RISK FACTORS FOR CEREBROVASCULAR DISEASE AND STROKE

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OXFORD

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Risk Factors for Cerebrovascular Disease and Stroke

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Foreword

THE DEVASTATING CONSEQUENCES of a stroke for the individual and for society are only too well known to the medical community. The Global Burden of Disease Stroke Experts Group recently reported in *The Lancet* that in 2010 there were 16.9 million people worldwide with a first stroke, 33 million stroke survivors, and about 6 million stroke-related deaths; in addition, 102 million disability-affected life years were lost. Of note, the global burden of stroke has increased substantially during the past two decades, with more than 75% of the burden being experienced in developing countries. Equally striking is the 3- to 10-fold variation in stroke burden across geographic regions. These are sobering figures that underscore the likelihood that the burden of stroke will likely escalate, given the aging of the world population. These data also point to the need for understanding the reasons for the geographic heterogeneity and varying burden of stroke worldwide.

Although these global trends seem alarming, they have to be juxtaposed against the major advances the medical community has made in the diagnosis of stroke and its prompt treatment and prevention during the past 50 years. During this time, stroke mortality has declined substantially. The decline can be attributed to an improved understanding of key stroke risk factors (from epidemiological studies), a changing landscape of the evidentiary basis for treating the condition (as a result of large, randomized, controlled clinical trials), and as a result of the major advances in the clinical care of stroke patients in intensive care stroke units. Indeed, one important related concept that is worth highlighting is that the day we make a clinical diagnosis of stroke in the emergency room is not when the disease process began. Indeed, the conventional starting point of medical treatment of a patient with an acute stroke represents medical failure—a failure of preventing the disease. The disease process itself begins with an inborn genetic susceptibility to the disease at birth, and continues to evolve throughout the entire adult life course, with continuous accrual of and exposure to key risk factors for stroke and the development of subclinical cerebrovascular disease that culminates in a clinical event one fine (or not so fine) day when a threshold is crossed. Several of these key risk

factors are lifestyle related. Thus, stroke is a life course and lifestyle-related disease condition that is eminently preventable.

To that end, this book is an outstanding attempt to elucidate carefully the panoply of risk factors for stroke, their synergistic interactions, and the spectrum of disease conditions encompassed by the simple term *stroke*, including variations with age and sex. The editors have compiled a comprehensive and exhaustive set of chapters that trace the evolution of disease propensity throughout the life course under the combinatorial influence of environmental and genetic risk factors. Each of the major sections, authored by experts in their respective domains, is complete by itself, provides state-of-the-art information on the subject matter, and integrates nicely with the other sections to offer a holistic view of how the disease condition evolves and how best we can predict, prevent, and treat stroke and its subtypes. The chapter on integrative approaches to disease prevention is consistent with the need of the hour—a combinatorial approach to disease risk prediction and prevention. Overall, the book is a goldmine of key information for a wide spectrum of readership—from medical students to residents and fellows to academic and practicing clinicians and neurologists. I congratulate the authors and editors on this landmark achievement.

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I

Introduction

1

EPIDEMIOLOGY OF CEREBROVASCULAR DISEASE AND STROKE

Yannick Béjot and Emmanuel Touzé

Introduction

Evaluating the epidemiology of cerebrovascular disease and stroke is of major interest because it will help us to identify risk factors, will establish needs with regard to the implementation of dedicated services, and will guide and evaluate future prevention priorities.

This chapter provides methodological key points to understand the epidemiology of cerebrovascular disease and stroke, and presents updated data about the incidence, recurrence, mortality, and prevalence of the disease.

Methodological Issues in Epidemiological Studies of Cerebrovascular Disease and Stroke

DEFINITION OF STROKE AND TRANSIENT ISCHEMIC ATTACK

The use of a universally accepted definition of stroke is an essential requirement for the study of epidemiology. Stroke is defined classically using the World Health Organization (WHO) diagnostic criteria as "rapidly developing clinical signs of focal (at times, global) disturbances of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin."[1] Despite its apparently clear formulation, this definition raises some issues. First, if applied strictly, it would exclude patients with isolated symptoms, such as headache or paresthesia, but without neurological signs on examination, although some patients may have actually had a stroke. Consequently, it has been proposed that "symptoms" be substituted for "signs,"[2] and this somewhat modified definition is in fact applied in stroke epidemiological studies. Second, this definition excludes transient ischemic attack (TIA), which refers to patients with an acute focal loss of brain or monocular function with symptoms lasting less than 24 hours.[3] Recently, however, this

arbitrary 24-hour time limit has been challenged because a large majority of TIAs have a shorter duration (usually less than 1 hour) and are sometimes associated with ischemic lesions on brain imaging (especially diffusion-weighted magnetic resonance imaging), all the more so when symptom duration is long.[4,5] In 2002, these observations led to the redefinition of TIA as a "brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 h, and without evidence of acute infarction."[6] Although the new definition emphasizes that TIA is not a benign event, it is difficult to apply in epidemiological studies because the categorization of a cerebrovascular event as TIA or stroke is influenced considerably by access to diagnostic resources—the proportion of brain magnetic resonance imaging performed in patients with transient neurological symptoms, and also the sensitivity of diagnostic techniques, both of which are highly inconsistent among studied populations.[7] Consequently, the use of the classic definition of TIA and stroke appears to be more reliable for epidemiological studies.

WHAT IS MEASURED BY EPIDEMIOLOGICAL STUDIES?

Stroke epidemiological studies provide data on the incidence, prevalence, case fatality, and mortality rates of stroke (Box 1.1), all of which contribute to our understanding of the disease in different but complementary ways.

Hence, ascertaining stroke incidence is useful to establish the need for acute stroke services in a given area. Geographic comparisons of stroke incidence help to identify individual and environmental vascular risk factors, and determining temporal trends can reveal the efficacy of prevention strategies in reducing stroke occurrence. Case fatality rates reflect the severity of the disease and the efficacy of care management of patients with stroke; mortality rates identify the global burden of stroke in a population and thus allow comparisons with other diseases. As for incidence, geographic and temporal comparisons of case fatality rates are of a great interest. Stroke prevalence, which is the most difficult parameter to evaluate in epidemiological studies, is useful as it can be used to determine the need for poststroke facilities and to reveal the long-term complications of stroke, such as functional impairment, depression, and dementia.

More recently, the concept of disability-adjusted life years (DALYs) has been developed from the WHO Global Burden of Disease Project to measure the global burden of the disease and its consequences in terms of premature mortality and living with disability.[8,9] DALYs lost corresponds to the sum of years lost as a result of premature death, and years of healthy life lost because of disability. DALY is derived from population-based data on stroke incidence, prevalence, fatality, and disability levels. This measurement reflects explicitly the adverse consequences of stroke in a population and is useful for worldwide comparisons.[10]

HOW DOES ONE STUDY STROKE EPIDEMIOLOGY?

Prospective population-based stroke registries are the most reliable tools to provide accurate information on stroke epidemiology. Contrary to hospital-based studies, which are prone to referral bias, population-based registries contain an unbiased sample of incident cases. This makes it possible not only to calculate incidence rates, but also to obtain other important information, such as early and long-term case fatality rates, poststroke morbidity (handicap, epilepsy, depression, dementia), and recurrent events. They can also be used to assess and improve stroke management, measure the usefulness of investigations and the place of care, and provide a setting for case–control studies of risk

BOX 1.1
DEFINITION OF THE MAIN PARAMETERS MEASURED BY STROKE EPIDEMIOLOGICAL STUDIES

Incidence rate: the number of new cases of stroke in a given population in a given time period, usually expressed as the number of new cases per 100,000 population at risk per year. Because crude incidence rates are influenced by the structure of the studied population in terms of age and sex, standardization by applying age- and sex-specific rates to a "standard" population is necessary to allow reliable comparisons among studies.

Case fatality rate: the proportion of patients with stroke who die within a certain period of time. Early case fatality rates are usually expressed as the percentage of patients with stroke who die within the first 28 days or 1 month after a stroke occurrence.

Mortality rate: the number of deaths resulting from stroke in a given population in a given time period, usually expressed in units of deaths per 1000 individuals per year. To make the results of studies comparable with those in populations with different age and sex structures, the standardized mortality ratio represents a proportional comparison with the numbers of deaths that would have been expected if the population had been of a standard composition in terms of age and gender.

Prevalence rate: the number of people with a history of stroke in a given population at a given time, usually expressed in units per 1000 individuals per year. Prevalence is influenced largely by both the incidence and the case fatality of stroke—the greater the incidence, the greater the prevalence; and, inversely, the greater the case fatality, the lower the prevalence.

factors.[11] Several criteria for running "ideal" stroke incidence studies have been defined to make their findings comparable (Box 1.2).[2,11,12]

However, such studies are time-consuming and expensive, which explains why only 56 of these studies conducted by 47 centers were found in a recent review of published data on incidence and early case fatality from 1970 to 2008.[13] In addition, population-based registries are limited by the relatively small population covered, which may not reflect the composition of the entire population of a country. Indeed, differences among the various regions of a country, in terms of socioeconomic level of the population or access to medical services, including primary prevention of cerebrovascular diseases, may be considerable. In addition, population-based studies are conducted principally within urban areas, and it has been clearly established that the incidence rates of stroke differ between urban and rural populations, in part as a result of variations in the distribution of vascular risk factors.[14,15] Last, only limited data from population-based registries are available for low- to middle-income countries, where stroke incidence rates are high.[13] For this last reason, a stepwise approach for the development of stroke registers (STEP Stroke) has recently been implemented by the WHO.[16] This stroke surveillance system begins with patients with stroke admitted to the hospital (step 1) and is completed, whenever possible, by the addition of stroke events identified outside the hospital. Events can be either fatal (step 2) or nonfatal (step 3). The feasibility of such a program has been demonstrated, and it will be helpful in obtaining reliable epidemiological data on stroke in low- to middle-income countries.[17]

BOX 1.2

CRITERIA FOR RUNNING HIGH-QUALITY INCIDENCE STROKE STUDIES

Use of standard definitions

- World Health Organization definition of stroke
- Classification into ischaemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage with at least 80% verification of diagnosis by computed tomography or magnetic resonance imaging.
- Classification of ischaemic stroke into subtypes (e.g., large-artery disease, small-artery disease, cardioembolic, other) if possible
- First-ever-in-a-lifetime only (for incidence calculations) and recurrent stroke

Standard methods for case ascertainment

- Complete population-based case ascertainment based on multiple overlapping sources of information: hospitals (including admissions for acute vascular problems and cerebrovascular imaging studies and/or interventions), outpatient clinics (including regular checking of general practitioners' databases), and death certificates
- Prospective study design, ideally with "hot pursuit" of cases
- Large, well-defined stable population
- Follow-up of patients' vital status for at least 1 month
- Reliable method for estimating denominators (census data not more than 5 years old)

Standard data presentation of the findings for comparisons among studies

- Complete calendar years of data to avoid the influence of seasonal fluctuations, and not more than 5 years of data averaged together
- Men and women presented separately
- Recommended reporting of age-specific estimates within standard mid-decade age bands (e.g., 45–54 years), including oldest age group (≥85 years)

Incidence of Stroke and TIA

CURRENT INCIDENCE OF STROKE WORLDWIDE

In 2005, the WHO estimated that, worldwide, approximately 16 million people sustained a first-ever stroke annually.[18] Data from population-based studies conducted at the beginning of the 21st century revealed considerable geographic variations in the incidence of first-ever stroke (Figure 1.1).[19–35]

Standardized incidence currently ranges from 66 to 220/100,000/year, and the highest rates are observed in low- to middle-income countries, although the data available in these areas are rather limited. Older studies also observed this excess in stroke incidence in Eastern Europe; it was 238/100,000/year in Uzhhorod, West Ukraine, in 1999 to 2000,[36] and 155/100,000/year in Novosibirsk, Russia, in 1992.[37] Of note, no studies that meet the quality criteria for the estimation of incidence have been conducted in Africa. Nonetheless, estimates suggest that 8% of all first-ever strokes occur on this continent,[18] and incidence rates were estimated to be, respectively, 109/100,000/year and 316/100,000/year in two rural area in Tanzania in a survey done between 2003 and 2006.[38]

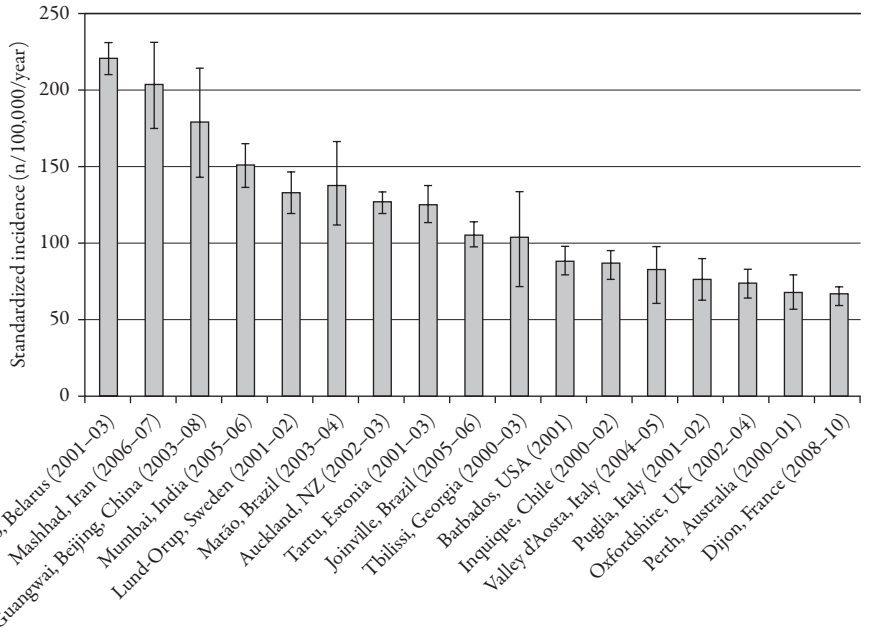

FIGURE 1.1 Worldwide stroke incidence according to contemporary, high-quality population-based registries. Incidence is age adjusted using the world population as the standard.

Sex differences in stroke incidence have been noted. Age-adjusted incidence rates are 1.5 times greater in men than in women in European registries (Figure 1.2).[19,32,39–41]

Similar results are found outside Europe.[42] However, the greater life expectancy of women, together with the increasing incidence rates with age, explain why more women sustain stroke in terms of absolute number. Of note, this excess in stroke incidence in men is particularly marked in people age 55 to 75 years old, whereas an inverse trend has been reported in older people.[43]

DISTRIBUTION OF STROKE SUBTYPES

Although ischemic stroke is the most frequent subtype, accounting for 55% to 90% of all cases, some worldwide variations in subtype distribution are observed (Figure 1.3).[19–25,27–35,39–41]

In contemporary population-based registries, the proportion of intracerebral hemorrhage reaches 22%. Older studies reported a greater proportion of hemorrhagic stroke in Asia, where they account for up to 35% of all strokes,[44,45] than in western countries. This disparity was attributed initially to a different distribution of genetic, environmental, sociocultural, and vascular risk factors. However, recent reliable data from a population-based study conducted in Beijing did not indicate an excess of intracerebral hemorrhage, and previous findings may, in part, have been distorted by poor methodology applied in these studies and/or changes in vascular risk factors over time.[21] Interestingly, in low- to middle-income countries, incidence rates of intracerebral hemorrhage and subarachnoid hemorrhage are almost twice those in high-income countries.[13]

Ischemic stroke itself is also a heterogeneous disease with different etiologic subtypes, usually classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[46] Population-based studies have demonstrated large differences in the distribution of these subtypes among ischemic patients with stroke, which may be the result of a number of reasons (Figure 1.4).[47–54]

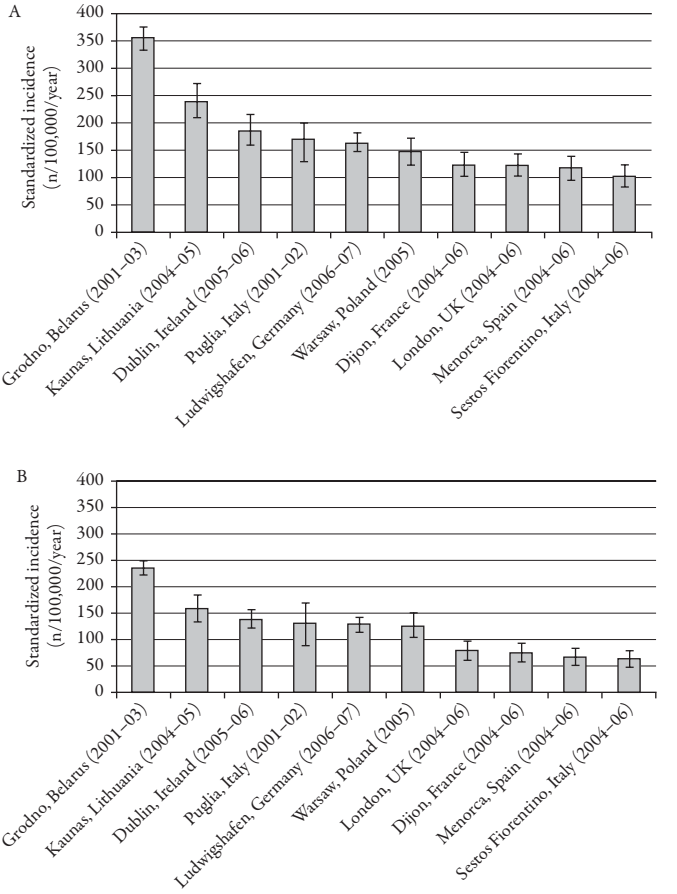

FIGURE 1.2 (A, B) Standardized incidence of stroke in men (A) and women (B) in contemporary European population-based registries. The European population is used as the standard.

First, the age structure of the study population is of major importance because the frequency of ischemic subtypes differs according to age. For example, the proportion of cardioembolic stroke increases sharply with age because of the rise in the prevalence of atrial fibrillation in elderly people.[55] Conversely, the category "other cause" is more frequent in young people, given the high proportion of cervical dissection at this age.[56] Second, race/ethnic discrepancies may also account for variations among studies in ischemic stroke subtype distribution, which can be explained by differences in the prevalence of vascular risk factors, and in both socioeconomic status and environmental status.[48,49,53] Last, because the TOAST classification requires the use of diagnostic procedures, discrepancies in access to medical resources can account for differences in the findings of studies. Consistent with this remark, the proportion of ischemic stroke of undetermined cause ranges from 22% to 52%. This category includes patients with insufficient diagnostic investigation.

TEMPORAL TRENDS IN STROKE INCIDENCE AND PROJECTIONS

In recent decades, few studies have evaluated temporal trends in stroke incidence. Stable incidence was observed in Dijon, France (1985–2006)[57]; and Rochester, Minnesota (1970–1989)[58]; whereas

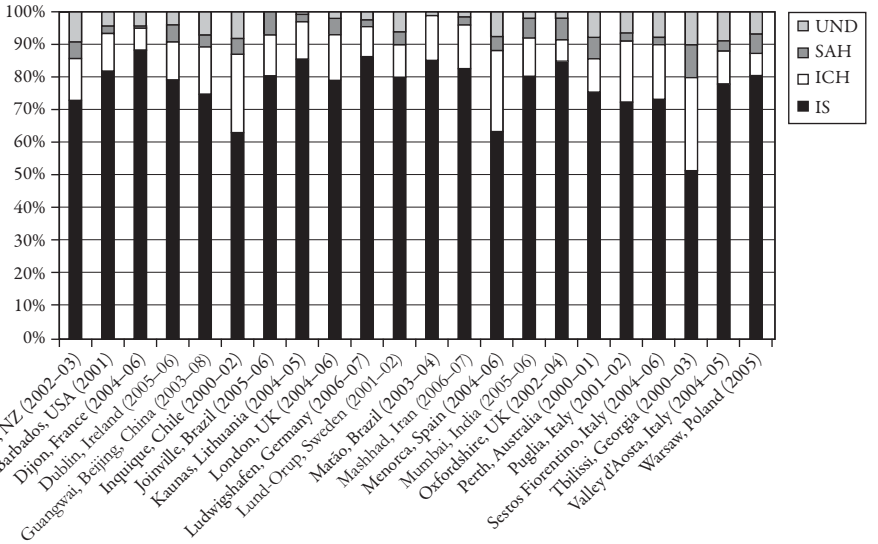

FIGURE 1.3 Distribution of stroke subtypes in contemporary stroke incidence studies. ICH, intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage; UND, undetermined stroke.

decreasing rates were noted in Oxfordshire, UK (between 1981–1984 and 2002–2004)[33]; Tartu, Estonia (between 1991–1992 and 2001–2003)[26]; Perth, Australia (between 1989–1990, 1995–1996, and 2000–2001)[34]; Auckland, New Zealand (between 1981–1982, 1991–1992, and 2002–2003)[25]; Val d'Aosta, Italy (between 1989 and 2004–2005)[31]; Joinville, Brazil (between 1995 and 2006)[59]; and Novosibirsk, Russia (from 1982–1992).[60] Conversely, stroke incidence increased in Lund-Orup, Sweden (between 1983–1985, 1993–1995, and 2001–2002).[23]

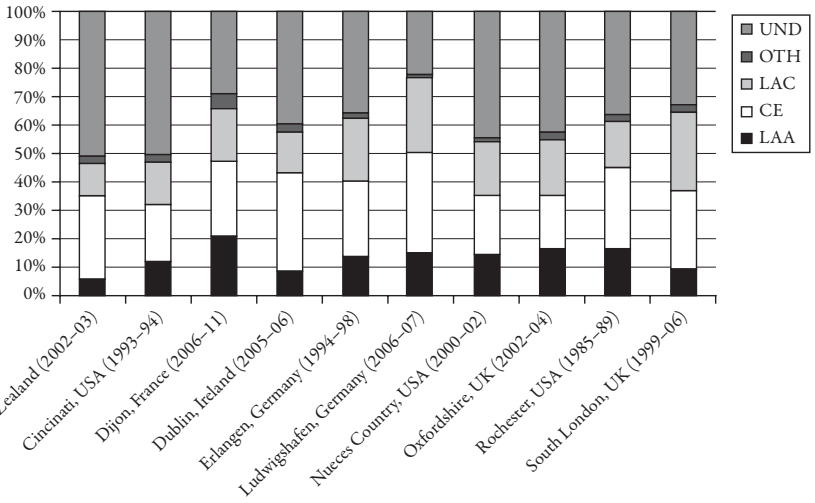

FIGURE 1.4 Distribution of etiologic subtypes of ischemic stroke in population-based studies. CE, cardioembolic; LAA, large-artery atherosclerosis; LAC, lacunar; OTH, other cause; UND, undetermined cause.

A meta-analysis of available data concluded there was a 42% decrease in stroke incidence in high-income countries from 1970 to 2008, whereas stroke incidence in low- to middle-income countries more than doubled during the same time.[13] Of note, these divergent trends were evident in both younger (<75 years) and older (≥75 years) individuals, although they were more pronounced in the older group. Improvements in preventive treatment and reductions in risk factors at the population level account for the reduction in stroke incidence in high-income countries, whereas the increase in stroke incidence observed in low- to middle-income countries could reflect the health and demographic transitions in these countries, and underlines the urgent need for the implementation of preventive strategies in these regions. Concomitant with these temporal trends in incidence, the mean age at stroke onset has increased over time in high-income countries, which may reflect the aging population and improvements in primary prevention leading to an increase in stroke-free life expectancy.[61]

Last, the WHO estimates indicate that the total number of first-ever strokes is expected to rise to 23 million annually by 2030 in the absence of additional populationwide interventions.[62]

INCIDENCE OF TIA

Only limited data about the incidence of TIA are available in the literature, probably because of the difficulty to investigate this disease reliably, resulting from the fact that diagnosis is sometimes difficult, and that a high proportion of patients with TIA do not seek medical attention, making it hard to obtain exhaustive case ascertainment. Recent population-based studies have estimated that age adjusted to the European population TIA incidence ranges from 28 to 59/100,000/year.[33,63–65]

Stroke Recurrence

After a first-ever stroke, the cumulative risk of recurrence ranges from 1% to 4% at 1 month, from 7% to 13% at 1 year, and reaches almost 40% at 10 years (Table 1.1).[66–70]

However, this risk may be underestimated, because studies excluded from the definition of stroke recurrence any stroke that occurred within 7 or 21 days in the same territory as the first event. Hence, when these patients with early recurrence were taken into account, the 3-month recurrence rate was substantially greater—about 15%—in the Oxford Vascular Study.[71]

Similar recurrence rates are observed for ischemic stroke and intracerebral hemorrhage, whereas patients with subarachnoid hemorrhage have a lower risk of stroke recurrence (<10% at 10 years).[66] The ischemic stroke etiologic subtype is associated strongly with recurrence. A meta-analysis of population-based studies revealed that 3-month recurrences were more frequent in ischemic stroke from large-artery atherosclerosis (14.3%) than in cardioembolic stroke (7.7%), lacunar stroke (2%), and ischemic stroke from undetermined cause (5.6%).[72] Patients presenting with a TIA are also at a high risk of subsequent stroke. The recurrence rates have been estimated at 5% at 7 days, and population-based studies demonstrated an annual risk ranging from 2% to 5% (although very early recurrences were excluded in these studies).[73]

Besides the risk of subsequent stroke, patients with stroke may also have other vascular diseases. The risk of myocardial infarction is 2.2%, and that of nonstroke vascular death is 2.1% (95% confidence interval, 1.9–2.4).[74] Very similar numbers are observed in patients with TIA.[73]

TABLE 1.1

Recurrence after first-ever stroke in population-based studies using a similar definition

Study place	Study period	Type of stroke included	Recurrence rates (%)					
			1 Month	6 Months	1 Year	2 Years	5 Years	10 Years
Erlangen, Germany	1994–1998	Ischemic stroke				10		
Northern Manhattan, New York	1990–1997	Ischemic stroke	2		8		18	
Oxfordshire, UK	1981–1986	Overall stroke		9	13		30	
Perth, Australia	1995–1996	Overall stroke	1	6	9		23	
Rochester, Minnesota	1975–1989	Ischemic stroke	4	9	12	17	29	39
South London, UK	1995–2004	Overall stroke			7		16	25

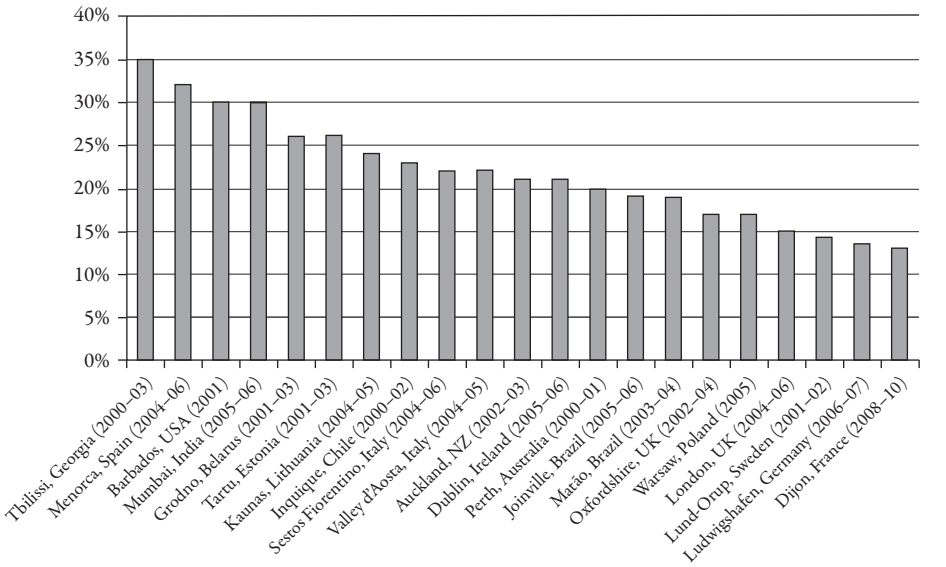

FIGURE 1.5 One-month case fatality rates of stroke in contemporary population-based registries.

Stroke Mortality

One-month case fatality rates of stroke range from 13% to 35% (Figure 1.5) in contemporary population-based registries.[19,22–24,26–32,33,34,40,41,75,76]

Rates are the highest for intracerebral hemorrhage (25%–61%) and subarachnoid hemorrhage (26%–48%), and the lowest for ischemic stroke (9%–19%). In addition, a poorer outcome is noted in low- to middle-income countries than in high-income countries. Less data are available for long-term mortality. Rates range from 25% to 38% at 1 year, 50% to 60% at 5 years, and up to 75% at 10 years.[24,75,77–84]

The prognosis of patients with ischemic stroke is heterogeneous and depends greatly on the underlying etiologic subtype. Worse survival is observed in patients with cardioembolic stroke (range, 40%–55% at 2 years) and, to a lesser degree, in those with stroke from large-artery atherosclerosis (range, 58%–80% at 2 years) compared with patients with lacunar stroke (range, 80%–90% at 2 years).[84–88]

Stroke is responsible for approximately 6 million deaths each year worldwide, and 85% of stroke deaths occur in low- to middle-income countries.[62] Age- and sex-adjusted mortality rates for stroke varies from 24 to 251/100,000/year.[10] The highest rates are observed in North Asia, Eastern Europe, Central Africa, and the South Pacific. According to WHO projections, 7.8 million stroke deaths per year are expected by 2030.[62]

Prevalence and Burden of Stroke

Scarce information exists on the prevalence of stroke. Studies revealed that age-standardized prevalence for people age 65 years or older ranges from 36 to 73/1000 population.[89–91] On the basis of a review of available data, Hankey and Warlow[92] estimated that, in a population of 1 million in a developed country, 12,000 individuals have had a previous cerebrovascular event: TIA

(n = 3000), stroke (n = 8000), or both (n = 1000). As for incidence, stroke prevalence is 40% greater among men than women. The male-to-female ratio peaks in the age range of 65 to 74 years, whereas it tends to decrease drop in the 75- to 84-year age range, and significantly so in the a range of 85 years or older.[42] From WHO data, the worldwide prevalence of stroke survivors was estimated at 62 million globally in 2005, and projections indicate that it will increase to 77 million by 2030.[62]

Besides its deleterious consequences on survival, stroke resulted in more than 50 million lost DALYs worldwide in 2005, accounting for 13% of the global burden of disease in the population older than 60 years, and 38% of the burden of cardiovascular diseases in the same age group.[62] DALY loss rates are almost four times greater in low-income countries than in middle-income and high-income countries, and a greater burden is observed in several areas such as Asia, Eastern Europe, Central Africa, and the South Pacific.[10]

Conclusion

Stroke and cerebrovascular diseases are very frequent and are associated with adverse consequences in terms of death and disability. Although recent improvements have been observed in high-income countries, stroke incidence is increasing dramatically in developing countries. Furthermore, the worldwide aging population will lead to an increase in the absolute number of patients experiencing a cerebrovascular event. These data clearly indicate the urgent need for a better identification and understanding of risk factors to improve both primary and secondary prevention.

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II

Genetic Risk Factors

2

INTRODUCTION TO GENETIC RISK FACTORS FOR CEREBROVASCULAR DISEASE

Bradford B. Worrall

Introduction

Reports of familial occurrence of cerebrovascular disease date to antiquity. During the seventh century BCE, two brothers who were successive Elamite kings appear to have had strokes that ended their reigns, and these familial strokes likely contributed to the Assyrian ascension and ultimate domination at the time.[1] Stroke remains a devastating personal and public health burden. Understanding the genetic contributors to stroke risk provides information on individual or population risk that may allow targeted intervention, prevention, or treatment. Perhaps more important, the investigation of genetic risk in cerebrovascular disease can provide insights into the fundamental biology and pathophysiology of these diseases, and this improved mechanistic knowledge can lead to new and better targeted therapies. Stroke and cerebrovascular disease present a classic "lumper" versus "splitter" conundrum. Ultimately, genetics may prove that lumping or splitting or both are appropriate, but for now this phenotypic heterogeneity presents a challenge for researchers and clinicians.[2]

Genetic conditions such as sickle cell and Fabry disease have long been recognized as having increased risk for stroke as part of these diseases.[3] In addition, specific monogenic stroke conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, and retinal vasculopathy with cerebral leukodystrophy (also known as hereditary endotheliopathy retinopathy nephropathy and stroke) manifest as ischemic stroke.[4] Genetic forms of intracerebral hemorrhage (familial amyloid angiopathies) and vascular malformations (cerebral cavernous malformations, Osler-Weber-Rendu, and so on) that include cerebral vascular malformations as a primary or secondary phenotypic component are also often monogenic or single-gene conditions.[5,6] Intracranial aneurysm can occur in syndromic connective tissue diseases (adult polycystic kidney disease, vascular Ehlers-Danlos, Loeys-Dietz syndrome, COL4A1 syndrome, or Marfan disease).[7] Newly described genetic disorders such as aortic aneurysm/Moyamoya disease associated with

mutations of the *ACTA2* gene have challenged our conceptualization of nonatherosclerotic arteriopathies, demonstrating a clear overlap among these phenotypes.[8] These monogenic conditions are rare individually; collectively, however, they account for an important clinical population and furthermore provide insight into the mechanisms and pathophysiologies of the corresponding common forms of cerebrovascular disease.[6]

The contributions of genetic variation to more common forms of cerebrovascular disease fall under the category of "complex genetics," in which genetic variants play a probabilistic rather than a deterministic role in risk for stroke. These genetic risks often interact with environmental exposures or other genetic or nongenetic heritable factors. Indeed, genetics may influence any complex phenotype through multiple mechanisms (Table 2.1). Genetic factors may directly alter the risk for a disease. Genetics may alter the severity of a disease (i.e., if you get the disease, you are affected more severely). Similarly, genetics may alter people's susceptibility to or severity of key risk factors such as hypertension or dyslipidemia. Gene-by-environment interactions can influence risk in the presence of an exposure such as cigarette smoking. Last, genetics may alter recovery from injury. Given that cerebrovascular disease represents multiple distinct and overlapping pathophysiological processes, the complexity quickly increases. Furthermore, as genetic researchers begin to identify novel mechanisms, the putative mechanism of genetic influence may change. For example, something thought to have a direct effect on risk may be discovered to mediate through a previously unrecognized interaction with a risk factor.

To date we have a handful of established or highly promising stroke genes for ischemic stroke[9] and ischemic stroke subtypes,[10–14] as well as intracerebral hemorrhage[15] and intracranial aneurysms.[16,17] Recent and ongoing efforts strive to amass an adequate number of stroke cases to have adequate

TABLE 2.1

Mechanisms by which genetic factors may influence complex phenotypes

General	Cerebrovascular specific	Example
Directly influence stroke risk	Harboring a particular genetic variant raises or lowers risk of stroke phenotype.	HDAC9
Influence severity	Harboring a particular genetic variant modifies the severity of the stroke phenotype if experienced.	Ischemic tolerance/ vulnerability
Influence likelihood of risk factor	Harboring a particular genetic variant raises or lowers the risk of a risk factor for a stroke phenotype.	Genetic determinants of T2DM
Influence response to risk factor	Harboring a particular genetic variant influences the likelihood of a cerebrovascular phenotype in the presence of a risk factor.	GWAS of CVD in T2DM
Influence response to an environmental exposure	Harboring a particular genetic variant influences the likelihood of a cerebrovascular phenotype in the presence of an environmental exposure.	Interaction of smoking and genetic burden in intracranial aneurysm
Influence recovery	Harboring a particular genetic variant influences recovery.	Neural plasticity

CVD, cerebrovascular disease; GWAS, genomewide association study; HDAC9, histone deacetylase 9; T2DM, type 2 diabetes mellitus.

power for discovery, as has been applied successfully to other complex genetic diseases and conditions using tens to hundreds of thousands of cases with substantial increases in yield with the successively larger data sets. The heterogeneity of mechanistic phenotypes included under stroke or even ischemic stroke rapidly partition even these larger samples into modest numbers at best. All of this occurs against a backdrop of waning enthusiasm for genomewide association studies (GWASs) as an approach. Next-generation genomics, gene expression, and epigenetics hold promise to help explain the "missing heritability" for stroke and other phenotypes.[18] Nevertheless, GWASs remain important and incompletely explored approaches for diseases such as stroke. Moving forward, GWASs will likely contribute in parallel to these and other newer approaches.

International efforts such as the International Stroke Genetics Consortium (ISGC) and METASTROKE provide venues for this important collaborative effort that bridge and supplement funded efforts such as the Wellcome Trust Case Control Consortium II—Stroke, the Australian Genetics Stroke Collaboration, and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium in ischemic stroke and related phenotypes. We anticipate the first results from the National Institute of Neurological Disorders and Stroke–funded Stroke Genetics Network in fall 2015, with cross-consortial meta-analyses and replication planned. Working groups in the ISGC focused on intracerebral hemorrhage and intracranial aneurysm genetic risk. This book represents a great deal of recent and ongoing work that is hot off the presses. It is an exciting but daunting time in stroke genetics.

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3

MONOGENIC DISEASES CAUSING CEREBROVASCULAR DISEASE AND STROKE

Anna Bersano

Introduction

Stroke represents a leading cause of mortality and long-term disability in developed countries.[1] Conventional and modifiable risk factors such as hypertension, atrial fibrillation, and smoking explain only a part of stroke risk, supporting the idea that risk factors not yet identified could contribute to stroke pathogenesis.[2,3] Evidence from epidemiological and twin studies support the contribution of genetic factors to stroke occurrence and outcome, although the extent of genetic predisposition is uncertain.[4–6] However, it is expected that the identification of such factors provides insights in understanding the pathophysiology of stroke aimed at developing new prevention strategies and drug therapies. The genetic contribution to common stroke is believed to be polygenic, and a monogenic basis is recognized in a small percentage of cases. However, although considered rare and believed to account for about only 1% to 5% of all strokes, monogenic diseases are probably underrecognized.[4,5] Despite some elements such as young age at onset, positive familial history, presence of specific associated clinical features, and absence of conventional vascular risk factors, which may support a suspicion of monogenic disease, the latter can be underdiagnosed simply because physicians may not include them in the differential diagnoses. Also, there may be a pleiomorphic phenotypic spectrum, in which stroke may be only one part of a systemic disorder.[7] Although rare, the diagnosis of monogenic conditions causing stroke is important for the implementation of correct management, including genetic counseling, preventive measures, and therapeutic decisions, because they are often either life-threatening or complex chronically debilitating diseases with difficult management.[8–10] Moreover, understanding the pathophysiology of these disorders may provide insight into the mechanisms underlying multifactorial ischemic stroke.

A large number of single-gene disorders have been described so far as well-known causes of stroke. However, in the literature they are not classified in a standardized and homogeneous way as a result of the phenotype variability and the association with different stroke types and subtypes

(hemorrhagic or ischemic, cardioembolic, small-vessel disease, and large-vessel disease).[8] Other than the most common monogenic diseases associated with stroke—such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); Fabry disease; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); and Marfan syndrome—other rarer single-gene diseases, associated particularly with the cerebral small-vessel disease feature, such as collagen 4A1 (COL4A1) syndrome, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), and hereditary endotheliopathy, retinopathy, nephropathy, and stroke, have been identified more recently.

In this chapter, we provide an updated review of monogenic stroke disorders associated with ischemic and hemorrhagic stroke, including a detailed description of their epidemiology, clinical and neuroradiological presentation, genetic and pathophysiological aspects, diagnostic features and therapeutic measures. We do not discuss in detail inherited connective disorders such as vascular Ehlers–Danlos syndrome (type IV), arterial tortuosity syndrome, Marfan syndrome, *Pseudoxanthoma elasticum*, and about Moyamoya disease, which are quite rare diseases that can also lead to ischemic stroke but are associated more frequently with cervical artery dissection (with or without ischemic stroke), carotid–cavernous fistula, intracranial dissections, and aneurysms potentially causing subarachnoid or intracerebral hemorrhage.

Table 3.1 summarizes the main clinical features of monogenic disorders associated with stroke.

Small-Vessel Diseases

CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY

CADASIL (Online Mendelian Inheritance in Man [OMIM] 125310-600276) is an autosomal dominant disease involving small cerebral arteries, and it affects middle-age adults.[11,12] It is the most common Mendelian cause of stroke.

Epidemiology

CADASIL has been reported in more than 500 families worldwide, but its overall prevalence remains uncertain probably as a result of underrecognition of the variable phenotypic expressions. The estimated prevalence in populations of European descent varies from 2 to 4/100,000.[13–15]

Clinical Presentation

Although clinical presentation of CADASIL varies substantially among and within families, the disease is characterized by four main clinical features: migraine with aura, subcortical ischemic events, mood disorders, and cognitive impairment. These symptoms vary with patient age and disease duration.[16,17] Migraine with aura, which has been observed in 20% to 40% of patients, is often the presenting clinical manifestation (onset around 30 years; range, 6–48 years). The most frequent manifestations in CADASIL are recurrent, subcortical ischemic events (transient ischemic attack [TIA] or stroke) and have been reported in 60% to 85% of patients (mean age at onset, 49 years; range, 20–70 years).[18] Ischemic events are almost invariably subcortical and occur typically in the absence of common cerebrovascular risk factors, although the concomitant presence of such risk factors (e.g., smoking and high cholesterol levels) may condition for an earlier stroke onset.[19,20] Ischemic events are generally recurrent (range, 2–5 events) and lead progressively to gait difficulty, urinary urgency, and pseudobulbar palsy.[16,21] The secondmost frequent clinical manifestation is cognitive impairment, which was observed in nearly all patients by the age of 50 years[22] and involves mostly executive

TABLE 3.1

Monogenic Disorders Associated with Stroke: Mode of Inheritance, and Clinical and Neuroradiological Features

Disease	CADASIL	CARASIL	HERNS	*COL4A1*	Fabry's disease	SCD	NF1	MELAS
Incidence	4–15:100,000	Exceptionally rare (50 cases)	Exceptionally rare	Rare	1:40,000–117,000	1:2500	1:3500	18.4 per 100,000
Pattern of inheritance	AD	AR	AD	AD	X-linked recessive	AR	AD	Maternal inheritance
Gene	*NOTCH3* (600276)	*HTRA1* (602194)	*TREX1* (606609)	*COL4A1* (605595)	α-GAL A gene (GLA; 300644)	β globin	NF1	80% tRNA Leu (UUR), (*MTTL1*)
Chromosome	19	10q25	3p21.3-p21.2	13q34	Xq22	11p15.5	17q11.2	mtDNA
OMIM	125310	60142	192315	120130	301500	603903	162200	540000
Clinical manifestations								
Stroke	60–85%	50%	Yes	17.3%	24–48% (M), 7–32% (F)	Yes, 25% by 45 years	Yes, rare	Yes, strokelike
Age at onset, y	49 (range, 20–70)	32 (range, 20–44)	40–50	36.1 (range, 14–49)	33–46 (M), 40–52 (F)	Childhood	Childhood	<40 years
Stroke subtype								
Small-vessel disease	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Large-vessel disease	1 report	No	No	No	Yes	Yes	Yes	Yes
Cardioembolic	No	No	No	No	Yes	No	No	Yes
Hemorrhagic	Rare	Rare	No	Yes	Yes	Yes	Yes	No
Other neurological manifestations								
Psychiatric disturbance	20%	Yes	Yes	Yes; depression, 4%	Yes, depression	Yes	No	Depression, 31%
Migraine with aura	20%–40%	Yes	Yes (70%)	Yes (19%)	No	No	Yes	Headache, 77%–91%
Seizures	5%–10%	No	Yes	Yes, 21%	Yes	Yes	Yes	Yes

(*continued*)

TABLE 3.1

Continued

Disease	CADASIL	CARASIL	HERNS	*COL4A1*	Fabry's disease	SCD	NF1	MELAS
Cognitive impairment	Vascular dementia	Vascular dementia	Yes	Yes, 4%; developmental delay	Yes, learning and growth delay	Yes	Yes, learning disabilities	Yes; memory problems, 71%–90%; learning deficits
Acute encephalopathy	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Extraneurological manifestations								
Neuropathy	No	No	No	No	Yes, small-fiber neuropathy	No	Yes; neurofibroma, schwannoma	Yes
Dysautonomic features	No	No	No	No	No	No	No	No
Myopathy	No	No	No	Yes	No		No	Yes; weakness, 89%; exercise intolerance, 93%
Renal disease	No	No	Yes	Yes	Yes	Yes	No	Occasionally reported
Skin involvement	No	No	Yes	No	Yes, angiokeratoma	No	Yes, neurofibroma	Vitiligo pigmentary changes
Ocular involvement	No	No	Retinopathy with progressive visual loss; later stages of the disease, occlusion of branches of large retinal arteries	Yes, 47.6%; cataracts, retinal vessels tortuosity, retinal hemorrhages	Yes, cornea verticillata	No	Yes, ocular glioma, Lisch nodules	Yes, rare optic atrophy, pigmentary retinopathy

Gastrointestinal involvement	No	No	Yes	No	Yes, 19%–52%	No	No	Yes, 64%
Cardiac involvement	No	No	No	No	Yes; MI, valvular diseases, HCM, rhythm disturbances	No	No	Heart disease, 21%; conduction defects
Others	No	Alopecia, pseudobulbar palsy, spondylosis deformans, and acute lumbago with lumbar disc herniation, less common ataxia, ophthalmoplegia	Raynaud's phenomenon, 80%			Pain vaso-occlusive crises, acute chest syndrome, asthma, pulmonary artery hypertension, cholelithiasis priapism	Skeletal abnormalities, endocrine system (pheochromocytomas), CNS tumors, or malignant peripheral nerve sheath tumors	Hearing loss, 50%–77%; short stature, 33%; diabetes, 33%
Instrumental findings								
Cerebral MRI								
Stroke	Lacunar	Lacunar	Lacunar	Lacunar	Lacunar, subcortical, cortical	Lacunar and large vessel	Large vessel	Cortical
White matter lesions	Yes	Often relatively spared	Yes	Yes; white matter lesions, 63.5%; microbleeds, 52.9%; lacunar infarction, 13.5%; enlarged perivascular spaces, 19.2%	Yes, periventricular hyperintensities, multiple hyperintensities on T2- and FLAIR-weighted images affecting deep white matter	Yes, frontal and parietal lobes	UBOs	Yes
Aneurysms	No	No	No	Yes, 44.4%	Yes, basilar artery dolichoectasia	Yes, vertebrobasilar	Yes	No

(*continued*)

TABLE 3.1

Continued

Dise-ase	CADASIL	CARASIL	HERNS	COL4A1	Fabry's disease	SCD	NF1	MELAS
Age (complete expression), y	35	20–40	40–50	Perinatal/adults	54	20–49	—	20–40
Peculiar findings	Temporal lobe hyperintensities, external capsule involvement	Diffuse white matter abnormalities with small foci of lacunae similar to that observed in classic Binswanger encephalopathy	Subcortical contrast-enhancing lesions with surrounding edema	Porencephaly, 46.1%	Pulvinar hyperintensities on T1-weighted-images, 24%	Moyamoya disease	Moyamoya disease, UBOs, or "T2 hyperintensities" in at least 60% of children with NF1; neurofibromas, carotid artery stenosis	No classical vascular distribution, asymmetric cortical involvement (temporal, parietal, and occipital lobes), peculiar fluctuation of lesions over time
Laboratory findings								
Proteinuria	No	No	Yes	Yes	Yes	No	No	Yes
Lactic acidosis	No	No	No	Yes	no	No	No	Yes
Skin biopsy	GOM on electron microscopy (Sn, 85%–95%; Sp, 95%–100%	No GOM	Multilayer basement membranes beneath endothelial cells of capillaries, arterioles, and venules	Interruption and thickening of basement membrane	Typical cytoplasmic lipid inclusions	No	No	No

Brain biopsy	Diffuse demyelination of the cerebral white matter/small-vessel pathology	Diffuse demyelination of the cerebral white matter with some preservation of U fibers (consistent with small- vessel disease)	Subpial and subcortical white matter gliosis in the absence of inflammation or vasculitis	No	Deep matter lesions that may include lacunar infarctions or may be associated with small-arteriole narrowing	Stenosing arteriopathy and vasculopathy hypertrophy of the intima and media layers of large arteries	Neurofibroma usually consisting of a mixture of cell types including Schwann cells, fibroblasts, endothelial cells, pericytes, mast cells, and perineural cells; abnormal proliferation of spindle cells and of intima with fibrous thickening and mesodermal dysplasia or fibromuscular hyperplasia; micronodular formations of smooth muscle aggregates on the walls of vessels	No
Muscle biopsy	No	No	No	Normal	No	No	No	Ragged red fibers; cytochrome *c* oxidase activity (complex IV) only partially reduced

AD, autosomal dominant; AR, autosomal recessive; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; F, female; FLAIR, fluid-attenuated inversion recovery; GOM, granular osmiophilic material; HERNS, hereditary endotheliopathy retinopathy nephropathy and stroke; M, male; *MELAS*, Mitochondrial myopathy, encephalopathy, lactic acidosis and strokelike episodes; MI, myocardial infarction; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NF1, neurofibromatosis type 1; SCD, sickle cell disease; tRNA, transfer RNA; UBO, unidentified bright object.

functions and processing speed,[23] but may be associated with deficits in memory and attention. Cognitive decline is commonly progressive and worsens with recurrent stroke. Mood disorders are reported in 20% to 31% of patients and are characterized primarily by severe depression and apathy, which are the onset clinical symptoms in 1.2% to 9% of cases.[16,24,25] The origin of these disturbances is still unknown, although vascular damage of cortical–subcortical circuits has been suggested.[26] Other less common clinical manifestations are seizures, which have been reported in 5% to 10% of patients, intracerebral heamorrhage,[27,28] deafness and parkinsonism.[22]

Brain Imaging

Magnetic resonance imaging (MRI) changes, characterized mostly by leukoencephalopathy and lacunar infarcts, can be detected in all patients with CADASIL after the age of 35 years and generally precede symptom onset by 10 to 15 years. The earliest changes are diffuse hyperintense lesions on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images affecting the periventricular areas and centrum semiovale. Lacunar infarcts are located mostly in subcortical white matter, basal ganglia, thalamus, internal capsule, and brainstem. These lesions were found in 75% of patients age 30 to 40 years, and their appearance increased with age.[29] Cortical microinfarcts have also been observed with high-resolution MRI in postmortem cerebral tissues.[30] Involvement of the anterior temporal lobe and external capsule is highly suggestive of CADASIL,[31,32] with a sensitivity and specificity of 90% and 100%, respectively. Lesional patterns become more severely diffuse with disease progression, and confluent hyperintensities on FLAIR images in the thalamus have been observed in about 12% of patients with CADASIL that were found to be associated significantly with age and related independently to the volume of white matter hyperintensities.[25,33] Other radiological features reported in CADASIL are subcortical microbleeds and cerebral atrophy.[34] Lacunar infarcts, but also microbleeds and ventricular volume, have been identified as the most important MRI parameters associated with cognitive disfunction,[26,35] whereas the association between cerebral atrophy and cognitive impairment in CADASIL is controversial.[34,36]

Genetics, Pathogenesis, and Pathological Aspects

CADASIL is an autosomal dominant disease caused by a mutation in the *NOTCH3* gene on chromosome 19q12 encoding a 2321-amino acid single-pass transmembrane receptor with an extracellular domain containing 34 epidermal growth factor repeats (EGFRs) with six cysteine residues, three Notch/Lin12 repeats, a single transmembrane domain, and an intracellular domain.[37,38] CADASIL results from mutations in exons encoding EGFRs (exons 2–24), with clustering in exons 3 and 4. However, a variation in mutational spectrum among CADASIL populations has been described.[39–41] Missense mutations account for 95% of cases, but small in-frame deletions or splice-site mutations have also been reported, all leading to a gain or a loss of a cysteine residue within the EGFR, thus altering the number of cysteine residues and leaving one unpaired.[22,42–45] Cysteine-sparing mutations of uncertain pathogenic significance associated with a CADASIL-like phenotype have been reported in a few patients.[46–49] The exact function of the *NOTCH3* gene is unknown. *NOTCH3* is expressed predominantly in vascular smooth cells of small arteries and pericytes of the brain,[50] as confirmed by microscopic and ultrastructural investigations, and *NOTCH3* knockout mice have been shown to have structural defects of small arteries resulting from altered differentiation of smooth cells and impaired autoregulation of cerebral blood flow.[51,52]

The Notch3 signaling pathway has been shown to be crucial to the structural and functional integrity of small arteries, and *NOTCH3* knockout mice have abnormally enlarged brain arteries with a thinner muscular coat and smaller smooth muscle cells.[51] It has been hypothesized that CADASIL mutated *NOTCH3* may interact with adjacent mutant receptors or other proteins

by anomalous disulfide bond formation, leading to spontaneously forming oligomers and higher multimeric complexes. This may lead to a selective accumulation of extracellular domain of Notch3 within the small artery in the proximity of vascular smooth muscle cells, ultimately resulting in vascular smooth muscle cell degeneration.[53] Microscopic and ultrastructural examination show an arteriopathy that affects mainly penetrating cerebral and leptomeningeal arteries, but also other organs such as spleen, kidney, muscle, aorta, and skin, although clinical manifestations are only cerebral. The arteriopathy is characterized by thickening of the arterial wall, leading to lumen stenosis, and by the presence of nonamyloid granular osmiophilic material within the media extending into the adventitia.[22,54]

Diagnosis

Although migraine, a familial history of stroke before the age of 60 years, the presence of diffuse white matter changes with anterior temporal lobe involvement and external capsule involvement, and lacunar infarcts were shown to be strong predictors of *NOTCH3* gene mutations in subjects with a clinical suspicion of CADASIL, the extremely variable phenotype hampers the identification of standardized, pregenetic screening clinical criteria.[31]

Skin biopsy showing, on electron microscopy, the presence of granular osmiophilic material within the vascular smooth cells is a highly specific diagnostic tool, but the sensitivity of this test is variable.[55–58] Immunostaining of skin samples with a NOTCH3 monoclonal antibody, which can detect accumulation of Notch3 in the vessel wall, seems to improve sensitivity up to 95%.[58] However, DNA sequencing of exons 2 to 24 of *NOTCH3* remains the gold standard for the diagnosis of CADASIL, with a 100% specificity in detecting a mutation that changes the number of cysteine residues in an EGFR. Genetic testing is indicated in patients presenting with a characteristic clinical syndrome, in combination with characteristic neuroimaging features and a positive familial history.

Treatment

Currently, there are no specific treatments of proven efficacy for patients with CADASIL. General therapeutic measures to relieve symptoms can be administered, whereas some drugs or proceedings should be avoided or used carefully because of their side effects.[59] Prophylactic drugs for migraine attack prevention such as beta blockers, flunarizine, amitryptiline, and topiramate should be used carefully, considering their potential side effects on cognition and mood, whereas sodium valproate can be used if there is coexisting epilepsy. Acetazolamide was proposed as a promising prophylactic treatment, probably providing an increase in cerebral perfusion, although it needs to be tested formally in a randomized controlled trial (RCT).[60,61] Because there is no specific drug for acute stroke in CADASIL, patients have to be treated similarly to other stroke patients. Common treatments for vascular risk factors and stroke prevention are recommended, given the possible role of risk factors in accelerating disease progression. Tissue plasminogen activator should be administered when patients meet clinical criteria. Conversely, it is unknown whether antiplatelet agents are effective in secondary stroke prevention, and their administration should be individualized based on patient risk factor profile and tolerance; antiplatelet use has been related to intracerebral hemorrhage in patients with CADASIL.[62] Posada et al.[63] conducted an open pivot trial on galantamine in four patients with CADASIL, without conclusive results. The first (and so far only) RCT of CADASIL randomized 168 patients with cognitive impairment to receive either 10 mg donepezil per day or placebo. Donepezil had no effect on the primary end point—the Alzheimer's Disease Assessment Scale cognitive subscale. Improvements were noted on measures of executive function, but the very short follow-up limits the clinical relevance of these findings.[64] Although the efficacy of selective serotonin

reuptake inhibitors in relieving depression or pseudobulbar syndrome have been demonstrated, there are no available studies that have tested drugs related mood disorders in patients with CADASIL.[59]

Last, supportive care and proper genetic counseling are necessary for patients with CADASIL and their family to help them in making informed medical and personal decisions, and minimizing potential psychological distress related to symptomatic or presymptomatic genetic testing.[59,65]

CEREBRAL AUTOSOMAL RECESSIVE ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY

CARASIL (OMIM 192315) is an autosomal recessive single-gene disorder affecting cerebral small arteries.

Epidemiology

The exact prevalence of CARASIL is unknown. To date, approximately 50 cases have been reported, mainly in Asian populations,[66,67] with the exception of one recently reported white (Spanish) patient.[68] Genetically, no founder haplotype has been identified, and thus CARASIL is expected to be underdiagnosed.[69]

Clinical Presentation

CARASIL was reported originally in two brothers who presented with juvenile onset of progressive encephalopathy with pyramidal and extrapyramidal signs, dementia, and alopecia.[70] In 1995, Fukutake and Hirayama[71] reviewed 17 patients with CARASIL. Alopecia was the first clinical symptom, present in approximately 90% of patients during adolescence. Hair loss is confined to the head and is diffuse. The second most common and early manifestation is a progressive encephalopathy, with onset from 20 to 44 years (mean, 32 years). Acute ischemic stroke, typically lacunar, mainly in the basal ganglia or brainstem, is reported in about half the patients. One patient developed a cerebral hemorrhage during an advanced course of the disease.[69] Severe back pain attacks with lumbar disc herniation were also reported to occur in the same time frame as the onset of encephalopathy.[71] Dementia is another common clinical feature, developed by age 30 to 40 years, and is characterized by memory impairment followed by disorientation in time, calculation deficits, and emotional lability up to severe memory deficits and abulia.[69]

Additional manifestations are pseudobulbar palsy, personality changes, pyramidal signs, gait disturbance, and spondylosis deformans; less commonly, patients presented with ophthalmoplegia, ataxia, and brainstem signs. The disease affects males predominantly (3:1) and the average illness duration is 20 to 30 years, although most patients became bedridden within 10 years from onset.[71,72]

Brain Imaging

T2-weighted cerebral MRI shows, by age 20 years, diffuse and symmetric high-signal intensity lesions more often in the periventricular and deep white matter with lacunar lesions in the basal ganglia and thalamus, which usually precede symptom onset.[71] Lesions extend during the disease course into the basal ganglia, thalami, brainstem, and cerebellum, and sometimes involve temporal lobes and external capsules as CADASIL. Atherosclerosis has been described in about half the patients on cerebral angiography.

Genetics, Pathogenesis, and Pathological Aspects

In 2009, Hara et al.[72] reported mutations in the *HTRA1* gene on chromosome 10q25 as causative of CARASIL. *HTRA1* encodes a 480-amino acid serine protease belonging to the chymotrypsin

family, conserved from prokaryotes to humans. Its structural complexity reflects its ability to act as chaperone and protease in various processes, including breakdown of the extracellular matrix, cancer, modulation of signaling pathways, osteoarthritis, age-related macular degeneration, and spinal disc degeneration. HTRA1 represses signaling by transforming growth factor (TGF)-β family members, with the protease domain located in exons 3 to 6. Mutations described in patients with CARASIL are mostly homozygous mutations in *HTRA1* exons 3 and 4, thought to cause dysregulation of TGF-β signaling.[72] Indeed, mutant proteins appeared unable to suppress TGF-β activity, leading to increased expression of *TGFB1* in the tunica media of affected small arteries. Increased expression of fibronectin, induced by TGF-β signaling, was found in the intima of patients with CARASIL.[67] Neuropathological examination revealed focal and diffuse demyelination with sparing of U fibers and severe arteriosclerotic changes in the small penetrating and leptomeningeal arteries, with fibrous intimal proliferation, hyalinosis, and intima splitting with concentric narrowing of the lumen.[70] Oide et al.[73] found sclerotic changes, with almost a complete disappearance of medial Smooth muscle cells (SMCs) in many arteries, thinning of adventitia, and increasing fragility of arterial walls, leading to collapse of arterial structure. No granular osmiophilic material or amyloid deposition were found.

Diagnosis

Although some clinical features of CARASIL are similar to CADASIL, early disease onset, mode of inheritance, presence of alopecia, and absence of migraine and mood disorders support the suspicion of CARASIL. Given the low involvement of extracerebral small arteries, genetic testing is the only diagnostic tool.

Treatment

No effective treatment is currently available. The efficacy of antiplatelet agents or anticoagulants for secondary stroke prevention is unclear. Genetic counseling and supportive care, as well as symptomatic drugs for dementia and cerebrovascular risk factors are suggested.[69]

AUTOSOMAL DOMINANT RETINAL VASCULOPATHY WITH CEREBRAL LEUKODYSTROPHY

Hereditary endotheliopathy with retinopathy, nephropathy, and stroke; cerebroretinal vasculopathy (CRV); and hereditary vascular retinopathy (HVR), originally reported as distinct disorders, have recently been found to be allelic variants of the same spectrum of disorders grouped under the name *retinal vasculopathy with cerebral leukodystrophy* (RVCL; OMIM 192315).[74–76]

Epidemiology

First described in 1988,[77] currently only a few patients and families have been described with RVCL.[74–83] Moreover, although RVCL is actually a known, heritable small-vessel disease, no epidemiological studies or systematic screening have been conducted so far.

Clinical Presentation

RVCL is a rare, adult-onset autosomal dominant disorder involving the small vessels and is associated with cerebral, ocular, and, less frequently, systemic vascular involvement. The clinical phenotype consists of progressive visual loss resulting from retinopathy followed by neurological involvement occurring during the third or fourth decade of life and consisting of stroke (mostly lacunar), seizures, migrainelike headache, psychiatric disturbances (personality disorders,

depression, and anxiety), or cognitive decline.[74,75,77–83] Typical clinical hallmarks are ophthalmologic findings characterized by retinopathy early during the course of the disease, with capillary dropouts and microaneurisms (particularly in the macular region and detectable on retinal fluorescein angiograms), leading to loss of central vision, prominent juxtafoveolar capillary obliteration, and telangiectasias.[83–85] Systemic vascular involvement manifests as mild liver dysfunction, with autopsy report of nodular regenerative hyperplasia and renal dysfunction of glomerular origin, with proteinuria and elevation of creatinine and renal histopathology suggestive of accelerated arteriolonephrosclerosis. Raynaud's phenomena, chronic anemia, and gastrointestinal symptoms, but also small-vessel bleeds, were also seen. Disease onset is during the fourth or fifth decade and there is 100% mortality over a 5- to 10-year period secondary to progressive neurological decline.[83]

Genetics, Pathogenesis, and Pathological Aspects

RVCL is an autosomal dominant disorder resulting from a *TREX1* gene mutation on chromosome 3p21.1-21.3. The *TREX 1* gene encodes a 314-amino acid 3′-5′ exonuclease DNAase III, which is part of the SET complex, a reticulum-associated complex translocating to the nucleus in response to superoxide generation by granzyme A. The latter is an activator of a caspase-independent pathway leading to apoptosis. TREX 1 and the endonuclease NM23-H1 are involved in DNA degradation.[86] A heterozygous 1-bp insertion (3688_3689insG) leading to a premature stop codon causes CRV and HVR, whereas a heterozygous 4-bp insertion (3727_3730dupGTCA) resulting in a frameshift has been shown to cause hereditary endotheliopathy with retinopathy, nephropathy, and stroke. Frameshift mutations affecting the C terminus of *TREX1* were found in families with RVCL, and in three of them the alteration was the same as that found in the CRV and HVR pedigrees.[87] Homozygous mutations in the *TREX1* gene have also been reported to cause Aicardi-Goutières syndrome, a rare, familial, early-onset, progressive encephalopathy with basal ganglia calcifications and cerebrospinal fluid lymphocytosis. Mutations associated with Aicardi-Goutières syndrome result in disruption of the enzymatic sites in TREX1 with loss of exonuclease function, which is likely to cause accumulation of altered DNA, triggering a destructive autoimmune response.[88] Heterozygous mutations observed in RVCL spare the region coding the catalytic function without altering the exonuclease function. Histopathology demonstrates coagulative necrosis secondary to an obliterative vasculopathy and minimal inflammatory infiltrate. Ultrastructural examination of the brain and other tissues including the kidney, gastrointestinal tract, and skin, showed multilayer basement membranes beneath endothelial cells of capillaries, arterioles, and venules.[74]

Brain Imaging

Computed tomography (CT) scans often show tumorlike lesions with displacement of the surrounding structures, and central contrast enhancement commonly in the frontoparietal region. Cerebral MRI findings usually consist of multiple subcortical hyperintense lesions on T2-weighted sequences involving the periventricular and deep white matter and corpus callosum, as well as contrast-enhancing tumorlike lesions with surrounding edema that may change over time and occur even in the absence of a neurological deficit.[74] Multiple cerebral calcifications on brain CT and MRI were also found.

Diagnosis

Currently, genetic testing is the only diagnostic tool, because clear, standardized clinical criteria have not been established.

Treatment

Given the few cases identified, no disease-specific treatment is available. Genetic counseling and secondary preventive measures such as antiplatelet agent use can be suggested based on empirical arguments.

COL4A1 SYNDROME

Mutations in the *COL4A1* gene have been identified recently as a cause of autosomal dominant hereditary cerebrovascular disease (COL4A1 syndrome [OMIM 605595-120130]). In addition, a broad range of systemic injuries affecting the eyes, kidneys, and muscles has been related to *COL4A1* gene mutations.

Epidemiology

Reports of a total of 65 patients and 13 families with an identified mutation have been published to date.[89,90] However, given its recent identification and its variable clinical expression, COL4A1 syndrome is probably largely underestimated.

Clinical Presentation

Pediatric forms of *COL4A1* gene mutations include children of all ages, with onset starting as early as during the prenatal period. One of the most frequent disease phenotypes is infantile hemiparesis or congenital porencephaly, which is probably a result of perinatal intracerebral hemorrhage (as reported in two preterm siblings with *COL4A1* mutation born after an uneventful pregnancy and delivery except for mild antenatal trauma in one,[91]) but is also seen in childhood. Intracerebral hemorrhage has also been described in adults, in the absence of any perinatal events or infantile hemiparesis or porencephaly.[92] Systematic exploration of mutation carriers, both children and adults, in families with porencephaly or infantile hemiparesis or perinatal intracerebral hemorrhage, showed a variable cerebrovascular phenotype including asymptomatic porencephaly, diffuse brain white matter lesions, intracerebral hemorrhage, TIA, and, rarely, brain infarction.[91–99] Asymptomatic cerebral aneurysms, often multiple, were observed in 44% of subjects submitted to appropriate investigations. Clinical features of cerebral small-vessel disease are quite common findings in *COL4A1* mutation carriers. Stroke occurred in 17.3% of subjects, with a mean age at onset of 36.1 years (range, 14–40 years). All ischemic strokes were small subcortical infarcts (33%) and the other strokes were hemorrhagic (67%). Mental retardation, migraine with and without aura, and epilepsy are the other neurological manifestations of COL4A1 syndrome, sometimes even in the absence of any history of vascular clinical events.[95,99,100]

Extraneurological symptoms include retinal arteriolar tortuosity,[101] venule tortuosities, retinal ischemic changes, or visual loss, but also hereditary angiopathy with nephropathy, aneurysms, and muscle cramps.[102–104] Retinal vascular lesions are inconstant within families with mutations and, when present, they are either asymptomatic or responsible for retinal hemorrhage and transient visual loss. *COL4A1* mutations have also been associated with other ocular manifestations such as cataract formation and anterior segment dysgenesis (Axenfeld-Rieger anomaly), microcornea, congenital cataract, retinal detachment, high intraocular pressure, and optic nerve atrophy or excavation.[89,101] Kidney involvement includes frequent microscopic hematuria with, sometimes, episodes of severe hematuria, small or large bilateral renal cysts, and mild renal failure in some older patients. Muscular symptoms consist of painful cramps, with onset during early childhood, that are spontaneous or provoked by exercise. Patients have persistent elevated serum creatine kinase levels of usually

moderate intensity, and electromyography and muscular biopsy are negative.[104] Less common findings are Raynaud's phenomenon, supraventricular arrhythmias, and mitral valve prolapse.[92]

Genetics, Pathogenesis, and Pathological Aspects

Type IV collagen is a major component of basement membranes and it consists of six homologous, but genetically distinct, α chains that are expressed selectively in different membranes and at different stages of embryonic development.[105] Three different networks have so far been identified. The α1–α2 network is widely expressed, whereas the α3–α4–α5 and the α5–α5–α6 networks show tissue-specific expression.[105–108] Collagen type IV, α3, α4, and α5 has been reported to be associated with Alport's syndrome and benign familial hematuria.[109–111] Collagen IV, α1 (COL4A1 [OMIM 120130]), is an essential component of basal membrane stability. All the reported mutations, except for the one described by Bilguvar et al.,[97] cause a glycine substitution, resulting in a destabilization of the triple helical domain, which is essential for macromolecular structure integrity. Mutations in the collagen IV genes are associated with reduced stability and defects of the basement membrane that, according to the different patterns of distribution of the different chains, may result in a tissue-restricted pathology when chains α3 to α6 are involved, and in a more diffuse disease when mutations occur in the α1 gene.

Brain Imaging

The wide spectrum of MRI findings associated with *COL4A1* gene mutations, including diffuse leukoencephalopathy (63.5%), lacunar infarcts (16.5%), microbleeds (52.8% with gradient echo sequences), dilated perivascular spaces (19.2%), and deep cerebral hemorrhages, suggest an underlying cerebral small-vessel disease. The leukoencephalopathy, which is the most common neuroradiological finding, is usually bilateral and symmetric, and of variable severity. It involves mainly supratentorial regions, predominantly the frontal and parietal lobes, the periventricular regions, and the centrum semiovale, sparing the temporal and occipital lobes and arcuate fibers.[90,95,106] Brainstem, especially the pons, and cerebellar deep white matter may also be affected. Silent microbleeds are located mainly in the basal ganglia, supratentorial white matter, and cerebellum. Small, deep lacunar infarcts and dilated perivascular spaces have also been observed, as well as multiple microcalcifications in the basal ganglia. MRI may show recent or old intracranial hemorrhages, especially in the basal ganglia, centrum semiovale, and pons.[89,91,92] Asymptomatic carotid intracranial aneurysms, usually multiple and located on the extra- or intradural carotid siphon, are particularly frequent in the *COL4A1* phenotype.[92]

Diagnosis

Genetic testing is currently the only diagnostic tool. Although only a few cases have been described, some combinations of neurological and/or extraneurological symptoms have been recognized as highly suggestive and should support genetic testing in clinical practice: (a) any deep intracerebral hemorrhage of unknown cause in association with diffuse white matter abnormalities on brain MRI suggestive of diffuse small vessel disease or with one of the cardinal extraneurological symptoms of the disorder in the patient or in a family member, (b) any bilateral and symmetric leukoencephalopathy of unknown cause in the presence of one of the cardinal extraneurological symptoms of the disorder in the patient or a family member, (c) any intracranial aneurysm if associated with diffuse small vessel disease of the brain in the absence of hypertension and particularly in younger patients, and (d) any infantile hemiparesis and/or porencephaly of unknown cause.[89] The diagnostic pathway should include a comprehensive multisystemic exploration including neurological, extraneurological

(ophthalmologic and renal, especially), vascular, and extravascular investigations, and a careful family history collection.

Treatment

No specific therapeutic measure has yet proved to be effective in this disorder. However, all patients with this mutation should be monitored systematically. Risk factors of hemorrhagic stroke are head trauma, intensive exercise, and the use of anticoagulants. Classic vascular risk factors such as hypertension should be prevented and treated carefully. Prophylactic interventions for sporadic, unruptured intracranial aneurysm should be discussed individually by a specialized multidisciplinary team. As in other autosomal dominant neurological disorders, genetic counseling of symptomatic and asymptomatic patients, and their close relatives is needed. Any at-risk pregnancy requires specific follow-up with repeated ultrasound evaluation of the fetus, and cesarean delivery may be the best option to decrease the risk of perinatal hemorrhagic events.[89]

Small-Vessel and Large-Artery Diseases

FABRY DISEASE

Fabry disease (FD; Anderson-Fabry disease, OMIM 301500) is a multisystem X-linked lysosomal storage disorder resulting in lysosomal glycosphingolipid (globotriaosylceramide [Gb3]) deposition from α-galactosidase A enzyme (α-Gal A) absence or deficiency caused by a mutation in the *GLA* gene.[112,113]

Epidemiology

The estimated prevalence ranges from 1:40,000 to 1:117,000, or 1:476,000 live male births worldwide.[114,115,116–122] In Portugal (population, approximately 10,000,000), it is estimated that as many as 3000 cases of FD are diagnosed every year in a population age 18 to 55 years.[123–125] Screening of 37,104 newborn males for deficient α-Gal A activity in Italy identified FD in 1:3100 subjects.[126] A high frequency of FD in newborn males was also found in Taiwan (approximately 1:1500).[127]

In a prospective study of 721 stroke patients (age, between 18 years and 55 years), the prevalence of FD was 4.9% among males and 2.4% among females.[128] The PORTYSTROKE study reported a 2.4% incidence of FD in 493 young Portuguese stroke patients, independent of age and sex.[129] Recently, researchers engaged in the Belgian Fabry Study screened 1000 patients with ischemic stroke, TIA or intracranial hemorrhage, unexplained white matter lesions, or vertebrobasilar dolichoectasia for FD. In that study, Gal A deficiency was demonstrated to play a role in up to 1% of young patients presenting with cerebrovascular disease.[130] Similar results were reported in the Zurich Fabry study, in which the genetic screening of 150 patients, age 18 to 55 years with stroke or TIA of undetermined origin, was negative.[131] In both studies, the results were incongruous with enzymatic activity, which was reduced respectively in 3.5% and 9% of cases, suggesting that this analysis may be false positive in some patients. Recently, the Stroke in Young Fabry Patients, or SIFAP1, study assessed a diagnosis of FD in 0.5% in a cohort of 5023 young stroke patients, supporting the idea that FD is not a frequent cause of young stroke.[131]

Clinical Presentation

Although Gb3 storage begins prenatally, clinical symptoms do not manifest until childhood. Burning pain in the extremities, gastrointestinal disorders, and hypohidrosis are the most common

presenting features. Learning and growth delay have been reported as well.[132] In general, progressive renal involvement—mostly proteinuria, leading to renal failure—and cardiac and cerebrovascular disease develop after age 20 years. Neurological manifestations other than cerebrovascular accidents (TIA or ischemic and hemorrhagic stroke) include small-fiber neuropathy and dysautonomic disorders. In general, cerebrovascular complications, which are not uncommon in FD, develop after the age of 20 years, with a mean age at onset of 33 to 46 years in males and 40 to 52 years in females.[133–135] The reported prevalence ranges from 24% to 48% in affected males and from 7% to 32% in affected females.[133–136] Ischemic episodes (stroke or TIA), resulting from damage to small and large blood vessels, but also from cardiogenic embolism, occur mainly in the posterior circulation.[136] The reason for this distribution is unclear. Rolfs et al.,[137] in 2005, reported a new phenotype characterized only by cryptogenic stroke, primarily in the posterior circulation, and proteinuria. Mitsias and Levine[136] also described cerebral hemorrhage resulting from aneurysmal deformity of blood vessels. Stroke is associated with a more severe disease progression, with reported stroke recurrence and mortality rates as high as 76% and 55%, respectively.[133–138] The disease has a progressive clinical course, characterized by recurrent cerebrovascular episodes and an accumulation of cerebral lesions, increasing with age. Neurological manifestations other than cerebrovascular accidents include small-fiber neuropathy and dysautonomic disorders. Neuropathic involvement, which can be as high as 80% in FD,[138–140] is characterized by painful, distal, small-fiber sensory peripheral neuropathy conditioning acroparesthesia; burning dysesthesia; sensory loss (primarily temperature); and tenderness. Symptoms can manifest as a constant, burning neuropathic pain or, alternatively, as episodes of severe and disabling paroxysmal pain in the hands and feet with dysautonomic features, lasting from hours to several days. Stress, physical exercise, fever, or temperature variation can act as pain triggers. Multisystemic manifestations include kidney involvement, which often begins with microalbuminuria and proteinuria during the second and third decade of life. It is characterized first by alterations in tubular reabsorption, secretion, and excretion, and is masked initially by glomerular hyperfiltration; from third to fifth decade it is dominated by tubular fibrosis and sclerosis.[141] Cardiac symptoms including left ventricular hypertrophy, arrhythmia, valvular structural abnormalities, conduction disturbances, and coronary artery disease are reported in 40% to 60% of patients.[142] Other frequent manifestations include characteristic skin lesions (angiokeratomas), which are typically small, reddish, raised skin lesions; corneal opacity—which usually does not affect vision and is detectable by slit-lamp examination (cornea verticillata), occurring almost in all hemizygous males—gastrointestinal disorders; and hypohidrosis. Learning and growth delay have been reported as well.[143]

Brain Imaging

Accumulation of cerebral lesions, increasing with age, is detectable on neuroimaging.[135,143] T2- and FLAIR-weighted images typically show multiple hyperintensities affecting the deep hemispheric white matter and brainstem, often preceding the occurrence of neurological symptoms.[144,145] Cerebral involvement is usually widespread, although a predominant posterior involvement has been reported; however, the anterior circulation, particularly the parietal and frontal lobes, may also be affected.[137,145] In recent studies, some patients with FD who experienced stroke presented brain hemorrhages. Bleeding occurred in the anterior circulation territory and frequently affected patients with hypertension.[138] Microbleeds but also intracerebral hemorrhage, in association with classic mutations have also been detected in patients with FD.[146,147] Additional radiological findings are tortuosity and abnormal ectasia of large vessels (dolichoectasia). Pulvinar hyperintensities on T1-weighted images, detectable in 23% of patients with FD by the third decade of life, is the only specific radiological feature of this disease. Because they appear as hyperdensities on cerebral CT, it has been supposed that they may represent calcification and mineralization induced by increased blood flow in the posterior circulation rather than local accumulation of Gb_3.[148,149]

Genetics, Pathogenesis, and Pathological Aspects

FD is an X-linked trait resulting from a mutation in the lysosomal *alfa-galactosidase A* (*GLA*) gene, located on chromosome Xq22. The disease occurs primarily among hemizygous males. However, a significant proportion of heterozygous (carrier) females also develop symptoms and signs of classic FD, usually at an older age.[150,151] Although an X inactivation mechanism has been involved, it cannot fully explain the presence of symptomatic heterozygous females[152]; therefore, the clinical variability is probably a result of other genetic or environmental factors. More than 585 mutations, mainly missense and nonsense point mutations, but also splicing mutations and small and large deletions, have been identified in the *GLA* gene.[153–155] The majority of these mutations lead to a loss of function of the enzyme. Although most families share unique mutations, there is an important intrafamilial variability in residual enzyme activity and disease course, which are strongly related. Although a clear genotype–phenotype correlation has not been demonstrated, mutations leading to a complete loss of function are generally associated with the classic phenotype. Although most clinical manifestations can be explained by the deposition of glycosphingolipids, particularly Gb3, in different tissues and organs, with predominant involvement of the vascular endothelium and smooth muscle cells, the pathophysiology of some clinical aspects such as cerebral vasculopathy is still poorly understood. The prevailing hypothesis is that a cardioembolic pathogenesis underlies only a small proportion of strokes in patients with FD, and that most cerebrovascular accidents derive from a more complex, multifactorial systemic vascular dysfunction, probably involving changes in vessel wall angioarchitecture, endothelial dysfunction, and abnormalities in blood constituents. Supporting this theory, increased markers of endothelial activation levels such as soluble vascular cell adhesion molecule, soluble intercellular adhesion molecule, P-selectin, E-selectin, and plasminogen activator inhibitor, as well as nitric oxide pathway dysfunction, have been reported in several studies to be associated with FD.[156–159] Polymorphisms of genes encoding proteins involved in the inflammatory response, vascular wall pathophysiology, and coagulation cascade (e.g., interleukin 6, endothelial nitric oxide synthase, factor V Leiden, and protein Z) have been shown to act as genetic modifiers of cerebral lesions.[160,161]

Diagnosis

Small- and large-vessel cerebrovascular disease and/or cardiovascular involvement with cerebral embolism and small-fiber neuropathies with specific associated signs and symptoms, such as angiokeratoma, proteinuria, cornea verticillata, and echocardiographic alterations suggestive of hypertrophic myocardiopathy, often not reported spontaneously by the patient, should alert physicians to the possibility of FD. However, the heterogeneous disease presentation and the similarity of some signs and symptoms to other common diseases make it challenging to recognize early manifestations of FD in clinical practice.[155] Thus, a diagnosis of FD may be delayed by as long as 15 years, if not overlooked.[162] Diagnostic guidelines suggesting a standardized clinical workup have been published.[163,164] However, given the availability of a specific treatment, early diagnosis of FD is necessary to prevent complications and disease progression, improve patients' quality of life, and avoid unnecessary additional investigations to detect the origin of stroke or neuropathies.[162,165]

Enzymatic assays demonstrating reduced alfa-galactosidase activity in plasma or leukocytes have been suggested to screen affected males systematically. However, plasma assays may occasionally lead to a false-positive diagnosis[166,167] or may fail to detect all cases of FD. Direct molecular analysis allows one to confirm the diagnosis and to identify the precise mutation. It should always be performed in females, given the high frequency of false-negative enzymatic activity assays. Plasma and urinary Gb3 dose have been also proposed, but the validity of this test is still uncertain.[168] Skin biopsy observed by electron microscopy may be a useful diagnostic tool when interpreted by an expert pathologist.[169]

Treatment

Enzyme replacement therapy (ERT) has revolutionized the care of patients with FD. In Europe, where this therapy was approved for clinical use in 2001, two different preparations of the α-Gal A enzyme are available (REPLAGAL® [agalsidase alfa], Shire Human Genetic Therapies, Boston, MA; and Fabrazyme [agalsidase beta], Genzyme Corporation, Cambridge, MA). Agalsidase-α is produced from a human fibroblast cell line, and agalsidase-β from a Chinese hamster ovary host cell line. Theoretically, replacing the missing enzyme and reducing the abnormal systemic accumulation of Gb3 should lead to clinical improvement. The treatment is safe except for some adverse effects that may occur especially during the first 3 months of treatment, consisting mainly of allergic reactions. Both preparations are administered as infusions. Differences also exist with respect to dosage (0.2 mg/kg for agalsidase-α and 1.0 mg/kg for agalsidase-β) and infusion time (40 minutes independent of body weight for agalsidase-α and 15 mg/hour for agalsidase-β). Although the two proteins differ in the glycosylation pattern, which depends on the originating cell line, and provide different reduction in Gb3 storage (agalsidase-α at a dose of 0.2 mg/kg and agalsidase-β at a dose of 1.0 mg/kg), currently there are no convincing data supporting substantial differences between the two preparations. Given their similar biological properties, any reported difference is likely a result of different dosing. The response to ERT is heterogeneous and not predictable.[170] Studies with both agalsidase-α and -β reported decreased cardiac mass, and clearance of storage in skin and kidneys, which improved renal dysfunction and delayed heart disease, and also relief of painful neuropathy, hearing loss, vestibular dysfunction and hypo-/anhidrosis. The greatest benefit has been shown when treatment is started during an early disease stage, before myocardial fibrosis has developed, thereby allowing the achievement of long-term improvement.[162] However, despite expectations, ERT has not been shown to affect the progression of white matter disease significantly,[171] nor to reduce the frequency of cerebrovascular events significantly,[172–174] and many questions on the effectiveness of this therapy still need to be answered, some of which stem from the fact that most of the studies conducted were observational and/or uncontrolled. There is a need for further studies of higher quality with more adequate outcome selection and follow-up duration.[162]

The results of the Stroke in Young Fabry Patients, or SIFAP2 study, involving a 36-month follow-up of stroke patients with proven FD treated with different prophylactic therapeutic approaches, will help to provide clearer information for the management of patients with FD.[132]

Currently, other therapeutic options such as gene therapies and restriction of Gb3 synthesis are under investigation.[175,176] Recent experimental results have highlighted the role of chaperone therapy. Chaperones are small molecules that are supposed to cross the blood–brain barrier (unlike ERT); these molecules have been shown to increase residual enzyme activity in FD animal models and in cultured cells from patients with FD. Chaperone therapies offer the advantage of oral administration, reducing the negative impact on quality of life caused by biweekly infusions of ERT. Migalastat (1-deoxygalactonojirimycin) was shown to be safe and well tolerated in a trial of 27 patients treated for 2 years, and seemed to improve α-Gal A activity in 24 patients.[177,178]

Other preventive measures, including administration of antithrombotic agents and control of vascular risk factors in patients with cerebrovascular manifestations, are indicated. However, given the still unclear pathogenetic mechanism, currently it is not known whether pharmacological treatments such as antiplatelet, anticoagulant, antihypertensive, or lipid-lowering agents may provide concrete benefits for patients with FD.[179]

SICKLE CELL DISEASE

Sickle cell disease (SCD; OMIM 603903) refers to a group of heterogeneous disorders that are unified by the presence of at least one β globin gene affected by the sickle mutation. Homozygotes for the

sickle mutation have sickle cell anemia or hemoglobin (Hgb) synonym of sickle cell anemia (SS) disease, which accounts for 60% to 65% of cases of SCD. Heterozygous sickle mutations associated with other β globin gene mutations lead to distinct forms of SCD. The most common associated mutation is HgbC, which leads to sickle HgbC disease, accounting for 25% to 30% of all cases of SCD. Coinheritance of a β-thalassemia mutation with the sickle mutation leads to sickle β thalassemia (Sb0 or sickle bþ, in relation to no or diminished β globin production), which accounts for 5% to 10% of all cases of SCD.[180]

Epidemiology

In the United States, sickle cell trait is carried by 7% to 8% of people of African ancestry, and the sickle hemoglobinopathies are estimated to affect 90,000 to 100,000 people. U.S. newborn screening data suggest that 1 in 2500 newborns is affected by SCD.[181]

Clinical Presentation

SCD can affect every organ or tissue in the body. Stroke is one of the most severe complications of SCD and it affects the pediatric population (ischemic subtype) and young adults (hemorrhagic subtype) primarily. The incidence of stroke in children with sickle cell anemia is roughly 1% per year.[182] However, in individuals with increased velocities in the distal internal carotid artery or middle cerebral artery, identified by transcranial Doppler imaging, the annual risk of stroke increases to 10%.[183] The risk of stroke increases with age in young adults: 11% by age 20 years, 15% by age 30 years, and 25% by age 45 years. Ischemic stroke accounts for approximately 75% of cases and hemorrhagic stroke for the remaining 25%.[184] The presenting symptoms of acute stroke in SCD include hemiparesis, facial droop, aphasia, and more generalized symptoms, including stupor and, rarely, seizures. The acute event is most often precipitated by severe anemia resulting from exacerbation of the steady-state values. Recurrence is frequent and 20% of acute stroke victims will experience a second acute stroke. The long-term outcome of acute stroke is variable; many patients lack significant motor impairment but may demonstrate impaired executive functioning. Moreover, 10% to 30% of patients with SCD have silent brain infarcts and diffuse white matter disease associated with cognitive deficiencies.[184–187] Neurocognitive impairment, including deficits in general intelligence, attention and executive functioning, memory, language, and visual–motor performance, have been also detected by neuropsychiatric and neurobehavioral testing in SCD and are associated with anemia and age.[188,189] Other frequent clinical manifestations are hematologic abnormalities, infections, and episodic pain crises. Anemia is the primary hematologic manifestation of SCD. After the transition to adult β globin expression, which occurs during the first year of life, children with SCD typically maintain stable baseline Hgb levels, with significant fluctuations occurring usually during acute disease complications. Leukocytosis and mild thrombocytosis were observed, too. Infections, mostly by *Streptococcus pneumoniae*, resulting from functional asplenia, have long been recognized in children with SCD, particularly before the introduction of vaccination and antibiotic prophylactic measures.[181] Severe, episodic pain crisis are another clinical hallmark of SCD. They are commonly referred to as *vaso-occlusive crises*, probably as a result of bone marrow ischemia with resulting infarction. Other clinical manifestations include acute chest syndrome characterized by fever, tachypnea, dyspnea, hypoxia, and chest pain, but also asthma, pulmonary artery hypertension, cholelithiasis, and priapism.

Brain Imaging

The distribution of infarctions seen on CT, MRI, and pathological examination seems to support the pathogenetic role of large-vessel disease of the internal carotid artery, middle cerebral artery, and

anterior cerebral artery in symptomatic stroke. However, the location of silent infarcts suggests that these strokes are the result of occlusion of smaller, penetrating arteries. These lesions are typically small (85% are <1.5 cm) and are distributed mainly in the white matter of the frontal and parietal lobes.[190] Fewer are present in the basal ganglia or thalamus; none has been reported in the brainstem or cerebellum.[190,191,192] Attributed to small-vessel disease, these lesions have been designated as lacunes by some authors.[191] However, their spatial distribution is clearly distinct from lacunes seen in adult hypertensive patients, and classic lacunar syndromes have not been described in children with SCD. When multiple, small, adjacent white matter lesions in the centrum semiovale are seen on MRI, this may be the result of proximal large-artery occlusive disease and not primarily the result of penetrating artery disease. Intracranial hemorrhage is not uncommon in adult patients with SCD. The pattern of cerebral infarction in childhood and hemorrhage in adulthood mimics that of Moyamoya disease, and is probably the result of the bursting of fragile collateral vessels. There have been various reports of subarachnoid hemorrhage in patients with SCD. Intracranial aneurysms in these patients are often multiple and occur in greater frequency in the vertebrobasilar system.[193–195]

Genetics, Pathogenesis, and Pathological Aspects

SCD is an autosomal recessive condition caused by a point mutation in exon 1 of the *β globin* gene (codon GAG changes to codon GTG) on chromosome 11p15.5, resulting in the substitution of glutamic acid by valine at position 6 of the β globin polypeptide chain.[180] This single-point mutation renders the sickle gene pleiotropic in nature, with multiple phenotypic expressions associated with complex genetic interactions and modifiers that are not well understood. The point mutation leads to its pathological polymerization, red cell rigidity, hemolytic anemia, and poor microvascular blood flow with consequent tissue ischemia and infarction.[196] When it is deoxygenated, HgbS polymerizes reversibly to form a network of fibrous polymers that stiffen the erythrocyte membrane, increase viscosity, and cause dehydration resulting from potassium leakage and calcium influx. These changes also produce the characteristic sickle shape of the red cells, which lose the pliability required to traverse small capillaries successfully. Reticulocytes have altered expression of adhesion molecules and adhere abnormally to the endothelium of small vessels.[197] These phenomena cause episodes of microvascular occlusion and premature red blood cell destruction, which leads to chronic, severe hemolytic anemia and vascular occlusion.[197,198] Other pathophysiological mechanisms in patients with SCD have been observed, including activation of the vascular endothelium, leukocytosis, leukocyte activation, platelet activation, and oxidative stress from tissue reperfusion. The pathogenesis of acute stroke is not completely understood, but it includes a noninflammatory stenosing arteriopathy of the intracranial vessels, particularly those forming the circle of Willis, and a vasculopathy characterized by hypertrophy of the intima and media layers of large arteries mostly in the anterior cerebral circulation (primarily the middle cerebral arteries) and decreased cerebral blood flow. An elevated production of thrombin, platelet activation, and proinflammatory mediators as well as low levels of protein C and protein S have been described in SCD, suggesting the presence of an underlying procoaguable state.[199] An increased production of angiogenic factors occurs in response to severe stenoses, which promotes the development of newly formed collateral vessels (Moyamoya disease). These new collaterals are fragile and prone to rupture, causing intracerebral hemorrhage. Patients with SCD may also experience cerebral sinus venous thrombosis and cardioembolism.

Diagnosis

Before newborn screening, the diagnosis of SCD was made only after a potentially devastating complication prompted medical attention. Universal newborn screening with Hgb electrophoresis or other methods has become the standard in the United States. The confirmation of SCD is given by

DNA sequencing. As with most genetic conditions, prenatal diagnosis of a fetus with SCD is possible during the first trimester through chorionic villus sampling or during the second trimester through amniocentesis.[180]

Treatment

The suppression of endogenous red blood cell production by regular transfusion of donor red blood cells has the longest therapeutic history. The clearest indications for chronic transfusions are for both primary and secondary stroke prevention.[200] Blood transfusion improves oxygen saturation via increasing arterial oxygen pressure and Hgb–oxygen affinity, thereby reducing red cell sickling. There is an immediate hemodynamic effect and increase in hematocrit,[201] with reductions in middle cerebral artery velocities. The progression of large-vessel stenoses can also be curtailed by transfusion therapy, as proved with angiography.[202] With a periodic transfusion regimen, a significant reduction of stroke risk has been shown when compared with the natural history of close to 70%.[203] However, the optimum duration of transfusion therapy has not been established. Several potential complications are associated with chronic transfusion therapy, including transmission of viral infection and hemosiderosis. Iron loading occurs primarily in the liver, heart, and endocrine glands, and prevention with parenteral desferrioxamine is expensive and associated with visual and acoustic neurotoxic effects and growth retardation. Hydroxyurea (HU) is the only medication approved by the Food and Drug Administration for the treatment of SCD. HU was recognized to increase expression of fetal Hgb and thereby inhibit the polymerization of HgbS. A recently completed RCT of HU for infants with SCD (BABY-HUG) demonstrated that HU reduces rates of hospitalization, blood transfusion, and vascular occlusive crises.[204] Thus, HU has been proposed as an alternative option to periodic transfusion for stroke prevention. The Stroke with Transfusions Changing to Hydroxyurea trial was a noninferiority study designed to compare standard treatment (transfusions plus chelation) with HU plus phlebotomy in children with SCD and iron overload, with a composite primary end point allowing an increased risk of stroke but requiring superiority for removing iron. This study was terminated prematurely after interim analysis revealed equivalent liver iron content, indicating that transfusions and chelation remain a better way to manage children with SCA, stroke, and iron overload.[205] American Heart Association/American Stroke Association stroke prevention guidelines recommend the use of antiplatelet agents and vascular risk factor control along with regular blood transfusion, with the goal of reducing HgbS to 30% to 50% for adults with SCD and a history of stroke.[206] Bone marrow transplantation is the only potentially curative treatment currently available for SCD; however, this option is currently restricted to individuals with human leukocyte antigen-matched siblings, and its efficacy in stroke prevention has not been demonstrated.[207]

Large-Artery Diseases

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 (NF1; OMIM 162200), also called *von Recklinghausen disease* or *peripheral neurofibromatosis*, is an autosomal dominant multisystem disorder involving tissue of mesodermal and ectodermal origin.[208]

Epidemiology

The incidence of NF1 was estimated to be approximately 1/3500 individuals.[208–213]

Clinical Presentation

NF1 can affect nearly every organ system, and the complications vary among individuals, even within a single family but also even within a single person at different times in life. Various manifestations of NF1 have different characteristic times of appearance. However, the average life expectancy of individuals with NF1 is reduced by about 15 years, and the most important causes of early death in individuals with NF1 are malignant peripheral nerve sheath tumors and vasculopathy.[214–216]

The most frequent clinical manifestations are alterations of skin—in particular, café-au-lait spots, neurofibromas, and intertriginous freckling. Café-au-lait spots are usually the first manifestation of NF1. They are often present at birth and increase in number during the first years of life. They are most common in the skin but may affect virtually any organ in the body. Neurofibromas are benign tumors arising from the Schwann cells that surround peripheral nerves of all sizes. They can occur anywhere in the peripheral nervous system. Additional features include Lische nodules in the eye iris, but people with NF1 also frequently have learning disabilities, headache, and hydrocephalus or seizures and may develop skeletal abnormalities (scoliosis, dysplasia), endocrine system tumors (pheochromocytomas), central nervous system tumors, or malignant peripheral nerve sheath tumors. Stroke in patients with NF1 is rare. In a series of 158 patients with NF1,[215] neurological manifestations were observed in 55% of these patients, and only one had a history of stroke. However, the vascular manifestations are underestimated among patients with NF1, because the affected individuals are often asymptomatic. Cerebrovascular abnormalities may present in children with NF1 as stenoses or occlusions of the internal carotid, middle cerebral, or anterior cerebral arteries. Small telangiectasic vessels form around the stenotic area and appear as a "puff of smoke" (Moyamoya) on cerebral angiograph.[218,219] One recent study of 419 children with confirmed NF1, of whom 266 (63%) received neuroimaging, cerebral arteriopathy (including Moyamoya) and supraclinoid internal carotid artery stenosis were seen in at least 6% and were associated with young age and optic glioma.[217] Ectatic vessels and intracranial aneurysms also occur more frequently in individuals with NF1 than in the general population.[221]

Brain Imaging

The "target sign" in plexiform neurofibroma, resulting from a central fibrocollagenous core (T2 hypointense) surrounded by myxomatous tissue (T2 hyperintense), is an important diagnostic sign for NF1. MRI and magnetic resonance angiography sequences, but also cerebral angiography, are used to identify cerebrovascular abnormalities such as vessel stenosis or occlusion, ectasiae, and aneurysms. Unidentified bright objects (UBOs), which are sometimes called *T2 hyperintensities* or *focal areas of signal intensity*, can be visualized on T2-weighted MRI of the brain in at least 60% of children with NF1, but the clinical significance is uncertain. UBOs show no evidence of a mass effect and are not seen on T1-weighted MRI or on CT. They may disappear with age. Some studies have suggested that the presence, number, volume, or location of UBOs correlate with learning disabilities in children with NF1, but the findings have not been replicated consistently.[220] The value of performing routine brain MRI in individuals with NF1 at the time of diagnosis is controversial.[221]

Genetics, Pathogenesis, and Pathological Aspects

NF1 is an autosomal dominant disorder with complete penetrance but variable expression. It results from mutations in the *NF1* gene on chromosome 17q11.2. The gene spans more than 350 kb of genomic DNA and encodes a messenger RNA of 11 to 13 kb containing 57 constitutive exons and four alternatively spliced exons.[222] One hundred sixty-eight *NF1* pseudogenes occur on chromosomes 2q21.1,

14q11.1, 14q11.2, 15q11.2, 18p11.21, 21q11.2–q21.1, and 22q11.1, complicating the design of molecular assays for *NF1* mutations. The inheritance of NF1 follows an autosomal dominant trait, and all affected individuals are apparently heterozygous for an *NF1* mutation because persons with constitutive inactivation of both alleles of the *NF1* gene have not been found. More than 500 different mutations of the *NF1* gene have been identified; most are unique and are related to a particular family. Many mutations have been observed repeatedly, but none has been found in more than a few percent of families studied. However, the large size of the *NF1* gene alone does not explain the high frequency of de novo mutations. Nonsense mutations, amino acid substitutions, deletions (which may involve only one or a few base pairs, multiple exons, or the entire gene), insertions, intronic changes affecting splicing, alterations of the 3′ untranslated region of the gene, and gross chromosomal rearrangements have been detected. NF1 is presumed to result from loss-of-function mutations, because 80% of germline mutations described cause truncation of the gene product. In addition, deletion of the entire gene causes typical, although often severe, NF1.[223,224] The *NF1* gene product is termed *neurofibromin*. Its function is not fully understood, although it is known to activate ras-guanosine triphosphate-ase, which promotes the hydrolysis of active ras-guanosine triphosphate to inactive ras-guanosine diphosphate.[225] Histological features of affected blood vessels are an abnormal proliferation of spindle cells, and intima with fibrous thickening and mesodermal dysplasia or fibromuscular hyperplasia. Micronodular formations of smooth muscle aggregates appear on the walls of vessels. The vascular abnormalities involve both small and large vessels and lead to stenosis, occlusion, or rupture of the blood vessels.[227]

Diagnosis

The National Institutes of Health (NIH) diagnostic criteria for NF1, developed at a consensus conference in 1987, are met in an individual who has two or more of the following features in the absence of another diagnosis: (a) six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in greatest diameter in postpubertal individuals, (b) two or more neurofibromas of any type or one plexiform neurofibroma, (c) freckling in the axillary or inguinal regions, (d) optic glioma, (e) two or more Lisch nodules (iris hamartomas) or a distinctive osseous lesion such as sphenoid dysplasia or tibial pseudoarthrosis, or (f) a first-degree relative with NF1 as defined by the previous criteria.[226,228,229] It has been suggested that a pathogenic mutation in the *NF1* gene be added to the list of diagnostic criteria. A comprehensive *NF1* mutation screen can detect gene mutations in more than 92% of tested patients, fulfilling NIH diagnostic criteria.

Mutation analysis is especially important in very young children with a negative family history and who fulfill the NIH diagnostic criteria only in part. Molecular testing for NF1 is also useful for diagnostic confirmation in the case when an adult patient with café-au-lait macules and axillary freckles has no neurofibromas. A multistep mutation detection protocol that identifies more than 95% of pathogenic *NF1* mutations in individuals fulfilling the NIH diagnostic criteria is available. This protocol, which involves analysis of both messenger RNA and genomic DNA, includes real-time polymerase chain reaction, direct sequencing, microsatellite marker analysis, multiplex ligation-dependent probe amplification, and interphase fluorescence in situ hybridization. Because of the frequency of splicing mutations, and the variety and rarity of individual mutations found in people with NF1, methods based solely on analysis of genomic DNA have lower detection rates. Prenatal diagnosis for pregnancies at increased risk for NF1 is available by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling.[230,231]

Treatment

No medical treatment is available to prevent the characteristic lesions, and surgery, chemotherapy, and radiotherapy are currently the only treatment options for cutaneous or subcutaneous neurofibromas that are disfiguring or in inconvenient locations.[221,232] There is no specific therapy for the

cerebrovascular complications. A phase I trial of Lovastatin showed improvement in memory, recall, and recognition.[233] Several drugs are currently at different stages of clinical evaluations. A majority of the trials, including Pirfenidone, Peg-Interferon Alpha-2b, Imatinib, Sirolimus, Vinblastine with Methotrexate, and photodynamic therapy are aiming for patients with plexiform neurofibroma.[233]

Mitochondrial Disorders

MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKELIKE EPISODES

MELAS (OMIM 540000) is a phenotypically and genetically heterogeneous mitochondrial disorder.

Epidemiology

MELAS is the most prevalent inherited mitochondrial disorder. The estimated prevalence of a 3243A>G mutation in mitochondrial DNA (mtDNA), which is responsible for 80% of MELAS cases, ranges from 5 to 236 per 100,000 in the white population.[234,235] One study, however, quantified the prevalence of this mutation in northern Finland as high as 1/9800 individuals in the adult population.[236,237]

Clinical Presentation

Hirano and Palavkis[238] first described the MELAS clinical spectrum, which allowed distinguishing MELAS from two other similar mitochondrial diseases: Kearns–Sayre syndrome and myoclonic epilepsy with ragged red fibers. The age of onset of initial symptoms is usually between 2 years and 20 years.[239] Strokelike episodes (usually characterized by aphasia, cortical blindness, hemianopia, and hemiparesis), which are usually transient, fluctuating, and not disabling, are the clinical disease hallmark. The strokelike lesions can evolve over weeks, resembling the spreading pattern of a cardioembolic or thrombotic stroke.[240] They are usually misdiagnosed as stroke, vasculitis, or encephalitis.[238] Multiple strokelike events may contribute to progressive disability and dementia.[241,242] Additional features, including seizures, normal early development followed by cognitive decline, short stature, hearing loss, psychosis, lactic acidosis, migraine, visual impairment, diabetes, and myopathy are also found in myoclonic epilepsy with ragged red fibers and Kearns–Sayre syndrome. Patients with MELAS often present acutely with a febrile illness and/or focal neurological deficits and/or seizure with a history of cataract and sensorineural deafness. Focal and generalized seizures are reported in 85% to 100% of patients with MELAS, often originating from the occipital lobe and during the strokelike episodes. They are initially infrequent and easy to treat, and during the disease course became more frequent and untreatable, probably contributing to disease progression.[242,243] Migraine is another common feature described in 77% of patients, and in 15% of cases may be the initial symptom.[238] Cognitive deficits include learning disability, decreased language and memory capabilities, and sometimes executive function impairment. Patients are, however, able to perform daily living activities until the later stages of disease.[244] Cardiomyopathy, conduction defects, or chronic heart failure, as well as diabetes mellitus and gastrointestinal disturbance, are also frequent complications of MELAS. Other nonspecific manifestations such as myopathy with easy fatigability and exercise intolerance, ophthalmic complications (ophthalmoplegia, pigmentary retinopathy, optic atrophy), and renal disturbances have been observed.[238] However, the presentation is variable as a result, at least in part, of the heteroplasmy phenomenon, with different levels of mutant and wild-type mtDNA in different tissues.[239]

One recent study with 10 years of follow-up of patients with MELAS showed neuropsychological decline and worsening of MRI abnormalities in patients with MELAS but not in carrier relatives (with the m.3243A>G mutation). Patients also had a greater risk of death than carrier relatives.[249]

Brain Imaging

Cerebral CT has revealed aspecific areas of cerebral infarction or bilateral basal ganglia calcifications.[238] However, infarction areas do not correspond to a definite vascular territory. In general, the posterior territories, particularly the temporoparieto-occipital lobes, are affected more frequently than the anterior regions.[244] MRI features are now the cornerstone of diagnosis, along with genetic studies and muscle biopsy.[243] Although there are no specific neuroradiological diagnostic features, hyperintensities on T2- and diffusion weighted imaging-weighted sequences that are not restricted to distinct arterial territories and migrate over time are highly suggestive of a metabolic disorders. The deep gray matter such as the thalamus may be involved, whereas cortical lesions generally spare the deeper white matter, reflecting the high metabolic demand of these regions. Some authors have reported an increased apparent diffusion coefficient (ADC) on MRI,[246] but these findings are controversial and the recent consensus is probably that there is restricted diffusion and therefore reduced ADC, as in ischemic stroke. The discrepancy in ADC findings is probably related to different time intervals between strokelike episodes and MRI[247]; longer time intervals are associated with greater ADC values related to the development of intracellular edema after the cytotoxic edema of the acute phase. ^{1}H magnetic resonance spectroscopy shows a decrease in N-acetylaspartate and an increase in lactate within strokelike lesions, whereas single proton emission computed tomography is characterized by a trend of hyperperfusion in acute, and hypoperfusion in chronic, disease phases.[247]

Genetics, Pathogenesis, and Pathological Aspects

MELAS is caused mostly by a point mutation in mtDNA, which is—in 80% of cases—a mutation (m.3243A>G) of the tRNALeu gene[248] Sato et al.,[249] in 1992, demonstrated the maternal pattern of inheritance of the mutation in a number of pedigrees. It should be emphasized that only a minor portion of subjects with the m.3243A>G mutation have clinical symptoms because, for the heteroplasmia phenomenon, each mitochondria has many copies of mtDNA, but the number of mutated mtDNA is variable. Thus, cell types and tissues within an individual have different amounts of abnormal mtDNA and it differs over time, explaining variable penetrance and clinical expression differences. Another important concept is the threshold effect: a threshold level, variable among individuals and based on the balance of oxygen supply and demand of mutated mtDNA, triggers the expression of disease symptoms. Given these peculiar aspects of mitochondrial heritability, a negative genetic test and muscle biopsy does not rule out the diagnosis definitively.

Other mtDNA mutations in *MTTL1* and other transfer RNA genes (*MTTF, MTTv, MTTQ*), as well as mutations in other subunits of complex 1, such as *MTND1, MTND5*, and *MTND6*, have also been identified as causing MELAS.[250] The mutations in MELAS most commonly disrupt mitochondrial protein synthesis, leading to decreased activity of respiratory chain elements and, finally, to an imbalance between energy requirements and the available energy of the cell. Dysfunction of complex I (43% of patients), II (29% of patients), and IV (23% of patients) has been mostly detected.[240] Mitochondrial mass increases inside the cells to compensate for respiratory chain failure, appearing on muscle biopsy as ragged red fibers.

Other mechanisms, including increased production or reactive oxygen species that are converted in toxic compounds or abnormal calcium and nitric oxide levels, have been described to play a role in the pathogenesis of MELAS.[240] Two theories have been hypothesized to explain the pathogenesis of strokelike episodes: the mitochondrial cytopathy theory and the mitochondrial angiopathy theory. According to the mitochondrial cytopathy theory, the leucine transfer RNA mutation decreases protein synthesis and causes oxidative phosphorylation failure, leading, ultimately, to adenosine triphosphate (ATP) depletion and energy failure. The mitochondrial angiopathy theory proposes that the accumulation of abnormal mitochondria in the endothelium and smooth muscle leads to cerebral

small-vessel dysfunction. In addition, it has been recently proposed that the strokelike episodes in MELAS result from neuronal hyperexcitability, which increases the energy demand in a neuronal population with mitochondrial dysfunction. This, along with the increased capillary permeability, causes vasogenic edema involving the cerebral cortex primarily.

Diagnosis

Although clinical criteria for MELAS diagnosis are available in the literature, the diagnosis of MELAS is one of exclusion.[238,241] The diagnostic workup includes a combination of clinical and radiological findings in association with laboratory and genetic testing, which should include mtDNA sequencing. The latter may be performed by using tissues other than peripheral blood, such as skeletal muscle, hair follicles, buccal mucosa, or urine sediment, and may include the screening of other nuclear, possibly involved genes. Lactate levels, pyruvate levels, and the lactate-to-pyruvate ratio are elevated in serum and cerebrospinal fluid of patients with MELAS. Serum lactate levels can be normal during the early disease stages but increase during the disease course (particularly during strokelike episodes). Elevated lactate levels were found in more than 90% of patients sera whereas in 50% to 100% of patients, high lactate levels were detected in the cerebrospinal fluid.[237,241,242]

On skeletal muscle biopsy, patients with MELAS typically present ragged red fibers (80%–100% of specimens) that show positive staining for modified Gomori trichrome but also cytochrome *c* oxidase-negative fibers, succinate dehydrogenase hyperreactivity, and, at a ultrastructural level, abnormally shaped mitochondria with paracrystalline inclusions.[242]

Treatment

Although many treatment options for MELAS, which include lifestyle modifications and pharmacological options, have been proposed, there is no U.S. Food and Drug Administration–approved drug or protocol therapy for this disease. The rarity of MELAS makes clinical trials and large-scale drug studies challenging. Thus, most of the therapeutic strategies used in MELAS have been adopted from case reports and/or studies with heterogeneous populations. A variety of pharmacological options, mostly nutritional supplements and vitamins, used alone or in different combinations, have been tried with different level of success but without consistent benefits. Treatment focuses on increasing respiratory chain activity by administering antioxidants, respiratory chain substrates, and cofactors that augment the production or use of ATP.[241] Coenzyme Q10 (CoQ) is the most widely used treatment in patients with mitochondrial disorders. CoQ is a mitochondrial substrate with antioxidant properties and may provide benefits through multiple mechanisms, including enhancement of the activity of respiratory chain or increase of ATP production, or by antioxidant activity.[241] In small trials and case reports, CoQ used alone or in combination with creatine and lipoic acid decreased the level of lactic acid, improved cardiac conduction defects, reduced muscle weakness, and improved neurological function.[251] In the only RCT that reached level II status, only 16 patients completed the treatment with daily 120 mg Coq 10, 300 mg lipoic acid, and 3 g creatine for 2 months. Patients had low levels of serum lactate, and neuromuscular deficits improved modestly. However, the long-term clinical effects remain to be proved.[251,252,253] Idebenone, which is a synthetic analog of CoQ and has better central nervous system penetration, has been used to improve cerebral mitochondrial metabolism and decrease the frequency of strokelike episodes in patients with MELAS.[254] However, the drug use has been approved in Japan, but not in the United States, for the treatment of MELAS.

L-arginine (L-Arg) is a semiessential amino acid and a substrate of nitric oxide synthase involved in growth, urea detoxification, and nitric oxide synthesis. L-Arg also plays an important role in endothelial-dependent vascular relaxation. Several anecdotal reports have suggested L-Arg may

enhance vascular reactivity in patients with MELAS.[255] The early infusion of L-Arg in the acute phase of strokelike episodes was associated with decreased severity and duration of strokelike events, reduced ischemic injury, and improved microcirculation, as evidenced on single proton emission computed tomography.[255,256] In addition, Koga et al.[255] reported that the oral supplementation of L-Arg (2–24 g/day or 150–300 mg/kg/day) decreases significantly the frequency and severity of strokelike episodes without major adverse effects.

Vitamins of complex B (thiamine B1, riboflavin B2, and nicotinamide B3) are considered a first-line treatment for MELAS. The active form of thiamine—thiamine pyrophosphate—is a coenzyme that increases acetyl coenzyme A, a substrate need for the proper functioning of the respiratory chain. A dosage ranging from 50 to 300 mg/day can be administered both to adult and pediatric patients. Riboflavin is a cofactor for electron transport in complexes I and II, finally enhancing ATP production. Last, nicotinamide, by increasing the supply of nicotinamide adenine dinucleotide in the respiratory chain, has also been shown to be somewhat beneficial.[240]

Dichloroacetate (DCA) is an indirect activator of the pyruvate dehydrogenase, a key enzyme complex that participates in the aerobic metabolism of pyruvic acid. By enhancing the activity of this complex, DCA increases the consumption of pyruvate and decreases the levels of lactic acid.

A randomized, placebo-controlled trial using DCA in patients with MELAS did not show treatment benefits and was terminated prematurely because of peripheral nerve toxicity.[257] Other treatments, including corticosteroids, carnitine, creatine, and antioxidants, such as vitamin E and C, have been proposed, but their beneficial effects have not been established.[237,240]

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4

HERITABILITY OF ISCHEMIC STROKE AND INTRACEREBRAL HEMORRHAGE

Annie Pedersén and Christina Jern

Introduction

The extent of hereditary influence on the pathophysiology of stroke has been investigated for several decades, and conflicting results have been presented throughout the years. Today, there is compelling evidence for a hereditary component to stroke risk, although compared with other complex vascular diseases such as coronary heart disease, it appears to be weaker.[1]

When investigating the heritability of a trait, the questions to be answered are: To what extent are differences in incidence the result of genetic variation? And to what extent are they the result of environmental differences? The genetic contribution could be the result of a single-gene mutation, as in monogenic or Mendelian disorders, or a combined action of a large number of genetic factors, each of which makes only a small contribution (i.e., a polygenic inheritance). In most instances, stroke is a so-called *multifactorial* or *complex disease* caused by a polygenic inheritance interplaying with different environmental factors. A number of monogenic forms of stroke exist; however, these uncommon conditions account collectively for only a small percentage of all stroke patients and are not addressed in this chapter.

Traditionally, investigation of heritability has been done in two principle ways: twin studies and family history studies. In twin studies, monozygotic (MZ) and dizygotic (DZ) twins are compared to determine how often affected twins have a cotwin that is affected by the same disease. Because MZ twins share all their genes and DZ twin share, on average, half their genes, a greater concordance among MZ twins means evidence for a genetic contribution. Twin studies have the advantage over family history studies in that they are better suited to separate genetic influences from environmental ones. A problem, however, is the difficulty in recruiting enough twin pairs with a late-onset disease such as stroke. Accordingly, the number of reported twin studies in stroke is very limited. Using data from a twin registry of U.S. veterans, Brass et al.[2] found a relatively strong genetic contribution to stroke risk, with a 17.7% concordance rate for MZ twins compared with 3.6% in DZ twins.

However, less convincing results have also been presented.[3,4] In 2005, Flossmann et al.[5] summarized these results in a meta-analysis. Overall, a genetic contribution to stroke risk was seen, with MZ twins being 1.65 times more likely to be concordant compared with DZ twins.[5]

In family history studies, the relatives of affected probands are compared with unrelated persons to determine whether they are more likely also to be affected. As opposed to twin studies, the number of published family history studies on stroke is quite numerous. In the systematic review and meta-analysis by Flossmann et al.[5] from 2005, results from family history studies, both case–control and cohort studies, supporting a genetic contribution to stroke risk were presented. However, the reliability of these results was questioned by the authors because of heterogeneity between studies and several methodological issues. More recent data supporting the heritability of ischemic stroke were presented from the Framingham study in 2010 and in a large, register-based Swedish study from 2012.[6,7]

Several aspects have to be taken into account when studying heritability and interpreting results from family history studies on stroke. These factors could probably explain a lot of the contradictory results seen throughout the years, and even if most people today agree that there is a hereditary component to stroke risk, there remain several gaps in our understanding of the hereditary patterns. First, associations seen in family history studies could be the result of genetic factors, familial shared environmental factors, or both. Similarly, interactions between genes and environmental factors could occur at various levels. There might be differences resulting from ethnicity, age, and sex. Not only does the risk of stroke have to be considered, but hereditary factors could also cause differences in a person's response to stroke therapy and the individual's capacity to recover after injury, as well as the brain's ability to withstand ischemia and the resulting severity of the stroke event. In addition, the inheritance patterns are likely to differ among the main stroke types—ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage—a fact that has been disregarded in many family history studies in which where stroke has been handled as one entity. Moreover, within each stroke type, different etiologic subtypes might further show different inheritance patterns. Last, rather than influence stroke risk directly, the genetic contribution could be mediated through intermediate phenotypes or risk factors, such as elevated blood pressure or diabetes. In the following sections, these matters are discussed further.

Ethnicity

Genetic susceptibility factors in complex diseases such as stroke are low pathogenic variants that have been able to segregate over generations in different populations. As a consequence, these factors are more likely to be shared by people of common ancestry. Therefore, ethnicity is fundamental in genetic epidemiological research. What is valid for one ethnic group is not necessarily true for another, and data from one ethnic group are not sufficient to draw conclusions in other groups. Furthermore, when it comes to family history and heritability, we have to be even more cautious, because not only genes, but also environmental and cultural factors might differ among ethnic groups.

There is a relative lack of family history studies on stroke patients with other than European or North American origin. There are a few studies from China and Taiwan supporting a relation between family history and stroke risk.[8–10] Likewise, one study from Russia and one from Korea have found associations.[11,12] In Japan, the results have been more diverse, with results contradicting a relation between family history and stroke,[13,14] as well as supporting a role for family history in cerebral hemorrhage, but not ischemic stroke.[15,16] There is also one study from Japan that reported that family history of stroke is an independent predictor of stroke recurrence after first-ever ischemic stroke.[17] A study from Pakistan also found that in patients with hypertension, diabetes, and obesity, a positive family history resulted in an increased stroke risk, with most strokes in this study being ischemic.[18]

On the other hand, a study from India did not detect any association between family history and *hemorrhagic* stroke.[19]

There are also a few studies that have made comparisons among different ethnic or regional groups. Lisabeth et al.[20,21] have observed a stronger familial influence on stroke risk in Mexican American stroke patients compared with white ischemic stroke or transient ischemic attack patients in Texas. A study from Singapore found that ethnic South Asian ischemic stroke patients had a greater frequency of positive family history compared with Chinese patients.[22] In a European multicenter study on ischemic stroke patients, no regional differences were seen when comparing southern, central, and northern European centers.[23] Last, American family history studies with mixed study populations including both white and black patients have found no racial differences in their results.[24,25]

To conclude, ethnic differences in the heritability of stroke are not unlikely. However, current knowledge is insufficient to permit any comprehensive conclusion.

Age

It has been suggested frequently that age influences the heritability of stroke, and there is some evidence that genetic factors are more important in stroke that occurs earlier in life.

When examining the age influence on familial aggregation of stroke there is a possibility of either looking into the age of onset in the affected relatives or in the patients themselves. A couple studies have found that an early age of onset in relatives increases the risk of stroke or death from coronary or cerebrovascular disease in probands.[7,26] In line with this, one of the most powerful studies supporting an association between family history and stroke risk has restricted a positive family history to that occurring before the age of 65 years.[6] Several studies have found a stronger familial aggregation of stroke in patients of younger age. This has been the case in European,[27–30] American,[24,31] and Asian[32,33] populations. These results are in line with results in studies including only younger subjects.[23,34]

To conclude, although there are a small number of studies suggesting the opposite,[35,36] the predominant evidence today points toward a stronger familial component in stroke occurring at younger ages.

Sex

As is the case with age, sex differences have likewise been suggested frequently to influence the hereditary pattern of stroke risk. However, here the results are more inconsistent.

In 2007, evidence for a greater heritability of ischemic stroke in women compared with men was presented from the Oxford Vascular Study (OXVASC) study.[37] The following year, the authors published a meta-analysis supporting their results. This study, which was not on ischemic stroke exclusively, showed that women with stroke were more likely than men to have a parental history of stroke, which was accounted for by an excess maternal history.[38] However, there is heterogeneity in design among the studies supporting a stronger female contribution to stroke risk, with some putting emphasis on the influence of relatives' sex, some on patients' sex, and some on both. There are also several studies that observed a stronger paternal as opposed to maternal influence on stroke risk or no sex differences at all.[7,22,39]

As in all family history studies on stroke, there is a risk of missing the true relations when mixing different stroke types because hereditary patterns might differ depending on etiology. This circumstance was observed in a small Asian study in which lifetime risk of stroke was increased significantly

in parents and siblings of both ischemic and hemorrhagic stroke, except for fathers of ischemic stroke patients and sisters of hemorrhagic stroke patients, although limited power could also explain these differences in part.[8] Thus, to sort out clearly the influence of sex on stroke hereditary patterns, further studies accounting for both relative and proband sex, as well as stroke subtypes, are warranted.

Stroke Severity and Outcome

The familial contribution to stroke might not only influence stroke incidence, but also possibly the brain's ability to withstand ischemia and an individual's capacity to recover from a stroke event. However, only a few studies have investigated family history in relation to stroke severity or outcome.

With regard to stroke severity, an American study found that a sibling history of stroke was associated with more severe strokes (as assessed by the Barthel index, Oxford Handicap Scale, and Glasgow Outcome Scale, but not the National Institutes of Health Stroke Scale), but no such association was found for parental or offspring history of stroke.[40] Another study found that a parental history of stroke was associated with subclinical, but not clinical, stroke.[41] In addition, a study conducted on middle-age British men found an association with nonfatal, but not fatal, stroke.[42] Some investigators found a lack of association between family history of stroke and stroke severity[12,26,35] or stroke volume.[43]

With respect to stroke outcome, the results presented to date have been diverse. One study measuring outcome at discharge found that a positive family history of stroke was associated with a poor functional outcome measured by the modified Rankin Scale.[35] Family history of stroke has also been shown to increase the risk of stroke recurrence.[17,44] In contrast, another study measuring outcome at discharge suggested an association between family history and an increased frequency of discharge to home care, as well as increased ability to ambulate independently at discharge in patients with a positive family history.[31] Moreover, a Swedish study measuring outcome 3 months after stroke found that a family history of stroke was associated with a favorable outcome, as assessed by the modified Rankin Scale.[34] Last, a study from Korea, also measuring outcome 3 months after stroke using the modified Rankin Scale, found no association with family history.[12]

In summary, the number of studies investigating hereditary influence on stroke severity and outcome are limited to date, and there is clearly a need for further research in this field.

Ischemic Stroke and Etiologic Subtypes

Stroke is a heterogeneous disease and could, in fact, be regarded as a syndrome rather than a single disease. Despite this, a large proportion of family history studies, and all published twin studies to date, have handled the two main causes of stroke—ischemia and bleeding—as one. Ischemic stroke is the most common stroke type, accounting for approximately 85% of stroke cases, which makes it the stroke type to which the results from mixed studies are most applicable. It is also the stroke type that has been studied most extensively. As for overall stroke, today there is predominant evidence for a hereditary component in ischemic stroke risk, which has been demonstrated in studies from Europe,[7,34] the United States,[6] and Asia.[12] Interestingly, new support for a hereditary component to ischemic stroke was demonstrated by using genomewide association study data, which provide genotyped single nucleotide polymorphisms (SNPs) over the whole genome. Heritability can then be approximated by assessing the proportion of variation in case–control status explained by those SNPs simultaneously.[45] Using this approach, and the so-called applied genomewide complex trait analysis, the "heritability" (or phenotypic variance explained by SNPs) of overall ischemic stroke was estimated to be 38%.[46]

Even within the group of ischemic stroke, disease etiology shows heterogeneity, and there is, likewise, a lack of studies that have taken this into account. The most frequently used subtype classification systems for ischemic stroke is the Trial of Org. 10172 in Acute Stroke Treatment, which includes the following etiologic subtypes: large-vessel disease, cardioembolism stroke, small-vessel disease, other determined etiology (a mix of specified unusual causes), and undetermined etiology.[47] Because the etiology and, consequently, the spectrum of risk factors differ among the different subtypes of ischemic stroke, it is likely that different genetic and environmental factors are involved. Accordingly, family history studies that have looked into ischemic stroke subtypes have found subtype-specific differences. A pattern of stronger familial aggregation in large-vessel and small-vessel disease compared with cardioembolic and undetermined stroke has been observed in European and American studies,[34,39,48] as well as in Asian studies.[8,49] Similar results were shown in a meta-analysis in which the results from some of the previously mentioned studies were added to results from the OXVASC and Oxford Community Stroke Project (OCSP) samples.[27] Other studies have also found a quite strong familial aggregation in large-vessel disease, whereas the association for small-vessel disease was weaker or even absent.[12,50] In contrast, a study with a mixed study population of whites and Mexican Americans found that family history was most frequent in small-vessel disease and least frequent in large-vessel disease.[35] In one study that specified a group of cryptogenic stroke (i.e., when the etiology remains unknown despite extensive workup), an association with family history was also found for this subtype.[34] Interestingly, the study described earlier that estimated the "heritability" of overall ischemic stroke from genomewide association data also confirmed that this "heritability" varies by ischemic stroke subtype.[46] It was estimated to be 40% for large-vessel disease stroke, 33% for cardioembolic stroke, and only 16% for small-vessel disease stroke.[46]

A problem when collecting family history data is that the stroke subtype among affected family members is very difficult to ascertain, and therefore most studies have made no attempt to do so. This fact could mask stronger associations of less frequent stroke subtypes. However, one study that looked into stroke subtypes in probands and affected siblings found that the occurrence of one subtype in a proband was not associated with a greater likelihood of the same subtype in the sibling.[51] The sample size of this study was very small, though. Larger studies are warranted and, although challenging to reach adequate sample sizes, twin studies would also be of great interest.

Many studies not only included family history of stroke, but also history of myocardial infarction. Associations between a positive family history of myocardial infarction and the subtype of large-vessel disease have been observed, which could reflect a shared genetic susceptibility for atherosclerotic disease in coronary arteries and large arteries supplying the brain.[27,34]

To conclude, ischemic stroke is the most common and best-studied stroke type with regard to family history. There is convincing evidence for a familial contribution to the risk of overall ischemic stroke, but this contribution seems to vary depending on etiologic subtype.

Hemorrhagic Stroke

As mentioned in the previous section, many studies on family history of stroke have combined hemorrhagic and ischemic stroke, and among those that have not, the majority have been on ischemic stroke alone. However, there is evidence that the genetic influences on ischemic and hemorrhagic stroke differ.[52]

With regard to the most common type of hemorrhagic stroke—intracerebral hemorrhage—there are studies that show an association between a positive family history and stroke risk,[16,39] but contradicting results exist.[19,53] It has been reported that family history of overall stroke is a predictor of ischemic stroke versus intracerebral hemorrhage,[50] and that family history of overall stroke is more frequent in ischemic stroke compared with intracerebral hemorrhage.[54] In contrast, another study

did not observe any difference in offspring risk of death from coronary or cerebrovascular disease in patients with ischemic stroke compared with patients with intracerebral hemorrhage.[26]

Noteworthy, in the abovementioned studies, a family history of stroke was considered positive, independent of stroke type. This might lead to underestimations of the familial influence on patients with intracerebral hemorrhage because ischemic stroke accounts for 85% of all stroke cases. The studies that have taken this into account have found mainly positive results,[15,52,55] except for one older study that found no association between cerebral hemorrhage and siblings' risk of death from cerebral hemorrhage, with the exception of the brothers of female patients.[56] Another fact that might cause difficulties in the interpretation of these studies is that a few did not separate distinctly intracerebral hemorrhage from subarachnoid hemorrhage.[26,50,56] Subarachnoid hemorrhage is a topic beyond the scope of this chapter. However, it should be noted that genetic factors clearly have a role in subarachnoid hemorrhage as well, which accounts for approximately 5% of all strokes. Aneurysms are the main cause of subarachnoid hemorrhage. In brief, first-degree relatives of patients with aneurysmal subarachnoid hemorrhage are at an approximately fourfold increased risk of ruptured intracranial aneurysms compared with the general population.[57] It has also been shown that the prevalence of asymptomatic intracranial aneurysms is approximately 10 times greater in subjects with a family history of intracranial aneurysms than in the average population,[58,59] and genomewide association studies have identified some loci associated with intracranial aneurysms.[60,61] Increased knowledge in this field will ultimately contribute to a better identification of persons at an increased risk of subarachnoid hemorrhage, and thus to a better selection of persons who may benefit from intracranial aneurysm screening.

Subtypes of intracerebral hemorrhage have been even less studied. However, Woo et al.[55] investigated family history and the risk of lobar and nonlobar intracerebral hemorrhage. A positive family history was found to be an independent risk factor for both subtypes; but, among cases of nonlobar intracerebral hemorrhage, this risk was seen predominantly in subjects younger than 70 years. No such age difference was seen among patients with lobar intracerebral hemorrhage.[55]

Intermediate Phenotypes

After the familial aggregation of a trait has been stated, the next question is: What does this aggregation stand for? Its content and nature need to be explored. It appears that the heritability of stroke is accounted for, to a certain degree, by the inheritance of intermediate phenotypes and risk factors, such as hypertension and atherosclerosis. This concept is in line with the fact that both the heritability patterns and the specific risk factors differ among stroke types and subtypes. Furthermore, coexistence between stroke and myocardial infarction, and the family history of these diseases have been observed frequently,[34,62–65] which could be explained by the inheritance of etiologic factors, common to both diseases, such as a genetic predisposition to arterial atherosclerosis in the case of large-vessel disease, or hypertension in the case of small-vessel disease. In line with this, family history of ischemic heart disease, stroke, diabetes mellitus, and hypertension have been shown to be associated significantly with each other in a large American population.[66]

The most commonly observed risk factor that has been shown to aggregate in families affected by stroke is hypertension. An association between hypertension and family history of stroke has been reported in many studies.[30,31,67,68] These results suggest that familial susceptibility to stroke is, in part, attributable to a predisposition to hypertension. Accordingly, associations between heritability of stroke and hypertension were found in a systematic review on family history of ischemic stroke and potential confounders.[69] It was further noted that family history of ischemic heart disease was associated mainly with stroke as a result of large-vessel atherosclerosis.[34] In contrast, family history of diabetes was not associated with stroke.[69,70] Other risk factors that have been pointed out as possibly

related to family history of stroke are atrial fibrillation,[71] left ventricular hypertrophy,[71,72] congestive heart failure,[70] and the level of C-reactive protein.[73]

As demonstrated by the previously mentioned studies, some of the familial contribution to stroke risk seems to be accounted for by the inheritance of risk factors. On the other hand, a common inherited risk factor such as hypertension often leads to differential pathological manifestations, such as ischemic versus hemorrhagic stroke, that appear to aggregate in different families. Furthermore, family history has frequently been shown to associate with stroke independent of risk factors. Thus, it seems that disease-specific factors are clearly at play. There is probably an interplay between genetic and environmental factors, some disease specific and others shared. To what extent needs further clarification.

Future and Clinical Applicability

As illustrated in the previous sections, current knowledge supports a familial component in both ischemic and hemorrhagic stroke risk, although many details need to be elucidated further. For this knowledge to be useful in a clinical setting, one way would be to incorporate it in a readily available and practical tool. An illustrative example of this approach is the Systematic COronary Risk Evaluation (SCORE) algorithm, originating from the Framingham risk score, including age, sex, systolic blood pressure, smoking status, and cholesterol levels to predict vascular death.[74] Stroke-specific risk scores for clinical use have likewise been constructed, such as concerning stroke risk after transient ischemic attack, the ABCD2 score; and in patients with atrial fibrillation, the CHADS2 score.[75,76] The Framingham stroke-specific score is widely used for overall stroke risk prediction.[77] Interestingly, a recent Framingham study on family history suggests that parental stroke status and age of parent at stroke might be worth incorporating into future revisions of the Framingham and other stroke risk prediction algorithms.[6] In fact, a couple Asian studies attempting to construct stroke prediction scores have already included family history in their models.[9,10] To evaluate and, possibly, to incorporate family history in a risk score could make up a future way to achieve clinical benefits from the results of this research field. In addition, it is worth noting that obtaining a family history is recommended to help identify persons at increased risk of stroke based on the American Heart Association's guidelines for primary prevention of stroke from 2011.[78]

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5

GENETIC DETERMINANTS OF ISCHEMIC STROKE

Steve Bevan and Hugh S. Markus

Introduction

The term *stroke* is used to represent a clinical syndrome rather than a single disease and can be defined as "a focal neurological loss of function, usually of sudden onset, resulting from disturbance in the blood supply to the brain." In 80% to 85% of cases, stroke results from the occlusion of a cerebral vessel (called an *ischemic stroke*), whereas the remaining 15% to 20% result from vessel hemorrhage (called *hemorrhagic stroke*). Each of these phenotypes can be divided further into subtypes depending on the causative pathology determined by investigations, including brain and vascular imaging, and cardiac evaluation.

Stroke is a major health burden in the developed world, currently ranked as the third most common cause of death and single largest cause of adult chronic disability. Every year in the United States, almost 800,000 people experience an incident or recurrent stroke; mortality data from 2008 shows that 1 in 18 deaths are the result of this condition.[1] Data from the Framingham study showed that one in five women and one in six men age 55 to 75 years of age will experience a stroke sometime during their life.[2] Stroke mortality is also expected to double worldwide by 2020 as a result of the aging population and increasing incidence in developing countries. Cerebrovascular disease also causes vascular dementia and appears to act synergistically with Alzheimer's disease pathology, increasing the chance of resulting clinical dementia.[3] This is of particular significance given the high prevalence of both cerebrovascular and Alzheimer's pathology in the aging population. Any treatment that could reduce the incidence of stroke or subsequent pathologies, including vascular dementia, would therefore have significant patient and economic benefits.

Evidence for Genetic Risk of Stroke

Conventional risk factors for stroke are well known and include factors such as hypertension, diabetes, smoking, and high cholesterol, among others. Together, however, these conventional risk factors

account for only 50% to 60% of stroke risk,[4] with the rest thought to be the result of genetic predisposition. The clearest evidence for this genetic predisposition comes from known forms of monogenic stroke—conditions resulting from a single gene that displays Mendelian patterns of inheritance and has a high penetrance. The most well studied of these is the condition known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. This phenotype is the result of specific mutations within cysteine residues of the *NOTCH3* gene, leading to aberrant binding of the gene product as a homodimer and causing small-artery stroke and small-vessel disease vascular dementia.[5] Stroke is also known to be a secondary presenting feature of other Mendelian single-gene disorders, such as Fabry disease (resulting from mutations in the α-galactosidase gene) and sickle cell disease (resulting from mutations in genes coding for hemoglobin). Although important to the individual patient, monogenic cases account for only a small percentage of overall stroke incidence and, to date, common variants in the same genes have not been associated with sporadic common polygenic stroke.[6]

Additional evidence in support of genetic risks for stroke come from both twin and family history studies.[7] Monozygotic twins share 100% of their DNA whereas dizygotic twins share 50%. An increased incidence of stroke in monozygotic twins therefore strongly implicates a genetic contribution to disease. Similarly, an increased risk in first-degree relatives over the general population risk implicates a genetic basis to stroke incidence. There is also evidence that the risks of the three main ischemic stroke subtypes—large-artery stroke, cardioembolic stroke, and small-vessel disease—have differing familial risks and hence discrete genetic risk profiles.[8] There is also evidence in support of genetic predisposition to stroke from the study of animal models of disease, with the stroke-prone, spontaneously hypertensive rat having been studied extensively. A number of loci have been proposed to harbor causative genes, although no specific mutation has yet been identified.[9]

As the end result of a progressive etiology, ischemic stroke can also be examined in terms of intermediate risk factors, the presence of which increases the likelihood of an ischemic stroke event in the future. Two such examples are the thickness of the carotid artery wall, known as *carotid artery intima media thickness* (IMT), and white matter abnormalities observable on magnetic resonance imaging of the brain and known as *white matter hyperintensities* (WMHs). Increased IMT and WMH are both associated with increased risk of future stroke, and both show significant heritability (the proportion of risk attributable to genetic risk factors). These estimates range from 55% to 75% for IMT[10–12] and 30% to 68% for WMH.[13–15] Identification of genetic risks for these intermediate phenotypes may allow intervention prior to more serious ischemic events occurring, as well as identify an at-risk population that would benefit from increased monitoring and lifestyle intervention to reduce later disease incidence.

Identification of Genetic Risk Variants in Ischemic Stroke

The human genome comprises some 3 billion base pairs and contains approximately 20,000 genes, many of which are alternatively spliced. Therefore, identification of, potentially, a single base change within the genome is not a trivial task. Until recently, the mainstay of stroke genetics was the candidate gene approach. Given the size and complexity of the genome, only small portions of it could be examined in a single experiment. Genetic variants (usually single nucleotide polymorphisms [SNPs]) were identified in a "candidate gene" that was hypothesized to be involved in stroke risk. The frequency of the SNP was then compared in stroke patients and stroke-free control subjects, with increased incidence in cases taken as evidence of a genetic risk.[16] Many hundreds of candidate gene studies have been performed in stroke with rather disappointing results. This picture is similar to many other complex diseases, and the underlying reasons for lack of success have been explored in detail.[17] In stroke in particular, important factors have included small sample sizes, a failure to

replicate positive findings within the same study, a positive publication bias, and a lack of accurate phenotypic subtyping. An additional problem with candidate gene studies is that associations can be identified only in genes already discovered and implicated in stroke pathology; completely novel genes cannot be identified. Although meta-analysis can overcome some of these limitations, and results in considerable cohort sizes for meaningful investigation,[18] candidate gene studies have now been largely superseded by alternative investigative techniques such as genomewide association studies (GWASs).

The other mainstay of genetic investigation, the linkage study, is not typically applicable to stroke given the late age of onset of an ischemic event. The only documented linkage studies in common polygenic ischemic stroke have come from Iceland, where samples collected for genealogical purposes can be combined with phenotypic data for retrospective analysis. These studies identified the only linkage-defined gene for ischemic stroke—phosphodiesterase 4D, or *PDE4D*[19]—although subsequent meta-analyses and replication have failed to confirm this finding outside the Icelandic population.[20]

Although a candidate gene study is a hypothesis-driven approach to genetic investigation, a GWAS can be considered to be nonhypothesis driven. A GWAS allows up to 1 million or more SNPs, which provide coverage of the whole genome to be genotyped in a single individual. Using a case–control methodology similar to a candidate gene study, but with rigorous statistical methods to account for the multiple comparisons made, associations between novel chromosomal loci and disease can be identified. The close proximity of genotyped SNPs also allows nongenotyped SNPs to be inferred or "imputed" with a high degree of accuracy, providing further access to genomic regions not targeted originally. GWASs can be considered as 1 million candidate gene studies in a single experiment, which can then be examined as a whole to provide additional information about intervening loci as a consequence of linkage equilibrium. This is an approach that has revolutionized complex disease genetics and is now being applied to ischemic stroke.

First reported in 2005 examining the complement factor H gene in macular degeneration,[21] the technique really gained prominence when applied to seven common diseases as part of the Wellcome Trust Case Control Consortium Study.[22] Since then, more than 1600 GWASs identifying more than 10,000 genetic loci in excess of 1×10^{-5} have been published, with GWASs becoming the current mainstay of genetic investigation in complex disease (www.genome.gov/gwastudies).

GWASs and Stroke

The GWAS as a technique was applied to other cardiovascular diseases before it was applied to ischemic stroke. As a consequence, the first GWAS findings for stroke came either via replication of variants associated with other cardiovascular phenotypes in a stroke cohort or as part of larger analyses looking for shared genetic determinants of cardiovascular and cerebrovascular risk. The 9p21 locus across *CDKN2A* and *CDKN2B* identified in coronary artery disease was the first GWAS-identified region to be replicated in large-artery stroke,[23,24] followed closely by replication in cardioembolic stroke of the atrial fibrillation-associated gene *PITX2*.[25,26] Another locus on 16q22 around *ZFHX3* was identified subsequently in a joint analysis of atrial fibrillation and cardioembolic stroke.[27]

The first reported study investigating the genetic basis of ischemic stroke directly via GWAS was performed in 2007 in 249 ischemic stroke patients and 268 control subjects, although we now realize this was underpowered.[28] A GWAS in 2009 from the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium investigated incident stroke in 1164 patients from a prospective community population, and associated the *NINJ2* gene on chromosome 12 with ischemic stroke risk.[29] This cohort examined ischemic stroke as a whole, without subphenotyping however, and a

subsequent large replication study using a cross-sectional case–control cohort design in 8763 patients and 8733 control subjects failed to confirm the association.[30]

Experience from other diseases has shown that although a GWAS is a powerful technique, it requires very large and, most important, well-phenotyped cases series—usually in the thousands of samples—to be successful. Even then, typically identified odds ratios have been in the region of 1.2 to 1.5 for single GWASs. More recent studies have relied on meta-analysis of multiple GWAS data sets of a common phenotype to identify smaller risks.

The collection of large, well-phenotyped case series is challenging in stroke, given the late age of onset of the condition. In particular, the detailed phenotyping that we now realize is essential is both expensive and time-consuming. As in other complex diseases, the collection of sufficient case numbers for meaningful study requires international collaboration. The GWAS has led the field of genetics into a collaborative research model in a way that has not been seen before—not just in stroke, but in a wide range of phenotypes. Within stroke itself, the formation of the International Stroke Genetics Consortium (www.strokegenetics.com) in 2007 was for the express purpose of furthering our understanding of the genetic basis of stroke through large, well-powered GWASs.

This consortium reported the first large GWAS in ischemic stroke, including subtypes, in 2011, identifying histone deacetylase 9, or *HDAC9*, on 7p21.1 as a risk factor for large-artery stroke, with the association being specific to this stroke subtype.[31] This finding was well powered, with a discovery cohort of, overall, 3548 ischemic stroke patients and 5972 control subjects, and replication totaling 9856 patients and 40,344 control subjects. A second GWAS from the same consortium in 2012 further identified a locus on 6p21.1 in a discovery analysis of, overall, 1162 ischemic stroke patients and 1244 control subjects, and replication in 1715 patients and 52,695 control subjects.[32] This association was again with the large-artery subtype of ischemic stroke. Both of these findings were within the expected odds ratios for GWAS—1.42 and 1.62, respectively—and both were replicated robustly in larger sample cohorts than the discovery analysis. Despite the impressive cohort sizes in these studies, both associations have been identified with subtypes of ischemic stroke rather than with ischemic stroke as a whole, and the sample sizes in these subgroups were smaller. Although lending strength to the argument that specific stroke subtypes have distinct genetic risks, it is likely that with larger numbers of each subtype, additional genetic risks will be identified. A number of other GWASs in ischemic stroke are ongoing at the time of writing.

In addition to internal replication of GWAS findings, meta-analysis of GWASs can be a useful tool in confirming postulated genetic risks. Validation of GWAS-identified hits in ischemic stroke and its subtypes has been performed via the meta-analysis of GWAS cohorts in the METASTROKE study comprising 12,389 patients and 62,004 control subjects.[33] This study confirmed the previously reported associations with *HDAC9, PITX2*, and *ZFHX3*, as well as identified an additional 12 potentially novel loci that require further efforts to replicate. As has been shown in other complex diseases, it is likely that, as sample sizes increase, additional associations will be identified, although the effect size of these new loci tends to decrease as larger sample sizes are required to identify them. It should also be noted that the effects of genetic risk variants in stroke, and a number of other complex diseases, tend to be smaller than individual conventional risk factors such as family history or hypertension. The real challenge is how to translate these genetic discoveries into patient benefit through functional biology.

Functional Investigation of GWAS Findings in Ischemic Stroke

Identification of genetic risks does little for patient benefit alone. Although isolation of risk variants can identify at-risk patients for targeted screening, increased surveillance, and early intervention, the current variants account for only a small proportion of total genetic risk and are, therefore, not useful

for risk prediction. A more tangible benefit to identifying genetic risk comes from novel insights into disease pathogenesis that may allow the development of better treatments. In general, this requires an understanding of the altered pathological mechanism of disease such that therapeutic intervention may be applied.

The genes *PITX2* and *ZFHX3* have been shown to regulate normal heart rhythm, with *PITX2* null +/– knockout mice shown to develop atrial arrhythmias and atrial flutter.[34] This abnormal heartbeat leads to altered blood flow, coagulation, and cardiac emboli formation, with these emboli circulating and blocking arteries within the brain, resulting in ischemia.

The 9p21 region, associated with coronary artery disease and subsequently large-artery stroke, has been associated with vascular smooth muscle cell (VSMC) proliferation, reduced expression of genes within the 9p21 region, and greater VSMC content within atherosclerotic plaques.[35] This altered plaque morphology is the source of large-artery stroke, during which plaque rupture leads to thrombus and formation of circulating emboli that block blood vessels within the brain and cause ischemia.

How variants within *HDAC9* may cause large-artery stroke exclusively is not yet known. Initial studies have shown that the *HDAC9* protein is expressed in both intracranial and systemic large arteries, including the carotid and middle cerebral arteries, with abundant staining found in both endothelial cells and VSMCs.[36] *HDAC9* messenger RNA expression was also shown to be upregulated in carotid atherosclerotic tissue. The *HDAC9* genetic variant associated with large-artery stroke has also been associated with both carotid artery IMT and asymptomatic carotid plaque in large-community populations.[36] The commonly used antiepileptic drug sodium valproate has been shown to have an *HDAC* inhibitory action. It has been shown to inhibit atherosclerosis in animal models.[37] Although its lack of specificity for *HDAC9* may make its use in stroke therapy less attractive, in a large-community study, sodium valproate was associated with lower stroke and myocardial infarction incidence when compared with other antiepileptic drugs.[38] Thus, although functional studies are required to determine exactly how *HDAC9* variants result in increased stroke risk, initial evidence suggests that *HDAC9* might offer a novel approach to stroke prevention.

How Has the GWAS Altered Our Understanding of Stroke Genetics?

The GWAS was devised initially to address the assumption that common variants in the human genome contribute to common disease. This common variant common disease theory informed the design of GWAS technology and chip design, as well as informed methods of data analysis. It is becoming increasingly clear, however, that the contribution of common, high-penetrance alleles to disease risk is less than originally envisaged, and that, in reality, most common diseases have been associated with a small number of loci contributing modest disease risk. As sample sizes have increased, smaller effect sizes have been detected; but, for most complex diseases, the overall genetic contribution to disease identified by GWASs is significantly less than that suggested from epidemiological studies.

GWASs result in the accumulation of vast amounts of genetic information, which with imputation can run to more than 10 million individual variants. Each of these is typically investigated as an individual risk factor with high stringency for multiple testing, but techniques have now evolved to examine global variance in this data, treating the data set as a whole. In this way, estimates of "global" genetic heritability can be made reflecting more accurately the totality of available genetic data, rather than focusing on single point estimates. It should be noted that these estimates are still restricted to the genetic information that can be genotyped or imputed directly based on the GWAS chip used, rather than all possible genetic information, however. Genomewide complex trait analysis provides such a tool to investigate the heritability of complex phenotypes[39] and has been applied to ischemic stroke.[40] This has shown the heritability of ischemic stroke when considering available

GWAS data was 37%, close to the 40% heritability figure estimated when considering the contribution of conventional risk factors. Intriguingly, the heritability of ischemic stroke subtypes showed considerable variability, being as high as 40% for large-vessel disease and as low as 16% for small-vessel disease. Cardioembolic stroke showed an intermediate genetic heritability of 32%.[40] Whether this variation reflects the underlying genetic architecture of these phenotypes or the certainty with which the phenotypes can be determined accurately is currently unclear, with the tighter the phenotype, the greater the underlying genetic contribution is likely to be when comparing patients and control subjects. One explanation for the lower heritability for small-vessel disease, which is at odds with the significant associations found in epidemiological family history data,[8] is that this subtype is heterogeneous and has more than one underlying pathology. These pathologies themselves have different genetic risks, diluting the phenotypic definition of small-vessel disease. Whichever is the true cause for differences in heritability, these heritability estimates add weight to the suggestion that individual ischemic stroke subtypes have different underlying genetic risk profiles.

The finding that the common-variant-common-disease hypothesis is not entirely accurate has led to a renewed interest in rare variants and their contribution to disease. It has been hypothesized that disease risk could be composed of a pool of common low-risk alleles together with a smaller number of rarer but high-risk alleles that are private to an individual or restricted to family members. In this manner, multiple risk alleles combine to produce the final phenotype, but the rare, highly penetrant alleles account for the observed familial aggregation of cases and increased incidence in related individuals. Such an occurrence would not lend itself to traditional linkage analysis because such genetic risks are not monogenic and would not be expected to display Mendelian patterns of inheritance, but nor would this disease model lend itself to a GWAS in which individual high-risk alleles would not be common enough in the general population to be detectable on currently used GWAS arrays. Identification of these high-risk alleles is best served by taking a sequencing approach to gene identification.

The Future of Gene Identification in Stroke

It is entirely feasible to sequence the entire genome. Currently, the limiting factor is primarily financial rather than technological. So-called *next-generation sequencing* originally referred to sequencing of the whole genome, but has recently become synonymous with the sequencing of the exome—the 1% of the genome that codes for protein. It is argued that a large proportion of disease-causing mutations is likely to affect protein-coding regions. Exome sequencing is viable financially, although the extent of the disease-relevant sequence outside the exome cannot yet be estimated in the absence of large-scale, whole-genome sequencing. Despite this, exome sequencing is growing in popularity, particularly in smaller cohorts, such as in the search for modifiers of disease presentation in familial clusters or in the search for known mutations in suspected carriers.[41] This latter approach is particularly attractive in that it enables areas of known or suspected relevance to be sequenced preferentially—a form of candidate gene sequencing. Such targeted sequencing approaches capture all the genetic variability within a genetic region but present a number of technological issues that must be overcome, including depth of coverage (how many times a region should be sequenced to be certain the sequence is accurate), the frequency a variant should have in a population to be defined as pathogenic or simply rare, and whether pooling of samples represents a viable method of reducing cost without reducing scientific robustness.

At the time of writing, published exome sequencing studies in stroke are limited, encompassing a study on intracranial aneurysm[42] and an exome pilot study identifying rare variants in ischemic stroke[43] using the search terms *stroke, exome*, and *sequencing* in PubMed. The evidence from other diseases, however, suggests that exome sequencing is increasing in importance. Whether

this is related to familial aggregation and stroke will suffer from a late age of onset in the same way linkage studies bypass the condition is possible, although the applicability of exome sequencing to cohort studies being constrained by financial rather than technical limitations suggests that, as costs decrease, the popularity of next-generation sequencing is likely to increase. Sequencing studies of stroke and stroke-related endophenotypes have been undertaken as part of the National Heart, Lung and Blood Institute's Grand Opportunities Exome Sequencing Project http://www.ncbi.nlm.nih.gov/projects/gap/cgi- bin/study.cgi?study_id=phs000546.v1.p1), which sequenced select sib pairs and community samples of ischemic stroke patients and control subjects, and the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium; these results are expected during the next 1 to 2 years.

Beyond the Genome

The central dogma of DNA leading to RNA leading to protein has been challenged in recent years, largely through efforts such as the human genome sequencing project and our increased understanding of genomic regulation. Although DNA is still the template in which an organism is encoded, control of expression of this DNA sequence through transcriptional, translational, and posttranslational regulation is providing an additional dimension to both normal and disease processes. Although still in their infancy compared with our understanding of DNA sequence, techniques such as transcriptional profiling, RNA sequencing, and proteomic analysis are beginning to be examined to further our understanding of genetic regulation and biological process.

Biomarkers of disease have long been examined as indicators of disease pathogenesis, with varying degrees of success. In ischemic stroke, the search for acute biomarkers of ischemia has been extensive but with little successful clinical utility.[44] More recent searches for panels of biomarkers are ongoing, but the major limitation of biomarkers remains the time lag to define a physiologically relevant pathology when compared with techniques such as imaging. As such, biomarkers are likely to be an adjunct to acute clinical care, but may be useful outside the acute setting, such as predicting recovery or secondary events.

One class of biomarkers receiving increased attention currently are microRNAs (miRNAs)—a class of small, noncoding RNAs typically 22 to 25 bp in length that regulate protein expression by binding to complementary messenger RNA sequences. These miRNAs were detected originally in intracellular locations, but have also been shown to circulate in the blood stream and to be remarkably resistant to degradation by exonucleases. This ability to circulate, and the implied stability of miRNAs, have led to their examination as biomarkers of disease, including cardiovascular disease[45] and stroke.[46] Although not a focus of this review, it is worth noting that DNA sequence changes that are often associated with disease do not explain the mechanism by which these associations manifest disease. The role of transcriptional, translational, and posttranslational regulation may yet prove to be of more relevance than DNA sequence change itself.

Conclusion

There is considerable epidemiological evidence that genetics plays an important role in stroke risk. Initial candidate gene studies failed to identify robust associations, in part as a result of small sample sizes, lack of power, failure to replicate, and inappropriate or limited phenotyping. Although meta-analysis of candidate gene studies identified some robust associations, these studies are very prone to positive publication bias. The advent of GWASs is beginning to transform our understanding

of stroke genetics and, for the first time, are being used identify robust genetic risks of ischemic stroke directly. GWASs have also identified novel candidates for therapeutic investigation. There remains an ongoing role for additional GWASs, particularly in specific stroke subtypes and nonwhite populations, and identification of further risk loci is likely. Despite the success of GWASs, a large proportion of genetic risk could still be considered to be unaccounted for in terms of individual risk alleles. The contribution of rare variants is currently the focus of renewed investigation through techniques such as next-generation sequencing, but this type of study is not yet fully developed and is costly. When combined with additional biological processes such as examination of transcriptional and translational processing and control, our understanding of the molecular basis of disease risk is improving all the time. The key will be to translate these advances into patient benefit.

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6

GENETIC RISK FACTORS OF INTRACEREBRAL HEMORRHAGE

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Introduction

Intracerebral hemorrhage (ICH) causes approximately 15% of all incident strokes in the United States and as much as 40% in East Asia.[1] The number of ICH cases is expected to increase in coming years as the population ages and the use of antithrombotic therapy among the elderly rises. This condition generates a substantial public health burden; it is the severest form of stroke, with a 90-day mortality that ranges from 30% to 50%. Moreover, only 10% to 25% of survivors achieve functional independence,[2,3] and they are also at increased risk of recurrent ICH. From a therapeutic standpoint, the only treatment demonstrated to decrease ICH risk is appropriate management of hypertension.[4,5] However, current population-attributable risk estimates suggest that only one third of all ICH cases in the elderly would be prevented by control of hypertension.[6] Furthermore, given the severity of ICH when it occurs, no acute therapy is likely to alter clinical outcome substantially on a population basis. Therefore, novel primary and secondary preventive strategies are needed.

Given that there are limited modifiable risk factors for this condition, the identification of genetic variants with a role in ICH is especially urgent, offering the possibility of novel targets for both prevention and treatment of ICH. In recent years, new technologies have revolutionized the field of genetics, offering the possibility of comprehensibly interrogating the genome (DNA), the transcriptome (RNA), and the proteome (proteins). Producing massive amounts of data, these high-throughput approaches have greatly accelerated the pace of identification of associations between phenotypes (outcomes) and variants in genetic sequence, RNA transcript levels, and levels of circulating proteins, yielding scores of new biological pathways for common diseases.

ICH is the final, acute result of a chronic and progressive process that damages the cerebral vasculature.[2] Infrequently, the underlying condition is a vascular malformation. Most of the ICH cases in subjects older than 55 years, however, take place in the context of cerebral small-vessel disease.[2] ICH is categorized based on the location of the bleeding. Lobar ICH corresponds to hemorrhages that occur

at the junction of the cortical gray matter and subcortical white matter, and deep (or nonlobar) ICH refers to hematomas located in the thalamus, basal ganglia, brainstem, or cerebellum. In general, each ICH location correlates with a different pathological finding. Because chronic hypertension is the leading risk factor for deep ICH, lipohyalinosis of the small vessels has been found to be the corresponding pathology.[7] Cerebral amyloid angiopathy (CAA), on the other hand, has been identified as the main determinant of lobar ICH, with chronic hypertension having a much more limited role.[8–10]

Role of Genetic Variation in ICH

The relative contribution of genetic variation to risk of a given disease can be estimated by measuring either familial aggregation or heritability. Familial aggregation refers to increased risk in relatives of patients (of the outcome of interest) compared with risk in the general population.[11] Several studies have demonstrated that familial aggregation is elevated in ICH. The Greater Cincinnati/Northern Kentucky study, using a population-based case–control design, found that having a first-degree relative with ICH was strongly related to risk of ICH (odds ratio, 6.3) after adjustment for potential confounding factors. This effect of family history was equally strong in both deep and lobar ICH.[6] In addition, a population-based hospital discharge register in Sweden revealed that sibling history of hemorrhagic stroke more than doubled the incidence of ICH.[12] The effect of family history differed by age; no statistically significant effect was found among those younger than 50 years, whereas the greatest risk was observed in the age group 60 to 69 years.

Heritability for a given condition is defined, formally, as the quotient between the total variability observed and the variability resulting from genes.[13] In other words, it is the proportion of the variation for the disease of interest that is explained by genetic variation. Until recently, heritability could be estimated only through twin studies. Unfortunately, no studies of this sort are available for ICH. Recent advances in the field of statistical genetics, however, now allow the estimation of heritability in unrelated individuals through the analysis of genomewide data.[14] Data from such an analysis for ICH are forthcoming from the International Stroke Genetics Consortium (ISGC).

Familial ICH

Rare mutations in several genes have been identified in families whose members develop ICH at a relatively young age. These disorders cluster within families and follow a clear Mendelian pattern of inheritance, almost always autosomal dominant (one mutated allele is sufficient to cause the disease). Although multiple familial syndromes have been described, each produced by a specific gene mutation, these conditions account for a negligible proportion of all ICH in the general population.

We describe familial disorders that produce ICH by affecting the small vessels of the brain, thus mirroring what happens in sporadic ICH. It should be noted, however, that a few familial disorders produce intracerebral bleeding by contributing to the development of large-vessel vascular malformations, as is the case of familial cerebral cavernous malformations and mutations in the *CCM1* and *CCM2* genes.[15]

FAMILIAL CAA

CAA occurs both as a familial and sporadic disorder, and definitive diagnosis of both forms requires pathological examination. Sporadic CAA, nonetheless, can be diagnosed noninvasively during life combing neuroimaging and clinical data, according to the Boston criteria (Table 6.1).[16]

TABLE 6.1

Boston Criteria for the Diagnosis of Cerebral Amyloid Angiopathy

1. Definite CAA

Full postmortem examination demonstrating

- Lobar, cortical, or corticosubcortical hemorrhage
- Severe CAA with vasculopathy[a]
- Absence of other diagnostic lesion

2. Probable CAA with supporting pathology

Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating

- Lobar, cortical, or corticosubcortical hemorrhage
- Some degree of CAA in specimen
- Absence of other diagnostic lesion

3. Probable CAA

Clinical data and MRI or CT demonstrating

- Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
- Age ≥55 years
- Absence of other cause of hemorrhage[b]

4. Possible CAA

Clinical data and MRI or CT demonstrating:

- Single lobar, cortical, or corticosubcortical hemorrhage
- Age ≥55 years
- Absence of other cause of hemorrhage[b]

CAA, Cerebral Amyloid Angiopathy; MRI, Magnetic Resonance Imaging; CT, Computed Tomography.
Note: International Normalized Ratio 3.0 or other nonspecific laboratory abnormalities are permitted for the diagnosis of possible CAA.
[a]As defined in Von Sattel et al.[17]
[b]Other causes of intracerebral hemorrhage include excessive warfarin dosing (International Normalized Ratio > 3.0), antecedent head trauma or ischemic stroke, central nervous system tumor, vascular malformation, central nervous system vasculitis, blood dyscrasia, and coagulopathy.
CAA, cerebral amyloid angiopathy; CT, computed tomography; MRI, magnetic resonance imaging.

Within this diagnostic framework, a probable diagnosis of CAA can be made, in the absence of pathological examination, based on the tendency of CAA-related hemorrhages (identified through neuroimaging) to be multiple and lobar. The specificity and sensitivity of this diagnostic scheme exceed 90%.[16]

For both forms of CAA—familial and sporadic—the underlying biological mechanism is the deposition of the amyloid beta (Aβ) peptide in small and medium-size vessels within the brain.[8,9] Familial forms follow a Mendelian (usually dominant) pattern of inheritance, present earlier in life, and purport a more severe clinical course as well as an earlier age of death (Table 6.2).[18–22] Most forms of familial CAA are produced by mutations in the Aβ precursor protein (*APP*) gene. All these variants cluster within the Aβ coding region of the gene (exons 16 and 17).[10] The most frequent mechanism of genetic variation is a point mutation within the *APP* gene. Duplication of the *APP* locus, however, has also been described in families with familial early-onset Alzheimer's disease and CAA.[23]

TABLE 6.2

Familial Cerebral Amyloid Angiopathies

Amyloid peptide	Precursor protein	Chromosome	Disease	Features	CAA-ICH
Aβ	APP	21	CAA related to familial AD	Associated with presenilin 1, presenilin 2 and APP mutations	+
Aβ	APP	21	CAA in Down syndrome	Lobar ICH has been reported in some cases	+/–
Aβ	APP	21	CAA in APP duplication	CAA pathology prominent, increased risk of lobar hemorrhage, also causes early-onset autosomal dominant familial AD	+
Aβ	APP	21	Hereditary cerebral hemorrhage with amyloidosis: Dutch type	Described in 2 large families from the Netherlands; age at onset, 50 years; lobar hemorrhages, focal neurological deficits, dementia, and leukoencephalopathy	+
Aβ	APP	21	Hereditary cerebral hemorrhage with amyloidosis: Italian type	Described in 3 Italian families; age at onset, 50 years; lobar hemorrhages and dementia	+
Aβ	APP	21	Hereditary cerebral hemorrhage with amyloidosis: Flemish type	Described in a Dutch family (discovered in Belgium, therefore called *Flemish*) and a British family; age at onset, 45 years; progressive AD-like dementia, in some patients associated with a lobar hemorrhage	+/–
Aβ	APP	21	Hereditary cerebral hemorrhage with amyloidosis: Iowa type	Described in an Iowa family and a Spanish family; age at onset, 50–66 years; memory impairment, expressive language dysfunction, personality changes, myoclonic jerks, short-stepped gait, no clinically manifest ICH (family from Iowa) or lobar hemorrhages (family from Spain)	+/–

Aβ	APP	21	Hereditary cerebral hemorrhage with amyloidosis: Piedmont type	Described in one family from Piedmont, Italy; age at onset, 50–70 years; recurrent lobar hemorrhages, cognitive decline	+
Aβ	APP	21	Hereditary cerebral hemorrhage with amyloidosis: Arctic (Icelandic) type	Described in one family from northern Sweden; age at onset, ~60 years; progressive cognitive decline (no strokes)	–
ACys	Cystatin C	20	Hereditary cerebral hemorrhage with amyloidosis: Icelandic type	Described in 9 subfamilies in Iceland; causes systemic amyloidosis; age at onset, 20–30 years; recurrent lobar hemorrhages	+
ATTR	Transthyretin	18	Meningovascular amyloidosis	Polyneuropathy is the main clinical symptom; rarer findings are ataxia, spasticity, and dementia; systemic amyloidosis	In some families (rare)
AGel	Gelsolin	9	Familial amyloidosis: Finnish Type	Progressive corneal lattice dystrophy, cranial and peripheral neuropathy, cutaneous amyloidosis, systemic amyloidosis	–
PrPSc	Prion protein	20	Gerstmann–Sträussler–Scheinker syndrome	Described in 1 family, progressive cognitive decline	–
ABri	ABri precursor protein	13	Familial British dementia	Described in 4 families; age at onset, 45–50 years; progressive dementia, cerebellar ataxia, spastic tetraparesis	–
ADan	ABri precursor protein	13	Familial Danish dementia	Described in 1 family from Denmark; age at onset, 30 years; cataracts, deafness, progressive ataxia, dementia (previously known as *heredopatia ophthalmo-oto-encephalica*)	–

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage.

Histopathologically, CAA is identified by deposition of a 39- to 43-amino acid proteolytic fragment of amyloid precursor protein (APP) in the vessel walls of capillaries, arterioles, and small and medium-size arteries of the cerebral cortex, leptomeninges, and cerebellum. This "vascular amyloid" is similar to that observed in amyloid plaques in Alzheimer's disease. Involvement ranges from mild (amyloid accumulates at the border of the media and adventitia of the vessel) to severe (there is total replacement of the smooth muscle media with amyloid, accompanied by vasculopathic changes that can include microaneurysm formation, concentric splitting of the vessel wall, chronic inflammatory infiltrates, and fibrinoid necrosis).[9]

Familial CAA can be classified further, depending on the nature and source of the accumulating peptide. Peptide accumulation in cerebral vessels can be found in all familial CAA syndromes (both Aβ and non-Aβ forms), although only in rare instances does lobar ICH represent the main clinical manifestation of non-Aβ CAA (with non-Aβ Icelandic type being the exception). Pleiotropy has been observed for the familial Aβ-CAA mutations; different subjects carrying the same mutation may have different clinical phenotypes. An example can be found for the Iowa mutation (replacement of asparagine for aspartate at position 23), in which one kindred had a history of recurrent ICH whereas a second presented with dementia and leukoaraiosis, but not ICH.[24] These observations demonstrate that additional genetic or environmental factors modify the effect of this mutation, and possibly other forms of familial CAA.[25]

COL4A1-RELATED INTRACEREBRAL HEMORRHAGE

Both familial and sporadic forms of ICH have been described for mutations in the *COL4A1* gene. This gene encodes the α1 chain of type IV collagen, a subtype of collagen that forms basement membranes of all tissues, including the vasculature, and contributes to their strength. Rare mutations within this gene cause autosomal dominant syndromes manifesting with perinatal intracerebral hemorrhage and porencephaly, adult-onset ICH (all locations), small foci of chronic blood products in normal brain tissue known as *microbleeds*, lacunar strokes, and leukoaraiosis.[26–28] Electron microscopic observations found that mice carrying *COL4A1* mutations have uneven and inconsistent basement membranes, with localized disruptions. Ultimately, these changes lead to increased fragility of vessel walls and ICH.[29]

Most disease-causing mutations in *COL4A1*-related cerebrovascular disease are missense variants affecting a highly conserved hydrophobic glycine residue. This genetic alteration results in inhibition of heterotrimer deposition into the vascular basement membrane, with a consequent alteration of its structural properties. In addition to the ICH-related phenotypes described earlier, the consequences of these structural changes are evident when observing the role of *COL4A1* in determining cerebral vessel tolerance to minor head trauma. Surgical delivery of mouse pups bearing a mutated *COL4A1* allele can prevent the severe perinatal cerebral hemorrhages that occur in spontaneous live births. This finding could have important implications for human disease, because impaired responses to even mild trauma could result in several clinical manifestations that could range from subclinical microbleeds to subarachnoid hemorrhage and ICH.[29]

Sporadic ICH: A Role for Rare and Common Genetic Variants

Both rare and common genetic variants appear to influence risk of ICH without producing the clear familial pattern of Mendelian inheritance. Individuals carrying these variants are at increased risk of sustaining an ICH, but pedigree and genotype data are not enough to predict accurately who will experience an ICH, as is the case with Mendelian disorders. Evidence for this type of non-Mendelian association is generated through candidate gene and genomewide association studies.

CANDIDATE GENE STUDIES

Common genetic variants are those that have a minor allele frequency greater than 5%. These variants presumably have a much smaller effect on disease susceptibility than rare mutations that cause familial (Mendelian) diseases; as a result, they are found in both affected and unaffected individuals. Candidate gene association studies aim to assess the hypothesis that a particular common genetic variant—or a limited number of them—is related statistically to the outcome of interest. The key to the success of candidate gene studies is prescient selection of the genetic variant to be evaluated. Selection strategies usually pursued examination of common variants at loci known to cause Mendelian forms of the outcome, extrapolation of evidence from animal models, and selection of genes known to participate in biological pathways related to the phenotype of interest (e.g. testing association with ICH of common variants for genes that encode proteins involved in the coagulation cascade). Candidate gene studies have yielded mostly negative results in ICH—as is the case for many other complex diseases. Moreover, most of the associations published have been not replicated in subsequent studies.[30] This is probably a result of the limitations observed in these studies: small sample size, application of *p* value thresholds that are insufficiently stringent, and inability to account for confounding as a result of population structure.

APOLIPOPROTEIN E AND RISK OF SPORADIC CAA

An association that has proved robust in candidate gene studies is that for apolipoprotein E, *APOE*, and sporadic ICH related to CAA—a finding that reflects the biological overlap with Alzheimer's disease. In the population-based, Greater Cincinnati/Northern Kentucky study, possession of the *APOE* ε2 or ε4 allele accounted for the largest proportion of lobar ICH cases, with a population-attributable risk of 30%. Moreover, multiple studies have described associations between the ε2 and ε4 alleles of the *APOE* gene and CAA-ICH.[31–33] Until recently, the small size and, perhaps, the lack of control for confounding resulting from population stratification of all candidate gene studies of *APOE* and CAA-ICH yielded inconsistent results.[34,35]

In 2010, the ISGC was able to accumulate a sample of sufficient size, as well as apply methods to control for population structure, to establish an association between *APOE* variants and lobar ICH at the level needed to account for testing of all common variants across the human genome. In this multicenter meta-analysis, which included more than 2000 patients with ICH and more than 4000 control subjects,[36] both the ε2 and ε4 alleles were associated with lobar ICH risk at genomewide significance levels ($p < 5 \times 10^{-8}$). This association was strengthened when the analysis was restricted to subjects with probable CAA (based on Boston criteria)—a reflection of the link between *APOE* ε2 and ε4 and CAA. In addition to influencing risk of first ICH, both ε2 and ε4 have also been shown to be associated with risk of recurrent ICH,[37] whereas ε2 alone increases the volume of ICH at presentation,[38] as well as the risk of contrast extravasation on neuroimaging (i.e., the "spot sign", see Figure 6.1.)[39] and ICH expansion.[40] These results are in line with previous pathological studies of *APOE* and ICH related to CAA. These reports provided evidence for a distinct role of the ε2 allele in increasing the risk of CAA-related bleeding, possibly through increased damage to small-vessel walls.[41,42] Of note, *APOE* alleles ε2 and ε4 have a very limited relationship with disease risk and clinical evolution over time in familial CAA—a finding that may reflect the overwhelming effect of rare (Mendelian) mutation in causing amyloid accumulation.

COLLAGEN TYPE 4, α1

The role of variation in *COL4A1* in sporadic (nonfamilial) forms of ICH was investigated recently by a sequencing study that followed the candidate gene approach. All coding and flanking intervening

sequences at this locus were sequenced in 96 patients with sporadic ICH and 145 ethnically matched control individuals. The study identified two mutations that were present only in patients with ICH: *COL4A1*^{P352L} and *COL4A1*^{R538G}. These variants resulted in missense changes in amino acids that are highly conserved across species.[43]

Collagen type IV, α1 (the product of *COL4A1*), is related structurally and functionally to the collagen type IV, α2, encoded by *COL4A2*. Leveraging this functional relation, another recent study assessed the effect of variants at the *COL4A2* locus on the risk of ICH. All coding and flanking regions of *COL4A2* were sequenced in 96 patients with sporadic ICH and 145 control individuals. Three rare, nonsynonymous coding variants affecting evolutionary conserved amino acids were observed in four patients that were not present in any of the control subjects. The same study showed, using cellular assays, that these variants caused intracellular accumulation of COL4A1 and COL4A2 at the expense of their secretion, providing additional support for their pathogenic role.[44] Of note, a similar approach, examining the role of *APP* mutations in sporadic CAA-related ICH did not identify any mutations.[45]

COMPLEMENT RECEPTOR 1

Identification of the complement receptor 1, or *CR1*, gene as a risk factor for ICH related to CAA arose through the examination of loci that have been implicated in Alzheimer's disease. Accumulated evidence suggests that rs6656401, a common variant within the *CR1* gene, known to increase risk for Alzheimer's disease, influences Aβ amyloid deposition in brain tissue.[46] Prompted by the biological overlap between Alzheimer's disease and CAA, a recent study investigated whether rs6656401 increases the risk of first and recurrent CAA-related ICH in 89 individuals with CAA-related ICH and 324 ICH-free control subjects. rs6656401 was associated with CAA-ICH (odds ratio, 1.61; $p = 8.0 \times 10\text{-}^{4}$) as well as with the risk of recurrent CAA-ICH (hazard ratio, 1.35; $p = .02$).[47] (p. 1)

GENOMEWIDE ASSOCIATION STUDIES

Genomewide association studies are comprehensive, unbiased searches for common genetic variants that affect specific traits or diseases. They are now possible because of the availability of affordable high-throughput technologies for genomewide genotyping, specific statistical tools, and publicly available data on single nucleotide polymorphisms (SNPs) and other forms of common genetic variation (HapMap and 1000 Genomes projects).[48–50] Investigators applying this study design make no a priori assumptions about the location or causal role of the genetic variants being interrogated. The combination of available genotyping technologies with advanced imputation techniques allows the evaluation of several million SNPs known to exist within the human genome.

Fundamental to the success of recent whole-genome association studies has been the assembly of large numbers of well-characterized patients by collaborating groups of investigators. Although a number of genomewide association scans have been reported for ischemic stroke, no such study aimed specifically at assessing ICH (or hemorrhagic stroke) has yet been completed. A large, international, multicenter genomewide study of ICH is currently being undertaken by the ISGC. An interim analysis of this study failed to identify loci associated with ICH at a genomewide level of significance (5.0×10^{-8}), but genotyping and analyses are ongoing.[51]

Magnetic Resonance Imaging-Detectable White Matter Hyperintensities: A Potential Endophenotype for ICH

Endophenotypes are measurable traits that are hypothesized to be along the causal pathway from genetic variation to disease expression.[52] Identification of endophenotypes can

facilitate the study of genetic risk factors because they are more frequent and easy to identify than the final outcome of interest. Potential endophenotypes for ICH can be obtained by observing other forms of brain injury related to the small-vessel pathologies responsible for ICH. Notable among these are white matter hyperintensities (WMHs; also known as *leukoaraiosis*), which are white matter rarefactions detected sensitively by computed tomography or magnetic resonance imaging. WMHs are common in the aging population, readily quantifiable through neuroimaging, and are strongly heritable, with estimates that range from 55% to 80%.[53–55] More important, WMH is associated with symptomatic ICH in both lobar and nonlobar locations.[56–58]

WMHs can be observed in almost all familial forms of ICH attributable to small-vessel disease. One such example is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a monogenic, autosomal dominant disorder caused by mutations in the *NOTCH3* gene. The protein encoded by *NOTCH3* seems to have a role in blood vessel development and corresponds to a cell-surface receptor expressed on the surface of vascular smooth muscle cells. The majority of mutations associated with CADASIL modify the number of cysteine residues within the extracellular domain of the protein. Mutations at this locus cause a familiar syndrome characterized by migraines with aura, recurrent strokes, progressive cognitive impairment, psychiatric disturbances, and, occasionally, ICH. It should be noted, however, that this condition produces mainly small, usually asymptomatic, microhemorrhages, and that the occurrence of clinically evident ICH is infrequent. From a radiological standpoint, the distinctive findings of CADASIL include microbleeds and diffuse WMH, with preferential, bilateral involvement of the external capsule and anterior temporal lobes (Figure 6.1).

Common genetic variants can also influence WMH burden in a non-Mendelian fashion. A recently completed genomewide association study identified six WMH-associated SNPs on one locus on chromosome 17q25. This locus encompasses six genes: *WBP2, TRIM65, TRIM47, MRPL38, FBF1*, and *ACOX1*. Variant alleles at this locus conferred a small increase in WMH burden—4% to 8% of the overall mean WMH burden in the sample.[59] These genes, together with their corresponding cellular processes, are appealing targets to be assessed for association with ICH and are being actively explored.

Clinical Implications

Recent genetic discoveries in ICH raise the promise of clinical applications.[60] Recognition of subjects carrying rare mutations that cause Mendelian diseases is crucial. These Mendelian

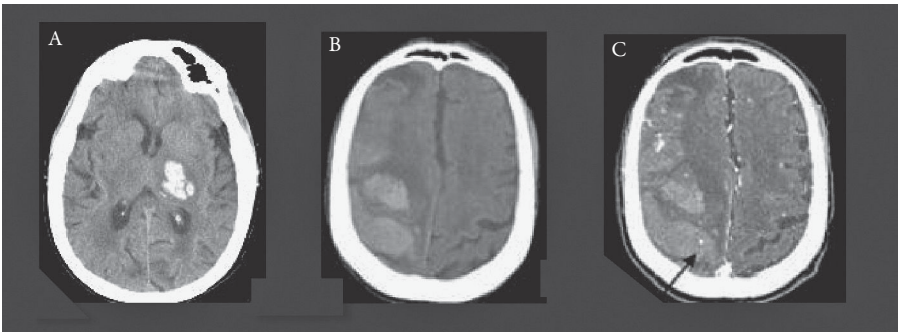

FIGURE 6.1 Radiological findings in intracerebral hemorrhage (ICH). (A) Deep ICH. (B) Lobar ICH. (C) Contrast extravasation within the intracranial hematoma—the "spot sign" (arrow).

conditions can be recognized by their clear pattern of familial aggregation and, in terms of ICH, by a younger age of onset, more severe clinical course, and higher rate of recurrence. Identification of subjects carrying these mutations is important to provide appropriate genetic counseling. In addition, making an accurate genetic diagnosis may improve clinical care, because specific preventive measures can be implemented based on the known natural evolution of each disease. It should be noted, however, that when the possibility of a Mendelian disease has been considered, clinical management should probably be deferred to a geneticist, because genetic testing is not always indicated, and to ensure optimal genetic counseling if the disease is confirmed.

A second important application of genetics to ICH may be in decision making for chronic anticoagulation. Use of warfarin increases both the frequency and the severity of ICH. Thus, even at the annual rate of 0.2% to 0.6% observed in randomized trials of conventional-intensity anticoagulation,[61] warfarin-related ICH exerts a major effect on clinical decision making. Therefore, it is plausible that even relatively weak risk factors for patients with ICH on warfarin might sway the balance in favor of or against treatment. In this regard, an important discovery has been that as much as 35% of the variability observed in the response to warfarin is related to common genetic variants occurring at the *VKORC1*[62] and *CYP2C9*[63] genes.[64–66] Based on these findings, in 2010 the U.S. Food and Drug Administration included in the warfarin product label dose recommendations based on the *CYP2C9* and *VKORC1* genotypes.

Several warfarin pharmacogenetic algorithms that combine clinical and genetic factors are currently available.[64,65] These approaches have already demonstrated their superiority, when compared with standard management, in estimating the correct dosing scheme at the beginning of anticoagulation.[67] Furthermore, the results of a recently published randomized study showed for the first time that warfarin pharmacogenetic algorithms also provide benefit in terms of clinical outcome.[68] In that study, the proportion of serious adverse events at 3 months was 4.5% versus 9.4% for the pharmacogenetic-guided and standard approaches, respectively. Four other clinical trials currently underway will provide important additional information to complement these findings.[69]

Future Directions

The genetic underpinnings of ICH are likely to emerge in the coming years from ongoing studies of related phenotypes as well as ICH itself. A large meta-analysis of genomewide association studies of blood pressure levels has revealed that the burden of these variants is associated with both ischemic and hemorrhagic stroke.[70] This same approach is likely to be applied to other ICH risk factors and endophenotypes for which common genetic variants have been identified, such as body mass index, alcohol abuse, and WMH.

Genomewide data for ICH will soon be available from the ISGC[71] as well as the Risk Assessment of Cerebrovascular Events study. In addition to offering the promise of novel genetic discoveries, these data will be used to estimate ICH heritability; assess, through pathway analysis, the role of specific metabolic and functional cellular pathways; and evaluate interactions between genes and medication exposure.

Genetic risk factors for ICH are available from birth, constant over time, and easy to measure reliably. In the end, the combination of genetic and clinical information is likely to lead to a more precise stratification of ICH risk, aiding in identifying high-risk individuals who may benefit from specific forms of prevention. Furthermore these risk factors are likely to highlight entirely new biological pathways, yielding just the kind of mechanistic insights necessary for the development of effective treatments.

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7

RELEVANCE FOR STROKE OF GENES ASSOCIATED WITH OTHER VASCULAR PHENOTYPES

Rainer Malik and Martin Dichgans

Introduction

This chapter provides an overview of genes that have been identified for established phenotypes in cardiovascular disease (CVD), whether the specific genes or loci are also implicated in stroke, and whether shared mechanisms between vascular phenotypes can be determined.

It has long been thought that stroke and other CVD phenotypes, and especially arterial disease, share a common etiology.[1,2] Genomewide association studies (GWASs) have been highly successful in identifying susceptibility loci for coronary artery disease (CAD) and myocardial infarction (MI). However, for stroke and other arterial diseases, these efforts have not been as successful so far—mostly because of small sample size and, more important, reduced power to detect associations in subtypes for stroke. This is especially important, because it has been established that genetic risk loci are specific to certain stroke subtypes.[3–7] In this chapter, we highlight the successes in related phenotypes and show how these findings could be related to stroke. We also discuss how to further GWASs to increase the number of risk loci for stroke.

We focus primarily on GWAS findings in predominantly white populations. When this is not the case, either for candidate gene studies or GWASs in nonwhite populations, this is noted in the text.

Coronary Artery Disease

CAD has been the most intensely studied cardiovascular phenotype with regard to GWASs. Pathologically, CAD is characterized by atheromatous plaques in the coronary arteries, with the end point of MI after plaque rupture. It has been speculated that CAD and stroke, and here, especially, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype of large-artery stroke (LAS), share a common etiology because the pathophysiological mechanisms of these diseases both

encompass—to varying degrees—the formation and rupture of atherosclerotic plaques with a misbalanced lipid profile and a pathological immune response.

Key risk factors for CAD are elevated cholesterol levels, smoking, diabetes, and hypertension,[8] and have been well established over time.[9] Less established risk factors such as homocysteine levels, triglyceride levels, C-reactive protein, and others have not proved to be useful indicators of CAD so far.

Recently, a large number of risk loci for CAD have been discovered through GWASs and have been replicated stably over time.[10–21] During past years, the number of patients and control subjects in GWASs has grown steadily so that even variants affecting CAD risk with only moderate impact have been discovered. The major loci for CAD, the associated genes, and their respective references are listed in Table 7.1.

TABLE 7.1

Overview of Coronary Artery Disease/Myocardial Infarction-Associated Loci

Locus	Gene/nearest gene	Additional cardiovascular phenotypes showing association
1q21.3	*IL6R*	AAA[22]
1p32.3	*PCSK9*	—
1p32.2	*PPAP2B*	—
1p13.3	*SORT1*	AAA[23]
1q41	*MIA3*	—
2q33.1	*WDR12*	—
2q22.3	*ZEB2-AC074093.1*	—
2p24.1	*APOB*	—
2p21	*ABCG5-ABCG8*	—
2p11.2	*VAMP5-VAMP8- GGCX*	—
3q22.3	*MRAS*	—
4q32.1	*GUCY1A3*	—
4q31.23	*EDNRA*	ICA[24]
5q31.1	*SLC22A4-SLC22A5*	—
6q25.3	*PLG*	—
6q25.3	*SLC22A3/LPAL2/LPA*	—
6q23.2	*TCF21*	—
6p24.1	*PHACTR1*	—
6p21.31	*ANKS1A*	—
6p21.2	*KCNK5*	—
7q32.2	*ZC3HC1*	—
7p21.1	*HDAC9*	LAS[3,25]
7q22	*7q22*	—
8q24.13	*TRIB1*	—
8p21.3	*LPL*	—
9q34.2	*ABO*	LAS, CES, IS26

TABLE 7.1

Continued

Locus	Gene/nearest gene	Additional cardiovascular phenotypes showing association
9p21.3	*CDKN2BAS*	LAS, PAD, ICA[5,24,27]
10q24.32	*CYP17A1/CNNM2/NT5C2*	ICA[28]
10q23.31	*LIPA*	—
10q11.21	*CXCL12*	—
10p11.23	*KIAA1462*	—
11q23.3	*ZNF259/APOA5/APOA1*	—
11q22.3	*PDGFD*	—
12q24.12	*chr12q24/SH2B3*	—
13q34	*COL4A1/COL4A2*	—
13q12.2	*FLT1*	—
14q32.2	*HHIPL1*	—
15q26.1	*FURIN-FES*	—
15q25.1	*ADAMTS7*	—
17q21.32	*UBE2Z*	—
17p13.3	*SMG6*	—
17p11.2	*RAI1-PEMT-RASD1*	—
19p13.2	*LDLR/SMARCA4*	PAD[27]
19q13.32	*ApoE-ApoC1*	—
21q22.11	gene_desert/*KCNE2*	—

Note: Data from CARDIoGRAMplusC4D Consortium.[21] These should be considered the most stable risk loci for coronary artery disease/myocardial infarction.
AAA, abdominal aortic aneurysm; CES, cardioembolic stroke; ICA, intracranial aneurysm; IS, ischemic stroke; LAS, large-artery stroke; PAD, peripheral artery disease.

One of the most intriguing findings associated with CAD is a locus at chromosome 9p21. The first discovery of this locus dates back to 2007.[12] The same region on chromosome 9 was found subsequently also to be associated with diabetes,[29–31] glioma,[32,33] and open-angle glaucoma.[34,35] Throughout the years, this finding has been replicated in various related CVDs (as discussed later) as well as in other CAD studies.[13,14,17–19,36,37] This locus shows a strong association consistently with CAD and other CVD phenotypes, and also mediates the largest effect on CAD risk, normally being reported in the range of an elevated risk per allele (odds ratio) of 1.2 to 1.4. As is the case for all GWAS findings, the clarification of the impact of this risk locus on certain pathways leading to onset or progression of atherosclerosis is a daunting task.

To elicit the biological role of this locus further, biochemical and molecular biology evidence has been published on how this locus might affect CVD risk through interferon-γ signaling.[38] This work has shown that the 9p21 region encompasses a cluster of transcriptional enhancers, with the GWAS signals for CAD in this region being located in one of the enhancers. It has also shown that, in human vascular endothelial cells, the enhancer interval containing the CAD risk locus interacts

physically with *CDKN2A/B* (the main transcript at the risk locus), the *MTAP* gene, and an interval downstream of interferon-α.[21] In addition, it is suggested that interferon-γ activation strongly affects the structure of the chromatin and the transcriptional regulation in the 9p21 locus, including STAT1 binding, long-range enhancer interactions, and altered expression of neighboring genes.

Furthermore, different variants of *ANRIL*, a long, noncoding RNA that is found at the 9p21 locus, can affect different sets of genes[39] independent of *CDKN2A/B*. Different variants of *ANRIL* affect downstream targets, most notably *CHD5, HBEGF, BCL2A1*, and *SERPINE1*. These genes are important in mechanisms related to apoptosis and proliferation—both pathways thought to be involved in atherosclerotic processes. *ANRIL* is also known to inhibit *CDKN2B* transcription epigenetically, painting a picture of an intricate genomic interplay between *CDKN2A/B, ANRIL*, and downstream targets affecting multiple mechanisms related to atherosclerosis and subsequent CAD.[40]

These data provide a first view of this genomic locus and the pathways that may act downstream of these variants. Because all these findings are novel, they need to be refined, and the true meaning and exact molecular genetic mechanism of this risk locus in CAD needs to be elicited even further before diagnostic or even therapeutic consequences can be drawn.

For stroke, the association of the 9p21 region could be replicated. Associations have been found with all ischemic stroke (IS),[41–43] as well as with LAS, specifically.[5] However, for IS some investigators have also reported no association with 9p21.[44] This is most likely a result of the fact that the 9p21 risk region is subtype specific to LAS. The normal prevalence of LAS cases in an IS cohort is around 20%[45] and, given the suggestive subtype-specific association, it does not come as a surprise that the association is not observed for all ISs when the subtype distribution is biased against LAS. There is, indeed, evidence that the 9p21 locus is specific to LAS; however, correlated effects over other stroke subtypes cannot be ruled out.[3] Hence, it seems possible that the 9p21 locus is a region associated with other stroke subtypes, but given current sample sizes, the clearest association is observed for LAS. Similarly, a CAD risk region at another locus on chromosome 9 (*ABO*) was also shown to be associated with IS and, interestingly, several stroke subtypes.[26] This is the first demonstration of genetic variants showing evidence of association with multiple subtypes of stroke (LAS and cardioembolic stroke [CES]). ABO is the main component that determines the blood type in humans and is also implicated in many other disease phenotypes[46–48] (Table 7.2[49–71]).

In the opposite direction—LAS risk variants in CAD—single nucleotide polymorphisms near *HDAC9* that were first found to be associated significantly with LAS in a subtype-specific manner[3,25] have also now been observed and replicated for CAD.[21] Together, these findings lead to a novel study investigating the shared genetic component of CAD and IS/LAS[72] using all available GWAS results from IS/LAS and CAD. Here, signals could be identified that are thought to be shared between the two phenotypes but have not been associated with stroke on a genomewide level, most likely as a result of the absence of power to detect these signals. Of note, variants in the *CYP17A1/CNNM2/NT5C2* region on chromosome 10, variants in the *RAI1-PEMT-RASD1* region on chromosome 17, and variants in a risk region for multiple related diseases on chromosome 12 were associated significantly with both CAD and IS, or both CAD and LAS, or all three phenotypes. It was made clear in the study that the genetic overlap between CAD and IS/LAS is, indeed, significant. It will be exciting to see in the near future if—given extended sample sizes—these proposed risk regions will be discovered for IS/LAS at the genomewide level.

In contrast to the discussed CAD risk loci, other risk regions found in CAD GWAS efforts are often identified, not for the CAD phenotype itself, but rather for risk factors for CAD. It can be concluded that these loci do not affect risk for CAD independently, but rather act as confounders through mechanisms affecting risk factors for CAD. Many GWAS loci identified in CVD show a high degree of pleiotropy, meaning the gene affected has influence on multiple diseases that are not necessarily related. As an example, one locus identified at chromosome 11q23 (*ZNF259*; Table 7.2) is also associated significantly with elevated low-density lipoprotein cholesterol levels. It is, therefore,

TABLE 7.2

Association of Coronary Artery Disease Loci with Cardiovascular Disease-Related Risk Factors

Chromosome	Gene	Association with other cardiovascular phenotypes
1p13.3	*SORT1*	LDL cholesterol[49–53]
1p32.3	*PCSK9*	LDL cholesterol[50,51,54]
2p24.1	*APOB*	Total cholesterol[51] and lipid metabolism[55]
2p21	*ABCG5-ABCG8*	Total cholesterol[51,56] and lipid metabolism[55]
4q32.1	*GUCY1A3*	Diastolic blood pressure[57]
6q25.3	*SLC22A3/LPAL2/LPA*	Lipoprotein(a) levels and LDL cholesterol[51,58,59]
8q24.13	*TRIB1*	Total cholesterol[51]
8p21.3	*LPL*	HDL cholesterol[51] and lipid metabolism[55]
9q34.2	ABO	Venous thromboembolism, ACE enzyme activity, plasma E–selectin level, and plasma vWF level, among others[13,51,60–65]
10q24.32	CYP17A1, CNNM2, NT5C2	Systolic blood pressure[66]
11q23.3	ZNF259/APOS5A/APOA1	Triglycerides and HDL cholesterol[49,50,67]
12q24.12	chr12q24/SH2B3	Diastolic blood pressure, platelet count, and plasma eosinophil count, among others[66,68,69]
15q26.1	FURIN-FES	Diastolic blood pressure[57]
19p13.2	LDLR/SMARCA4	LDL cholesterol[50–53,56,70,71]
19q13.32	ApoE-ApoC1	Total cholesterol,[51] among others

ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein; vWF, von Willebrand factor.

easy to speculate that the increased risk of developing CAD is mediated through this risk factor. Another example is a locus at chromosome 10q24 (*CYP17A1*; Table 7.2), which is associated significantly with hypertension, and thus the risk for CAD may be conferred via high blood pressure.

A summary of variants found in CAD associated with confounders (adapted from Voight et al.[73] and Schunkert et al.[13]) can be seen in Table 7.2. From here it becomes visible that a moderate percentage of loci are associated with either lipoprotein (cholesterol) levels or hypertension—two of the main risk factors for CAD. However, many loci found to be associated with CAD are not associated with a related disease, so these may act independently of risk factors or through mechanisms not yet fully understood. It will be paramount in the future to dissect the dependent from the independent loci to broaden our understanding of mechanisms contributing to CAD and, subsequently, to IS/LAS.

In a recent publication,[21] the first efforts have been conducted to unravel the pathways associated with CAD, incorporating all found genomewide signals. The top three pathways—atherosclerosis signaling, liver X receptor/retinoid X receptor (RXR) activation, and farnesoid X receptor/RXR activation—all harbor genes involved in lipid metabolism, including 10 CAD risk loci. Notably, three of the top four pathways also contain genes involved in inflammation. In addition to the atherosclerosis signaling and liver X receptor/RXR activation pathways, the acute phase response signaling pathway, which includes four CAD risk loci (*APOA1, MRAS*, interleukin 6 receptor [*IL-6R*], and *PLG*), is involved in inflammation and, more specifically, the rapid inflammatory response that is triggered, among other factors, by tissue injury.

Myocardial Infarction

MI has often been studied together with CAD because MI is the direct clinical end point of CAD. Therefore, GWASs aimed directly at MI are scarce,[36,54] and most loci are also reported for CAD alone or for a combined CAD/MI phenotype (as mentioned earlier).

Recently, there has been a large-scale effort to study whether variants associated specifically with MI are also relevant in IS.[74] The authors selected 11 loci previously associated with MI and tried to replicate these findings in an independent stroke cohort.

They found that, for IS, two loci (*PCSK9* at 1p32.3 and *SH2B3* at 12q24.12) show evidence of association, but statistical significance was found to be nominal. Furthermore, they also evaluated the association of MI genes in stroke subtypes and found that the previously identified CAD risk gene (Table 7.1), *MRAS*, is associated with CES, *MIA3* is associated with small-vessel stroke, and *SH2B3* is associated with strokes stemming from an unknown origin, although the associations are, again, at a nominal level only. Their study, although limited by a lack of power, still can serve as an interesting design for future efforts to discover shared disease mechanisms, similar to the study performed on IS/LAS and CAD.[72]

Peripheral Artery Disease

Peripheral artery disease (PAD) affects large arteries supplying the limbs or internal organs. A clinically usefully diagnostic criterion is the ankle–brachial pressure index, which is also used as an endophenotype in GWAS analyses. PAD has a prevalence of around 6%in the general population.[75] Because atherosclerosis is also a hallmark of PAD, risk factors are similar to CAD/MI and include smoking, diabetes, dyslipidemia, obesity, and hypertension.[76,77]

Murabito et al.[27] have recently shown that the 9p21 locus also plays a large role in PAD. In addition, they report that another suggestive CAD-related gene (*LDLR*; Table 7.1) shows borderline genomewide associations with PAD.

Other GWASs have shown that a variant in the neuronal acetylcholine receptor subunit α3, or *CHRNA3*, gene (a nicotinic acetylcholine receptor) is associated with PAD, but this association is most likely mediated by smoking behavior,[78] the main risk factor for PAD and not exclusive to PAD itself. The variant rs7025486 in the disabled homolog 2 interacting protein isoform (*DAB2IP*) gene also showed suggestive association with PAD[79] in a study for a whole array of CVDs. This region, however, shows a more significant association with abdominal aortic aneurysms (AAAs; discussed later).

A classic approach in genetics—complementary to GWAS—is the study of candidate genes, usually genes situated in pathways relevant to the disease phenotype. Zintzaras and Zdoukopoulos[80] show, in their extensive review of candidate gene studies in PAD, that variants in 22 potential PAD genes show a consistent effect over all studies (Table 7.3). They classified the genes in their study according to the biological pathway to which they belong. Pathways considered are the coagulation cascade (factor V Leiden, factor II Leiden), the folate–homocysteine pathway (methylenetetrahydrofolate reductase [MTHFR]), the renin–angiotensin system pathway (angiotensin-converting enzyme [ACE], angiotensinogen), the leukocyte transendothelial migration pathway (matrix metalloproteinase 9 [MMP9], intercellular adhesion molecule 1, and the cytokine–cytokine receptor interaction pathway (IL-6), all of which have been implicated for CVD in general.

Because the threshold for statistical significance is lower for candidate gene studies and, usually, the sample size in candidate gene studies is significantly smaller, these findings need to be confirmed independently using a case–control setup and more markers being tested. However, they still can serve as a good starting point for future studies. MMP9 is of special interest for stroke genetics

TABLE 7.3

Genes Identified for Peripheral Artery Disease Using a Candidate Gene Approach

Gene symbol	Full name	Pathway
F5	Coagulation factor V	Coagulation cascade
F2	Prothrombin	Coagulation cascade
MTHFR	Methylenetetrahydrofolate reductase	Folate pathway
ITGB3	Integrin, β3	Extracellular matrix receptor interaction pathway
ACE	Angiotensin-converting enzyme	Renin–angiotensin system pathway
AGT	Angiotensinogen	Renin–angiotensin system pathway
IL-6	Interleukin 6	Cytokine–cytokine receptor interaction pathway
ICAM1	Intercellular adhesion molecule 1	Leukocyte transendothelial migration pathway
MMP9	Matrix metalloproteinase 9	Leukocyte transendothelial migration pathway
CHRNA3	Neuronal acetylcholine receptor subunit α3	Other

because it is a prognostic marker for poor outcome after stroke,[81] probably through activation of neutrophils in the ischemic brain.[82]

In a different approach using previously discovered regions implicated in telomere length, Raschenberger et al.[83] showed in patients with PAD that their mean telomere length is significantly shorter than in their healthy counterparts. This phenomenon has been already reported for CAD[84] and other CVDs, but no evidence exists to date that this is also true for IS.

Another interesting finding that was communicated by Khandanpour et al.[85] is that elevated homocysteine levels mediated by a variant in the *MTHFR* gene are associated with PAD. As stated earlier, the role of homocysteine levels in stroke and other CVDs is disputed, and the effects might also be restricted to low-folate populations.[86] This is, indeed, a very active area of research and will, hopefully, lead to a complete picture on how folate levels affect stroke risk.

Apart from the 9p21 locus, no gene associated with PAD has been associated with stroke, as is stated specifically for *DAB2IP*[79] and *CHRNA3*.[87]

Intracranial Aneurysm

Intracranial aneurysms (ICAs) occur in up to 6% of the general population, in which subarachnoid hemorrhage after aneurysm rupture is a potentially fatal event. ICAs can occur in every brain artery, but are most common in the anterior cerebral artery and the anterior communicating artery. IS (and here, specifically, LAS), CAD/MI, and PAD on the one side and ICA on the other side are thought to have distinct etiologies, with atherosclerosis being considered a risk factor for the former group, but not for the latter (ICA).[88–90] Therefore, risk loci are not thought to overlap between those two categories. Nevertheless, it is also important to mention that risk factors for ICA overlap with those of stroke and other atherosclerotic diseases—namely, smoking[91] and hypertension[92]—possibly leading to a weakening of the vessel walls and potentially promoting aneurysm rupture in ICA. In summary, risk loci identified for both ICA and IS might affect a broader phenotype of arterial disease and not necessarily via atherosclerotic mechanisms.

This is signified by the 9p21 locus, which also has been identified as a risk region for ICA.[93,94] Furthermore, the *SOX17* cluster on chromosome 8 has also been replicated stably and can be associated with ICA.[28,93] *SOX17* encodes for a member of the Sry-related HMG box transcription factor family and has been implicated in vascular biology and angiogenesis.[95,96] It is of special interest because it ensures endothelial integrity. Suggestive evidence in an Asian population was also found at a region on chromosome 2, namely for a locus encompassing the *BOLL* and *PLCL1* genes.[93] In this work, the authors state that the *PLCL1* gene is of interest because it has significant homology to phospholipase C, which lies downstream of VEGFR2 signaling, suggesting a role in endothelial mechanisms because VEGFR2 plays an essential role in the regulation of angiogenesis, vascular development, vascular permeability, and embryonic hematopoiesis.

In a purely Japanese population, the *EDNRA* gene has been identified as a risk gene for ICA.[97] *EDNRA* is a known and potent mediator of vasoconstriction,[98] and the same locus has also been associated with plaque size in an analysis of carotid intima media thickness and atherosclerotic plaques.[99] In addition, it was also found to be a major risk locus for CAD (Table 7.1).

Yasuno et al[28] identified three novel risk loci for a mixed European and Japanese population, with variants near *RBBP8, STARD13/klotho* (a locus associated with renal failure and arterial stiffening), and *CNNM2* (a CAD risk locus; Table 7.1) being associated with the phenotype. They state that these candidates are implicated in cell cycle progression, potentially affecting the proliferation and senescence of progenitor cell populations that are responsible for vascular formation and repair.

In a recent publication, a variant in the *PRDM6* gene was found to be associated with ICA, but this association is mediated through hypertension and, more specifically, through elevated systolic blood pressure.[100] This comes as no surprise, because PRDM6, a histone methyltransferase that acts as a transcriptional repressor of smooth muscle gene expression, could potentially predispose to elevated systolic blood pressure by an altered vascular wall structure.

The latest and biggest meta-analysis of ICA,[24] using 32,000 patients and 84,000 control subjects, confirmed the assumption that chromosome 9p21, the *SOX17* cluster, and *EDNRA* are the most reliable risk regions for ICA. Interestingly, two of the three major loci are also known to be risk regions for CAD. Other loci could not be replicated. Using a complementary approach, van't Hof et al.[101] showed that a genetic risk profile composed of risk variants for hypertension is associated with ICA, but other, related risk profiles for lipids and CAD are not.

Abdominal Aortic Aneurysm

AAAs are dilations in the abdominal aorta. Ninety percent of these aneurysms occur infrarenally and may spread to the pelvic arteries. Similar to ICAs, they are potentially lethal when aneurysm rupture occurs. Regarding etiology, AAA is thought to occur more frequently in patients with atherosclerosis. It is still debatable whether this association is causal or the result of common risk factors, with most studies suggesting that AAA formation is independent of atherosclerosis.[102,103] The other main risk factors for AAA include advanced age, male gender, smoking, and family history.[104]

As stated earlier, the *DAB2IP* gene[79] and the 9p21 locus[94] have both been associated with AAA, suggesting partly overlapping disease-causing mechanisms related to atherosclerosis. The association of *DAB2IP* with AAA was the most convincing compared with other CVD phenotypes, and therefore should be considered the main risk locus for AAA. DAB2IP is a suppressor for the PI3K-Akt and RAS pathways, and an enhancer of apoptosis. The Akt pathway is known to act in vascular homeostasis and angiogenesis.[105] Furthermore, DAB2IP is also thought to affect VEGFR2-mediated signaling (as mentioned earlier).[106]

In a recent study,[107] an association of variants within the *LRP1* gene with AAA was found. Because LRP1 is a binding partner of apolipoprotein E, a gene implicated primarily in lipid metabolism and

a risk candidate for a plethora of CVDs, it would be an ideal candidate also to mediate stroke risk. Apolipoprotein E has proved to be a risk gene for hemorrhagic stroke,[108] but the evidence for IS is still unreliable.[109] Another known CAD risk gene (*SORT1*) was also found to be an independent genetic risk factor for AAA.[23]

A region at chromosome 3p12 near *CNTN3*[110] was identified as an additional risk variant for AAA. This contactin 3-gene product is responsible for cell surface interactions during nervous system development. This finding might also be an indicator of a confounder for smoking behavior, as the authors state in their publication.[110]

In a recent publication, Harrison et al.[22] found that variants in *IL-6R* associate significantly with AAA. One specific variant is responsible for an amino acid shift (Asp358Ala) in IL-6R, leading to a lower risk of AAA. Variants in *IL-6R* have also been reported as increasing risk for CAD (Table 7.1).

Thompson et al.[111] hypothesize in a candidate gene study that gene products in the transforming growth factor β pathway might play a role in AAA, and this was further replicated independently.[112] Transforming growth factor β research has a long-standing tradition in stroke genetics because it has been proved to play a role in angiogenesis after stroke[113] and to act as a neuroprotective agent.[114] Interestingly, associations with *MMP9, ACE*, and *MTHFR* have been show by Thompson et al.[111] also to be associated with AAA through meta-analysis of candidate gene studies. Because these are also thought to be associated with PAD (as discussed earlier), this points toward a broader arterial mechanism involved.

In the same mold, Jones et al.[115] have performed a candidate gene study and found a nonsynonymous single nucleotide polymorphism in the angiotensin II receptor type 1, or *AGTR1*, gene, which belongs to the angiotensin–renin system similar to *ACE* and angiotensinogen in PAD. This is of interest because the angiotensin system, and especially angiotensin II, is the major causative factor of cerebrovascular effects of hypertension.[116] The renin–angiotensin system is thought to have some influence on stroke, but not solely via hypertension; the exact mechanisms are not known thus far. Renin–angiotensin inhibitors have shown some previous success in stroke treatment.[117]

Interestingly, genetic risk profiles of lipid factors and CAD show an association with AAA, but not with ICA—the reverse of what is shown for genetic risk profiles of hypertension.[101] This could lead to the conclusion that genetic variants in these pathways all contribute with small effects toward the risk phenotype.

Conclusion

The chromosome 9p21 locus represents a major risk locus associated with a range of CVDs. Efforts are already being made to elicit further the role of this locus in a broader vascular disease model with regard to the actual biochemical and biological processes involved. There are multiple other candidate loci, many of them plausible biologically, that should be examined further in the future, regardless of whether they also serve as regions implicated in stroke. Most notable, the overlap between CAD and LAS risk variants is encouraging and might lead to the discovery of shared genetic risk regions in the future. Similarly, other related CVDs also show genetic overlap with CAD to some extent (Table 7.1), leading to the hypothesis that these genetic risk factor act on a broader vascular phenotype implicated in several disease etiologies.

One reason why some of these risk regions are, to date, not found as risk regions in stroke could be that stroke, as a complex CVD, is a much more heterogeneous phenotype. Most risk regions identified for stroke (9p21, 6p21 and 7p21 for LAS, and 4q25 and 16q22 for CES) have been identified for subphenotypes only, making it more likely that different stroke subphenotypes have distinct, nonoverlapping genetic risk profiles. One risk region for stroke (*ABO*) is currently the only one identified for multiple subtypes of stroke.[26] These distinct etiologies may share greater similarities with

related CVD phenotypes, as is the case, for example, with LAS and CAD. As an additional point, this division into stroke subphenotypes decreases drastically the number of patients studied. With a more homogenous phenotype like CAD, patient numbers of 100,000 are reached in the largest studies, such as CARDIoGRAMplusC4D.[21] These numbers have not been reached yet in the stroke field, with the METASTROKE[25] study being the biggest so far, with 12,000 stroke patients. When studying subphenotypes, this number gets continuously lower, and therefore the discovery of novel risk regions is hampered. Thus, the numbers of cases in each subphenotype needs to be increased dramatically in the future.

Another reason might be the existence of rare variants in the regions identified for related CVD phenotypes. It is still disputed whether the majority of genetic heritability is captured via common variants (frequency, >1%–3% in the general population) or low-frequency/rare variants (frequency, <1%–3%). It could be that rare variants in similar genes/pathways like the ones identified for related diseases play a role in stroke. Therefore, new methods such as targeted deep sequencing, exome sequencing, or even whole-genome sequencing are needed to test these hypotheses further and to identify more risk variants for stroke.

Using these approaches, several risk loci found for related diseases, and especially CAD, might prove to be bona-fide risk regions for IS or its subtypes.

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8

GENES ASSOCIATED WITH RARE SUBTYPES OF STROKE

Cervical Artery Dissection

Stéphanie Debette

Introduction

Cervical artery dissection (CeAD) is one of the most common causes of ischemic stroke (IS) in young and middle-age adults,[1] occurring at a mean age of 44 years.[2,3] Although the disease can occur in children as well, it is very rare beyond age 65. Carotid dissections are more common than vertebral dissections, with a ratio of approximately 1.7:1 in populations of European origin.[3] A predominance of vertebral dissection has been described in Asian cohorts.[4,5] A slight male predominance was reported in European cohorts (53%–57%).[6] Men more often have carotid dissection and are, on average, 5 years older when CeAD occurs.[6–8]

In the general population, the incidence of CeAD is relatively low—estimated between 2.6/100,00 per year and 3/100,000 per year,[3,9] which makes it a major challenge to study large samples of patients with this disorder. Pathologically, CeAD is associated with a hematoma in the wall of a cervical artery (carotid or vertebral), secondary either to an intimal tear or to direct bleeding within the arterial wall from ruptured vasa vasorum. The most severe complication of CeAD is intraluminal thrombus formation, leading to cerebral—or more seldom retinal—ischemia. CeAD can also present with "local" symptoms or signs only, including headache, cervical pain, Horner's syndrome, and cranial nerve compression, or can be asymptomatic.

Although mechanisms and risk factors of CeAD are poorly understood, neck trauma is an important predisposing factor for CeAD. Rarely, CeAD can occur with major penetrating or nonpenetrating traumas.[10] Often, patients with CeAD report a minor trauma,[11–13] such as chiropractic manipulation, whiplash injury, or extreme neck movements, in the days or weeks preceding the dissection. However, a causal relationship is often difficult to establish, reported traumas are often trivial, occurring very often in a lifetime, and many cases of CeAD occur without any trauma at all, suggesting that there must be other susceptibility factors. Recently, hypertension was shown to be associated with a moderately increased risk of CeAD,[14,15] whereas hypercholesterolemia and

overweight appear to be associated inversely with the disease.[7,16] Other putative risk factors include recent infection,[17,18] hyperhomocysteinemia,[19–21] and migraine.[22,23]

A number of arguments suggest that patients with CeAD could have an underlying arterial wall weakness, and that genetic factors may play a role in the pathophysiology of CeAD (Figure 8.1). Indeed, various concomitant structural and functional arterial abnormalities were described in association with CeAD, including larger aortic root diameter,[24] increased carotid stiffness,[25] endothelial dysfunction,[26–28] and arterial redundancies.[29] Pathological changes predominating at the media–adventitia border, including vacuolar degeneration, capillary neoangiogenesis, and erythrocyte extravasation, were detected in temporal arteries of patients with CeAD, but not in control subjects.[30] There is also an intriguing overlap of CeAD with other nonatherosclerotic vasculopathies, such as fibromuscular dysplasia[31–33] or reversible cerebral vasoconstriction syndrome.[34–36] Moreover, a number of arguments suggest that this putative underlying arterial wall weakness could reflect, more largely, a weakness of the connective tissue (Figure 8.1). Indeed, more than half of patients with CeAD have ultrastructural skin connective tissue abnormalities on electron microscopy, the most common pattern being Ehlers-Danlos type III-like composite collagen fibrils and fragmentation of elastic fibers.[37] Skin biopsies performed in healthy relatives of index patients with CeAD have suggested that these connective tissue changes may be inherited according to an autosomal dominant pattern.[38] In addition, CeAD is a classic complication of some rare inherited disorders of connective tissue, as detailed next.

Monogenic Disorders and CeAD

In rare instances, CeAD can occur as part of a known monogenic disorder.[39] Arterial dissection is, indeed, a common feature of certain rare inherited disorders of connective tissue, such as vascular Ehlers-Danlos syndrome (vEDS), Marfan syndrome (MFS), or Loeys-Dietz syndrome (LDS).[40]

VASCULAR EHLERS-DANLOS SYNDROME

vEDS is a rare autosomal dominant disease, resulting from a mutation in the *COL3A1* gene on chromosome 2q31 (OMIM 130050). The prevalence is estimated at 0.2 to 1/100,000,[41] and the median survival is 48 years (in older series).[42] The diagnosis is suggested clinically by the presence of at least two of four major clinical criteria[43]: easy bruising, thin skin with visible veins, characteristic facial features, and rupture of arteries, uterus, or intestines. In addition, the diagnosis must be confirmed by the demonstration of either an abnormal type III procollagen synthesis or of a mutation in the *COL3A1* gene. Phenotypic features can be subtle, and most patients are unaware of the diagnosis at the time of their first major complication.[42] The latter usually occurs at a young age, before age 40 years in 80% of patients.[42] Neurological complications of vEDS are essentially cerebrovascular,[44] including CeAD, carotid cavernous fistula, intracranial aneurysms, and arterial rupture. The mean age at occurrence of the first cerebrovascular complication was reported to be 28 years (range, 17–48 years).[44] In the two largest, partly overlapping, series of biologically confirmed patients with vEDS, 2% of them had a history of CeAD (of note, only carotid and not vertebral artery dissections were reported in the most recent study).[42,44] The reported frequency of vEDS cases in large published series of consecutive patients with CeAD is very low, around 0.5% to 2%.[45–48]

Although vEDS seems to be extremely rare among patients with CeAD at the general population level, being aware of and screening for the main clinical diagnostic criteria are important. Indeed, diagnosing vEDS has major consequences for the patient's management. Endovascular investigations are contraindicated in patients with vEDS, given the high risk of iatrogenic arterial dissection and rupture, resulting from the vulnerability of the arterial wall. To prevent primary or recurrent ischemic

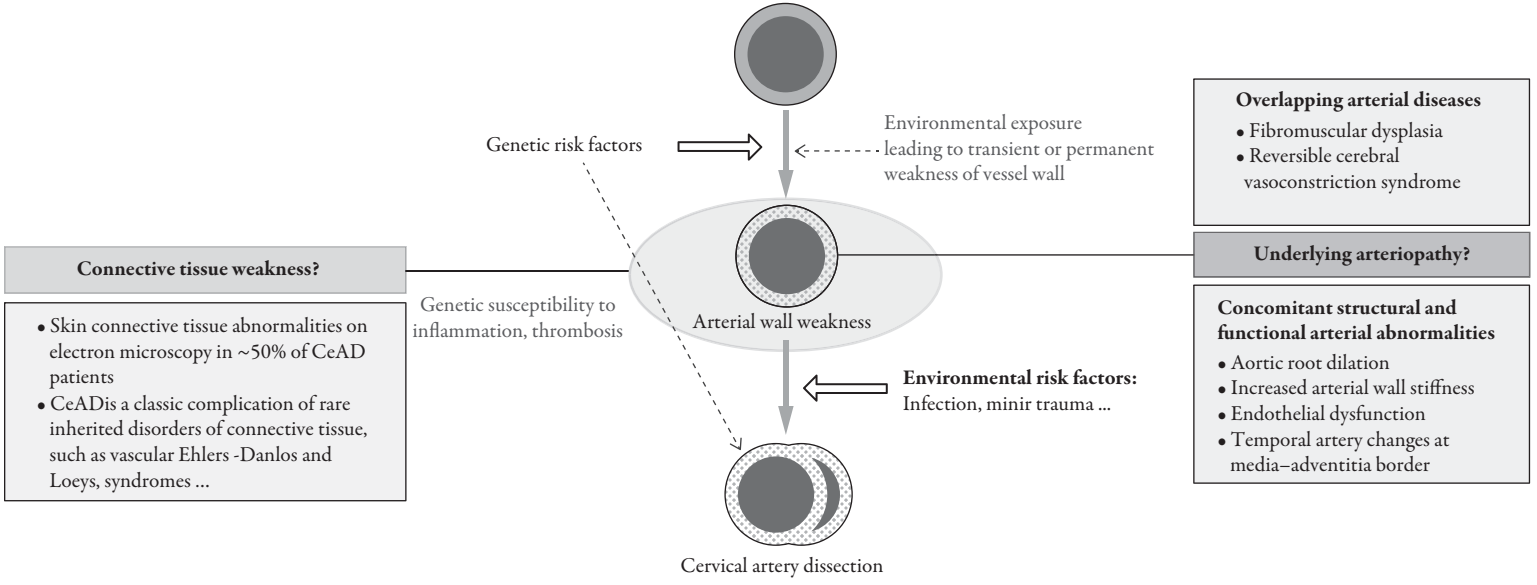

FIGURE 8.1 Pathophysiology of cervical artery dissection (CeAD), a multifactorial model.

events, either anticoagulants or antiplatelet agents are prescribed at the acute phase of CeAD, in the general population; their efficacy has not been compared in a randomized trial.[6,48,49] In patients with vEDS, antiplatelet agents might perhaps be the preferred treatment, because fatal bleeding may occur with anticoagulants.[41] Prophylactic treatment with celiprolol is also recommended for patients with vEDS, to prevent recurrences of dissection or arterial rupture.[50]

MARFAN SYNDROME

MFS is an autosomal dominant disease resulting from a mutation in the *fibrillin-1*, or *FBN1*, gene on chromosome 15q21.1 (OMIM 154700). The prevalence is estimated at 1/5000.[51] Clinical signs of MFS include musculoskeletal, ocular, and cardiac complications with aortic and mitral valve anomalies; aortic aneurysms; and dissections conditioning the outcome. The diagnostic criteria have been revised recently.[52] Large series of consecutive patients with CeAD report very low frequencies of MFS (0.6%–0.9%)[2,45,48] without details on how the diagnosis of MFS was confirmed. Many large series do not report any patient with MFS. In patients with a proven diagnosis of MFS, spontaneous CeAD seems to be exceptional and must be differentiated from proximal aortic dissections extending into the brachiocephalic arteries. In a retrospective analysis of neurovascular complications in 513 patients with MFS, not a single case of CeAD was found.[53]

LOEYS-DIETZ SYNDROME

LDS is a recently identified group of extremely rare autosomal dominant disorders (OMIM 609192, OMIM 610380, OMIM 610168, OMIM 608967) caused by mutations in the *transforming growth factor β receptor 1* (*TGFBR1*) and *2* (*TGFBR2*) genes (chromosome 9q22 and 3p22), of unknown prevalence,[54] the phenotypes of which overlap with MFS and vEDS.[55] Three quarters of affected individuals have LDS type I with craniofacial manifestations (ocular hypertelorism, bifid uvula and cleft palate, craniosynostosis); the remaining quarter have LDS type II with cutaneous manifestations (velvety and translucent skin; easy bruising; widened, atrophic scars).[55] The disease is characterized by aggressive arterial aneurysms and a high incidence of pregnancy-related complications, including uterine rupture and death.[55,56] Arterial tortuosity involving head and neck vessels is frequent in patients with LDS. CeAD is a classic complication of LDS, although aortic dissections are more common.[57]

OTHER MONOGENIC DISORDERS

A number of observations have suggested an association of CeAD with other monogenic conditions, including alpha$_1$-antitrypsin deficiency, arterial tortuosity syndrome, osteogenesis imperfecta, autosomal dominant polycystic kidney disease, or hereditary hemochromatosis,[34,58–66] as well as with rare chromosomal disorders such as Turner's syndrome[67,68] or William's syndrome.[69] It is, however, unclear whether the simultaneous occurrence of these disorders is more common than would be expected by chance, and these conditions may not be risk factors for CeAD at the community level.

Last, it cannot be formally excluded that some patients with CeAD have mild forms of inherited disorders of connective tissue with incomplete penetrance or CeAD as the first isolated symptom,[6,70] because patients were not screened systematically for mutations in genes such as *COL3A1, FBN1, TGFBR1*, or *TGFRB2*, which are responsible for vEDS,[42] MFS,[52] and LDS.[55] In earlier studies, a systematic search for mutations in *COL3A1* among 53 patients with CeAD,[71–74] and in *TGFBR1* and *TGFBR2* among 56 consecutive patients with CeAD,[70] identified potentially deleterious mutations in *COL3A1* among two cousins with CeAD,[71] and in *TGFBR2* in two unrelated patients with

CeAD,[70] but none of them fulfilled the clinical diagnostic criteria of vEDS or LDS, possibly pointing to mutations with incomplete penetrance.[43,55,75] Whether identifying such mutations is clinically relevant—especially in terms of risk for CeAD recurrence, other vascular complications, and familial risk—is unclear to date.

Genetic Predisposition to CeAD

In the majority of CeAD cases, there is no clinical evidence for an underlying monogenic disease, and CeAD is believed to occur as part of a multifactorial predisposition (Figure 8.1).[39] Heritability estimates are not available. In one single-center study that addressed the frequency of family history of CeAD systematically, in 200 patients with CeAD,[76] 10 patients from 8 families had a family history of dissection. Of these, five patients (2.5%) from three families (1.5%) had a family history of dissection in the cervical arteries (the remaining being in the intracranial arteries, aorta or renal artery), and in four patients the family history of CeAD was in a first-degree relative (2.0%).[76] Another study, of 181 patients with CeAD, reported the presence of a family history of CeAD in less than 4 (2.2%) of their patients,[77] but familial occurrence of CeAD was not the main scope of that article, thus no details are provided on the degree of relatedness of affected individuals. On the one hand, these scarce reports of family history of CeAD could be an overestimation resulting from recruitment bias through tertiary referral centers, and because several CeAD cases from multiple affected families were included. On the other hand, a family history of CeAD is likely to be underreported because CeAD can be asymptomatic, or clinical signs can be subtle and the diagnosis tricky, especially before magnetic resonance imaging became widely available. Overall, even though familial occurrence of CeAD seems to be rare, it is slightly more common than would be expected by chance given the low incidence of the disease.[78] Familial cases of CeAD usually do not appear to occur in the context of a known, inherited connective tissue disorder.

Genetic factors could, theoretically, predispose to CeAD at various levels, such as (a) by contributing to a weakening of the vessel wall (on top of which environmental factors such as trauma or acute infection could act as triggers); (b) by increasing vulnerability to environmental factors that could have an impact on vascular wall integrity, such as by modulating inflammatory response to infection; and (c) by influencing the occurrence of environmental susceptibility factors of CeAD, such as hypertension, low lipid levels, and body mass.

Different approaches have been used to identify genetic variants contributing to CeAD risk. It should be noted that genetic susceptibility variants for multifactorial diseases such as CeAD usually have modest effects, with odds ratios typically less than 1.5.[79] The main objective, when searching for genetic risk factors of a complex, multifactorial disease, is to improve our understanding of the molecular mechanisms involved in the pathophysiology of this disease and thereby identify novel potential drug targets and optimize preventive strategies.

LINKAGE STUDIES

Linkage studies are family based and consist of testing whether genetic markers cosegregate with a given disease (in this case, CeAD) within families. This is done by examining simultaneously the transmission across generations of both CeAD and marker alleles, either genomewide or in a specific genomic region. Although linkage studies are particularly suited to discover genes causing monogenic disorders, they have also been implemented in some instances to identify genes contributing to complex diseases in family-based studies. Linkage studies for CeAD have been limited by the small number of large families with several members affected by the disease. They have not identified any significant linkage peak to date, but their power was limited.[39] One linkage analysis was performed in a family including three

individuals affected by CeAD, using markers flanking the *COL3A1* locus.[74] Other linkage studies have been performed in families with only one member affected by CeAD, but several members presenting skin connective tissue abberrations described as being associated with CeAD.[38,80,81] These studies used microsatellite markers for candidates genes involved in the synthesis of extracellular matrix components,[80,81] and one study performed a whole-genome linkage analysis.[38] Despite some suggestive findings, none of these studies could confirm formally the presence of genetic linkage.

Genetic Association Studies

Genetic association studies consist of comparing the frequency of genetic variants between patients and control subjects. Until recently, genetic association studies were candidate gene based (i.e., genetic variants were selected through a priori hypotheses about the underlying pathophysiology of the disease). One or more genetic variants (usually single nucleotide polymorphisms) from a candidate gene were genotyped in a group of unrelated patients and control subjects, and the association of allele frequencies was compared between patients and control subjects.

In total, 18 genetic association studies testing the association of CeAD with candidate genetic variants have been published, on relatively small samples.[39,82,83] Of these, five have reported significant associations with three different candidate genes: *ICAM-1* (rs5498),[84] *COL3A1* (3′ UTR 2-bp deletion),[74] and *MTHFR* (*MTHFR*-C677T).[20,21,85] The first two were not replicated.[39] Three studies, of which two overlap, found a positive association between the *MTHFR* 677TT genotype and CeAD,[20,21,85] whereas four others did not report any association.[19,83,86,87] A meta-analysis of these studies (comprising 440 patients with CeAD) suggested an overall significant association of the *MTHFR* 677TT genotype with an increased risk of CeAD.[39] However, given the small sample size of individual studies and the publication bias favoring candidate gene studies with significant results, it seems crucial to replicate this finding in a larger, independent sample. The *MTHFR* 677TT genotype is associated with elevated homocysteine levels,[19–21,87] which may contribute to endothelial damage or influence elastic properties of the arterial wall.[20]

Overall, published candidate gene association studies have been markedly underpowered, mainly as a result of the low prevalence of CeAD, which made it difficult to reach sufficient sample sizes. Moreover, candidate gene association studies are unable to identify novel genetic variants involved in unsuspected pathways, because they are based on what is already known or suspected about the pathophysiology of the disease.[79]

Definitive data can be obtained only from much larger multicenter genetic association studies, with replication of positive associations in independent samples.[88] International efforts, as part of the CADISP consortium (www.cadisp.com),[89] have recently enabled the collection of DNA samples from close to 2000 patients with CeAD, and have led to the first genomewide association study (GWAS) of CeAD. GWASs offer an unbiased approach, consisting of genotyping very large numbers of genetic variants (100,000–5,000,000) distributed across the chromosomes using high-throughput genotyping, without requiring any a priori hypothesis. During the past few years, this approach has been applied to a number of complex diseases with major successes, leading to the identification of hundreds of novel genes conferring increased risk of many complex diseases, including stroke (see Chapter 5).[90–92]

Conclusion and Perspectives

To summarize, apart from exceptional cases of CeAD occurring as a complication of rare inherited disorders of connective tissue, and apart from very rare familial cases (<3%), CeAD appears to be mostly a multifactorial disorder. Despite important efforts, no consistent, robustly replicated genetic

association with CeAD has been identified to date. Published studies have been markedly underpowered. Results of the first GWAS of CeAD are awaited.

Additional GWASs on larger samples will likely be needed to expand the search further for genetic susceptibility factors of CeAD, if additional patients can be recruited during the coming years. Collecting large samples of dissection patients of non-European ethnicity will also be important to refine our understanding of the genetic architecture of CeAD. Indeed, so far, most genetic studies have been performed in populations of European descent. Interestingly, clinical and demographic characteristics of CeAD differ in part in other ethnic groups.[88,93]

As has been experienced with other complex diseases, GWASs will likely identify only a minor proportion of genetic susceptibility factors for CeAD, even when much larger samples can be collected in the future. Indeed, GWASs focus mostly on single nucleotide polymorphisms, and more recently also on small insertions and deletions. Investigating other types of genetic variation, such as copy number variants, rare variants, or epigenetic modifications, will be another important step. Efforts are already underway to explore these types of variation in CeAD, leveraging available data from existing data sets.

Last, further insight into the biological pathways underlying CeAD may be obtained by exploring the pleiotropy, or shared genetic variation, between CeAD and other arterial diseases showing important phenotypic correlation, such as fibromuscular dysplasia[31,32] or reversible cerebral vasoconstriction syndrome.[35,36]

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9

GENES ASSOCIATED WITH RARE SUBTYPES OF STROKE

Cerebral Venous Thrombosis

Thomas Marjot and Pankaj Sharma

Introduction

Cerebral venous thrombosis (CVT) is a rare form of cerebrovascular disease that accounts for less than 1% of all cases of stroke. The condition was first recognized by French physician Ribes back in the early 19th century[1] and was largely regarded as arising from local or systemic septic conditions. Clinically, CVT was traditionally believed to follow a reliable course of rapidly progressing focal neurological deficit, seizures, coma, and inevitable death. Even up until the middle of the 20th century, CVT remained a postmortem diagnosis, with confident diagnosis based on clinical grounds alone emerging only during the 1940s. Now our understanding of this complex condition has broadened substantially. Modern magnetic resonance imaging and computed tomography have allowed more rapid confirmation of diagnosis and have paved the way for investigation into the treatment, prognosis, and risk factors for this disease.

Anatomy

The venous drainage of the cerebrum can be separated broadly into deep and superficial systems. The superficial system, which lies on the surface of the brain, is composed of venous sinuses, the walls of which are composed of dura mater as opposed to venous endothelium, The superior sagittal sinus is the largest contributor to the superficial system and runs posteriorly and inferiorly toward the confluence of sinuses. Two transverse sinuses travel laterally and inferiorly from this confluence and twist into an S shape, where they form the sigmoid sinuses before ultimately becoming the internal jugular veins bilaterally. The deep venous system is composed of vessels lined by traditional endothelium and has branches that penetrate the deep cerebral structures. These branches come together behind the midbrain to form the vein of Galen. At this point, the vein of Galen joins the inferior sagittal

sinus, becoming the straight sinus, which then enters to the confluence of sinuses, the junction where deep and superficial systems meet. Thrombosis within any of these drainage structures constitutes a diagnosis of CVT, and it is therefore not surprising that this disease presents with a wide-ranging variety of signs and symptoms. An important clinical correlate of the venous anatomy is that bilateral cerebral involvement is not infrequent. For example, deep venous thrombosis can cause bilateral thalamic damage and reduced consciousness with little focal neurological deficit. Similarly, bilateral motor impairment is often found in sagittal sinus thrombosis in which the circulatory dysfunction may affect both hemispheres.

Diagnosis and Treatment

Definitive diagnosis relied traditionally on autopsy investigation, which revealed that venous thrombosis often coexisted with hemorrhagic lesions, which for a long time was thought to contraindicate the therapeutic use of heparin. However, recent guidelines, compiled largely from Cochrane reviewed evidence, state that concomitant intracranial hemorrhage is not a contraindication for anticoagulants. Body weight-adjusted, subcutaneous low-molecular weight heparin or dose-adjusted intravenous heparin is now used first line in acute CVT management.[2] The rationale for anticoagulation is to recanalize the occluded sinus or vein, to prevent further development of the thrombus, and, possibly in some cases, to reduce the risk of thromboembolic events elsewhere, such as pulmonary embolism (PE) or deep vein thrombosis (DVT).

CVT is thought to cause neurological damage via two distinguishable mechanisms: (a) thrombosis of the cerebral veins, which leads to local effects caused by venous obstruction; and (b) thrombosis of the major sinuses, which triggers intracranial hypertension.[3] The lasting damage these two processes cause has been largely unappreciated, and robust evidence evaluating long-term prognosis has only become available during the past 10 years. The large, prospective International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) containing 642 adult cases has proved invaluable in this respect because it documents patients' clinical profile over time.[4] Although the study offers a much less fatalistic impression of CVT than early case reports—for example, more than half of patients had no symptoms present at 16 months—there was still a significant proportion of patients (13%) who met the primary outcome of death or dependence at the end of follow-up.[4]

Despite accumulating literature and vast improvements in our understanding of the pathology, treatment, and prognosis of CVT, the disease still remains a diagnostic and therapeutic challenge. Mortality is still significant—hovering consistently around 10%—the disorder may worsen occasionally despite optimal anticoagulation, and any age group can be affected. CVT in neonatal and pediatric groups is of increasing scientific and clinical interest. Compared with adult CVT, neonatal and pediatric CVT is estimated to bring about far more severe long-term neurological outcomes, including developmental delay, cerebral palsy, and lasting seizure disorders.[5] It is also more common, with rates as high as 26 cases per 1 million, as opposed to 4 per 1 million in the adult population.

Diagnostic testing and safe/effective treatment still remain to be evaluated systematically for neonatal/pediatric patients, and current guidelines, unfortunately, are based on scant evidence. Etiology and pathophysiology of CVT in these groups is also still poorly understood, although two prospective studies have concluded that the prevalence of prothrombotic risk factors varied between 41% and 56.4%.[6,7]

More concerning, despite the ascendency of neuroimaging techniques during the past 25 years, CVT is still commonly overlooked, largely as a result of the diversity of clinical presentation and its multifactorial etiology.[8] Traditionally, CVT was regarded as occurring secondary to local or systemic infection, with the remaining proportion being regarded as "idiopathic." During the past 30 years, and although infection remains an important underlying pathology, the causes of CVT

have broadened significantly to include surgery, hematologic diseases, vasculitis, pregnancy and puerperium, arteriovenous malformations, cancer, acquired prothrombotic disorders, and oral contraceptive pill (OCP) use. Interestingly, OCPs seems to have altered the demographics of who is susceptible to CVT. Up until the 1970s, men and women were equally affected; however, since then, a definite female preponderance has developed. Both evidence from laboratory analysis[9] and the associations found in CVT case–control studies[10,11] lead us to hypothesize that increasing OCP use may have driven such a distinct epidemiological shift.

Etiology

Numerous etiology-minded case reports also exist that point to the influence of various underlying risk factors, including spontaneous intracranial hypotension,[12] thalidomide use in multiple myeloma,[13] inflammatory bowel disease,[14] altitude,[15] tamoxifen,[16] erythropoietin,[17] and phytoestrogens.[18] In addition, a systematic review has recently been conducted that evaluated a causal association between hyperthyroidism and acute venous thrombotic complications, of which CVT seems to be a particularly common manifestation.[19] As a result of the increasing realization of the numerous possible risk factors involved in CVT, the proportion of cases with no identified risk factors, what might be considered idiopathic, has reduced from ~35% in the year 2000[20] to less than 15% in the more recent and comprehensive ISCVT study.[4] The ISCVT study's "etiological workup" also showed that multiple predisposing conditions were present in 38% of patients, suggesting that risk factor interactions are likely to be important in CVT etiology. One potentially major underlying risk factor believed to predispose an individual to CVT, when a second risk factor is encountered, is that of a genetic thrombophilia.

Genetics

It is now approximated that inherited thrombophilias constitute 22.4% of CVT cases.[4] Genetic thrombophilias should, especially, be considered in the diagnostic workup of any patient with recurrent venous thrombosis, in those with a family history of venous thromboembolism, in the young, and in those with no obvious acquired risk factor. The diversity of proteins involved in the complex coagulation cascade and fibrinolytic system has led to numerous possible substrates being responsible for thromboembolic disease. Deficiency in antithrombin III was first discovered in 1965,[21] followed later by deficiencies of protein C[22] and protein S[23] in 1981 and 1984, respectively. In 1993, resistance to activated protein C was identified as the most common cause of inherited thrombophilia,[24] and 1 year later, a specific polymorphism in Factor V was acknowledged as the major cause for this resistance.[25] The polymorphism was identified as a substitution event in the factor V gene (G1691A), which caused the arginine in residue 506 to be replaced by glutamine (Arg506Glu/R506Q), yielding a protein known as *factor V Leiden* (FVL). Aberrant FVL reduces the rate of inactivation of factor Va by activated protein C, which leads to an increased production of thrombin and, ultimately, clot formation. The FVL genotype has been found to be highly prevalent within the general population, ranging from 0.45% in Asian Americans to more than 5% in white Americans.[26] In 1996, a mutation in the prothrombin (*PT*) gene (G20210A) was found to be a common genetic factor predisposing to thrombosis. The G20210A mutation was found to enhance blood prothrombin activity, thus augmenting thrombin generation. Meta-analysis has shown that both factor V and *PT* polymorphisms appear to be significant in the development of DVT and PE, and also in CVT.[27,28] In CVT, FVL conferred an odds ratio (OR) of 2.40 (95% confidence interval [CI], 1.75–3.30), and prothrombin G20210A an OR of 5.48 (95% CI, 3.88–7.74). These ORs for risk, however, are very different from

those found in peripheral venous thrombosis—namely, DVT and PE—with the PT mutation having a far greater impact on CVT than peripheral venous thrombosis. The inverse is true for FVL; this gene variant has a greater impact on peripheral, as opposed to cerebral, venous thrombosis. In this way, there seems to be region-specific mechanisms for thrombosis, with different vascular beds having their own unique susceptibility to the prothrombotic effects of certain gene variants.

Meta-analysis has also confirmed FVL and *PT* G20210A gene variants as being associated significantly with neonatal and pediatric CVT.[29] Kenet et al.[29] demonstrated an OR for risk from the FVL gene variant of 2.74 (95% CI, 1.73–4.34), which is comparable with adult studies. The *PT* G20210A polymorphism, however, had an OR of 1.95 (95% CI, 0.93–4.07) in pediatric CVT, which is markedly smaller than the association observed in adult populations. It may be that birth-related complications and greater incidence of sepsis may make CVT during early stages of life a more environmentally determined condition, with genes such as *PT* G20210A emerging only as predominant in adulthood.

Another established prothrombotic genetic risk factor involves alterations to the methylenetetrahydrofolate reductase (*MTHFR*) gene. The C677T polymorphism, leading to an exchange of alanine to valine, has long been implicated in ischemic heart disease and DVT.[30] Furthermore, meta-analysis has tried to evaluate risk specifically for the development of CVT.[31] In 2009, Gouveia and Canhao[31] found a nonsignificant OR, with considerable heterogeneity between individual studies. They concluded that there was insufficient data to support the risk of C677T *MTHFR* mutation. A 2011 meta-analysis that included five additional case–control studies showed similar conclusions, with no overall association being proved, and interpretations being limited by significant interstudy heterogeneity. Removal of one study, however, which corrected heterogeneity, did give a revised OR of 2.30 (95% CI, 1.20–4.42), suggesting that the *MTHFR* C677T gene variant should not be excluded completely as a genetic risk factor for CVT. In addition, the potential role of the novel *MTHFR* A1298C variant in CVT has recently been explored and has been shown to correlate positively with the disease (OR, 10.25; 95% CI, 5.6–18.7) in a small Tunisian cohort of patients.[32] MTHFR is of particular interest because of its role in homocysteine metabolism. MTHFR is necessary for the conversion of homocysteine to methionine, a less toxic amino acid. Increased blood homocysteine levels have been found to have a significant association with CVT (OR, 4.07),[33] thus providing a plausible etiologic link between *MTHFR* mutation and CVT. In 2005, a technique of "Mendelian randomization" was used to try and ascertain the causal relationships between MTHFR, homocysteine, and stroke.[34] It was noted that the observed increase in risk of stroke conferred by a homozygous *MTHFR* C677T mutation was close to the risk predicted by homocysteine-level changes conferred by such a mutation. These findings were consistent with a causal relationship between MTHFR, homocysteine, and ischemic stroke. These principles and meta-analytical techniques have been applied to CVT, in part using data linking homocysteine levels with DVT, and there is some statistical evidence to suggest causality between *MTHFR* C677T and CVT.

The quest for a more complete understanding of genetics in prothrombotic conditions, including CVT, has given rise to a host of other single nucleotide polymorphisms (SNPs) worthy of consideration. Plasma glutathione peroxidase (*Gpx-3*) T927C,[35,36] protein Z G79A,[37,38] and thrombin activatable fibrinolysis inhibition factor G438A, A505G, and C1040T[39] have all been postulated as conferring a risk for CVT, but no statistical evidence of association has emerged as yet. Several studies have shown a positive correlation of the *PAI-1* 4G allele with thrombotic disease such as DVT,[27,40] PE,[27] myocardial infarction,[41] and atherothrombotic stroke.[42] The 4G allele has been shown to have a gene–dose effect on circulating levels of *PAI-1*, a serine–protease responsible for inhibiting tissue plasminogen activator and urokinase, which together activate plasminogen and, hence, fibrinolysis. Studies in CVT populations, however, have yet to show any statistically significant association.[28,43–47] A gain-of-function mutation in the gene encoding the tyrosine–protein kinase, Janus kinase 2, is typically associated with myeloproliferative disorders, including polycythemia rubra vera, essential

thrombocythemia, and primary myelofibrosis. Evidence is accumulating to support the JAK2 mutation as a novel risk factor for thromboembolic disease, which would correlate with the major burden of mortality and morbidity in myeloproliferative disorders being accounted for by vascular events. Patients with CVT have been found to carry the *JAK2* mutation regardless of blood count,[48] and recently *JAK2* status was found to be an independent risk factor for CVT (OR, 5.47; 95% CI, 1.06–28.27) without overt myeloproliferative disorders in an Indian cohort.[49] In a similar Indian case series, the tissue factor pathway inhibitor, or *TFPI*, T33C gene variant is the only polymorphism shown to confer protection against the development of CVT (OR, 0.19; 95% CI, 0.04–0.98).[50] This gene variant is associated strongly with increased tissue factor pathway inhibitor levels, and therefore increased inhibition of factor Xa and thrombin in the coagulation cascade.

Determining accurately the contribution of genetic polymorphisms to vascular thrombosis has had its pitfalls. During the past three decades, there has been wide variation in the number and type of genetic tests available, and many case series have had limited and incomplete thrombophilia workups. Furthermore, thrombophilia testing is expensive and may not specifically guide treatment acutely. There is increasing evidence, however, that an understanding of the genetic susceptibility of a patient to thrombosis will allow clinicians to counsel patients regarding future exposure to environmental risk factors such as the OCP. Martinelli et al.[51] showed that the combination of the *PT* mutation and OCP use conferred a substantially greater risk for CVT (OR, 149.3; 95% CI, 31.0–711.0) than for the *PT* mutation alone (OR, 10.2; 95% CI, 2.3–31.0).

Candidate gene case–control models have formed the bulk of CVT genetic research, but many have failed to recruit sufficient numbers of patients with CVT to draw reliable conclusions of association. Repeated meta-analysis allows pooling of all available data and has provided better insight into the etiology of several vascular disorders.[27,52] Modern genetic epidemiological research must be placed within the context of genomewide association studies (GWAS). These studies are made possible by increasingly sophisticated gene-chip technology, which allows sequencing of more than 1 million SNPs simultaneously. The SNP profiles are then compared, and if one gene variant is more frequent in patients than in control subjects, it is said to be "associated" with the disease phenotype. In contrast to the candidate gene approach, the whole genome is investigated and, as a result, there is greater scope to identify novel polymorphisms that may confer risk for pathology. These SNPs may not necessarily fall within coding regions of known coagulation cascade proteins. Indeed, recent GWAS investigation into DVT and PE confirmed disease risk association with the ABO blood group loci as well as with the well-documented FVL gene variant,[53] whereas an international collaborative genomewide association study (Biorepository to Establish the Aetiology of Sinovenous Thrombosis, or BEAST) is currently underway. A GWAS of this kind in CVT is likely to advance substantially our understanding of the genetics of this type of stroke, guide risk stratification, and offer possible areas for therapeutic intervention.

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10

GENETIC RISK FACTORS FOR MRI MARKERS OF CEREBRAL SMALL-VESSEL DISEASE

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Introduction

Cerebral small-vessel disease (SVD) refers to damage to small vessels of the brain.[1] SVD is a leading cause for stroke, dementia, cognitive decline, and other age-related disabilities.[2–6] Only a fraction of SVD manifests as clinically overt disease such as stroke or dementia.[7] A far greater proportion of SVD remains clinically covert and is highly prevalent in the general population, particularly in older individuals, as has been revealed by brain imaging in large population-based samples.[8] Clinically "covert" SVD is often associated with subtle cognitive and motor dysfunction, and heralds an increased risk of future stroke and dementia.[2,3,9–12]

Parenchymal lesions on magnetic resonance imaging (MRI), which are thought to be caused by damage to cerebral small vessels, are being studied as markers of SVD.[1] Cerebral MRI is currently the best approach to visualize these lesions. MRI measures such as white matter hyperintensities (WMHs), small subcortical brain infarcts (SSBIs), and cerebral microbleeds are most commonly used.[13] Because factors leading to common SVD are largely unknown beyond aging and high blood pressure,[14–16] identifying genetic risk factors for MRI markers of SVD may help unravel molecular pathways and biological processes involved in SVD.

A detailed description of MRI markers of SVD is provided in Chapter 21. Briefly, WMHs correspond to signal abnormalities of variable size in the white matter, appearing as hyperintensities on T2-weighted or fluid-attenuated inversion recovery images, without cavitations.[13] Pathological correlates include myelin degeneration or rarefaction, proliferative astrogliosis, fibrinoid changes, and fibrosis to the vessel walls.[17,18] The underlying mechanisms are poorly understood, with chronic hypoperfusion of the white matter and disruption of the blood–brain barrier leading to chronic leakage of plasma into the white matter being the prevailing hypotheses.[2,13] WMHs are highly prevalent in older community persons, affecting 90% of individuals older than 80 years,[2] and up to 50% of

middle-age persons (44–48 years).[19] Lesion volume is highly variable, ranging between 0.3 cm^3 and 10 cm^3 or more in community persons age 45 to 75 years, on average.[19,20] It can be measured quantitatively using automated algorithms, or semiquantitatively based on visual scales.[21–24]

Brain infarcts (BIs) are hypointense foci (usually >3–4 mm) on MRI T1-weighted sequences, appearing hyperintense on T2-weighted sequences and hyper- or hypointense on fluid-attenuated inversion recovery sequences, in a vascular distribution.[25] Among BIs, SSBIs correspond to neuroimaging evidence of infarction in the territory of one perforating arteriole (i.e., <15 mm, and as large as 20 mm in some studies) located in the basal ganglia, the white matter, or the brainstem.[13] SSBIs are believed to reflect SVD primarily, and to account for 60% to 70% of all BIs.[13,26] The vast majority of BIs are "covert" (i.e., not associated with symptoms of acute clinical stroke).[7,27] Their frequency ranges between 10% and 30% in older community persons.[28]

Cerebral microbleeds are small (usually 2–5 mm and as large as 10 mm) hypointense lesions on gradient echo—T2*—or susceptibility-weighted images.[10,29,30] These correspond to hemosiderin deposits and likely represent small foci of blood cell leakage. In the general population, their frequency ranges between 5% and 15%, and increases with age, systolic blood pressure, and smoking.[31–35] They are frequently observed (~60%) in persons with a history of intracerebral hemorrhage (ICH).[32]

Evidence for Genetic Contribution to MRI Markers of Cerebral SVD

Evidence for a genetic basis of MRI markers of SVD, mainly for WMH burden and BIs, comes from heritability estimates based on twin and family studies, and from the observation of monogenic diseases causing SVD.[36,37]

HERITABILITY ESTIMATES FROM TWIN AND FAMILY STUDIES

Heritability of a complex trait can be measured by comparing the similarity of a trait among relatives, and by estimating to what extent differences in incidence are the result of genetic variation or environmental differences. Twin studies, comparing monozygotic and dizygotic twins, are best suited to separate genetic influences from environmental ones (Chapter 4). High heritability estimates suggest that a trait is influenced significantly by genetic factors, making it a compelling target for more specific genetic analyses. A study of older male twins (74 monozygotic vs. 71 dizygotic) found that the heritability of WMH burden was 71% (95% confidence interval, 66–76), after adjusting for age and head size.[38] The heritability for WMH burden remained high after adjustment for a family history score for stroke.[39] High heritability estimates for WMH burden have also been reported in the Framingham Heart Study (55%, $p < .0001$), in Mexican Americans from the San Antonio Family Heart Study ($72 \pm 11\%$, $p = 1.0 \times 10^{-14}$), and in hypertensive siblings from the Genetic Epidemiology Network of Arteriopathy (GENOA) study ($80 \pm 10\%$, $p < .0001$; and $67 \pm 11\%$, $p < .0001$ after adjusting for sex, age, systolic blood pressure, and brain volume).[40–42] The observation that individuals whose parents or siblings have had stroke are at increased risk for BIs also supports the role of genetic factors in SSBI occurrence.[43,44]

MONOGENIC DISORDERS CAUSING SVD

Several monogenic disorders display phenotypes similar to that of sporadically occurring SVD. The main monogenic diseases causing SVD are listed in Table 10.1[45–66] and are described in greater detail in Chapter 3 and Chapter 6. Genes underlying these disorders could also harbor genetic variants influencing sporadic forms of SVD, as has been observed for other diseases such as type 2 diabetes and obesity.[67]

TABLE 10.1

Monogenic Diseases Causing Small-Vessel Disease

Disease	Prevalence	Mode of inheritance	Causal gene	Reference
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, or CADASIL	1–9/100,000	Autosomal dominant	*NOTCH3*	Joutel et al.,[45] Chabriat et al.[46]
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, or CARASIL	Exceptionally rare	Autosomal recessive	*HTRA1*	Hara et al.,[47] Fukutake et al.[48]
Autosomal dominant retinal vasculopathy with cerebral leukodystrophy, or RVCL	Exceptionally rare	Autosomal dominant	*TREX1*	Jen et al.,[49] Terwindt et al.,[50] Ophoff et al.,[51] Richards et al.[52]
Hereditary cerebral amyloid angiopathy, or H-CAA	Rare	Autosomal dominant	*APP*	Revesz et al.,[53,54] Biffi et al.[55]
COL4A1 syndrome	Rare	Autosomal dominant	*COL4A1*	Gould et al.,[56] Volonghi et al.,[57] Lanfranconi et al.[58]
Fabry disease	1–5/10,000	X-linked recessive	*GLA*	Germain,[59] Pastores et al.,[60] Rolfs et al.,[61] Sims et al.[62]
Mitochondrial encephalopathy with lactic acidosis and strokelike episodes, or MELAS	Unknown	Mitochondrial inheritance	Mitochondrial DNA	Clayton et al.,[63] Hirano et al.,[64] Sproule et al.,[65] Majamaa et al.[66]

Linkage Studies

Linkage analyses are used to map genetic loci by use of observations of related individuals.[68] They are family based and test whether genetic markers cosegregate with a given disease within families. Although they are particularly suited to discover genes causing monogenic disorders, they also have been implemented in some instances to identifying genes contributing to complex traits in family-based studies. At least five studies have performed whole-genome linkage analysis for WMH burden.[42,69–72] Significant logarithm of odds scores for linkage with WMH burden have been reported only for the chromosome 4p16 region by the Framingham Heart Study in older community persons of European ancestry.[70,71] The 4p16 region harbors the gene for Huntington disease (*HTT*), a gene that has been associated with hypertension (*GRK4*) and also genes responsible for mitochondrial functioning. Chromosomal regions that have shown suggestive evidence for linkage include chromosomes 1, 5, and 11.[42,69,72] Interestingly, using bivariate whole-genome linkage analyses, two studies have found an indication of shared genetic loci for WMH volume and blood pressure measurements—the GENOA study and the San Antonio Family Heart Study—suggesting that genes with pleiotropic effects may be underlying both traits.[40,73] Overall, linkage studies are, however, much less powerful than genetic association studies for discovering genetic risk variants for complex diseases.[74]

Candidate Gene-Based Association Studies

Candidate gene association studies test the association of a disease with genetic variants selected through a priori hypotheses about the underlying pathophysiology. They consist of genotyping one or more genetic variants (usually single nucleotide polymorphisms [SNPs]) from a candidate gene in a group of unrelated persons, and test the association of their allelic frequencies with case–control status or with a quantitative trait. Numerous candidate gene-based association studies have been performed for WMH burden and MRI-defined BIs. Very few candidate genes have been studied in association with microbleeds.

Rather than presenting a comprehensive overview of all published candidate gene studies in association with MRI SVD, we provide a summary of the most robust findings in the text. All genes and variants that have shown significant association with one or more MRI markers of SVD in at least one publication are listed in Tables 10.2[75–93] and 10.3.[94–100]

CANDIDATE GENE-BASED STUDIES FOR WMH BURDEN

Genes of Cholesterol Regulation

Apolipoprotein E (APOE) is involved in the transport of cholesterol and other hydrophobic molecules. Common variants of *APOE* are well-established risk factors for dyslipidemia, cardiovascular disorders, ICH, and late-onset Alzheimer's disease (AD), as well.[55,101–106] The ε4 allele of *APOE* is associated with late-onset AD in a dosage-dependent manner. *APOE* ε4 has been investigated in a number of studies for association with WMH burden, but results were not conclusive. In 2009, a meta-analysis of 46 studies (19,000 subjects)[78] found no convincing evidence for association of *APOE* ε4 with WMH burden. A more recent, larger meta-analysis of 42 studies (29,965 participants), including unpublished data, found that *APOE* ε4 is associated with increased WMH burden.[88] Interestingly, this meta-analysis also found that the less frequent *APOE* ε2 allele, which is protective for AD but a risk factor for lobar ICH and ICH volume progression,[52,55,106,] was associated with increased WMH burden. Variants in other genes involved in cholesterol regulation (mainly,

TABLE 10.2

Candidate Gene Studies for WMH Burden

Gene	HGNC symbol	Pathway	Polymorphism	Sample size	Reference	Ethnicity	p Value (WMH GWAS)[a]
Calpain10	*CAPN10*	Arteriosclerosis and related pathways	rs7571442	777	Smith et al.[75]	European	NA
Coagulation factor III	*F3*	Arteriosclerosis and related pathways	rs3917643	777	Smith et al.[75]	European	NA
Intercellular adhesion molecule 1	*ICAM1*	Arteriosclerosis and related pathways	rs5498 (K469E)		Han et al.[76]	Chinese	.006
Kit Ligand	*KITLG*	Arteriosclerosis and related pathways	rs995029	777	Smith et al.[75]	European	.99
Matrix metalloproteinase 2	*MMP2*	Arteriosclerosis and related pathways	rs9928731	777	Smith et al.[75]	European	.37
Matrix metalloproteinase 3	*MMP3*	Arteriosclerosis and related pathways	rs679620 (K45E)	756	Fornage et al.[77]	European	.2
Matrix metalloproteinase 9	*MMP9*	Arteriosclerosis and related pathways	rs2250889 (P574R)	756, 671	Fornage et al.[77]	African and European	.12
Angiotensin-converting enzyme	*ACE*	Blood pressure	rs1799752 (I/D)		Paternoster et al.[78]		.62
Adducin 1	*ADD1*	Blood pressure	rs4961 (Gly460Trp)	1018	van Rijn et al.[79]	European	.68
Angiotensinogen	*AGT*	Blood pressure	rs699 (M235T)		Paternoster et al.[78]		.01
Angiotensin II receptor 1	*AGTR1*	Blood pressure	rs5186 (A1166 C)	231	Taylor et al.[80]	European	NA
Angiotensin II receptor 2	*AGTR2*	Blood pressure		231	Taylor et al.[80]	European	NA
Aldosterone synthase	*CYP11B2*	Blood pressure	rs1799998 (−344C/T)	510, 829	Brenner et al.,[81] Verpillat et al.[82]	European	.07

(*continued*)

TABLE 10.2

Continued

Gene	HGNC symbol	Pathway	Polymorphism	Sample size	Reference	Ethnicity	p Value (WMH GWAS)[a]
Methylenetetrahydrofolate reductase	*MTHFR*	Homocysteine metabolism	rs1801133 (C677T), rs1801131	68	Hassan et al.,[83] Kohara et al.,[84] Szolnoki et al.,[85] Paternoster et al.,[78] Linnebank et al.[86]		.73
Interleukin 6	*IL6*	Inflammation	rs1800795	532, 2905	Fornage et al.[87]	African and European	.09
Apolipoprotein E	*APOE*	Lipid metabolism	APOE ε4, APOE ε3, APOE ε2, rs7412, rs429358		Paternoster et al.,[78] Schilling et al.[88]		NA
Cholesteryl ester transfer protein	*CETP*	Lipid metabolism	rs1800775 (C-629A)	452	Qureischie et al.[89]	European	.66
Endothelial nitric oxide synthase	*NOS3*	Oxidative stress	rs1799983	93	Henskens et al.[90]	European	.19
Paraoxanase 1	*PON1*	Oxidative stress	rs854560	264	Schmidt et al.[91]	European	.47
Brain-derived neurotrophic factor	*BDNF*	Regeneration	rs6265 (Val66Met)	312	Taylor et al.[92]	European	NA
NA	*NOTCH3*	Vascular dysfunction	rs10404382	877	Schmidt et al.[93]	European	NA

[a] *p* Values for the association with WMH burden in the GWAS by Fornage et al.[20] are presented.
GWAS, genomewide association study; HGNC, HUGO Gene Nomenclature Committee; I/D, insertions/deletions; NA, not applicable; WMH, white matter hyperintensity.

TABLE 10.3

Candidate Gene Studies for BI

Gene	HGNC symbol	Pathway	Polymorphisms	Sample size	Reference	Ethnicity	p Value (BI GWAS)[a]
Apolipoprotein E	*APOE*	Lipid metabolism	APOE ε2		Schilling et al.[88]		NA
Lipoprotein lipase	*LPL*	Lipid metabolism	rs328 (S447X)	197/964	Morrison et al.[94]	Europeans	.50
Angiotensin I converting enzyme	*ACE*	Blood pressure	rs1799752 (I/D)		Paternoster et al.[78]		.60
Angiotensinogen	*AGT*	Blood pressure	rs699 (M235T)		Paternoster et al.[78]		.70
Adducin 1, alpha	*ADD1*	Blood pressure	rs4961 (Gly460Trp)		van Rijn et al.[95]		.40
Nitric oxide synthase	*NOS3*	Oxidative stress	786T>C, 4a4b, 894G>T	269/234	Song et al.[96]	South Koreans	NA
Interleukin 6	*IL6*	Inflammation	rs1800795, rs1800796	233/465, 2905	Jenny et al.,[97] Fornage et al.[87]	Europeans	.60/.80
Protein kinase C, eta	*PRKCH*	Vascular dysfunction	rs3783799 rs2230500	295/497	Serizawa et al.[98]	Japanese	NA
Fibrinogen gamma chain and alpha chain	*FGG, FGA, FGB*	Clotting	rs2066860, rs2066861, rs1049636, rs2070011, rs2070014, rs2070016, rs6050, rs1800787	213/864	van Oijen et al.[99]	Europeans	0.02–0.80
Micro RNAs	*miR-146a, miR-149, miR-196a2, miR-499*	Micro RNAs	miR-146aG, miR-149T, miR-196a2C, miR-499G	373/553	Jeon et al.[100]	South Korean	NA

[a] *p* Values for the association with the presence of BIs in the GWAS by Debette et al.[26] are presented.
BI, brain infarct; GWAS, genomewide association study; HGNC, HUGO Gene Nomenclature Committee; NA, not applicable.

rs1800775, *CETP*) have shown weak evidence of association with WMH burden in a small, single sample ($N = 452$), with no replication to date.[89]

Genes Involved in Blood Pressure Regulation

Elevated blood pressure is one of the most important known risk factors for WMH burden. Hence, genes that play an important role in blood pressure regulation could influence risk for WMH burden. Angiotensin-converting enzyme (ACE) and angiotensinogen (AGT) are part of the renin–angiotensin system, a major regulator of systemic blood pressure. The *ACE* insertions/deletions polymorphisms (rs1799752) and *AGT* Met235Thr polymorphism (rs699) have been examined in multiple studies for association with WMH burden, with heterogeneous findings. A meta-analysis of nine studies found that the *ACE* DD homozygote genotype was associated significantly with increased risk for WMH burden, whereas no association with *AGT* Met235Thr polymorphism (rs699) was observed in aggregate.[78] The latter polymorphism was, however, associated with WMH burden at a nominal significance level ($p = .01$) in a recent genomewide association study (GWAS) of WMH burden (see Section 10.5).[20] Aldosterone plays an important role in maintaining intravascular volume and blood pressure. Mutations in the aldosterone synthase gene (*CYP11B2*) cause either hypertension or hypotension. The TT genotype of the *CYP11B2* polymorphism rs1799998 was found to be associated with WMH burden in two relatively small, separate studies ($N = 510$ and $N = 829$), independent of hypertension.[81,82]

Genes Involved in Arteriosclerosis and Related Pathways

It has been hypothesized that hypertension might affect WMH burden by accelerating age-related processes such as arteriosclerosis. The GENOA study showed that matrix metalloproteinase (MMP) 3 (*MMP3*) variants were associated with WMH burden in Europeans, and *MMP9* variants with WMH burden in both Europeans and Americans (756 Europeans and 671 blacks).[77] Later, the GENOA study genotyped 1649 SNPs from genes known or hypothesized to be involved in arteriosclerosis and related pathways in 777 European individuals. The study revealed an association for variants in *F3, KITLG, CAPN10,* and *MMP2* variants with WMH burden.[75] A Chinese study has also revealed an association of a genetic variant (rs5498) in *ICAM1* with WMH burden,[76] and this association was replicated at a nominal significance level ($p = .006$) in a recent GWAS of WMH burden (see Section 10.5).[20]

Genes of Homocysteine Metabolism

Serum homocysteine levels have been shown to be correlated positively with WMH burden, whereas folate levels are correlated inversely[107] This has led to the investigation of methylenetetrahydrofolate reductase (*MTHFR*) gene polymorphisms with WMH burden, as the polymorphisms (rs1801133 and rs1801131) of *MTHFR* are associated with homocysteine levels. Three studies have shown an association of the variant rs1801133 (C677T) with WMH burden when comparing the homozygotes carriers of the T allele with the rest.[83,84,108] However a meta-analysis of these three studies for allele-based associations (additive model) did not find any significant association.[78]

Genes Involved in Vascular Dysfunction

NOTCH3 plays a key role in the functional and structural integrity of small arteries, and mutations in *NOTCH3* are causal for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a monogenic form of SVD. Schmidt et al.[109] sequenced all the 33 exons, promoter, and 3′ untranslated region of this gene in a subset of 277 subjects of ASPS.

They showed that four (rs1043994, rs10404382, rs10423702, and rs1043997) of the nine common variants detected by them were associated with WMH burden in subjects with hypertension ($N = 877$, present in their entire cohort), and replicated their most significantly associated SNP (rs10404382) in the Cohorts for Heart and Ageing Research in Genomic Epidemiology (CHARGE) Consortium, comprising 4773 individuals with hypertension who were stroke free. They also showed that subjects with severe WMH burden more often have *NOTCH3* nonsynonymous SNPs predicted to be deleterious.[109]

Most important, most candidate gene association studies were performed in small samples and did not include a preplanned replication in independent samples. Systematic reviews and meta-analyses have not been able to confirm associations of most candidate genes,[78,110] as has been the case for all complex traits.[111]

CANDIDATE GENE-BASED STUDIES FOR BIS

Because WMHs and SSBIs share common risk factors, especially age and hypertension, some of the candidate genes investigated in association with SSBIs overlap with those investigated in association with WMHs. Of note, several studies have examined associations with all BIs and not specifically SSBIs (a marker of SVD), although the latter represents a vast majority (>70%) of BIs in the general population (Table 10.3).

Genes of Cholesterol Regulation

A recent, large-scale meta-analysis of published and two unpublished studies has reported association of the *APOE* ε2 allele with all BIs.[88] The same meta-analysis did not observe any significant association of *APOE* ε4 with all BIs. Results on SSBIs were not available.

Genes Involved in Blood Pressure Regulation

Variants in *ACE, AGT,* and *ADD1* have been shown to be associated with BIs.[79,85,95,112,113] However a meta-analysis of these studies gives little support for the association of these genes with BIs and suggests publication bias resulting from small sample sizes.[110]

Genes Involved in Vascular Dysfunction

A study investigated associations of polymorphisms in *PRKCH* with BIs in a Japanese population (295 patients with BIs vs. 497 control subjects, no replication) and found the associations to be significant under a dominant model of inheritance.[98] *PRKCH* polymorphisms were also shown earlier to be associated with the SVD subtype of ischemic stroke in a Japanese population.[114] However, a recent, large-scale meta-analysis by the METASTROKE consortium[115] failed to replicate the association of *PRKCH* polymorphisms with the SVD subtype of ischemic stroke in populations of European origin. The association of *PRKCH* polymorphisms with MRI-defined SSBIs has not yet been verified in independent Asian and non-Asian samples, to our knowledge.

Genes Involved in Clotting

Fibrinogen has both inflammatory and hemostatic properties, and its higher plasma levels have been associated with an increased risk of coronary artery disease, ischemic stroke, and dementia.[116,117] In the Rotterdam scan study, one haplotype spanning seven common polymorphisms in the fibrinogen genes (*FGG* and *FGA,* "GATAGTG") was found to be more frequent in 213 subjects with MRI-defined BIs than in 864 control subjects.[99] One variant in this haplotype (rs2066861) reached

nominal significance ($p = .04$) in association with MRI-defined BIs in a GWAS of MRI-defined BIs (see Section 10.5).[28]

MicroRNA Genes

MicroRNAs (miRNAs) are a class of endogenous, small, noncoding RNAs that play an important role in gene regulation. Four polymorphisms in four miRNAs (miR-146aG, miR-149T, miR-196a2C, and miR-499G) have been shown to be associated with cancer and Moyamoya disease,[118–121] and to affect response to vascular damage.[122–125] A study investigated association of these four polymorphisms with silent BIs in a South Korean population (373 patients with SSBI vs. 553 control subjects).[100] Although none of the four polymorphisms was associated with BIs individually, combinations of their alleles into a genetic risk score was associated with BIs. This result has not yet been confirmed.

CANDIDATE GENE-BASED STUDIES FOR CEREBRAL MICROBLEEDS

Two large meta-analyses have found the *APOE* ε4 allele to be associated strongly with the risk of cerebral microbleeds.[88,126] This association was stronger for microbleeds in the lobar region of the brain and is in agreement with the strong association of the *APOE* ε4 locus with ICH and cerebral amyloid angiopathy.[101,106,127–129] Large studies on the association of other genetic variants with microbleeds are lacking. Homozygous carrier status of variant alleles in four SNPs (rs1699102, rs3824968, rs2282649, and rs1010159) near *SORL1*, another gene in the amyloid pathway, was found to be associated with microbleeds in a small family-based sample from a genetically isolated Dutch population ($N = 129$), but these findings have not yet been replicated.[130]

Genomewide Association Studies of SVD

Candidate gene association studies are unable to identify novel genetic variants involved in unsuspected pathways because they are based on what is already known or suspected about the pathophysiology of a disease.[131] GWASs offer a solution to this problem by genotyping large numbers of SNPs (up to 5 million) distributed across the chromosomes without requiring any a priori hypothesis. During the past 7 years, they have been applied to a number of complex diseases and they enabled the identification of thousands of robust genetic associations with more than 300 complex diseases and traits, including various age-related neurological disorders.[115,132–135] Some of these discoveries have also resulted in the identification of drug targets and in improved disease classification, although clinical applications are still limited.[136,137] This new approach may be equally well suited to MRI markers of SVD, if sufficiently large populations can be collected. So far, only two GWASs of MRI markers of SVD have been completed—one on BIs and another on WMH burden.[20,26]

The GWAS meta-analysis on BIs included 9401 participants (1822 patients with BI vs. 7579 control subjects) from seven population-based cohorts of European origin participating in the CHARGE Consortium.[26] This first GWAS meta-analysis of MRI-defined BIs did not include specific analyses of SSBIs. This GWAS identified variants with suggestive association on chromosome 20p12. The index SNP in the locus 20p12 (rs2208454) is located in intron 3 of the MACRO domain containing 2, or *MACROD2*, and is downstream of fibronectin leucine-rich transmembrane protein 3, or *FLRT3*. However, the association of rs2208454 was not replicated in an independent sample of Europeans and blacks. Four SNPs in weak LD with rs2208454 were associated nominally with BIs in the independent black sample.[26]

The GWAS meta-analysis of WMH burden was also performed on the same seven population-based cohorts as the BI GWAS and included 9361 study participants.[20] Because WMH burden was estimated on different scales (microliters or unitless grades) in the various cohorts, the association statistics of individual studies were combined using random effect meta-analysis. This GWAS identified variants on chromosome 17q25 to be associated significantly with WMH burden ($p = 4 \times 10^{-15}$) and replicated the same successfully in two independent cohorts comprising 3024 subjects. Three other studies (two of European subjects and one of Japanese participants) have shown the same variants in this locus to be associated with WMH burden.[138–140] The 100-kb region of the 17q25 locus that is associated with WMH burden has several genes of various functions. The index SNP rs3744028 of this region is located in intron 2 of the tripartite motif-containing 65 gene, or *TRIM65*. Gene expression studies on HapMap lymphoblastoid cells have shown that the index SNP in this locus is associated with the expression of *TRIM47*.[140] The RING domain of TRIM47 has protein ubiquitination properties that promote proteolysis and cellular homestasis.[141] Ubiquitin–proteasome pathways play an important role in cerebral ischemic injury mechanisms and WMH expression profiles.[142,143] Other genes of interest in the 17q25 locus include *ACOX1* and *UNC13D*, which are associated with rare white matter diseases.[144] Fine mapping of the region (e.g., through targeted sequencing), as well as functional studies, are needed to dissect further the mechanisms underlying the relation between the chromosome 17q25 locus and WMH burden.

Of note, in this first GWAS of WMH burden, associations with 22 previously described candidate genetic variants were explored, in a much larger sample size than the original studies ($N = 9361$). This approach provided only weak evidence for replication of *AGT* polymorphism rs699 ($p = .01$) and *ICAM1* polymorphism rs5498 ($p = .006$), which did not withstand correction for multiple testing.

Lessons Learned, Future Perspectives, and Implications

Despite high heritability estimates, so far only a few genes have been identified that show robust associations with MRI markers of SVD. The lack of large, well-planned studies with preplanned replication, and heterogeneity in defining the phenotype, may have contributed to inconsistent findings across studies. Recently, this has prompted international expert panels to provide a uniform definition and terminology for MRI markers of SVD.[13]

Large collaborative efforts are ongoing as part of large consortia (CHARGE Consortium, International Stroke Genetic Consortium) to expand the search for common and rare variants associated with MRI markers of SVD. These efforts include additional GWASs on large samples, including cohorts of non-European ethnicity, as well as analyses of associations with rare variants through exome-chip genotyping and next-generation sequencing. Structural variants such as insertions/deletions, copy number variations, and repeat polymorphisms have been shown to be involved in many neurological conditions and should not be neglected as MRI markers of SVD. Last, exploring the genetic determinants of novel, cutting-edge MRI markers of SVD—such as subtle changes in white matter microstructure on diffusion tensor imaging or burden of dilated perivascular spaces, including in younger populations that have had less exposure to environmental risk factors—may provide important additional insight into the genetics of MRI markers of SVD.

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III

Environmental Risk Factors

11

INTRODUCTION TO ENVIRONMENTAL RISK FACTORS FOR CEREBROVASCULAR DISEASE

Didier Leys

DESPITE MAJOR IMPROVEMENTS made during the past 30 years in stroke prevention, overall stroke incidence is still increasing.[1] The major explanations are the longer life expectancy and increased survival rate after myocardial infarction and first-ever stroke. However, even after adjusting for age, the incidence of stroke is still increasing for ischemic stroke in men.[1] Besides genetic factors that cannot be modified, two categories of modifiable risk factors influence the incidence of stroke: (a) factors that can be modified by patients and physicians, and (b) environmental factors that can be influenced by the society.

Factors related to the patient, are the so-called "modifiable vascular risk factors." High blood pressure, diabetes mellitus, dyslipidemia, tobacco consumption, metabolic syndrome, obesity, excessive alcohol consumption, and estrogen therapy are the most important ones. These factors are major contributors to the occurrence of stroke, and their treatment is usually associated with a reduction of vascular events (i.e., stroke, coronary events, and vascular death). Interestingly, there are some indications that, for a few of these risks factors, their treatment is also associated with a reduction in stroke severity in case of such an event.[2] The management of these risk factors is the basis of primary and of secondary stroke prevention. In low-income countries, these factors can often be treated at a low cost. The effect of an optimal management of these factors is not dramatic at the individual level, and needs months or years to become statistically significant in trials. However, in the long-term, their management is probably the easiest, safest, and cheapest way to reduce the risk of both ischemic and hemorrhagic strokes. Unfortunately, many subjects in the population are not treated correctly, even after a first event.[3]

Factors related to the environment are diet, pollution, passive smoking, and climate. Individuals have almost no possibility of influencing these factors, but politicians can. For instance, campaigns against smoking, laws to prevent excessive intake of sugar in soft drinks, and campaigns promoting physical exercise are long-term measures that are supposed to prevent vascular events. The efficacy of these measures cannot be proved directly by randomized trials, but only by historical comparisons,

and cannot have the greatest degree of evidence. However, they are probably the most effective to prevent vascular events on a large scale at the population level.

These so-called *environmental factors* are important because they are the most important targets for vascular prevention. However, similar risk factors do not have the same effect in each of us. This effect depends, probably, on the interaction of modifiable risk factors with many other factors that cannot be modified, such as genetic factors, ethnicity, age, and their association.

Currently, many strokes can be prevented by optimal management of modifiable vascular risk factors. The decision to treat or not to treat a risk factor is currently based on large trials performed in subjects at risk or in the general population. In the future, a more personalized approach could be used, taking into account not only the risk factor that should—or should not—be treated, but also the combination with other risk factors and the presence of nonmodifiable risk factors. This is the domain of personalized medicine.

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12

HYPERTENSION

The Major Risk Factor for Stroke

Jennifer L. Dearborn and Rebecca F. Gottesman

Introduction

Hypertension affects millions of individuals worldwide and is a growing epidemic in middle- and low-income countries, as well as in the United States and Europe.[1–3] In the United States alone, approximately 30% of adults are diagnosed with hypertension.[4,5] We now recognize that hypertension is the single most important modifiable risk factor for cerebrovascular disease, including ischemic stroke, hemorrhagic stroke, and small-vessel disease. Because almost three quarters of the world's population with hypertension live in resource-limited settings, low awareness of health risks related to elevated blood pressure is of increasing concern.[6] This knowledge gap emphasizes the need to create health systems to identify and treat hypertension, particularly given its close links with cerebrovascular disease.

The ancient Egyptians observed how to palpate pulses, but it was not until the middle of the 18th century that blood pressure was measured, through the experiments of Stephen Hales.[7] As a veterinarian, he performed a set of experiments during which observations were made about the variation in pulse pressure using a glass tube inserted into the artery of a horse. Hundreds of years later, using a standard sphygmomanometer, we now better understand the risk that blood pressure poses for the spectrum of vascular disease—from myocardial infarction and heart failure to stroke. Many large-scale prospective studies have helped to establish the link between elevated blood pressure and cerebrovascular disease. In this chapter, we discuss mechanisms of hypertension leading to stroke, and review major results from observational studies, meta-analyses, and clinical trials, incorporating data about intracranial hemorrhage and subclinical cerebrovascular disease.

Population Impact of Hypertension and Stroke

Hypertension is exceedingly common. In the years 2005 to 2008, 68 million adults older than 18 years in the United States were diagnosed with hypertension, which represents a prevalence of 31%.[5] Worldwide, about 639 million adults with hypertension live in developing countries, and this number is expected to increase.[6] In the United States, 70% of patients with hypertension are receiving treatment for hypertension, but only 48% (31 million) have their condition controlled.[5] Elevated blood pressure is linked closely to all stroke subtypes. Thus, it is likely that the growing rate of hypertension in this country is a large contributor to the 795,000 people in the United States who experience a new stroke each year.[8, 9]

EVIDENCE LINKING HYPERTENSION AND STROKE

Hypertension is the risk factor for stroke with the largest population-attributable risk (PAR).[10] The PAR is the proportion of a cohort with the outcome (in this case stroke) that is caused by a specific risk factor (in this case, hypertension). It is therefore a good estimate of the burden that the risk factor places on a population attributable to the disease in question. In the case of hypertension, the adjusted PAR for ischemic stroke has been estimated at 26%, with a 95% confidence interval (CI) of 12 to 41. As a comparison, the risk factor with the second highest PAR is history of prior transient ischemic attack (TIA), which carries a PAR of 14% (95% CI, 11–17).[10] The evidence demonstrating associations between hypertension and stroke is reviewed in the next section; trials of antihypertensive treatment are reviewed later in this chapter.

OBSERVATIONAL STUDIES

Starting in 1949, a population-based sample of adults age 30 to 69 years on enrollment were recruited into the Framingham cohort; members were monitored for the development of cardiovascular outcomes.[11] Over 50 years, stroke incidence declined but lifetime risk did not, which could be attributed to increased life expectancy.[12] In 1970, a 14-year interim analysis showed that stroke was more common in subjects with hypertension than in those without[11,13] and, more important, there was no blood pressure threshold critical to risk of developing stroke. As other studies have shown, as blood pressure increased (either systolic or diastolic), there was a log-linear increase in the relative risk for stroke.[14,15] These initial and, at that time, somewhat unexpected data, were reproduced in several studies and meta-analyses.[16,17] It is now estimated that for every 9/5 mmHg increase in usual blood pressure, there is approximately a one-third increase in stroke rate, and this holds for persons with hypertension as well as persons with lower blood pressures that would not reach a threshold of hypertension.[14] This emphasizes that there was no critical threshold of "safe" blood pressure, and that relative risk of stroke increases with higher blood pressures (in the entire blood pressure range studied).[15]

One of the most important meta-analyses in this area was the Prospective Trials Collaboration, which combined data on 1 million adults with vascular risk factors from 61 trials to evaluate associations between blood pressure and mortality.[18] This study of adults age 40 to 69 years found a twofold difference in the stroke death rate for every 20 mmHg higher systolic blood pressure (SBP), and further confirmed that there was no threshold of increased risk, at least above the lower limit of SBP greater than 115 mmHg. This has important treatment implications, because it suggests there may be some benefit to lower blood pressure for preventing stroke mortality, even in normotensive adults. Trends are similar in the Asia Pacific region, as examined in a meta-analysis of 41 cohorts in which 82% of the subjects were Asian. There was a log-linear relationship between hypertension and stroke that closely paralleled the relationship between hypertension and cardiovascular disease.[19]

A controversy emerged when other observational studies demonstrated that a low diastolic blood pressure (DBP) was associated with increased risk of stroke. These data described a J-shaped curve between DBP and the risk of stroke—meaning, risk of stroke declined, before it increased again, as blood pressure increased, with the greatest risk of stroke at the extreme values of DBP. It was shown in the Rotterdam study that, in the subset of older adults (>55 years) who had treated hypertension, there was an increased risk of stroke in the lowest category of blood pressure.[20] The authors postulated that advanced atherosclerosis and stiff blood vessels could account for this difference, which was found only in the treated group; however, this relationship still held even with adjustment for cardiovascular risk factors, such as prior myocardial infarction. Several other small cohorts replicated this finding.[21] To address this discrepancy between studies showing a J curve and others that consistently showed a linear relationship, several meta-analyses were performed. One comprehensive meta-analysis of more than 48,000 subjects performed in 1991 showed there was not a consistent J-shaped relationship between DBP and stroke.[22] SBP components, however, have not been examined consistently across studies. A recent analysis found that all-cause vascular mortality followed a J curve with hypertension; however, the relationship between SBP and stroke did not follow this trend.[23] The current prevailing theory, as of the date of publication, is that the J curve may not hold for associations between blood pressure and stroke, and that there is not enough evidence of a critical threshold of blood pressure control beyond which harm is caused.[24]

Components of Blood Pressure in Relation to Stroke

The Framingham cohort also elucidated that, although SBP and DBP are related to stroke incidence, DBP did not add any additional risk over that measured by the SBP if the DBP was less than 95 mmHg.[25] In fact, in subjects with elevated SBP, there was no increased risk conferred by DBP in men, and in women there was only a modest increased risk. The case is different, however, for those with isolated diastolic hypertension. The Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial evaluated 923 individuals with a prior cerebrovascular event (defined as prior stroke or TIA, discussed later), of whom 315 had isolated diastolic hypertension.[26] Lowering blood pressure in those with diastolic hypertension prevented stroke recurrence. This is in accordance with data for other cardiovascular disease, for which it has been shown that the combination of SBP and DBP is superior in predicting the risk of cardiovascular disease than either component alone.[27]

The pulse pressure (PP) and the mean arterial pressure (MAP) are alternative means of expressing blood pressure. The PP is the SBP less DBP, or the pressure required to create the pulse. In younger subjects, a higher PP usually means that the left ventricular ejection fraction is increased, but in older subjects it can be a surrogate marker of arterial stiffness.[28] Blood pressure can also be understood as a steady component (the MAP), which is unchanged from heart beat to beat, and a variable component (the PP), which varies from beat to beat. The MAP is usually defined as the cardiac output times the systemic vascular resistance, which can be calculated directly by $\mathrm{MAP} = \mathrm{DBP} + \frac{1}{3(\mathrm{SBP} - \mathrm{DBP})}$.

There is some debate about whether the PP or the MAP, alone or together, are better predictors of stroke risk than SBP and DBP, and the data seem to suggest that the MAP may be a better measure for assessing risk of cerebrovascular disease than PP. In one study, however, the combination of the PP and the MAP was more robust in predicting cardiovascular disease than the PP, the MAP, SBP, or DBP alone. It was, however, only equivalent to SBP plus DBP in predicting risk.[27] The PP, however, may have an inverse correlation with stroke in women, and was not correlated significantly with stroke in men.[29] In another study, the PP and the MAP were associated independently with ischemic stroke, and the predictive value of the PP depended on the MAP.[30] One might expect that if the PP was, indeed, a good surrogate for arterial stiffness, or vascular disease, it would be more predictive of

increased risk of stroke, but this was not the case. Instead, it is the steady-state component that seems to contribute more to the overall risk of stroke.

Blood pressure variability may also be important in increasing an individual's risk of stroke. Variability is measured as differences in mean blood pressure over time (residual standard deviation), often described as visit-to-visit variability and average differences in adjacent blood pressure readings (successive variation).[31] This definition highlights that some patients have episodic hypertension, and some guidelines recommend 24-hour ambulatory monitoring when variability is detected.[32,33] An increased hazard of stroke has been shown both in studies of variability as detected by ambulatory blood pressure monitoring as well as visit-to-visit variability, and has been independent of mean SBP.[34] More specifically, certain patterns of blood pressure variability may increase risk the most: the "morning surge" in blood pressure has been associated with stroke risk,[35] as has variation in the standard nocturnal dip in blood pressure seen in most individuals (either extreme dipping or lack of nocturnal dipping).[36] Orthostatic hypotension, defined as a decrease in SBP by at least 20 mmHg or a decrease in DBP by at least 10 mmHg, has also been associated with a twofold higher hazard of stroke in observational cohorts, independent of other stroke risk factors.[37] Last, differences in the visit-to-visit variability of blood pressure may account for differences in outcomes seen among trials comparing different antihypertensive agents.[38] Taken together, these data suggest that current methods of following mean blood pressure may miss a subpopulation of patients with high variability, in whom stroke risk is also increased.

Other Characteristics of Blood Pressure Associated with Increased Risk of Stroke

A longer length of exposure to hypertension increases the likelihood of having a stroke.[39] There is an interesting interaction between hypertension and age, however, with the odds ratio of stroke (at some point in a given individual's life) being about 5 at younger ages (50 years) if a person is hypertensive. This decreases gradually until 90 years of age, until there is no increase in risk conferred by hypertension.[10] These data would suggest that there is little benefit, in terms of stroke prevention, to treating hypertension in the very elderly. It may be that "the damage is already done"; clinical trials, however, do not clearly show the lack of a benefit in elderly patients (details discussed later).

Blacks in the United States have higher rates of hypertension than white Americans, and are at a greater risk than the general population of having negative outcomes from hypertension, including stroke.[40] It is particularly important to identify and treat, either through lifestyle modification or drug therapy, hypertension throughout the life span in this population, to reduce the burden of disease including stroke. In the United States, the rates of stroke in Native Americans, multiracial persons, and blacks are greater than those of white Americans, Asian Americans, or Hispanics. Black Americans had a threefold greater rate of lacunar strokes than white Americans.[8]

Blood Pressure among Individuals with History of Stroke

There is evidence that hypertension is just as tightly tied to recurrent stroke as primary stroke, and that lowering blood pressure in this group is equally important as it is in individuals without history of stroke.[14] An analysis of a large cohort in the UK TIA and aspirin trial showed that each 10-mmHg decrease in SBP and 5-mmHg decrease in DBP after minor stroke or TIA was associated with about one third fewer recurrent strokes (34%; standard deviation, 7%).[41] This is a different result from several small studies that have shown a J-shaped relationship with blood pressure and recurrent stroke,[14] suggesting that a low blood pressure after stroke could actually increase risk for subsequent infarction.

These contradictory findings may be because the studies looked at different populations. It is also possible that low blood pressure immediately after stroke is detrimental to certain stroke subtypes, such as patients with a larger area of infarction, who are at risk of hypoperfusion to areas supplied by collateral blood flow. In addition, hypotension may be a marker of a more critically ill patient with a greater recurrent stroke risk because of underlying comorbidities. A typical TIA patient would not have any of these risks. Thus, in major stroke, it may be that low blood pressure is detrimental during the acute period (supported by the lack of a benefit in acute blood pressure lowering in stroke[42]), but in TIA or smaller volume strokes, or over a longer time period, there is a more linear relationship between blood pressure and stroke.

Stroke patients with major vessel intracranial stenosis are a unique subgroup who may have different blood pressure requirements for secondary prevention of stroke both acutely and long term. A decrease in blood pressure may, theoretically, cause hypoperfusion to a large territory of the brain, and therefore these patients may require a higher baseline blood pressure as their cerebral autoregulatory mechanisms are altered. How antihypertensives should be used in this population is uncertain. A meta-analysis of several trials has suggested that, although SBP is associated with recurrent stroke in moderate artery stenosis, this association disappeared with severe large-vessel stenosis (>70%).[43] This being said, an analysis of patients who received intravenous thrombolysis for acute stroke revealed that withholding antihypertensive therapy in known hypertensives in the 7 days immediately after stroke was associated with poor outcome.[44] All together, long-term blood pressure lowering in patients with prior stroke prevents recurrence, and how soon to initiate this therapy in certain subgroups remains to be determined.

Mechanisms of Hypertension and Stroke

There are different theories of how hypertension predisposes persons to an increased lifetime risk of stroke. Central to many of these theories is the idea that increased intraluminal pressure causes endothelial changes that lead to processes such as accelerated atherosclerosis, microthrombi formation, and structural changes in the blood–brain barrier.[45] Structural remodeling from chronic hypertension reduces the external diameter of the cerebral arterioles, which are characterized by a thickened media, a reduced lumen, and increased extracellular matrix.[46,47] Systemic hypertension induces structural changes that are manifest by increased expression of growth factors such as transforming growth factor β1, vasoactive factors such as angiotensin II, and matrix proteins collagenase and elastase.[47] In addition, the vasculature may have impaired relaxation responses as a result of changes in the endothelium-mediated vasodilation.[48]

Much of these data come from studies of two genetic breeds of rats: the stroke-prone spontaneously hypertensive rat (SHRSP) and the Wistar–Kyoto rat (WKY).[46] Stroke in the SHRSP rat is thought to be similar to clinical stroke in humans,[49] whereas the WKY rat is a normotensive strain. From these rats, we have learned that chronic hypertension does not simply reduce the internal lumen of blood vessels, but rather both the internal and external diameters (Figure 12.1). The result is impaired vasodilation from a hypertrophic vessel and, in addition, a smaller total vessel volume from vascular remodeling. A smaller vessel volume could lead to a greater predisposition to embolization or plaque formation, predisposing the cerebral tissue to global hypoperfusion and impaired oxygenation.

The vasodilator response is mediated by the endothelium, leading to release of a variety of growth factors and cytokines. In the SHRSP rat, the vasculature did not have a robust vasodilatory response to acetylcholine, adenosine diphosphate, or serotonin when compared with the WKY rat, suggesting that, likely secondary to remodeling, a different endothelial milieu exists.[46] From these rats we have also learned there is a difference in collateral blood vessel formation, which may relate to cerebral perfusion, and risk of surrounding cell death and ischemia in an infarct territory. With middle cerebral

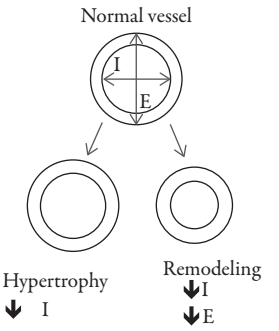

FIGURE 12.1 In hypertrophy, as the vessel wall thickens, the vessel diameter stays constant externally and reduces internally. In chronic hypertension, remodeling occurs, which causes a narrowing of the internal and external vessel diameter, effectively changing the flow dynamics and autoregulatory curve of the cerebral vasculature. E, external diameter; I, internal diameter.
Adapted from Heistad DD, Mayhan WG, Coyle P, Baumbach GL. Impaired dilatation of cerebral arterioles in chronic hypertension. *Blood Vessels* 1990;27:258–262.

artery ligation, the SHRSP rat has a larger territory infarct that progresses faster than the WKY rat,[50] which could be due to decreased blood flow from collaterals to the ischemic penumbra. The decrease in luminal size of these end vessels may also contribute to this finding.[51] The acute response to elevated blood pressure may be increased vessel permeability, leading to plasma leakage and edema. This process releases cytokines and growth factors, which, as described earlier, may lead to vascular remodeling in the long term. Studies of hypertensive rats support that, in the setting of hypertension, strokes could result from hyperplastic blood vessels, reduced collaterals, and thrombotic lesions.[49]

Cerebrovascular autoregulation is a process by which the brain vasculature carefully regulates intracranial blood flow so that the brain can operate at a range of systemic blood pressures. The high metabolic demand of the brain requires steady cerebral perfusion. This control is maintained by the constriction or dilation of small arteries or arterioles that respond to changes in pressure.[52] Regulation of this complex process occurs by the sympathetic nervous system, interactions with brain carbon dioxide and other brain metabolites, and neurovascular coupling. In normotension, this response occurs at approximately 60 to 160 mmHg SBP; but, in patients with hypertension, this range may be shifted to higher pressures.[53] Thus, this exquisitely sensitive system is "tuned" by chronic exposure to hypertension to respond at a higher range of blood pressure. This is further evidence that the "hypertensive brain" is structurally different from that of normotensive persons.

In humans, little about the vascular structure of the hypertensive brain is known. In one small, cerebral positron emission tomographic study, there were differences found in regional cerebral blood flow in patients with mild hypertension compared with normotensive patients, with patients with mild hypertension having reduced blood flow in the frontal cortex and basal ganglia.[54] Extrapolating from rats and from in vitro data, it seems that a constellation of vascular remodeling, impaired vasodilation from an altered endothelial response, and a shifted autoregulatory curve may begin to account for the mechanism of hypertension increasing one's risk of stroke.

Treatment Trials for Prevention of Stroke

PRIMARY PREVENTION

Given the clear association between hypertension and increased risk of stroke, there has been much interest in pharmacological management to reduce hypertension, and in whether this is associated

with a resulting decrease in stroke rates. Studies have covered both the issue of whether *any* antihypertensive treatment reduces risk of stroke, as well as whether there are differences between specific blood pressure regimens. Many of the trials that reviewed in this chapter examined all cardiovascular outcomes, with stroke outcomes as a subgroup analysis. Because of the large size and randomized design of many of the trials, there is still much knowledge to be gained from them about cerebrovascular disease specifically. Most of the primary studies discussed are summarized in Table 12.1.[55–66]

ANTIHYPERTENSIVE USE (IN GENERAL) AND STROKE

Several meta-analyses including large numbers of patients have shown that blood pressure reduction reduces the risk of stroke significantly, regardless of initial blood pressure.[67-69] These meta-analyses included selected trials that were required to have examined either antihypertensive drugs versus placebo, groups of different blood pressure goals, or comparisons of different classes of antihypertensive drugs. Some of the studies included in this analysis, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial and PROGRESS are also discussed separately.

The results of one collaboration showed that greater blood pressure reductions produced greater reductions in the risk of cardiovascular events or stroke. Calcium channel blockers (CCBs) reduced the risk of recurrent stroke compared with placebo (38% reduction; 95% CI, 18–53), as did angiotensin-converting enzyme inhibitors (ACE-Is), which were associated with a 28% risk reduction (95% CI, 19–36). Blood pressure lowering by any agent reduced the risk of recurrent stroke. Side-by-side comparisons of different regimens reached borderline significance, with ACE-I appearing to be inferior to beta blockers or CCB; however, these differences were most likely the result of differences in blood pressure management, and efficacy in blood pressure control between agents.[69] Later analysis confirmed that, although CCBs, appeared to reduce the risk of stroke preferentially (discussed further later), this effect was accounted for by interindividual variation in blood pressure reduction between agents,[68] or by the fact that the effect size was small and perhaps clinically insignificant with some regimens.[67]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Some of the motivation for evaluating distinct antihypertensive medication regimens evolved from the cardiac literature. For systolic heart failure, for example, there is benefit from ACE-I for reduction in mortality and symptomatic improvement.[70] The Heart Outcomes Prevention Evaluation was a trial designed to evaluate the effect of the ACE-I ramipril on cardiovascular events in patients without left ventricular dysfunction.[56] Individuals at high risk of cardiovascular disease were randomized to ramipril or placebo for 5 years. The major outcome showed that ramipril reduced the rate of death, myocardial infarction, or stroke; the relative risk of stroke was 0.68 ($p < .001$) in the treatment group.

ANGIOTENSIN RECEPTOR BLOCKERS

Another trial looked at angiotensin receptor blockers (ARBs) and their impact on cardiovascular mortality compared with beta blockers. The Losartan Intervention for Endpoint Reduction trial selected subjects with hypertension and left ventricular hypertrophy by electrocardiogram.[57] They were monitored for at least 4 years after randomization to a losartan-based or an atenolol-based regimen. Losartan prevented cardiovascular mortality compared with atenolol, and the relative risk for stroke was 0.75 ($p = .001$) in the losartan-based group. In another study, the ARB telmisartan showed no difference in effect compared with the ACE-I ramipril, or the combination of both medications, in terms of cardiovascular mortality.[65]

TABLE 12.1

Important Studies in Primary Stroke Prevention

Study	Year of publication	Type of study	Subjects	Intervention	Duration of follow-up	Outcome related to stroke
SHEP[55]	1991	Randomized, double-blind, placebo-controlled, step-care design	4736 persons age 60 years and older with hypertension	Diuretic (chlorthalidone), then beta blocker (atenolol) vs. placebo	Average follow-up, 4.5 years	Diuretic reduced risk of stroke by 36% compared with placebo.
Heart Outcomes Prevention Evaluation[56]	2000	Randomized, placebo-controlled, two-by-two factorial design	9297 individuals older than 55 years with vascular disease or diabetes plus one other risk factor, who do not have low ejection fraction or heart failure	ACE-I (ramipril) or placebo, monitored for 5 years	Average follow-up, 5 years	ACE-I reduced the rate of stroke or TIA (RR, 0.68) as well as overall death and myocardial infarction.
Losartan Intervention for Endpoint Reduction trial[57]	2002	Double-masked, randomized, parallel group	9193 participants ages 55 to 90 years with hypertension and left ventricular hypertrophy by electrocardiogram	ARB (losartan)-based or beta blocker (atenolol)-based treatment, monitored for 4 years	Average follow-up, 4.8 years	ARB therapy reduced the rate of stroke compared with beta blocker-based therapy (RR, 0.75).
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[58]	2002	Randomized, double-blind, active controlled	33,353 patients age 55 years and older with at least one cardiovascular risk factor and hypertension	CCB or ACE-I vs. diuretic (chlorthalidone) vs. CCB (amlodipine) vs. ACE-I (lisinopril)	Average follow-up, 4.9 years	ACE-I therapy had a 15% greater risk of stroke than the diuretic arm. There was no difference in stroke in the CCB vs. the diuretic arm.

Treatment Trials Collaboration[59]	2003	7 sets of prospectively designed overviews of 29 treatment trials	162,341 patients, mainly with hypertension or diabetes, vascular disease, heart disease or cerebrovascular disease	ACE-I, CCB, diuretics, and beta blockers (various)	Range of follow-up, 2–8.4 years	There were some differences in cerebrovascular treatment among medication types; however, these trends only approached significance and were primarily the result of differences in blood pressure.
Health outcomes of various antihypertensives[60]	2003	Network meta-analysis of long–term, randomized, controlled clinical trials from 1995 to 2002	41 trials that included 192,478 patients randomized to 7 treatment strategies	Diuretics vs. placebo, diuretics vs. CCBs, diuretics vs. ACE-I, diuretics vs. beta blockers, diuretics vs. alpha blockers	Variable	Low-dose diuretics were superior to placebo (RR of stroke, 0.71). None of the other agents were better than diuretics for any outcome.
CONVINCE[61]	2003	Randomized, double blind	16,602 individuals with hypertension and more than one cardiovascular risk factor	Randomized to CCB (verapamil) or investigators' choice of beta blocker (atenolol) or diuretic (hydrochlorothiazide) titrated	Median follow-up, 3 years	There were no significant differences in stroke among treatment groups, but nonischemic hemorrhage was increased in the CCB-based group.
Anglo-Scandinavian Cardiac Outcomes–Blood Pressure Lowering Arm[62,63]	2005	Randomized, step care, active treatment	19,257 patients with hypertension age 40 to 70 years who had at least 3 other vascular risk factors but no previous history of CAD	Randomized to CCB (amlodipine) +/– ACE-I (perindopril) vs. beta blocker (atenolol) +/– diuretic (adding bendroflumethiazide)	Follow-up, 5.5 years	Significantly lower rates of stroke in the CCB arm than in the beta blocker arm. After multivariate adjustment for differences in blood pressure, the residuals were no longer significant.

(*continued*)

TABLE 12.1

Continued

Study	Year of publication	Type of study	Subjects	Intervention	Duration of follow-up	Outcome related to stroke
Beta blockers and the treatment of primary hypertension[64]	2005	Meta-analysis of randomized, controlled trials	13 trials ($N = 105,951$), patients with hypertension compared treatment with beta blockers with other antihypertensive drugs, 7 studies ($N = 27,433$) compared beta blockers vs. placebo or no treatment in patients with hypertension	Beta blockers vs. other treatment or beta blockers vs. placebo	Variable	RR of stroke was 16% greater for beta blockers than for other drugs. Beta blockers had a 19% reduced risk of stroke compared with that of placebo or no treatment.
ONTARGET[65]	2008	Randomized, double-blind treatment trial, after a 3-week single, blind run-in period	17,118 patients with vascular disease or diabetes	ARB (telmisartan) vs. ACE-I (ramipril) vs. combination	Median follow-up, 56 months	There was no significant difference in stroke between groups.
ACCOMPLISH[66]	2008	Randomized, double blind	11,506 patients with hypertension at risk for cardiovascular events	ACE-I, CCB combination (benazopril–amlodipine) vs. ACE-I, diuretic (benazopril–hydrochlorothiazide)	Average follow-up, 30 months	There were no significant differences in stroke outcome.

ACCOMPLISH, avoiding cardiovascular events in combination therapy in patients living with systolic hypertension; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CONVINCE, controlled onset verapamil investigation of cardiovascular endpoints; ONTARGET, ongoing telmisartan alone and in combination with ramipril global endpoint trial; RR, relative risk; SHEP, systolic hypertension in the elderly program; TIA, transient ischemic attack.

DIURETICS

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial examined the effect of diuretics versus other regimens on cardiovascular mortality.[58] In this large trial, patients 55 years or older with at least one cardiovascular risk factor and hypertension were randomized to chlorthalidone (thiazide diuretic), amlodipine (CCB), or lisinopril (ACE-I). This study showed a clear benefit from diuretics in reducing cardiovascular end points and stroke with no difference in all-cause mortality. The risk of stroke was increased by 15% in the ACE-I (lisinopril) group compared with the diuretic arm ($p = .02$). This provided convincing data for the use of thiazide diuretics, which are inexpensive and well tolerated. These data were supported by another study showing that chlorthalidone reduced the risk of stroke compared with placebo in adults with hypertension age 60 years and older.[55] A meta-analysis performed in 2003 selected 42 trials of first-line antihypertensive therapy with cardiovascular outcomes as end points.[60] More important, this study also showed that low-dose diuretics were superior to placebo for all cardiovascular outcomes, including stroke. There was no other agent that was superior to diuretics.

CALCIUM CHANNEL BLOCKERS

CCBs seem to be neutral in comparison with other agents, showing neither increased benefit nor decrement associated with their use. The Anglo-Scandinavian Cardiac Outcomes–Blood Pressure Lowering Arm trial examined the effect of randomization of subjects between the CCB-based regimen (amlodipine) and an beta blocker-based regimen (atenolol) in subjects with hypertension and risk factors for cardiovascular disease.[62] The results showed a significantly lower rate of stroke in the CCB arm, but this was not significant after adjustment for blood pressure. Another trial showed a lack of effect with the CCB verapamil versus investigators' choice of blood pressure treatment for primary and secondary outcomes.[63] A comparison of combination regimens of the ACE-I benazopril with amlodipine versus benazopril with the diuretic hydrochlorothiazide showed no difference in outcome for stroke.[71] Specific hypotheses about the potential benefit of CCBs are based on the observed stroke risk associated with SBP variability, in that increased SBP variability is associated with greater risk of stroke. CCBs appear to be modestly more effective than other medications (particularly beta blockers) in reduction of SBP variability and thus may be more effective in stroke prevention in particular patients.[38,72]

BETA BLOCKERS

Beta blockers may not only fail to show a clear benefit, but also may be inferior first-line agents for hypertension treatment for primary prevention of stroke. A meta-analysis of 13 randomized, controlled trials showed a 16% increase in the rate of stroke (95% CI, 4–30) when beta blockers were used as primary therapy for hypertension compared with other agents.[64] This has helped to shape guidelines for antihypertensive selection.

From these trials, several important points have been learned, which are well summarized in a 2009 Cochrane review of first-line drugs for hypertension, for primary prevention.[73] This review compiled data from 57 trials of hypertension and cardiovascular outcomes, including 58,040 patients. Its results highlighted that there is evidence for low-dose thiazide diuretics as first-line therapy for hypertension, based on reduced mortality, cardiovascular disease, and stroke risk. It differentiated low-dose diuretics from high-dose diuretics, which do not have the same benefit in terms of cardiovascular disease. This meta-analysis also summarized that there seems to be less benefit to beta blockers (atenolol in all five trials) compared with low-dose thiazides, and suggested they should not be

used as first-line therapy. No difference was detected between groups for comparisons of ACE-I and CCBs with thiazides; but, independently, both classes reduced the risk of stroke.

MANAGEMENT OF HYPERTENSION IN OTHER PATIENT GROUPS

As discussed earlier in this chapter, data are less clear on the benefits of treating hypertension in older adults. A trial performed in persons older than 60 years showed a 15% (95% CI, 1–32) increase in stroke rate for every 10-mmHg increase in blood pressure, suggesting there is still an association in older adults.[74] The Prospective Studies Collaboration showed that increased blood pressure in the age group 80 to 89 years was still correlated positively with an increase in stroke mortality.[18] Treating blood pressure in the elderly was shown to have benefit in one trial of subjects older than 80 years. The Hypertension in the Very Elderly Study examined effects of treating subjects older than 80 years and was stopped prematurely because of a reduction in all-cause mortality in the treatment group. In this study, active treatment was associated with a 39% reduction in the risk of death from stroke (95% CI, 1–62).[75] These data support early and long-term treatment of hypertension even in the elderly.[76]

Despite these clinical trial results, the treatment target for blood pressure lowering in persons older than 60 year, and particularly in persons older than 80 years, is somewhat controversial. Recently released Joint National Committee on the Detection, Prevention Evaluation and Treatment of High Blood Pressure (JNC) 8 criteria[77] suggest that a more relaxed threshold of 150 mmHg systolic, rather than 140 mmHg systolic, may be a sufficient goal in older adults without diabetes or chronic kidney disease, although in persons who have achieved a lower blood pressure and have no treatment-related side effects, no change in treatment is recommended.

Data are also less clear on the benefit of treatment of mild hypertension for primary prevention of stroke. A Cochrane Database review from 2012 of 8912 total participants from four clinical trials demonstrated that short-term (4–5 years) use of any antihypertensive medication in individuals with mild hypertension (SBP, 140–159 mmHg, or DBP, 90–99 mmHg) was not clearly associated with a reduction in stroke risk (relative risk, 0.51; 95% CI, 0.24–1.08).[78] This may have been a result of the relatively short follow-up interval, because it might be hypothesized that risk of stroke is only increased substantially over a long-term interval in individuals with more modest increases in blood pressure. The Systolic Blood Pressure Intervention Trial is a large, ongoing study of primary prevention, randomizing individuals 55 years and older with borderline systolic hypertension (≥130 mmHg) and at least one cardiovascular risk factor to either "standard" blood pressure management (goal SBP, <140 mmHg) versus "intensive" blood pressure management (goal SBP, <120 mmHg). Enrollment for this study was ongoing at the time of publication of this chapter, but it is likely that results from this study, with a primary outcome including stroke as part of a composite cardiovascular outcome, will help elucidate optimal management in individuals with borderline or mild hypertension.

SECONDARY PREVENTION

Two studies in the 1990s provided the first evidence that reducing blood pressure in patients with stroke prevented recurrent cerebrovascular disease. The Poststroke Antihypertensive Study (PATS) was a study of 5665 Chinese persons with prior stroke or TIA who were randomized to placebo or the treatment group with the diuretic indapamide.[79] Blood pressure reduction of only 5/2 mmHg reduced recurrent stroke by 29% in the treatment group. Another collaboration, the Individual Data Analysis of Antihypertensive Intervention Trials, also showed benefit to blood pressure lowering for secondary prevention of stroke.[80]

Other trials examining the role of long-term blood pressure management in individuals with a history of stroke (Table 12.2[81–85]) have generally shown that lowering blood pressure is beneficial for

TABLE 12.2

Important Studies in Secondary Stroke Prevention

Study	Year	Type of study	Subjects	Intervention	Duration of follow-up	Outcome
Poststroke Antihypertensive Study[91]	1995	Randomized, double blind, placebo controlled	5,665 Chinese patients with prior stroke or TIA	Diuretic (indapamide) vs. placebo	Average follow-up, 2 years	A blood pressure reduction of only 5/2 mmHg by a diuretic reduced recurrent stroke by 29%.
Individual Data Analysis of Antihypertensive Intervention Trials[92]	1997	Meta-analysis of randomized, controlled trials	9 trials involving 6752 patients with prior stroke or TIA	Various antihypertensive strategies vs. placebo	Variable	The recurrent stroke rate was reduced in the treatment group (RR, 0.72).
Perindopril Protection against Recurrent Stroke Study[93]	2001	Randomized, placebo controlled	6105 individuals with prior stroke or TIA (both hypertensive and nonhypertensive)	ACE-I (perindopril) based therapy +/– diuretic (indapamide) vs. placebo	Average follow-up, 3.9 years	Treatment reduced risk of stroke in all subjects. The combination of ACE-I and a diuretic produced larger risk reductions (by 43%).
Blood pressure reduction and secondary prevention of stroke[93]	2003	Systematic review and meta regression of randomized, controlled trials	7 trials with 8 comparison groups of patients with prior ischemic or hemorrhagic stroke, or TIA	Diuretic, ACE-I, beta blocker, ACE-I and diuretic	Range of follow-up, 2–5 years	Lowering blood pressure reduced stroke (OR, 0.76). ACE-I and diuretics, especially together, as well as separately, reduced stroke; beta blockers had no discernible effect.
Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention study[77]	2005	Randomized treatment trial	1405 patients with hypertension with a cerebral event in the previous 24 months	ARB (eprosartan) vs. CCB (nitrendipine)	Follow-up, 2.5 years	Cerebrovascular events were significantly lower in the ARB group ($n = 102$ vs. $n = 134$)

(*continued*)

TABLE 12.2

Continued

Study	Year	Type of study	Subjects	Intervention	Duration of follow-up	Outcome
Prevention Regimen for Effectively Avoiding Second Strokes[94]	2008	Randomized, placebo controlled	20,332 patients who recently had an ischemic stroke	ARB (telmisartan) vs. placebo	Follow-up, 2.5 years	ARB did not reduce the rate of stroke.
Secondary Prevention of Small Subcortical Strokes study[95]	2013	Randomized, open label	3020 patients with recent symptomatic lacunar stroke randomized to 2 blood pressure targets (130–149 mmHg and <130 mmHg)	Various antihypertensive strategies to meet goal	Average follow-up, 3.7 years	There were nonsignificant reductions in stroke and vascular events.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; OR, odds ratio; RR, relative risk; TIA, transient ischemic attack.

secondary prevention after stroke. In PROGRESS, subjects who were hypertensive and nonhypertensive with a prior stroke or TIA were randomized to perindopril (ACE-I), with a physician choice to add indapamide (a diuretic), versus placebo.[86] The treatment arm had a significant reduction in recurrent stroke, even in patients without hypertension, and active treatment reduced major vascular events in those with isolated diastolic hypertension by 32% (95% CI, 17–45). This study is a persuasive one for future treatment studies aimed at reducing stroke rates in individuals with a history of stroke or TIA. A meta-analysis of seven trials confirmed that ACE-Is reduced secondary stroke risk, and they were especially synergistic with diuretics.

As a follow-up to PROGRESS, because of the hypothesis that inhibition of the renin–angiotensin system might reduce stroke recurrence in particular, ARBs were studied in relation to recurrent stroke. The Prevention Regimen for Effectively Avoiding Second Strokes investigated the effect of telmisartan versus placebo in patients who recently had a stroke or TIA,[87] with nearly three fourths of enrollees having a history of hypertension. In the follow-up of more than 2.5 years, telmisartan reduced the rate of recurrent stroke, but this difference was not statistically significant. The difference in blood pressure reduction between the two groups was also small. Other cardiovascular studies have showed no difference in stroke rates in patients on ARB therapy.[88–89]

A post hoc analysis of this trial evaluated whether there was a threshold of blood pressure that was "too low," in that it increased risk of stroke. Surprisingly, among these patients with noncardioembolic stroke, "low normal" blood pressure (<120 mmHg systolic) increased the risk of recurrent stroke.[90] This is evidence that, unlike in primary prevention, in a population with prior stroke the J-shaped relationship may indeed hold, suggestive of possible harm in lowering systolic blood pressure to less than 120 mmHg in this population. In contrast with this finding, however, the Secondary Prevention of Small Subcortical Strokes trial of patients with lacunar stroke found a trend toward fewer strokes in the "lower" blood pressure arm (<130 mmHg), compared with the arm less than 150 mmHg, but this difference did not reach statistical significance.[91] If there is, indeed, an optimal threshold for blood pressure in recurrent stroke, this needs to be confirmed in future studies so that accurate guidelines can be established.

The Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention study examined the effects of the ARB eprosartan with the CCB nitrendipine.[92] Cardiovascular and cerebrovascular events were reduced in the eprosartan arm, although there were similar rates of blood pressure control between the two groups, suggesting a benefit to treatment for secondary prevention with an ARB over a CCB.

Taken together, these data support that lowering blood pressure is an effective intervention in secondary stroke prevention. It is less clear how soon after stroke this should be initiated, because there is the potential for harm or no benefit if implemented immediately after an acute stroke in certain patients.[42] The recurrent rate of stroke may be reduced by as much as 27% (95% CI, 14–38) with adequate treatment.[56] Although the combination of an ACE-I and a thiazide diuretic seems to be beneficial in secondary prevention, data are lacking to allow recommendation of particular drug classes.

CURRENT GUIDELINES FOR BLOOD PRESSURE AND STROKE

In 2003, the guidelines for blood pressure management from the *Seventh Report on the Joint National Committee on the Detection, Prevention Evaluation and Treatment of High Blood Pressure* (*JNC7*) were released.[93] This report detailed new definitions of blood pressure and, for the first time, detailed a treatment goal of less than 140/90 mmHg, and for those with diabetes or renal disease, of less than 130/80 mmHg. This was a change from the previous blood pressure treatment goals that did not define blood pressures from 120 to 140 mmHg as prehypertensive. The JNC7

recommendations included the results of PROGRESS, which compared ACE-I-based therapy (perindopril) with or without a diuretic (indapamide) compared with placebo. Previous stroke or TIA was included as a "compelling indication" for agent-specific therapy. Based on this trial, a diuretic inhibitor or ACE-I is recommended as first-line therapy for those with prior stroke or TIA (Table 12.3[93,77]).

Results of the recently released JNC8 guidelines are more controversial, mostly secondary to the relaxed blood pressure guidelines in older adults.[77,94] The newer guidelines maintain previous recommendations for patients 60 years or younger, people with diabetes, and individuals with chronic kidney disease. They suggest a more relaxed blood pressure goal, for patients older than 60 years, of less than 150/90 mmHg, maintaining that if such patients are treated to lower than this goal without side effects, current treatment should be continued. The main dissenting opinion was that there was no clear evidence that the more strict goals were harmful, although relaxing blood pressure goals in the frail elderly, such as patients older than 80 years, may be warranted.

The American Heart Association's 2011 guidelines for the primary prevention of stroke mirror the JNC7 recommendations, as level Ia evidence.[95] Regular blood pressure screening, lifestyle modification, and, if necessary, appropriate pharmacological treatment are emphasized. The goal blood pressure set forth for primary stroke prevention is less than 140 mmHg systolic and less than 90 mmHg diastolic. For patients with diabetes or renal disease, the goal is less than 130 mmHg systolic and 80 mmHg diastolic.

TABLE 12.3

JNC7 and JNC8 Recommendations for Blood Pressure Management

Classification	SBP	DBP		
JNC7			Treatment without a compelling indication	Treatment with prior stroke
Normotensive	<120	And <80	None	None
Prehypertension	120–139	Or 80–89	none	Diuretic or ACE-I
Stage 1 hypertension	140–159	Or 90–99	Thiazide diuretic for most, may consider ACE-I, CCB, beta blocker, or combination	Diuretic or ACE-I, other classes as needed
Stage 2 hypertension	≥160	Or ≥100	2-drug combination for most, usually thiazide diuretic and ACE-I or ARB, or CCB or beta blocker	Diuretic or ACE-I, other classes as needed
JNC8			Nonblack	Black
≥60 years	<150; if treatment to <140/90 is without side effects, do not adjust	<90	Initiate therapy with thiazide diuretic, CCB, ACE-I, or ARB	Initiate therapy with thiazide diuretic or CCB
<60 years	<140	<90	Same	Same

Note: Data from Chobanian et al.[93] and James et al.[77]
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Guidelines put forth by the American Heart Association in 2006[96] and updated in 2010 are the current standard for treatment of hypertension in patients with stroke.[97] These guidelines provided standard evidence levels to the current recommendations. In the 2010 guidelines, there was level Ia evidence for the following two recommendations: (a) antihypertensive therapy is recommended for those who have had a stroke or TIA for secondary prevention beyond the first 24 hours and (b) some data support the primary use of diuretics or ACE-I as primary drug therapy for patients who have had a stroke or TIA; however, the optimal regimen is uncertain. There is level IIb evidence for treating patients without documented hypertension but with a stroke or TIA with a blood pressure-lowering regimen, if it is deemed safe. Less definitive than the JNC7 report, the recommendations provide level IIb evidence saying that the specific blood pressure goal is uncertain, but reductions of 10/5 mmHg blood pressure are effective in reducing risk, with normotension defined as less than 120/80 mmHg.

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) accounts for 15% to 30% of all strokes, and has a high mortality rate compared with ischemic stroke, with only 38% surviving the first year.[98] Hypertension may be the greatest risk factor for ICH, and has consistently shown an association in many case–control and cohort studies.[99] Similar to ischemic stroke, there is a linear increase in risk of hemorrhage for each level of SBP.[43] A study performed during the 1980s found retrospectively that 45% of patients with ICH had preexisting hypertension,[100] and the prevalence is now thought to be as high as 75%.[101] Hypertension results in an almost fourfold greater risk of developing lifetime ICH.[102] Primary ICH accounts for 78% to 88% of all ICH, and is the subtype most associated with hypertension.[98] Hypertension is much more common in nonlobar hemorrhage than in lobar hemorrhage, which has unique risk factors, such as cerebral amyloid angiopathy or underlying metastasis.[103]

One study showed that mortality in ICH was greater in subjects with hypertension who had ceased their blood pressure medication regimen, suggesting that those subjects may be especially prone to vessel rupture, possibly from changes in blood pressure induced by starting or stopping therapy.[104] ICH is often included in total stroke incidence and prevalence estimates, and total stroke risk has been noted to be reduced with antihypertensive therapy.[55,98] PROGRESS showed that, in addition to total stroke, the ICH recurrence rate was also reduced with blood pressure treatment with an ACE-I.[86,105]

Primary ICH occurs when a blood vessel ruptures, which is weakened from the long-term effects of hypertension, and can represent falling off the upper end of the cerebral autoregulatory curve, or can be the result of another intrinsic vascular process such as cerebral amyloid angiopathy. The long-term exposure to higher blood pressures may weaken the arterial wall through a process of lipohyalinosis, especially in smaller blood vessels, which are more prone to rupture in hypertension-related ICH.[101] This explains the predilection of hemorrhage related to hypertension to occur in small penetrating branches of the middle cerebral artery, the paramedian penetrators of the basilar artery, or the branches coming off the posterior cerebral artery, commonly involving subcortical structures such as the thalamus, basal ganglia, brainstem, and cerebellum.[105] Electron microscopy of vessels involved in ICH show a weakened vessel wall, which typically is near the branch points of vessels. This was first described as Charcot-Bouchard microaneurysms in 1868, as a pathological leakage from a damaged vessel at the site with a dilation in the vessel wall.[98] The current thinking is that this pathological change is secondary to the chronic effects of hypertension. We know that the cerebral autoregulatory curve is disordered in acute ICH, and it is possible that derangements in cerebral vasodilation from chronic hypertension predispose to the hemorrhagic event.[106]

White Matter Disease

With the use of magnetic resonance images becoming standard in the treatment and care of patients, white matter hyperintensities, or leukoaraiosis, which is used interchangeably in this chapter, is recognized more frequently (Figure 12.2). Leukoaraiosis is a word that originates from the Greek stem *leuko*, meaning "white," and *araiosis*, meaning "rarified."[107] The term was originally introduced 20 years ago, and today the cause is better understood. It is best understood as a part of the spectrum of small-vessel disease, and is often seen surrounding lacunar infarcts. One mechanism suggested for this is ischemia from continued hypoperfusion. This is observed through techniques such as magnetic resonance perfusion, but it is difficult to prove as a primary rather than a secondary effect. Another theory invokes breakdown of the blood–brain barrier, leading to leakage of toxic serum proteins that elicit a cytotoxic response. Last, there may be endothelial interactions that lead to altered blood flow patterns and breakdown of the blood–brain barrier, causing white matter changes.[107]

Some of the evidence for a vascular etiology of white matter changes is the observed strong association in the epidemiological literature between blood pressure and leukoaraiosis. In addition, greater white matter hyperintensity burden is associated with a greater burden of small-vessel stroke.[108] The Framingham Risk Score was related to white matter hyperintensities, suggesting a similar risk factor profile in both diseases.[109] Hypertension is strongly associated with subclinical infarcts detected on imaging.[110] Similarly, blood pressure has shown a strong association with leukoaraiosis, with higher blood pressures leading to a greater amount of white matter hyperintensities[111] or their progression.[112,113] One study showed a twofold increase in white matter lesions in subjects with moderate to high blood pressure variability in midlife.[114] Both SBP and DBP measured 20 years before imaging were associated with white matter changes, and this relationship was J shaped.[115] This suggests that aggressive blood pressure management may not be beneficial in some subgroups with underlying vascular disease in which the autoregulatory curve has been shifted.

The benefit of antihypertensive treatment in reducing progression of white matter lesions is less clear than these relationships. Although in the study on cognition and prognosis in the elderly (SCOPE, Study on Cognition and Prognosis in the Elderly), in which elderly normotensive subjects

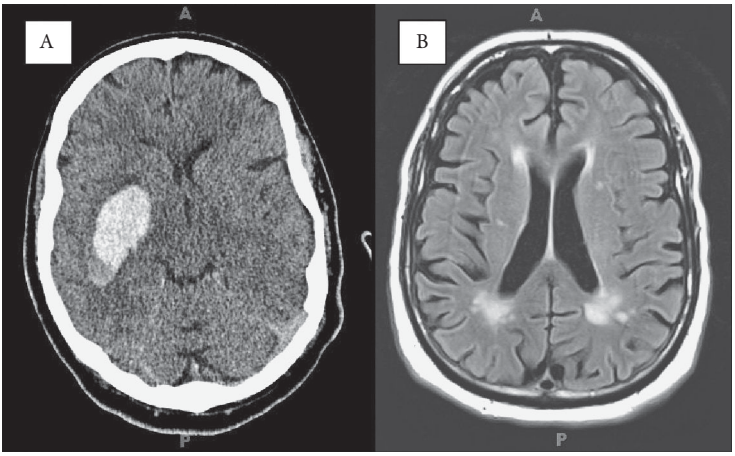

FIGURE 12.2 (A). Head computed tomographic scan showing right intracranial hemorrhage originating in the basal ganglia and extending into the temporal lobe. (B) Magnetic resonance imaging fluid-attenuated inversion recovery sequence demonstrating white matter changes surrounding the lateral ventricles and corona radiata as evidence of small vessel disease, or leukoaraiosis.

were randomized to candesartan therapy or placebo, the placebo group had a greater progression in white matter volume when compared with the candesartan group.[116] The recently published Prevention Regimen for Effectively Avoiding Second Strokes failed to show a difference in white matter lesion progression in individuals treated with telmisartan compared with placebo.[117] This trial had a very short follow-up, however, which might account for lack of a benefit because overall leukoaraiosis progression in both groups was minimal in this study. The PROGRESS trial, with a slightly longer follow-up, did find that individuals in the active antihypertensive arm had less extensive progression of white matter hyperintensities.[118] Despite these conflicting data, it is apparent that leukoaraiosis may be a magnetic resonance imaging marker that can be used to measure the impact of chronic hypertension on the brain, and its underlying causes may be similar to small-vessel stroke.

Conclusion

Hypertension is the greatest risk factor for all subtypes of stroke, including small-vessel stroke, embolic stroke, and hemorrhagic stroke. In addition, it is a significant risk factor for leukoaraiosis, which may represent a spectrum of microvascular disease in the brain. The contribution of hypertension is significant across all populations studied, and is a significant public health concern in developing countries, where access to consistent primary care may be variable. Epidemiological studies show that, although SBP and DBP contribute to the risk of stroke, there may be more to learn from the combination of the MAP and the PP or SBP and DBP in terms of predictive power for stroke. Lowering blood pressure at any level reduces risk of stroke, and there is no critical threshold below which one is "protected" from the log-linear risk of blood pressure and stroke.

Evidence supports the use of low-dose thiazide diuretics for primary prevention of stroke, and low-dose thiazides combined with ACE-I are shown to reduce recurrent stroke. All blood pressure agents reduce risk of stroke, but beta blockers may be less effective than other agents and thus, in the absence of other indications for beta blockers specifically, are not an ideal first-line therapy. The most recent JNC8 blood pressure guidelines maintain the previous JNC7 guidelines for a lower blood pressure goal in patients with diabetes and persons younger than 60 years (≤140/90 mmHg), but allows for a greater threshold in those older than 60 years and, as discussed earlier, this recommendation in older persons is controversial.

Understanding the autoregulatory curve in cerebral blood vessels is key to understanding the lifetime effect of hypertension on the vascular supply of the brain. As we move ahead in research, developing modulators of vascular remodeling may help mitigate the chronic effects on hypertension and the brain. Moving forward, we must integrate the solid epidemiological base of knowledge to target therapy in primary and secondary prevention. As is described, fewer large-scale trials exist in the secondary prevention of stroke, and optimal blood pressure regimens and timing of their initiation still remain to be determined. Hypertension may be the largest risk factor for stroke, but it is modifiable, and creating systems of care that allow for detection and treatment will continue to lower worldwide rates of stroke.

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13

DYSLIPIDEMIA AND RISK OF STROKE AND CEREBROVASCULAR DISEASE

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Introduction

Dyslipidemia refers to abnormal lipid levels, including high levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), or triglycerides (TGs), and low levels of high-density lipoprotein cholesterol (HDL-C).[1] The definition of thresholds for abnormal levels varies according to the number of associated vascular risk factors and history of vascular disease.[1–3] The lifetime risk for developing dyslipidemia in individuals age 50 years or older is 50% for high LDL-C, 25% (women) and 65% (men) for low HDL-C, and between 20% and 50% for both low HDL-C and high LDL-C.[4] Dyslipidemia, especially elevated LDL-C, is an important risk factor for cardiovascular disease.[5,6] Recent stroke guidelines also consider that dyslipidemia is a well-documented and modifiable risk factor for stroke,[3] but the relationship is less straightforward than for cardiovascular disease.[3,7] Indeed, in observational studies, LDL-C and TC appear less strongly associated with stroke and covert magnetic resonance imaging-defined cerebrovascular disease (CVD) than with coronary artery disease. This could be explained in part by the heterogeneity of stroke and the differential associations of lipid fractions with stroke subtypes, as high levels of LDL-C and TC have been reported as risk factors for ischemic stroke and protective factors for hemorrhagic stroke (intracerebral hemorrhage [ICH]).[8–12] Despite the weakness and complexity of associations between LDL-C and stroke in epidemiological studies, randomized controlled trials (RCTs) have demonstrated that reducing LDL-C reduces the risk of stroke.[13] Less data are available for the relationship of other lipid fractions (TG, HDL-C, non-HDL-C, and so on) with stroke, and on the relationship of dyslipidemia with covert MRI-defined CVD.

In this chapter, we review the literature on the association between lipid fractions or lipid-lowering therapy and CVD, including stroke and MRI markers of CVD.

Epidemiological Studies on LDL-C and Stroke

In contrast with coronary heart disease, which is associated strongly with high LDL-C, epidemiological studies have often failed to show a significant relationship between LDL-C and risk of stroke.[14–16] There are several potential explanations for this. First, heterogeneity of stroke may play a role because associations diverge between ischemic stroke and hemorrhagic stroke, and between ischemic stroke subtypes, as detailed below. Second, a survival effect resulting from competing risks cannot be excluded because individuals exposed to a high risk of vascular disease related to high LDL-C levels, such as myocardial infarction, may have died prematurely, thus attenuating associations with stroke, which often occurs later in life than coronary heart disease. Third, the length of exposure and the age at which exposure is measured may matter. Lipid levels measured in late life can decrease as a result of behavioral changes or because of the presence of comorbidities, as well as a result of the initiation of lipid-lowering drugs. Midlife lipid levels seem to reflect exposure to dyslipidemia over a life span more fully.[17,18]

The epidemiological evidence for an association of high LDL-C with an increased risk of ischemic stroke is relatively weak. The largest meta-analysis, comprising nine cohort studies ($N = 688,367$) and published 10 years ago, found that low LDL-C levels are associated with a significant reduction in the risk of ischemic stroke (by 15% per 1.0 mmol/L of LDL-C).[19] However, individual study results, including those in more recent studies, have been less consistent. The Prospective Epidemiological Study of Myocardial Infarction (PRIME) study, a large, multicenter, prospective cohort study in healthy European middle-age men ($N = 9711$), did not find any significant association between LDL-C and incident ischemic stroke during a 10-year period.[16] In the Northern Manhattan Study (NOMAS) study, among 2940 community-dwelling stroke-free individuals (mean age, 68.8 years), baseline LDL-C as a continuous variable was not associated with an increased risk of ischemic stroke after 7.5 years on average,[15] but LDL-C greater than 130 mg/dL predicted an increased risk of stroke (hazard ratio [HR] = 3.81; 95% confidence interval [CI], 1.53–9.51). In a cross-sectional analysis of baseline data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, carried out in 9795 patients with type 2 diabetes, high LDL-C at baseline was an independent risk factor for ischemic stroke or stroke of unknown type (HR = 1.14; 95% CI, 1.02–1.27).[20] When considering ischemic stroke subtypes, several studies have shown a significant association of elevated LDL-C with ischemic stroke resulting from large-artery atheroma,[16,21,22] and not with cardioembolic ischemic stroke.[14,21,22] The Etude du Profil Génétique de l'Infarctus Cérébral (GENIC) case–control study ($N = 984$) also reported a significant association of LDL-C with lacunar (small-vessel disease [SVD]) stroke (odds ratio [OR] per standard deviation [SD] increase = 2.71; 95% CI, 1.60–4.55).[22]

Regarding ICH, a recent meta-analysis of four observational studies ($N = 124,498$) showed a significant association between high levels of LDL-C (>3.62 mmol/L or 140 mg/dL) and a 38% reduction in risk of ICH.[23] An earlier meta-analysis of nine cohort studies examining the effect of statins ($N = 688,376$) reached a comparable conclusion, stating that a 1.0-mmol/L reduction in LDL-C was associated with a significant 19% increase in hemorrhagic stroke risk.[19] A meta-analysis of observational studies did not find an increased risk of recurrent ICH in patients with previous lobar hemorrhage receiving statins ($N = 117,948$).[24]

RCTs of LDL-C Management and Risk of Stroke

STATINS

Despite the lack of strong epidemiological associations of high LDL-C with ischemic stroke, and even indications of an increased risk of ICH in individuals with low LDL-C levels,[11,12,25] RCTs have shown

that reducing LDL-C levels reduces significantly the risk of all stroke, both in primary and secondary prevention. Statins are inhibitors of the 3-hydroxy-3-methyl-glutaryl-CoA reductase enzyme and are the most widely used drugs to lower LDL-C. Standard or low-potency statins (such as simvastatin 40 mg/day) reduce LDL-C by about 41% and TG by 21%, and increase HDL-C by 6%. Higher doses or high-potency statins (such as atorvastatin 40–80 mg/day or rosuvastatin 10–20 mg/day) decrease LDL-C by 41% to 63% and TG by 10% to 35%, and increase HDL-C by around 10%, although for the latter the results are variable.[12,26] Interestingly, it was suggested that statins may also have other properties beyond their impact on lipid level reduction,[13] such as atherosclerotic plaque stabilization, decreased inflammation, improved endothelial function, altered thrombogenicity,[13,27,28] and neuroprotective effects.[29]

Primary Prevention

Numerous RCTs have explored the effect of lipid-lowering drugs on the risk of stroke, mostly as secondary end points, with the primary end point often being a composite of vascular events. Most RCTs were performed primarily in individuals without a history of stroke. Overall, recent comprehensive meta-analyses of these RCTs, testing the effect of lipid-lowering drugs against placebo, usual care, or less intensive therapy, reported a significant 4.5% reduction of stroke incidence per 10-mg/dL reduction in LDL-C (N = 195,488),[30] or a 4% relative risk reduction for 10% reduction in LDL-C (N = 266,973).[7] Statins were associated with a 22% reduction in total stroke (fatal and nonfatal combined) in a population free of cardiovascular disease,[31] and with a 15% to 18% reduction in total stroke (n = 130,443–182,803) in populations without such restrictions.[13,24,32] Moreover, another recent meta-analysis of 47 RCTs (N = 175,232) using a Bayesian mixed-treatment comparison to combine direct and indirect (vs. placebo) comparisons of statin doses, showed that high statin doses (leading to an expected minimum of a 40% decrease in LDL-C) were associated significantly with a decreased stroke risk compared with low statin doses (leading to an expected maximum of a 30% decrease in LDL-C).[33] The beneficial effect of statin intake was significant only for nonfatal stroke, with a 19% (95% CI, 4%–32%) reduction (N = 80,711),[34] whereas no significant association was reported between statin intake and risk of fatal stroke.[12,31,34] This pattern did not seem to be modified by statin subtype when performing indirect comparisons between high-potency statins (rosuvastatin and atorvastatin) versus low-potency statins (pravastatin, simvastatin, fluvastatin, and lovastatin).[34]

When focusing on ischemic stroke, statin intake was associated with a significant 17% reduction in ischemic stroke risk in a large meta-analysis of RCTs of 130,443 participants.[24] Moreover, in a meta-analysis of RCTs in high-risk populations with coronary artery disease (N = 39,612), a more aggressive statin therapy (40–80 mg/day atorvastatin or 10–20 mg/day rosuvastatin) was associated with a significant 16% reduction in ischemic stroke when compared with less intensive therapy (20–40 mg/day simvastatin).[12] Intensive statin therapy was, however, also shown to be associated with a greater rate of adverse events, especially elevated liver enzymes and creatine kinase.[33,35]

Regarding hemorrhagic stroke, a subanalysis of a large meta-analysis revealed that statins had no effect on intracranial hemorrhage in a population free of cardiovascular disease (two RCTs, N = 25,634).[31] No significant association with ICH was found in large meta-analyses with and without individuals with preexisting history of cardiovascular disease (23 RCTs, N = 130,443, of which one was exclusively of patients with stroke or transient ischemic attack [TIA]; and 31 RCTs, N = 182,803, of which 11% had a history of stroke).[24,32] One of these meta-analyses also examined the relationship between degree of LDL-C reduction or achieved LDL-C level and ICH risk, showing no association[32] (Table 13.1[36–114]).

TABLE 13.1

RCTs and Meta-analyses Reporting Associations between LDL-Cholesterol or Statins and Stroke

Author/name of study	Year	*N*	Mean age, yr	Men, %	Follow-up duration, yr	Treatment	Effect estimate for all strokes
Primary prevention: RCT							
Baigent et al.[36]/ SHARP	2011	9270	62	63	4.9	Simvastatin, placebo	Rate ratio = 0.81; 95% CI, 0.66–0.99; p = .04
Ruggenenti et al.[37]/ ESPLANADE	2010	87/93	51	76	0.5	Fluvastatin 40–80 mg + benazepril–valsartan, benazepril–valsartan	Information not found in the article
Fassett et al.[38]/ LORD	2010	58/65	60	65	2.5	Atorvastatin 10 mg	RR = 0.22; 95% CI, 0.01–4.57; p = .33[a]
Fellström et al.[39]/ AURORA	2009	1389/1384	64	62	3.8	Rosuvastatin 10 mg, placebo	HR = 1.17; 95% CI, 0.79–1.75; p = .42, for nonfatal stroke
Armitage et al.[40]/ SEARCH	2009	6031/6033	64	83	6.7	Simvastatin 80 mg, simvastatin 20 mg	RR = 0.91; 95% CI, 0.77–1.08; p = .3
Ridker et al.[41]/ JUPITER	2008	8901/8901	66	62	1.9	Rosuvastatin 20 mg, placebo	HR = 0.52; 95% CI, 0.34–0.79; p = .002
Tavazzi et al.[42]/ GISSI-HF	2008	2285/2289	68	77	3.9	Rosuvastatin 10 mg, placebo	HR = 1.23 (0.89, 1.70), p = .21
Sato et al.[43]/OACIS lipid	2008	176/177	63.2	76.7	0.7	Pravastatin 10 mg, standard acute myocardial infarction therapy without pravastatin	p (article) = .252 RR = 0.20; 95% CI, 0.01–4.16; p = 0.30[a]
Bone et al.[44]	2007	604	59	0	1.1	Atorvastatin, placebo	RR = 2.93; 95% CI, 0.12–71.13; p = 0.51[a] (1 hemorrhagic stroke in the atorvastatin 80 group compared with none in placebo group)

(*continued*)

TABLE 13.1

Continued

Author/name of study	Year	*N*	Mean age, yr	Men, %	Follow-up duration, yr	Treatment	Effect estimate for all strokes
Kjekshus et al.[45]/ CORONA	2007	2514/2497	73	76	2.7	Rosuvastatin, placebo	RR = 0.89; 95% CI, 0.69–1.15; $p = .38$[a]
Deedwania et al.[46]/ SAGE	2007	446/445	72.5	69.4	1.0	Atorvastatin 80 mg, pravastatin 40 mg	RR = 0.33; 95% CI, 0.03–3.18; $p = .34$[a]
Knopp et al.[47]/ ASPEN	2006	1211/1199	61	66	4.0	Atorvastatin 10 mg, placebo	RR = 0.89; 95% CI, 0.56–1.40; $p = .60$[a]
Nakamura et al.[48]/ MEGA	2006	3866/3966	58	32	5.3	Pravastatin 10–20 mg, usual care	HR = 0.83; 95% CI, 0.57–1.21; $p = .33$
Amarenco et al.[49]/ SPARCL	2006	2365/2366	63	60	4.9	Atorvastatin 80 mg, placebo	HR = 0.84; 95% CI, 0.71–0.99; $p = .03$
Schmermund et al.[50]	2006	234/233	61.5	74.5	1.0	Atorvastatin 80 mg, atorvastatin 10 mg	RR = 0.33; 95% CI, 0.01–8.11; $p = .50$[a]
Sakamoto et al.[51]/ MUSUASHI-AMI	2006	237/244	64	80	2.0	Any statin, usual care	RR = 1.54; 95% CI, 0.26–9.16; $p = .63$[a]
Pedersen et al.[52]/ IDEAL	2005	4439/4449	62	81	4.8	Atorvastatin 80 mg, simvastatin 20 mg	HR = 0.87; 95% CI, 0.70–1.08; $p = .20$
LaRosa et al.[53]/TNT	2005	4995/5006	61	81	4.9	Atorvastatin 80 mg, atorvastatin 10 mg	HR = 0.75; 95% CI, 0.59–0.96; $p = .02$
Wanner et al.[54]/4D	2005	1254	66	54	3.9	Atorvastatin 20 mg, placebo	RR = 1.33; 95% CI, 0.90–1.97; $p = .15$
Anderssen et al.[55]/ HYRIM	2005	283/285	57	100	4	Fluvastatin 40 mg	NS
Yokoi et al.[56]/ ATHEROMA	2005	182/179	59	83	3.0	Pravastatin 10–20 mg, usual care	RR = 1.23; 95% CI, 0.34–4.50; $p = .75$[a]
Makuuchi et al.[57]/ PCABG	2005	152/151	59	84	4.5	Pravastatin 10–20 mg, usual care	RR = 0.20; 95% CI, 0.02–1.68; $p = .14$[a]

Stone et al.[58]	2005	96/103	—	86	1.0	Atorvastatin 80 mg, lovastatin 5 mg	RR = 1.07; 95% CI, 0.07–16.91; $p = .96$[a]
Koren and Hunninghake[59]/ ALLIANCE	2004	1217/1225	61	82	4.7	Atorvastatin 10–80 mg, usual care	HR = 0.87; 95% CI, 0.55–1.38; $p = .55$
Colhoun et al.[60]/ CARDS	2004	1428/1410	62	68	3.9	Atorvastatin 10 mg, placebo	HR = 0.52; 95% CI, 0.31–0.89
Cannon et al.[61]/ PROVE-IT	2004	2099/2063	58	78	2.0	Atorvastatin 80 mg, pravastatin 40 mg	Risk reduction = −9%, NS
De Lemos et al.[62]/A to Z	2004	2265/2232	61	76	2.0	Simvastatin 80 mg, simvastatin 20 mg	HR = 0.79; 95% CI, 0.48–1.30; $p = .36$
Asselbergs et al.[63]/ PREVEND-IT	2004	864	51	64.5	3.8	Pravastatin 40 mg, placebo	RR = 1.74; 95% CI, 0.51–5.91; $p = .37$[a]
Zanchetti et al.[64]/ PHYLLIS	2004	254/254	58	40	2.6	Pravastatin 40 mg, placebo	RR = 3.00; 95% CI, 0.12–73.30; $p = .50$[a]
Muldoon et al.[65]	2004	96/93/94	53.6	48	0.5	Simvastatin 10 mg, simvastatin 40 mg, placebo	RR = 3.03; 95% CI, 0.12–73.48; $p = .49$[a]
Nakagawa et al.[66]/ PCS	2004	54/66	60	92	5.0	Pravastatin 10 mg, usual care	RR = 0.92; 95% CI, 0.21–3.92; $p = .91$[a]
Nissen et al.[67]/ REVERSAL	2004	327/327	56.2	72	1.5	Atorvastatin 80 mg, pravastatin 40 mg	RR = 1.00; 95% CI, 0.06–15.92; $p = 1.00$[a]
Bae et al.[68]	2004	105/100	60.0	67.8	0.5	Atorvastatin 10 mg, usual care	RR = 0.95; 95% CI, 0.06–15.02; $p = .97$[a]
Sever et al.[69]/ ASCOT-LLA	2003	5168/5137	63	81	3.3	Atorvastatin 10 mg, placebo	HR = 0.73; 95% CI, 0.56–0.93; $p = .024$
Holdaas et al.[70]/ ALERT	2003	2102	50	66	5.1	Fluvastatin 40 mg, placebo	RR = 1.16; 95% CI, 0.83–1.63; for cerebrovascular event (fatal and nonfatal stroke, TIA, reversible ischemic neurological deficit, subarachnoid hemorrhage)

(*continued*)

TABLE 13.1

Continued

Author/name of study	Year	*N*	Mean age, yr	Men, %	Follow-up duration, yr	Treatment	Effect estimate for all strokes
Mohler et al.[71]	2003	120/120/114	68.0	77	1.0	Atorvastatin 80 mg, atorvastatin 10 mg, placebo	RR = 2.05; 95% CI, 0.10–42.29; p = 0.64[a]
Olsson et al.[72]/3T	2003	556/537	62.8	75.4	1.0	Atorvastatin 30 mg, simvastatin 35mg	RR = 2.90; 95% CI, 0.12–70.97; p = 0.51[a]
Scanu et al. / ALLHAT-LLT[73]	2002	5170/5185	66	51	4.8	Pravastatin 40 mg, usual care	RR = 0.91; 95% CI, 0.75–1.09; p = 0.31
Athyros et al.[74]/ GREACE	2002	800/800	59	79	3.0	Atorvastatin 10–80 mg, usual care	RR = 0.53; 95% CI, 0.30–0.82; p = .034
Liem et al.[75]/ FLORIDA	2002	265/275	60.5	83	1.0	Fluvastatin 80 mg, placebo	RR = 2.07; 95% CI, 0.19–22.75; p = .55[a] (all fatal stroke)
Craig et al. / HPS[76]	2002	10,269/10,267	65	75	5.0	Simvastatin 40 mg, placebo	Rate ratio = 0.75; 95% CI, 0.66–0.85; p < .0001
Taylor et al.[77]/ ARBITER	2002	79/82	60	71	1.0	Atorvastatin 80 mg, pravastatin 40 mg	RR = 3.11; 95% CI, 0.13–75.28; p = .48[a]
Shepherd et al.[78]/ PROSPER	2002	2891/2913	75	48	3.2	Pravastatin 40 mg, placebo	HR = 1.03; 95% CI, 0.81–1.31; p = .81
Serruys et al.[79]/LIPS	2002	844/833	60	83.8	3.9	Fluvastatin 80 mg, placebo	RR = 1.97; 95% CI, 0.18–21.73; p = .58[a]
Schwartz et al.[80]/ MIRACL	2001	1538/1548	65	65	0.3	Atorvastatin, placebo	RR = 0.50; 95% CI, 0.26–0.99; p = .045
Ito et al.[81]/PATE	2001	331/334	73	21	3.9	Pravastatin 10–20 mg; low dose, 5 mg	RR = 0.64; 95% CI, 0.31–1.29; p = .21[a]
Hedblad et al.[82]/ BCAPS	2001	198/199	61.9	46.8	3.0	Fluvastatin 40 mg, placebo	N = 8 strokes (the article does not distinguish between the 2 groups)

Brown et al.[83]/ HATS	2001	160	53.0	87.0	3.0	Simvastatin 10–20 mg, niacin (+/–antioxidants), placebo or antioxidants	RR = 0.11; 95% CI, 0.01–2.03; $p = .14$[a]
Schaefer et al. / GISSI-P[84]	2000	2138/2133	60	86	1.9	Pravastatin 20 mg, usual care	RR = 1.05; 95% CI, 0.56–1.96; $p = .88$[a]
Arntz et al.[85]/ L-CAD	2000	70/56	57	80	2.0	Pravastatin 20–40 mg, usual care	RR = 1.60; 95% CI, 0.15–17.19; $p = .70$[a]
Teo et al.[86]/SCAT	2000	230/230	61.0	89	4.0	Simvastatin 30 mg, placebo	RR = 0.57; 95% CI, 0.17–1.92; $p = .37$[a]
Kleemann et al.[87]/ CLAPT	1999	112/114	54	100	2.0	Lovastatin 20-80 mg, usual care	RR = 0.34; 95% CI, 0.01–8.24; $p = .51$[a]
Downs et al.[88]/ AFCAPS-TexCAPS	1998	3304/3301	58	85	5.2	Lovastatin 20–40 mg, placebo	RR = 0.82; 95% CI, 0.41–1.66; $p = .59$[a]
Joy et al. / LIPID[89]	1998	4512/4502	62	83	6.1	Pravastatin 40 mg, placebo	Risk reduction = 19%; 95% CI, $p = .048$
Barter et al. / Post-CABG[90]	1997	676/675	62	92	4.3	Lovastatin 40–80 mg, lovastatin 2.5–5 mg	$p = .15$ (article data); RR = 1.12; 95% CI, 0.58–2.18; p
Bertrand et al.[91]/ PREDICT	1997	347/348	58.3	83.7	0.5	Pravastatin 40 mg, placebo	RR = 3.01; 95% CI, 0.12–73.60; $p = 0.50$[a]
Besterhorn et al.[92]/ CIS	1997	254	49.3	100	2.3	Simvastatin 40 mg, placebo	No stroke
Sacks et al.[93]/CARE	1996	2081/2078	59	86	5.0	Pravastatin 40 mg, placebo	Risk reduction = 31% (3–52), $p = .03$
Shepherd et al.[94]/ WOSCOPS	1995	3302/3293	55	100	4.9	Pravastatin 40 mg, placebo	Risk reduction = 11% (–33 to 40)
Crouse et al.[95]/ PLAC-II	1995	75/76	63	85	3.0	Pravastatin 10–40 mg, placebo	RR = 0.51; 95% CI, 0.05–5.47; $p = .57$[a]
Salonen et al.[96]/ KAPS	1995	244/223	57	100	3.0	Pravastatin 40 mg, placebo	RR = 0.50; 95% CI, 0.09–2.69; $p = .42$[a]
Jukema et al.[97]/ REGRESS	1995	450/434	56.2	100	2.0	Pravastatin 40 mg, placebo	RR = 0.58; 95% CI, 0.14–2.41; $p = .45$[a]

(*continued*)

TABLE 13.1

(Continued)

Author/name of study	Year	*N*	Mean age, yr	Men, %	Follow-up duration, yr	Treatment	Effect estimate for all strokes
Pitt et al.[98]/PLAC1	1995	206/202	57.0	77.5	3.0	Pravastatin 40 mg, placebo	RR = 0.20; 95% CI, 0.01–4.06; $p = .29$[a]
Vermeer et al. / SSSS[99]	1994	2221/2223	58.6	82	5.4	Simvastatin 40 mg, placebo	RR = 0.70; 95% CI, 0.52–0.96; $p = .024$ for cerebrovascular events (stroke + TIA)
Furberg et al.[100]/ ACAPS	1994	919	62	52	2.8	Lovastatin 20 mg (+1 mg warfarin), placebo	RR = 0.09; 95% CI, 0.005–1.64; $p = .10$[a]
MAAS investigators[101] / MAAS	1994	193/188	55	89	4.0	Simvastatin 20 mg, placebo	RR = 0.49; 95% CI, 0.04–5.33; $p = .56$[a]
Waters et al.[102]/ CCAIT	1994	165/166	53	81	2.0	Lovastatin 20 mg, placebo	RR = 3.02; 95% CI, 0.12–73.55; $p = .50$[a]
Weintraub et al.[103]/ LR	1994	203/201	62.0	72	0.5	Lovastatin 80 mg, placebo	RR = 0.33; 95% CI, 0.01–8.05; $p = .50$[a]
Kato et al. / PMSG[104]	1993	530/532	55.0	76.5	0.5	Pravastatin 30 mg, placebo	RR = 0.14; 95% CI, 0.01–2.77; $p = .20$[a]
Blankenhorn et al.[105]/MARS	1993	134/136	58	91	2.2	Lovastatin 80 mg, placebo	RR = 0.14; 95% CI, 0.01–2.78; $p = .20$[a]
Bradford et al.[106]/ EXCEL	1991	6582/1663	55.8	59	0.9	Lovastatin 20–80 mg, placebo	$N = 11$ strokes, of which one was fatal; information not detailed in the article
Brown et al.[107]/ FATS	1990	83/81	66	32	2.7	Pravastatin 10 mg, usual care	No stroke
Primary prevention: MA							
Ribeiro et al.[33] (MA)	2013	175,232	49–74 (range, means)	—	3.0	Statins	High-dose statin intake was associated with a decreased risk in stroke (OR, 0.83; 95% CI, 0.68–0.99) compared with low dose ($N = 79{,}515$ for this analysis)

Taylor et al.[31] (Cochrane review)	2013	56,934/free of CVD	—	—	>0.5	Statins	-Statin intake was associated with a 22% (95% CI, 11%–32%) reduction in total stroke. -Statin intake had no influence on fatal stroke. -Statin intake had no effect on ICH
McKinney and Kostis[32] (MA)	2012	182,803	62.6 ± 5.2	67	—	Statins	-Statin intake was associated with a 16% (95% CI, 9%–22%) reduction in total stroke. -Statin intake was not associated with ICH incidence. -There was no association between the degree of LDL-C reduction or achieved LDL-C and hemorrhagic stroke risk.
Hackam et al.[24] (MA)	2011	130,443	—	—	3.9 (median)	Statins	Statin intake was associated with -15% (95% CI, 7%–22%) reduction in total stroke -17% (95% CI, 8%–25%) reduction in ischemic stroke risk Statin intake was not associated with ICH (median LDL-C reduction, 1.03 mmol/L).
Tonelli et al.[34] (MA)	2011	60,841	51–76 (range)	—	2 (median)	Statins	-Statin intake was associated with a 19% (95% CI, 4%–32%) reduction in nonfatal stroke. -Statin intake had no influence on fatal stroke.

(*continued*)

TABLE 13.1

(Continued)

Author/name of study	Year	*N*	Mean age, yr	Men, %	Follow-up duration, yr	Treatment	Effect estimate for all strokes
Baigent et al.[12]/CTT (MA)	2010	169,138	—	—	—	Statins	-Overall, the risk reduction in the incidence of stroke was 16% (95% CI, 11% – 21%) and was 21% (95% CI, 15% – 26%) for ischemic stroke for a reduction of 1.0 mmol/L of LDL-C, with no significant excess of hemorrhagic stroke. -A 1.0-mmol/L reduction in LDL-C was associated with a 23% (95% CI, 15% – 30%) reduction in first nonfatal ischemic stroke. -No effect on deaths resulting from stroke (ischemic, hemorrhagic, unknown, all strokes)
De Caterina et al.[7] (MA)	2010	266,973	—	—	3.5	Cholesterol-lowering treatment	-Statin intake was associated with a 15% (95% CI, 8% – 22%) reduction in the risk of stroke -4% reduction in RR of stroke incidence for 10% reduction in LDL-C
Labreuche et al.[30] (MA)	2010	195,488	—	—	—	Lipid-modifying drugs	4.5% (95% CI, 1.7% – 7.2%) reduction in stroke incidence for 10 mg/dL reduction in LDL-C
Amarenco and Lebreuche[13] (MA)	2009	165,792 (high risk for stroke)	55 – 75 (range, means)	31 – 100 (range)	0.3 – 6.7 (range)	Statins	18% (95% CI, 13% – 23%) reduction in all stroke incidence, no increase in hemorrhagic stroke
Amarenco and Lebreuche[13] (MA)	2009	83,205	58 – 66 (range,means)	31 – 86 (range)	0.3 – 6.1 (range)	Statins	Primary prevention of hemorrhagic stroke (RR = 0.81; 95% CI, 0.60 – 1.08)

Silva et al.[35] (MA)	2007	27,548	58.2 – 61.7 (range,means)	75.5 – 81.0 (range)	3.4	Atorvastatin or simvastatin 80 mg	-Intensive statin therapy is associated with a decreased stroke risk (OR, 0.82; 95% CI, 0.72 – 0.94). - Intensive statin therapy is associated with the risk of statin-induced adverse events[b] (OR, 1.44; 95% CI, 1.33 – 1.55) and with adverse events requiring discontinuation of therapy (OR, 1.28; 95% CI, 1.18 – 1.39).
Secondary prevention: RCT							
Nagai et al.[108] J-STARS	2014	1578	66.2	68.8	5.0	Pravastatin 10 mg, no statin	Ongoing trial of patients with noncardioembolic ischemic stroke
Milionis et al.[109]/ Athenian Stroke Registry	2009	794	67.0	68.4	10	Statins	Statin therapy after discharge is associated inversely with 10-year stroke recurrence (HRa= 0.65; 95% CI, 0.39 – 0.97)
Kennedy et al.[110]/ FASTER	2007	392	68.1	52.7	0.25	Aspirin, aspirin + clopidogrel, aspirin + simvastatin, aspirin + clopidogrel + simvastatin	RR = 1.5, p = .25 (for all strokes and TIAs)
Amarenco et al.[49]/ SPARCL	2006	4731 (stroke or TIA), 2365 (atorvastatin), 2366 (placebo)	63.0 (atorvastatin group), 62.5 (placebo group)	59.7	4.9 (median)	Atorvastatin 80 mg	Statin intake is associated with a 16% (95%CI, 1% – 29%) reduction in stroke recurrence.
Collins et al.[111]/HPS	2004	3280 (CVD)	40 – 80 (range)	75.0	5.0	Simvastatin 40 mg	91% (95% CI, – 8% to 395%) increase in hemorrhagic stroke risk, no effect of statins on stroke recurrence
White et al.[112]/ LIPID	1998/ 2000	369	31 – 75 (range)	83	6.0	Pravastatin 40 mg, placebo	Not available in the article (subanalysis)

(*continued*)

TABLE 13.1

(Continued)

Author/name of study	Year	*N*	Mean age, yr	Men, %	Follow-up duration, yr	Treatment	Effect estimate for all strokes
Sacks et al.[93]/CARE	1996	333	21 – 75 (range)	86	5.0	Pravastatin 40 mg, placebo	Not available in the article (subanalysis)
Secondary prevention: reviews and MA							
Feher et al.[28] (review)	2011	—	—	—	—	Statins	Marginal reduction of stroke recurrence with statin therapy
Amarenco and Labreuche[13] (MA)	2009	4731 (stroke or TIA) 8,011 (SPARCL + HPS)	63.0/62.5 (atorvastatin group / placebo group) 63.0/62.5 (atorvastatin group / placebo group, for SPARCL) – 40 – 80 (range for HPS)	59.7 59.7 – 75.0	4.9 (median) 4.9 (SPARCL) – 5.0 (HPS)	Atorvastatin 80 mg Atorvastatin, simvastatin	67% (95% CI, 9% – 156%) increase in hemorrhagic stroke risk (SPARCL) 73% (95% CI,19% – 150%) increase in hemorrhagic stroke risk (SPARCL + HPS)

Manktelow and Potter[113] (Cochrane review, MA)	2009	9224 (history of stroke or TIA), 8011 (history of stroke or TIA) (SPARCL + HPS)	18 + 63.0/62.5 (atorvastatin group / placebo group, for SPARCL) – 40 – 80 (range for HPS)	53 – 86 59.7 – 75.0	0.25 – 6.0 (range) 4.9 (SPARCL) – 5.0 (HPS)	Atorvastatin, pravastatin, simvastatin Atorvastatin, simvastatin	Statin intake was associated marginally with decreased stroke recurrence risk (OR, 0.88; 95% CI, 0.77 – 1.00). Statin intake was associated with decreased ischemic stroke recurrence risk (OR, 0.78; 95% CI, 0.67 – 0.92).
Bersano et al.[114] (review)	2008	—	—	—	—	Statins	- Statins reduce the risk of stroke occurrence in high-risk patients and also seem to reduce stroke recurrence. - The low incidence and reversibility of their adverse effects, and the unclear association with hemorrhagic events, support the safe use of these drugs.

[a]Calculated by authors based on the information provided in the article.
[b]Elevation in creatine kinase 10 or more times the upper limit of normal; elevation in alanine or aspartate aminotransferase three times or more the upper limit of normal; rhabdomyolysis; drug-induced adverse events requiring discontinuation; drug-induced events.
3T, Treat-to-Target; 4D, Deutsche Diabetes Dialyse Studie; 4S, Scandinavian Simvastatin Survival Study; A to Z, Aggrastat to Zocar phases; ACAPS, Asymptomatic Carotid Artery Progression Study; AFCAPS-TexCAPS, Air Force – Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of Lescol in Renal Transplantation; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARBITER, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ASCOT-LLA,

(*continued*)

TABLE 13.1

(Continued)

Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; ATHEROMA, Angiographic Intervention Trial Using an HMG-CoA Reductase Inhibitor to Evaluate the Retardation of Obstructive Multiple Atheroma; AURORA, Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; BCAPS, β-Blocker Cholesterol-Lowering Asymptomatic Plaque Study; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events; CCAIT, Canadian Coronary Atherosclerosis Intervention Trial; CI, confidence interval; CIS, Coronary Intervention Study; CLAPT, Cholesterol Lowering Atherosclerosis PTCA Trial; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; CTT, Cholesterol Treatment Trialists; ESPLANADE, European Study for Preventing by Lipid-Lowering Agents and ACE-Inhibitors Dialysis Endpoints; EXCEL, Expanded Clinical Evaluation of Lovastatin; FATS, Familial Atherosclerosis Treatment Study; FLORIDA, Fluvastatin on Risk Diminishment after Acute Myocardial Infarction; GISSI, Gruppo Italino per lo Studio della Sopravvivenza nell' Infarcto Miocardico (-P, Prevenzione; -HF, Heart Failure); GREACE, Greek Atorvastatin and Coronary-Heart-Disease Evaluation; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study; HR, hazard ratio; HRa, adjusted hazard ratio; HYRIM, Hypertension High Risk Management Trial; ICH, intracerebral hemorrhage; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS, Kuopio Atherosclerosis Prevention Study; L-CAD, Lipid Coronary Artery Disease; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study; LORD, Lipid Lowering and Onset of Renal Disease; LR, Lovastatin Restenosis Trial; MA, meta-analysis; MAAS, Multicenter Anti-Atheroma Study; MARS, Monitored Atherosclerosis Regression Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; MUSUASHI-AMI, Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction; NS, not significant; OACIS-LIPID, Osaka Acute Coronary Insufficiency Study- LIPID; OR: odds ratio; PATE, Pravastatin Anti-Atherosclerosis Trial in the Elderly; PCABG, Pravastatin Coronary Artery Bypass Graft Study; PCS, Prevention of Coronary Sclerosis; PHYLLIS, Plaque Hypertension Lipid-Lowering Italian Study; PLAC-1, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; PLAC-2, Pravastatin, Lipids, and Atherosclerosis in the Carotids; PMSG, Pravastatin Mutinational Study Group for Cardiac Risk Patients; Post-CABG, Post-Coronary Artery Bypass Grafting; PREDICT, Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty; PREVEND-IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; RCT, randomized, controlled trial; REGRESS, Regression Growth Evaluation Statin Study; REVERSAL, Reversal of Atherosclerosis with Aggressive Lipid Lowering; RR, risk ratio; SAGE, Study Assessing Goals in the Elderly; SCAT, Simvastatin/Enalapril Coronary Atherosclerosis Trial; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SHARP, Study of Heart and Renal Protection; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA, transient ischemic attack; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study; yr, year.

Secondary Prevention

A few RCTs have focused on the effect of lipid-lowering drugs in individuals with a history of stroke. A meta-analysis of four RCTs (N = 8713) on individuals with prior noncardioembolic stroke, TIA, or CVD found that statin intake was associated with a significantly reduced risk of stroke recurrence (risk ratio [RR] = 0.88; 95% CI, 0.78–0.99).[13] A Cochrane meta-analysis of five RCTs (N = 9224) of individuals with a history of stroke or TIA reported a marginal association between statin intake and a decreased risk in stroke recurrence (OR= 0.88; 95% CI, 0.77–1.00), which was more pronounced for ischemic stroke (OR= 0.78; 95% CI, 0.67–0.92; two RCTs, N = 8011).[113] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was designed to evaluate the effects of atorvastatin 80 mg/day in 4731 patients who experienced a noncardioembolic stroke or TIA in the previous 6 months (but who have no known coronary heart disease), and is the only completed trial that focuses exclusively on patients with a history of stroke. This RCT reported a 16% (95% CI, 1%–29%) reduction in stroke recurrence in patients in the statin arm compared with patients in the placebo arm,[49] which was found consistently in all age groups,[115] genders,[116] and stroke subtypes (the cardioembolic subtype being excluded in this RCT).[117]

In the SPARCL trial (N = 4731) and in a subanalysis of 3280 participants from the Heart Protection Study (HPS) (N = 20,536; comparing 40 mg simvastatin daily vs. placebo in patients with coronary disease, other occlusive arterial disease, or diabetes) with a history of cerebrovascular disease,[111] an increase in risk of hemorrhagic stroke was observed in patients randomized to statin treatment of, respectively, 67% (95% CI, 9%–156%) and 91% (95% CI, –8% to 395%); and this increase in risk was 73% (95 % CI, 19%–150%) when combining SPARCL and HPS (Table 13.1).[13] In the SPARCL trial, this finding remained significant even after adjusting for age, male gender, presentation with hemorrhagic stroke at inclusion, and uncontrolled hypertension.[25] This result was found to be stronger in the subgroup with ischemic stroke resulting from SVD as a qualifying event.[25] However, in these patients, the significant reduction in ischemic stroke risk associated with atorvastatin therapy offset the risk of hemorrhagic stroke, and the benefit in terms of all stroke risk remained significant.[25,117] There is no clear evidence concerning the beneficial effect on stroke recurrence related to statin intake in patients with previous hemorrhagic stroke.[28]

The benefit and safety of more intensive lipid-lowering drug regimens in secondary stroke prevention is currently being evaluated in the Treat Stroke to Target RCT, in which the usual target of 100 mg/dL LDL-C is compared with LDL-C less than 70 mg/dL in individuals with a recent ischemic stroke (<3 months).

EZETIMIBE

Ezetimibe is a cholesterol transporter inhibitor in the small intestine directly targeting Niemann-Pick C1-like 1, which is highly expressed at the surface of absorptive jejunal enterocytes.[118] It is prescribed to lower LDL-C levels when patients are intolerant to statins or do not achieve targeted LDL-C levels.[119] Ezetimibe (10 mg/day) was reported to reduce LDL-C by approximately 20% and TG by around 8%, and to increase HDL-C by approximately 5%.[118] It was tested in combination with statin therapy to obtain a more aggressive lipid-modifying effect, but although no adverse event was observed, the additional benefit of this combination and the effect of ezetimibe alone on clinical outcomes remain unproved.[120,121]

Guidelines for LDL-C management in primary or secondary stroke prevention are shown in Boxes 13.1[122] and 13.2.[123–125]

BOX 13.1

GUIDELINES FOR THE MANAGEMENT OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL AND STATIN THERAPY IN STROKE

Currently, low-density lipoprotein cholesterol (LDL-C) is the only lipid fraction that has an acknowledged guideline in stroke with precise aims.

Primary Prevention

- For patients with coronary heart disease (CHD) or high-risk conditions such as diabetes, statin therapy should be initiated, as well as therapeutic lifestyle modifications to reach fasting LDL-C goals as detailed in the National Cholesterol Education Program—Adult Treatment Panel III[2,3]:
  - No or one risk factor: ≤160 mg/dL
  - More than two risk factors (10-year Framingham CHD risk, ≤20%): <130 mg/dL
  - High-risk patients (CHD or CHD risk equivalents, 10-year Framingham CHD risk, >20%): <100 mg/dL
- In patients with diabetes, especially if they have additional risk factors, statin therapy should be initiated to decrease the risk of first stroke.[3]

Secondary Prevention

- According to the American Heart Association/American Stroke Association, statin therapy should be initiated in patients with ischemic stroke or transient ischemic attack (TIA) with evidence of atherosclerosis but without known CHD if LDL-C is ≥100 mg/dL.[122]
- Reduction of LDL-C levels of at least 50% (or target, <70 mg/dL) is recommended for patients with atherosclerotic ischemic stroke or TIA and without known CHD.[122]
- For patients with ischemic stroke or TIA who have high cholesterol levels or comorbid coronary artery disease, the National Cholesterol Education Program—Adult Treatment Panel III guidelines should be followed: lifestyle modifications, dietary guidelines, medication recommendation.[122]

Other Lipid Fractions and Stroke

Although the focus so far has been mainly on LDL-C lowering and statins, other lipid fractions have recently gained interest in association with stroke risk.

EPIDEMIOLOGICAL STUDIES

Total Cholesterol

TC corresponds to the sum of LDL-C, HDL-C, and very low-density lipoprotein. However, the biggest component of TC being LDL-C, associations of TC with stroke risk largely resemble those of LDL-C. In a meta-analysis of 45 prospective studies including 450,000 individuals, TC was not associated with an increased risk of stroke.[126]

Focusing on ischemic stroke, there was a significant association of the latter with TC levels of 7.0 mmol/L or more, in 28,519 stroke-free male smokers age 50 to 69 years,[10] and a trend toward

BOX 13.2
GUIDELINES CONCERNING LIPID-LOWERING DRUGS OTHER THAN STATINS IN STROKE MANAGEMENT, ACCORDING TO THE AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION[a]

Primary Stroke Prevention

- The use of fibrates alone might be considered for patients with diabetes to decrease the risk of first stroke, but usefulness and efficacy are not well established.[3]
- The use of fibrates in combination with a statin therapy in patients with diabetes is not useful.[3]
- Fibric acid derivatives might be considered for patients with hypertriglyceridemia, but their efficacy in the prevention of ischemic stroke is not established.[3]
- Niacin might be considered for patients with low high-density lipoprotein cholesterol levels or high lipoprotein a levels, but their efficacy is not established for the prevention of ischemic stroke in these patients.[3]
- The use of niacin, fibric acid derivatives, bile acid sequestrants, and ezetimibe in the prevention of ischemic stroke might be considered in patients who do not achieve targeted lows-density lipoprotein cholesterol levels or who are intolerant to statins, but there is a lack of evidence concerning their efficacy in decreasing the risk of stroke.[3]

Secondary Stroke Prevention

- Gemfibrozil, a fibrate acid agent, or niacin might be considered for patients with ischemic stroke or transient ischemic attack and who have low levels of high-density lipoprotein cholesterol, but their usefulness or efficacy is not well established.[122]

[a]Of note, these recommendations have not been updated yet after the publication of two recent negative niacin trials.[123–125]

a positive association with TC was reported in a meta-analysis of 18 Asian cohorts comprising 124,774 participants.[127] When considering ischemic stroke subtypes, a consistent association between TC and both the large-artery disease and the SVD subtypes has been described,[21,22,128,129] and no association[21,22] or even an inverse association has been noted between TC and cardioembolic stroke.[128]

A meta-analysis of 17 observational studies (N = 1,285,222) yielded a significant association between increasing TC and decreased hemorrhagic stroke risk, with an increase of 1 mmol/L TC being associated with a significant 15% reduction in the relative risk of hemorrhagic stroke, especially ICH, but not subarachnoid hemorrhage.[23]

Recent meta-analyses of 78 RCTs (N = 266,973; mean follow-up, 3.5 years), of which 49 tested the efficacy of statins and the remaining 33 tested various lipid-lowering drugs (13 on fibrates, 7 on dietary interventions, 12 on other drugs, and 1 on partial ileal bypass surgery), reported a significant association between reduction in TC and reduction in overall stroke risk, yielding a 0.8% relative risk reduction for each 1% reduction of TC (mostly a result of LDL-C reduction) in a population comprising 3.4% of patients with a history of stroke and 27% of patients with a history of myocardial infarction[7] (Table 13.2[130–149]).

TABLE 13.2

RCTs Studying the Association between Lipid-Lowering Drugs (Other Than Statins) and Stroke

Author/name of study	Year	*N*	Mean age, yr	Men, %	Mean follow-up duration	Treatment	Results
Fibrates: RCT							
Ginsberg et al.[130]/ACCORD study	2010	2765/2753	62	69	4.7 yr	Fenofibrate 160 mg, placebo	RR (95%CI) = 1.06 (0.72, 1.56)
Whitney et al.[131]/AFREGS	2005	71/72	62	92	2.5 yr	Gemfibrozil 600 mg, placebo	RR (95%CI) = 0.90 (0.73, 1.12)
Keech et al.[132]/FIELD study	2005	4895/4900	63	63	5.0 yr	Fenofibrate 200 mg, placebo	RR (95%CI) = 0.20 (0.01, 4.15)
Meade et al.[133]/LEADER study	2002	783/785	68	100	55.2 mo	Bezafibrate 400 mg, placebo	RR (95%CI) = 1.23 (0.85, 1.77)
Diabetes Atherosclerosis Intervention Study Investigators / DAIS[134]	2001	207/211	56.8	73	3.3 yr	Fenofibrate 200 mg, placebo	Not available in the article (*N* = 12 strokes)
BIP Study Group / BIP [135]	2000	1548/1542	60	91	6.2 yr	Bezafibrate 400 mg, placebo	RR (95%CI) = 0.93 (0.68, 1.27)
Rubins et al.[136]/VA-HIT	1999	1264/1267	64	100	5.1 yr	Gemfibrozil 1.2 g, placebo	RR (95%CI) = 0.73 (0.53, 1.00)
Frick et al.[137]/Helsinki Heart Study	1993	311/317	48.6	100	5.0 yr	Gemfibrozil 1.2 g daily, placebo	RR (95%CI)= 1.02 (0.06, 16.22), $p = .99$[a]b
Frick et al.[138]/Helsinki Heart Study	1987	2051/2030	47.3	100	5.0 yr	Gemfibrozil 1.2 g, placebo	RR (95%CI) = 1.10 (0.58, 2.07), $p = 0.77$[a]
Acheson et al.[139]	1972	95	NR	68	8.7/7.6 yr	Clofibrate 1–2 g, corn oil then placebo	RR (95%CI) = 1.07 (0.70, 1.63)

Veteran Administration Cooperative Study Group[140]	1973	268/264	NR	100	4.6 yr	Clofibrate 2 g, placebo	RR (95%CI) = 1.58 (0.97, 2.59)
Coronary Drug Project Research Group[141]	1975	3892	NR	100	6.2 yr	Clofibrate 1.8 g, placebo	RR (95%CI) = 1.11 (0.92, 1.34)
Committee of Principal Investigators[142] /	1978	5331/5296	46	100	5.3 yr	Clofibrate 1.6 g, olive oil placebo	RR (95%CI) = 1.18 (0.71, 1.96)
Research Committee of the Scottish Society of Physicians / Scottish[143]	1971	350/367	52.1	82.7	3.4 yr	Clofibrate 1.6 g or 2 g, placebo	Not available in the article (N = 5 strokes); secondary prevention trial
Fibrates: MA							
Zhou et al.[144] (MA)	2013	37,791	46–68 (range, means)	63–100 (range)	2.5–8.7 yr (range)	Fibrates	No association between fibrate intake and stroke risk; decrease in fatal stroke risk in patients with diabetes, cardiovascular disease, or stroke (RR (95%CI) = 0.49; 0.26, 0.93)
De Caterina et al.[7] (MA)	2010	39,890	45.9–68.2 (range, means)	—	2.5–6.2 yr (range)	Fibrates	No association between fibrate and stroke risk
Jun et al.[145] (MA)	2010	19,935	—	63–100 (range)	1.8–8.7 yr (range)	Fibrates	No association between fibrate intake and stroke risk (RR (95%CI) = 1.03; 0.91, 1.16)

(*continued*)

TABLE 13.2

(Continued)

Author/name of study	Year	*N*	Mean age, yr	Men, %	Mean follow-up duration	Treatment	Results
Niacin: RCT							
Guyton et al.[146]	2008	676/272	57	50	0.5 yr	Niacin 0.5–2 g + ezetimibe 10 mg + simvastatin 20 mg/ ezetimibe 10 mg + simvastatin 20 mg	OR (95%CI), 0.03 (0.00, 2.33); as reported in MA[149]
Whitney et al.[131]/AFREGS	2005	71/72	63	92	2.5 yr	Niacin 0.25–3 g + gemfibrozil 1.2 g + cholestyramine 2 g, placebo	Difference (percentage points) = 2.8 (–5.2 to 13.5); $p > .2$; OR (95%CI), 0.14 (0.01, 2.18); as reported in MA[149]
Taylor et al.[147]/ARBITER-2	2004	87/80	67	91	1.0 yr	Niacin 0.5–1.0 g + any statin, placebo + any statin	OR (95%CI), 0.12 (0.00, 6.27); as reported in MA[149]
Brown et al.[83]/HATS	2001	38/38	53	87	3.0 yr	Niacin 1–4 g + simvastatin 10–20 mg, placebo	OR (95%CI), 0.13 (0.01, 2.15); as reported in MA[149]
Carlson and Rosenhamer[148]/ STOCKHOLM	1988	279/276	60	80	5.0 yr	Niacin 3 g + clofibrate 2 g, usual care	OR (95%CI), 1.19 (0.36, 3.92); as reported in MA[149]
CDP[140]	1975	1119/2789	44	100	6.2 yr	Niacin 3 g, placebo	OR (95%CI), 0.75 (0.60, 0.94); as reported in MA[149]

Niacin: MA							
Bruckert et al.[149] (MA)	2010	6015	36–67 (range, means)	43–100 (range)	0.5–6.2 yr (range)	Niacin alone or in combination	26% (95%CI) (8–41%) reduction in stroke risk
HDL-C: MA							
De Caterina et al.[7] (MA)	2010	224,835	—	—	3.5 yr	—	No effect of HDL-C level change on stroke risk
TG: MA							
De Caterina et al.[7] (MA)	2010	243,875	—	—	3.5 yr	—	Inconsistent results
Labreuche et al.[30] (MA)	2010	96,807/98,681 placebo	34–72 (range, means)	0–100 (range)	1.0–6.2 yr (range)	—	No association with stroke incidence
TC: MA							
De Caterina et al.[7] (MA)	2010	266,973	—	—	3.5 yr	—	1% reduction in TC levels is associated with a 0.8% reduction in relative risk of stroke

[a] calculated by authors based on the information provided in the article; [b] according to raw data provided in [30]ACCORD: Action to Control Cardiovascular Risks in Diabetes; AFREGS, Armed Forces Regression Study; ARBITER-2, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2; BIP, Bezafibrate Infarction Prevention; CI, confidence interval; DAIS, Diabetes Atherosclerosis Invervention Study; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; HATS, HDL-Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; LEADER, Lowering Extremity Arterial Disease Event Reduction; MA, meta-analysis; mo, month; NR, not recorded; OR, odds ratio; RCT, randomized, controlled trial; RR, risk ratio; Stockholm CDP, Stockholm Coronary Drug Project; TC, total cholesterol; TG, triglyceride; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; yr, year.

Triglycerides

TGs are a complex lipid fraction, the levels of which vary considerably, and studies examining their association with stroke have yielded inconsistent results.[120]

A systematic review of epidemiological studies reported that high TG levels were associated with an increased risk of stroke (RR per 1 SD = 1.10; 95% CI, 1.07–1.13).[150] Similarly, in a large meta-analysis of RCTs (N = 195,488), a 10-mg/dL increase in baseline TG levels was associated with a significant increase in the risk of all strokes by 5.5%.[30] When focusing on ischemic stroke, a large meta-analysis of prospective studies carried out in individuals without coronary heart disease did not find any significant association between TG level and ischemic stroke (N = 302,430).[151] Interestingly, although TGs are generally measured in a fasting state, some studies found a significant association of higher nonfasting TG levels (but not fasting TG levels) with increased risk of stroke and ischemic stroke.[152] High levels of nonfasting triglycerides indicate the presence of increased levels of remnants from chylomicrons and very low-density lipoproteins; these may penetrate the arterial endothelium and promote the development of atherosclerosis. No clear differential association with ischemic stroke subtypes has emerged from two case–control studies comparing ischemic stroke patients with control subjects,[21,22] although one retrospective analysis conducted on 1049 patients with ischemic stroke or TIA reported that TG levels were associated with the large-artery disease subtype of ischemic stroke compared with other subtypes of ischemic stroke (OR = 2.69; 95% CI, 1.44–5.2; when comparing the highest TG quartile with the lowest).[153]

No strong association between reduction of TG levels through interventions and reduction of stroke risk has been shown.[135,144] A meta-analysis of RCTs reported inconsistent associations between change in TG levels and stroke reduction (70 RCTs, N = 243,875), although most of the tested multivariable models were in favor of a significant association between TG reduction and stroke risk reduction.[7] Another meta-analysis of RCTs did not report any association between TG change and stroke incidence (64 RCTs, n = 96,807 in the active group and n = 98,681 in the control group),[30] but did observe a trend for an association between TG lowering in fibrate and niacin trials and decreased risk of stroke[30] (Table 13.2).

When focusing on hemorrhagic stroke, large epidemiological studies revealed that low TG levels were a significant risk factor for incident ICH in several population-based studies, including in the 3C-Study (HR for TG ≤0.94 mmol/L = 2.35; 95% CI, 1.18–4.70; N = 8393),[154] and in a pooled analysis of the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) Study (relative rate for increasing TG = 0.45; 95% CI, 0.30–0.67; N = 21,680).[11] Similar nonsignificant associations were observed in other studies.[155–157] Of note, an earlier large meta-analysis of Asian prospective studies did not report any significant association between TG and the risk of hemorrhagic stroke (26 studies, N = 96,224).[158] In the SPARCL trial, there was no association between baseline TG level and risk of ICH in 4731 patients with previous stroke or TIA.[159]

High-Density Lipoprotein Cholesterol

A large systematic review of 18 studies on the relationship between HDL-C and risk of stroke found that 8 of 10 cohort studies and 3 of 8 case–control studies were in favor of an association between high HDL-C levels and decreased risk of stroke.[160] In prospective studies, an average increase of 10 mg/dL in HDL-C was associated with an 11% to 15% decrease in stroke risk.[160] When considering ischemic stroke, none of the 10 prospective cohort studies reported a significant association with HDL-C.[160] However, three of the eight case–control studies reported an inverse association between HDL-C levels and ischemic stroke, and two reported that increasing HDL-C levels were a significant risk factor for ischemic stroke.[160] There are more limited data and

a lack of consistency regarding associations of HDL-C with ischemic stroke subtypes. Increasing HDL-C was reported to be associated significantly with a reduced risk of SVD ischemic stroke (RR per SD = 0.62; 95% CI, 0.48–0.79)[161] and cardioembolic stroke (RR per SD = 0.65; 95% CI, 0.50–0.84)[161] in the ARIC study, a prospective, multicenter, population-based cohort study (N = 14,488). In a health maintenance organization-based case–control study from the Group Health Cooperative (N = 1555 stroke patients and 6455 control subjects),[129] the top quartile of HDL-C was reported to be associated significantly with a reduced risk of large-artery disease ischemic stroke (OR = 0.4; 95% CI, 0.2–0.7).[129]

Concerning hemorrhagic stroke, in a large systematic review of 18 studies, only limited data from one prospective cohort study and three case–control studies were available on the relationship between HDL-C and hemorrhagic stroke, none of which reported a significant association.[160]

A recent meta-analysis of 78 RCTs (N = 266,973), of which 49 tested the efficacy of statins and the remaining 33 tested various lipid-lowering drugs (13 on fibrates, 7 on dietary interventions, 12 on other drugs and 1 on partial ileal bypass surgery), reported no association of change in HDL-C levels with stroke risk (N =224,835) in a population comprising 3.4% of patients with a history of stroke and 27% of patients with a history of myocardial infarction.[7] (Table 13.2)

Others

ATHEROGENIC DYSLIPIDEMIA

Atherogenic dyslipidemia refers to the concomitant presence of low HDL-C (<40 mg/dL) and high TG levels, with exact thresholds varying across definitions for TG (>200 mg/dL or >150 mg/dL).[162] The definition may also include the presence of small and dense low-density lipoprotein particles.[163,164] Both low HDL-C and high TG levels have been associated with cardiovascular disease, but their combination might be even worse, by promoting a proinflammatory state and oxidative stress.[165,166] This condition is mostly seen in patients who are obese and have metabolic syndrome, insulin resistance, and type 2 diabetes.[167–169] In a cohort of 1471 patients with previous TIA or minor stroke, atherogenic dyslipidemia was associated significantly with a 4.8% increased risk of recurrent stroke after 90 days.[166] However, data are scarce and there are currently no specific therapeutic recommendations for this group.

NON-HDL CHOLESTEROL

Non-HDL-C corresponds to the measure of all atherogenic apolipoprotein B-containing lipoproteins, including LDL-C, very low-density lipoprotein, intermediate density lipoprotein, and lipoprotein a [Lp(a)].[170] It was reported to be associated with cardiovascular disease incidence and mortality in the general population,[151,171–173] and in individuals with diabetes. [174–176] A secondary analysis of the Cholesterol and Recurrent Events (CARE) trial, evaluating the effect of pravastatin in 2078 patients with myocardial infarction, revealed that baseline non-HDL-C was the only lipid marker that was associated significantly with the risk of incident stroke or TIA (HR = 1.76; 95% CI, 1.05–2.54).[177] Focusing on ischemic stroke, a large meta-analysis—carried out in 302,430 participants from prospective studies without known vascular disease—reported a significant association between non-HDL-C and ischemic stroke risk, but none with hemorrhagic stroke.[151] In a cohort of 1049 patients with ischemic stroke or TIA, the highest non-HDL-C levels were associated with the large-artery atherosclerotic subtype of ischemic stroke compared with all other subtypes (OR = 2.39; 95% CI, 1.40–4.11).[153] In summary, there are accumulating data suggesting an important role of non-HDL-C for the risk of stroke, but additional research is needed to characterize this relationship further and the impact of lipid-lowering therapy in patients with high non-HDL-C.

Lipoprotein(a)

Lp(a) is a low-density lipoproteinlike particle that contains apolipoprotein B-100 linked to the glycoprotein apolipoprotein(a) by a unique disulfide bond. It was reported that Lp(a) has atherogenic properties, possibly related to the plasminogenlike structure of apolipoprotein(a).[178–180] It has been known for a long time that Lp(a) is a risk factor for coronary heart disease and myocardial infarction,[181] which was largely confirmed by several subsequent meta-analyses.[182,183] A meta-analysis of 31 studies of fatal and nonfatal CVD (56,010 subjects, 4609 strokes) showed that high levels of Lp(a) are a risk factor for stroke when conducting a meta-analysis of 23 case–controls studies (N = 19,530, of which 2600 were strokes). The standardized mean difference was 0.39 (95% CI, 0.23–0.54) in studies using means and SD, and the OR was 2.39 (95% CI, 1.57–3.63) for studies using dichotomous values of Lp(a) (either considering the atherogenic threshold of 30 mg/dL or comparing the highest quintile vs. the lowest).[184] This was also the case when combining five prospective cohort studies (N = 37,098, with >1645 incident strokes): the RR was 1.22 (95% CI, 1.04–1.43) comparing the highest tertile of Lp(a) with the lowest one.[184] When considering stroke subtypes, increasing levels of Lp(a) were found to be associated with a significantly increased risk of ischemic stroke (RR = 1.11; 95% CI, 1.02–1.20; per 3.5-fold higher Lp(a) levels), but not hemorrhagic stroke (RR = 1.06; 95% CI, 0.90–1.26), in a large meta-analysis of prospective studies (1.3 million person-years at risk with 1903 incident ischemic strokes and 338 incident hemorrhagic strokes).[185] When focusing on ischemic stroke subtypes, in the ARIC study (N = 14,488), levels of Lp(a) greater than 174 μg/mL were a significant risk factor for nonlacunar stroke (RR = 1.42; 95% CI, 1.10–1.83; $p < .01$), but not for lacunar or cardioembolic subtypes.[161] In summary, available data suggest that high Lp(a) levels may increase the risk of stroke, particularly ischemic stroke, but there are currently no validated cutoffs to define abnormal levels of Lp(a) or intervention thresholds.

Drugs Aimed at Reducing Primarily Other Lipid Fractions than LDL-C

Several studies report that patients treated with lipid-lowering drugs (mostly statins) do not achieve normal lipid levels.[5,163,186] Therefore, other lipid-modifying drugs have received increasing attention, with the objective to reduce the residual risk defined as the presence of high TG levels or low HDL-C levels despite the lowering of LDL-C levels with statin therapy to provide additional vascular protection.[5,163,187]

Fibrates

Fibrates are agonists of the peroxisome proliferator receptor-α (PPAR-α), increasing the transcription of genes involved in cholesterol metabolism, including fatty acid binding proteins. These proteins increase lipolysis and induce fatty acid uptake by the liver, thus reducing TG production and increasing HDL-C production.[121,187–189] On average, fibrates are reported to reduce TC by 15% to 20%, TG by 32% to 45%, and LDL-C by 3% to 20%, and to increase HDL-C by 6% to 16% in patients with dyslipidemia.[121,190,191] In addition, fibrates were reported to have anti-inflammatory properties, which could confer vascular protection.[192] Fibrates were not associated significantly with stroke risk reduction in recent meta-analyses of RCTs[7,144] carried out respectively in populations comprising 3.4% of patients with a history of stroke and 27% of patients with a history of myocardial infarction,[7] and in patients with previous diabetes, cardiovascular disease, or stroke.[144,145] Noteworthy, in subgroup analyses, fibrate intake decreased significantly the risk of fatal stroke[144] (Table 13.2). In addition to statin therapy, fibrates were reported to be most beneficial for cardiovascular risk in patients with atherogenic dyslipidemia or high TG levels.[193]

Niacin

Niacin (or nicotinic acid) increases HDL-C levels by 30%, reduces TG and LDL by 20% on average,[162] and is the only available drug that modulates Lp(a).[149] A meta-analysis of 11 RCTs ($N = 6616$, mainly with a history of myocardial infarction or with established or suspected coronary heart disease) reported a significant 26% reduction in stroke risk in the treated group[149] (Table 13.2). However, two subsequent RCTs were negative. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized 3414 patients, of whom 720 had a history of stroke or CVD, to receive 1500 mg or 2000 mg niacin or placebo, and was interrupted prematurely because of the lack of benefit.[123] The Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial randomized 25,673 patients, of whom 8170 had a history of CVD or placebo, without significant benefit on the occurrence of major vascular events, and with various side effects, especially increased risk of myopathy in association with statins.[124,125]

Bile Acid Sequestrants

Bile acid sequestrants (e.g., cholestyramine) prevent bile acid reabsorption and reduce its recirculation to the liver, thus increasing transformation of cholesterol into bile acid through the LDL-C pathway, leading to a decrease in circulating LDL-C.[121] On average, bile acid sequestrants provide a decrease of 14% in TC and 21% in LDL-C, and a 3% increase in HDL-C and 2% to 5% in TG. It was suggested that bile acid sequestrants have a positive effect on clinical outcomes, but few studies have been carried out, and they have been restricted to coronary heart disease outcomes. Data concerning its effectiveness when associated with statins are lacking.[121] Moreover, they are not commonly prescribed because of numerous drug interactions and low patient tolerance, with mainly gastrointestinal side effects, leading to drug discontinuation.[121]

Other options were, until now, studied unsuccessfully because of major side effects. Other PPAR modulators that might help to reduce the residual risk associated with high TG levels in addition to LDL-C reduction belong to this category.[30,165,189] More specifically PPAR-γ agonists (the thiazolidinediones family, including rosiglitazone and pioglitazone), which were initially approved as antidiabetic treatments, were associated with an increased risk of congestive heart failure and myocardial infarction.[194,195] Cholesteryl ester transfer protein inhibitors, including torcetrapib, have been proposed to increase HDL-C levels.[30,196] However, torcetrapib—which raised HDL-C by approximately 70% and decreased LDL-C by approximately 24%—was associated with a paradoxical increase in major cardiovascular diseases and death of any cause, and increased blood pressure. [196,197] Moreover, the benefit of this molecule on atherosclerosis could not be established.[196,198,199] Other cholesteryl ester transfer protein inhibitors such as dalcetrapib or anacetrapib might be more promising, but their efficacy and safety remain to be proved.[196]

Dyslipidemia and MRI Markers of CVD

MRI markers of CVD, including MRI-defined WMHs, brain infarcts (BIs), and cerebral microbleeds (CMBs), are powerful predictors of stroke, both ischemic stroke and ICH.[200,201] These intermediate markers, which are mainly markers of SVD, are highly prevalent in the general population; more than 80% of community-dwelling adults have some degree of WMHs after 65 years of age, 8% to 28% have BIs in populations age 59 to 75 years on average, and 3.1% to 24.4% have some CMBs in populations age 52.9 to 60 years or more.[202–205] All these MRI markers of "covert" CVD predict an increased risk of stroke and dementia.[202,203,206,207] In this section, data are derived mainly from epidemiological studies and some post hoc analyses within RCTs.

EPIDEMIOLOGICAL STUDIES

MRI Markers of Ischemic CVD

LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Heterogeneous results have been published regarding the association of LDL-C with MRI markers of ischemic CVD, with positive associations being reported mostly in very small samples, which are therefore exposed to false discovery and publication biases. A small study in the general population reported LDL-C as a significant risk factor for deep WMHs ($N = 106$, $r = 0.24$, $p < .05$), but not for periventricular WMHs.[208] Two other small studies reported an association of LDL-C with BI, in the Seiryo Clin Study, a cohort of healthy Japanese men ($N = 324$; OR = 2.54; 95% CI, 1.03–6.27)[209] and in persons with essential hypertension (oxidized LDL subfraction, $n = 100$).[210] In the Leukoaraiosis and Disability (LADIS) study, carried out in nondisabled to mildly disabled elderly ($N = 396$) recruited in a hospital-based setting, no association between LDL-C and WMH progression or new lacunes was reported after 3 years of follow-up.[211] Similarly, in 349 volunteers free of neuropsychiatric disease age 50 to 70 years, from the Austrian Stroke Prevention Study (ASPS), LDL-C was not associated with MRI-defined ischemic CVD, a combination of deep WMHs and BIs.[212] LDL-C levels were associated inversely with worsening of WMH grade in 1919 community persons age 65 years or older from the CHS (OR = 0.81; 95% CI, 0.68–0.96),[213] but not with incident BIs after 5 years ($N = 1433$).[214] In line with these findings, recent analyses in the Three-City-Dijon (3C-Dijon) study and the Epidemiology of Vascular Aging (EVA) study—two large, prospective population-based studies in late-middle-age and older community persons—revealed a borderline significant inverse relationship between higher LDL-C levels and WMH volume ($N = 2608$; metaregression coefficient, -0.0243 ± 0.0122; $p = .047$), which was no longer significant after adjusting for other vascular risk factors, and there was no association between lacunar infarcts and LDL-C.[215]

Of note, in the CHS, statin intake was also associated with accelerated WMH progression (by one grade or more) in the group with severe WMHs at baseline (OR = 1.94; 95% CI, 1.06–3.58; $N = 538$),[213] and with a fourfold decrease in risk of silent infarct ($N = 1730$).[216] These results should be interpreted with caution, given the observational design.

Overall, available studies do not suggest a consistent association of LDL-C with MRI markers of ischemic CVD.

TOTAL CHOLESTEROL

A study reported a significant inverse association between hyperlipidemia (defined by hypercholesterolemia, hypertriglyceridemia, or use of lipid-lowering drugs) and WMH severity in 1135 acute ischemic stroke patients from two independent hospital-based cohorts, [217] which was confirmed by the LADIS study, reporting hypercholesterolemia as a significant protective factor against severe, age-related white matter changes (including BIs and WMHs) evaluated on MRI ($N = 639$; OR = 0.56; 95% CI, 0.34–0.94).[218] No association was observed between TC and WMH progression or new lacunes in the LADIS study.[211] In summary, data on the association of TC with MRI markers of ischemic CVD are scarce, but seem to be consistent with a trend toward an inverse association between LDL-C and MRI markers of ischemic CVD. Confirmation from large, population-based studies is lacking.

TRIGLYCERIDES

Several large, community-based studies have found significant associations of higher TG levels with larger WMH volume, although others have not confirmed this association. A study carried out in healthy Japanese volunteers reported a significant association of hypertriglyceridemia with larger WMH burden ($N = 1030$; OR = 1.94; 95% CI, 1.37–2.73),[219] as did the National

Heart, Lung, and Blood Institute Twin Study ($N = 1028$, $r = 0.22$, $p < .05$).[220] The LADIS study ($N = 396$) found an association of increasing TG levels with greater risk of new lacunar infarct (OR = 1.2; 95% CI, 1.0–1.5; $p < .05$), but not with WMH burden.[211] In the population-based 3C-Dijon and EVA studies ($N = 2608$), higher TG levels were associated with larger WMH volume (metaregression coefficient, = 0.0810 ± 0.0300; $p = .007$) and with lacunar infarcts (meta-OR = 1.54; 95% CI, 1.04–2.28; $p = .03$), after adjusting for vascular risk factors.[215] Increased inflammation,[221,222] as well as blood–brain barrier dysfunction, were suggested as possible explanations for these results.[223] Of note, other population-based studies (ASPS, $N = 349,119$; CHS, $N = 1,433,121$) did not report any significant association with WMH burden or BIs, respectively, but they were performed either on a smaller sample or did not focus specifically on lacunar BIs—a less heterogeneous phenotype than all BIs, which is believed to reflect mostly cerebral SVD. Hence, although a formal meta-analysis of published data is needed to draw a conclusion, data from several independent studies suggest an association of increasing TG levels with MRI markers of ischemic SVD.

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

Published results of associations between HDL-C and WMHs are heterogeneous. In the National Heart, Lung, and Blood Institute Twin Study, greater midlife HDL-C levels were associated with a lower WMH burden ($N = 514$, $r = -0.20$, $p < .05$).[220] In the LADIS study ($N = 396$), there was no association between HDL-C and WMH progression, but there was a significant inverse one with new lacunes (OR = 0.6; 95% CI, 0.5–0.8).[211] In contrast, in the CHS, increased late-life HDL-C was reported as a significant risk factor for WMH progression ($N = 1919$; OR = 1.24; 95% CI, 1.05–1.48).[213] In the ARIC study ($N = 14,488$), HDL-C was not associated with silent brain infarcts.[224] Similarly, in the 3C-Dijon and EVA studies ($N = 2608$), no association was found between HDL-C measured in late life and WMHs or lacunar infarcts.[215] In summary, large population-based studies in older individuals do not support a protective effect of high HDL-C on MRI-defined CVD. Additional data in younger and larger samples are needed.

MRI Marker of Hemorrhagic CVD (CMBs)

LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Available literature seems to agree on the absence of a relationship between LDL-C and CMBs. No association was observed in community participants age 55 years and older from the Rotterdam study.[225] Similarly, in a nested MRI substudy of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, an RCT designed to examine the effect of cholesterol-lowering therapy on vascular events, LDL-C was not associated with CMBs ($N = 439$).[226] Two small studies have examined the relation of LDL-C with CMBs in patients with ICH ($N \leq 163$). Both found no significant association,[227,228] but one of them described an association of statin intake with the presence and increased number of CMBs (OR = 2.72; 95% CI, 1.02–7.22), especially corticosubcortical CMBs, which are associated with cerebral amyloid angiopathy (OR = 4.15; 95% CI, 1.54–11.20); $N = 163$).[228] Again, caution is required in interpreting this finding, given the observational design of this study.

TOTAL CHOLESTEROL

In the Rotterdam study, a significant inverse association between higher TC levels and decreased risk of deep or infratentorial incident microbleeds (OR = 0.66; 95% CI, 0.44–0.98) was reported,[205] as well as an association between a TC level less than 4.42 mmol/L and risk of CMBs (OR = 2.01; 95% CI, 1.24–3.26; $N = 1062$).[229] In contrast, no association was found in the Framingham Heart Study

or in the nested MRI substudy of the PROSPER study.[211,215] A study carried out in 105 persons with ICH also did not reveal any significant associations between TC and CMB.[227] In a Korean study of 172 patients with stroke (n = 107) or other neurological diseases (n = 65), TC was a risk factor for CMBs (OR = 10.91; 95% CI, 3.98–25.57).[230] Overall, available data are inconsistent. Additional studies are needed to explore the relation of TC with CMBs overall and according to their lobar or deep location.

TRIGLYCERIDES

Literature reports on the association between TGs and CMBs is scarce and conflicting. The Rotterdam study reported a significant inverse relationship between high levels of TG and risk of deep or infratentorial CMBs (OR = 0.37; 95% CI, 0.14–0.96), but not for lobar CMB.[225] However, in the nested MRI substudy of the PROSPER trial, TGs were not associated with CMBs.[226] Similarly, a small study carried out in persons with ICH did not show any significant association between TG and CMB (N = 105).[227]

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

HDL-C was not associated with CMBs in the population-based Framingham Heart Study,[231] the Rotterdam study,[225] or the PROSPER study.[226] Similarly, a study carried out in persons with ICH did not show any significant associations between HDL-C and CMBs (N = 105).[227] In a Korean study of 172 patients with stroke (n = 107) or other neurological disease (n = 65), HDL-C levels greater than the 75th percentile (=1.47 mmol/L) were reported as a significant risk factor for CMBs (OR = 3.46; 95% CI, 1.45–8.29).[230] Hence, except for one small study in an high-risk Asian population, available studies seem to agree on the absence of a relationship between HDL-C and CMBs at the community level.

RCTs TESTING THE IMPACT OF LIPID-LOWERING DRUGS ON MRI MARKERS OF SVD

No trial to date has been designed specifically to test the impact of lipid-lowering drugs on MRI markers of CVD. However, post hoc ancillary studies of the Regression of Cerebral Artery Stenosis (ROCAS) and PROSPER trials have looked at the association of simvastatin and pravastatin intake on progression of ischemic lesions on brain MRI.

In the ROCAS trial (N = 208), which aimed at evaluating the impact of a 20-mg/day simvastatin intake on the progression of asymptomatic middle cerebral artery stenosis in stroke-free individuals, simvastatin intake was associated significantly with a reduced progression of WMHs in individuals who already had severe WMHs at baseline (regression coefficient, −0.214; p = .043),[232] and with less incident infarcts (N = 227; OR = 0.09; 95% CI, 0.01–0.82),[233] after 2 years of follow up. The PROSPER trial (N = 535) did not find a significant association between a 40-mg/day pravastatin intake and progression of ischemic lesion load after 3 years of follow-up.[234]

Given the lack of robust data from randomized trials, there are currently no available guidelines on how to manage dyslipidemia in individuals with MRI SVD.

Conclusions

Overall, despite inconsistent associations in epidemiological studies, there is strong evidence that lowering LDL-C reduces the risk of stroke—mainly, ischemic stroke. Despite a modest increase in a risk of ICH when lowering LDL-C, the overall benefit in terms of all-stroke prevention remains significant. Statins are currently the only drug recommended in primary and secondary stroke prevention, validated in large RCTs. The optimal therapeutic target (LDL-C

< 0.7 mmol/L vs. <1.0 mmol/L) is currently under evaluation. Their benefit is not demonstrated in patients with a history of ICH. Although there is mounting evidence for a residual risk of stroke associated with high TG levels and low HDL-C levels, it is currently unclear whether therapeutic interventions aiming at modifying TGs and HDL-C have a significant impact on the risk of stroke, and which drug category would be most appropriate. More trials are needed to address this important issue. Another area of uncertainty is the relation of lipid fractions with MRI markers of covert CVD, and whether lipid-lowering drugs should be prescribed in persons with such lesions and no history of clinical vascular disease. No consistent association has been described between most lipid fractions and MRI markers of CVD, although several studies seem to report an increased burden of ischemic SVD in individuals with high TG levels. Additional studies and meta-analyses of published results are needed to understand these associations more fully and to evaluate whether information of MRI markers of SVD should be incorporated in therapeutic algorithms for management of dyslipidemia to reduce the burden of CVD and cognitive decline at the population level.

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14

METABOLIC DYSFUNCTION AS A RISK FACTOR FOR STROKE

Obesity, Metabolic Syndrome, and Diabetes Mellitus

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Introduction

In this chapter, we discuss diabetes mellitus, metabolic syndrome, and obesity as they pertain to the development of ischemic and hemorrhagic stroke. We begin with an overview of these conditions, then their pathophysiology in relation to stroke, stroke risk and outcomes in persons with these disorders, and management decisions to decrease the risk of stroke. We do not discuss individually, other related stroke risk factors such as hypertension, dyslipidemia, and smoking.

DIABETES MELLITUS

Diabetes is a chronic disease characterized by ongoing hyperglycemia resulting from either glucose intolerance/peripheral resistance to insulin or insufficient levels of insulin. Its definition requires a fasting plasma glucose level of 126 mg/dL or more (≥7 mmol/L) or, according to the World Health Organization (WHO), impaired glucose tolerance as defined by a 2-hour postglucose load test level of 199 mg/dL or more (≥11 mmol/L). In addition, a glycated hemoglobin level of 6.5% or more also determines diabetes. These tests should be replicated at least once to confirm the diagnosis.[1,2] Diabetes is preceded by prediabetes—a prolonged, presymptomatic stage characterized by mild hyperglycemia, insulin resistance, and early decrease in insulin secretion. Prediabetes is determined by a fasting plasma glucose level of 100 to 125 mg/dL (5.6–6.9 mmol/L) or a glycated hemoglobin level of 5.7% to 6.4%.[2]

Type 1 Diabetes

Type 1 diabetes accounts for approximately 5% to 10% of all cases of diabetes and is accompanied by extensive long-term clinical complications, given its lifelong duration. Most cases of type 1 diabetes

are the result of a cell-mediated immune response against pancreatic β cells, leading to an absolute or near-absolute deficiency of insulin. Genetic susceptibility mediated mainly through human leukocyte antigen DR and DQ genotypes plays a role in its pathogenesis, as do environmental triggers that alter immune function, such as viral infections, environmental toxins, and exposure to certain foods early in life. A strong indication that environmental factors play an etiologic role in this disease is the observation that migrant populations carry the same incidence of type 1 diabetes as that of the local population.[3]

Type 2 Diabetes

Type 2 diabetes is caused by relative insulin deficiency resulting from impaired insulin production in addition to peripheral insulin resistance. Type 2 diabetes accounts for 90% of all cases of diabetes and has a strong genetic component. A family history of type 2 diabetes increases the risk of disease 2.4 times. Sedentary lifestyle, obesity, and overeating may also trigger disease onset; therefore, environmental factors are fundamental in the pathogenesis of this disease.[1] Type 2 diabetes is often associated with other metabolic abnormalities, including hypertension, dyslipidemia, and metabolic syndrome. Frequently, type 2 diabetes develops gradually over a prolonged period of time with nonspecific symptoms, thus leading to underdiagnosis of this condition.[1]

Metabolic Syndrome (Syndrome X or Insulin Resistance Syndrome)

Metabolic syndrome is comprised of a combination of disease states that lead to a significantly increased risk for cardiovascular disease, stroke, and diabetes. A recent consensus to define metabolic syndrome was determined using definition points from the WHO, the National Cholesterol Education Program's Adult Treatment Panel III, and the International Diabetes Federation. It includes three or more of the following: (a) central obesity (waist circumference ≥102 cm in men or ≥88 cm in women for white populations, or waist circumference ≥94 cm in men or ≥80 cm in women for nonwhite populations), (b) hypertriglyceridemia (triglycerides ≥150 mg/dL or medication use), (c) low high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men and <50 mg/dL in women or medication use), (d) hypertension (blood pressure [BP] ≥35/85 mmHg or antihypertensive use), and (e) a fasting plasma glucose level of 100 mg/dL or more, or medication use.[4] When three of these risk factors are present, the risk of cardiovascular disease and diabetes is increased 1.5 to 2 times. Insulin resistance, promoted mainly by excess free fatty acids and visceral obesity, is key in the role of metabolic syndrome as a risk factor for cardiovascular disease.[5]

Obesity

Obesity is a chronic pathological condition characterized by the accumulation of excess adipose tissue. It is associated with an increased risk of multiple morbidities and mortality. Obesity is a consequence of a neurochemical imbalance and can be defined operationally by the body mass index (BMI), which is a ratio of weight to height. Normal BMIs range from 18.5 to 24.9 kg/m^2, overweight BMIs range from 25 to 29.9 kg/m^2, and the obesity BMI is 30 kg/m^2 or more. Additional factors weigh into the relevance to health of an individual's weight status, such as age, stability of the BMI, activity level, and distribution of adiposity. Cardiovascular risk is increased with a higher BMI at an earlier age, an increasing BMI, low physical activity, and central adiposity as measured by the waist circumference. Obesity is associated with decreased life expectancy and a higher risk of mortality, diabetes, insulin resistance, and metabolic syndrome.[6]

Epidemiology

Diabetes and metabolic syndrome have become worldwide epidemics, with an impressive impact on cardiovascular disease burden and healthcare costs across the globe. Furthermore, these diseases, once considered mainly conditions of adulthood, have been seen progressively in children and teenagers as well, increasing the magnitude of the epidemic.

DIABETES MELLITUS

According to WHO, there are approximately 346 million people worldwide with diabetes (type 1 and type 2 combined). Diabetes has a very high impact on mortality; there were 3.4 million deaths in 2004 attributed to diabetes, of which 80% were in middle- to lower income nations.[7] A large systematic analysis of national heath surveys and epidemiological studies involving 370 country-years and 2.7 million participants showed an age-standardized prevalence of diabetes of 9.8% in men and 9.2% in women (yielding approximately 173 million affected persons worldwide of each sex), indicating an increase of nearly 194 million cases of diabetes from 1980 to 2008. The countries with the highest fasting plasma glucose levels and highest prevalence of diabetes were in Oceania, North Africa, the Middle East, and the Caribbean. Seventy percent of the additional cases of diabetes from 1980 to 2008 are the result of population growth and aging, and the remainder is a result of an increase in age-specific prevalence.[8] It is also estimated that many patients with diabetes are undiagnosed. In the United States, data from NHANES suggests that 2.2% of noninstitutionalized Americans have undiagnosed diabetes.[9]

The healthcare costs associated with diabetes are significant and, unfortunately, escalating. Persons with diabetes use two to three times more healthcare resources than persons without diabetes, which in some countries can amount to 15% of healthcare expenditures.[10] According to a statement from the American Diabetes Association, in 2007, U.S. healthcare costs attributed to diabetes were US$ 176 billion, of which US$ 116 billion were the result of excess medical expenditure (50% from hospitalizations) and US$ 58 billion were from reduced national productivity (US$ 27 billion from loss of lifetime productivity resulting from early mortality).[9]

Type 1 Diabetes

Type 1 diabetes is considered a disease of the young, with 50% to 60% of cases diagnosed before 16 to 18 years of age and, subsequently, continuing at low incidence rates through adulthood. Unfortunately, the global incidence of type 1 diabetes has also been increasing steadily at about 2% to 5%/year.[3] Based on a Swedish population study, the annual incidence rate of type 1 diabetes was reported to be 16.4/100,000 in men and 8.9/100,000 in women. The incidence decreased by 1%/year of increasing age.[11] These data underscore the known susceptibility to type 1 diabetes of postpubertal men compared with postpubertal women, also reported in other studies (with male-to-female ratios of 1.2–2.1). In addition, there also appears to be a seasonal variation in disease incidence, with a larger number of cases reported in autumn, winter, and early spring.[11]

Type 2 Diabetes

Estimates of the world prevalence of type 2 diabetes indicate approximately 141.9 million persons in the year 2000, corresponding to a crude prevalence of 3.8% of adults older than 20 years. It is estimated that in 2025, there will be 285.4 million persons with type 2 diabetes worldwide.[12]

Type 2 diabetes affects both sexes equally. It presents predominantly in middle and late life, with prevalence rates higher in patients older than 65 years. However, the proportion of middle-age

individuals with type 2 diabetes has increased in the United States during the past 20 years.[9,13] In the Framingham Heart Study, during a 30-year period there was a near doubling of the prevalence of type 2 diabetes in individuals age 40 to 55 years. Compared with the 1970s, the age- and sex-adjusted odds ratio for diabetes during the 1980s was 1.40 (95% confidence interval [CI] 0.89–2.22), and 2.05 (95% CI, 1.33–3.14) during the 1990s (p value for trend = .0006). Most of the persons who developed type 2 diabetes had BMIs greater than 30 kg/m^2, highlighting the importance of obesity and lifestyle in the disease pathogenesis.[14] Hispanics and blacks are at particularly high risk for type 2 diabetes.[9] It is estimated that the net number of people with diagnosed diabetes in the United States is growing by 1 million each year.[9] From 1988 to 2008 there has been an increase in the incidence of type 2 diabetes in Mexican Americans and other Hispanic populations in the United States, whereas the incidence has decreased in non-Hispanic whites. In 2008, the prevalence of diabetes in the United States was 6.1% for non-Latino whites, 11.6% for Mexican-Americans, and 12.6% for blacks. In addition, Hispanics and blacks with type 2 diabetes were 50% more likely to have worse glycemic control than non-Hispanic whites.[13] Native Americans are also at a very high risk for type 2 diabetes, with reported estimates of disease prevalence ranging from 47% to 73%.[15] Regarding control of vascular risk factors, 54% of persons with type 2 diabetes in the United States maintained poor control of two or more associated cardiovascular risk factors.[13]

METABOLIC SYNDROME

As with diabetes, metabolic syndrome is also becoming a worldwide epidemic, with great variation in prevalence in different countries and according to race. It appears to affect both sexes equally in whites, but women are affected more commonly among blacks and Hispanics.[16] As an example, reported prevalences in men vary from 8% in India to 39% in the United States; and in women, from 7% in France to 43% in Iran. The disease affects more Mexican-Americans than non-Hispanic whites. The prevalence also increases significantly with age, especially in the 60- to 69-year age group. Because the disease is linked directly to obesity, it is becoming more frequent in obese children and teenagers; its prevalence has been reported, in different populations, to affect up to 50% of severely obese children.[5,17]

OBESITY

Initially a disease of developed nations, obesity has become a worldwide epidemic affecting both adults and children.[18] In the United States, the prevalence of obesity was 16.9% in children and 35.5% among adult men and 35.8% among adult women in 2009/2010, according to data from NHANES.[6,19,20] Furthermore, more than two thirds of Americans are overweight or obese. Worldwide, 23.2% of adults are overweight and 9.8% are obese. It is projected there will be 1.35 billion overweight and 537 million obese adults worldwide in 2030.[21] More females are overweight than males at any given age, and obesity increases with age. Interestingly, obesity has increased more in younger than older women, whereas the reverse has occurred in men. Hispanics and blacks have a greater prevalence of obesity than whites.[6]

Pathophysiology of Metabolic Dysfunction and Stroke

DIABETES

Hyperglycemia may contribute to stroke and worsened stroke outcomes through various mechanisms. Hyperglycemia has been shown to be associated with larger infarcts in animal models. Similarly, in humans there is reduced penumbral salvage in acute stroke patients who are hyperglycemic on

admission.[22,23] Hyperglycemia may impair arterial recanalization via abnormalities in the coagulation cascade and impaired fibrinolysis, mediated through higher levels of PAI-1 and tissue-type plasminogen activator antigen. Furthermore, chronic hyperglycemia may lead to reduced efficacy of pharmacological fibrinolysis, abnormal blood flow patterns, and impaired vascular reactivity. Other potential mechanisms for worse stroke outcomes include increased reperfusion injury and increased risk of hemorrhagic complications after thrombolysis.[23] Diabetes is known to promote atherosclerosis in the cervical and coronary arteries. Furthermore, diabetes is associated with a 40% increased risk of atrial fibrillation.[24]

METABOLIC SYNDROME

The key aspect of metabolic syndrome, leading to its contribution to cardiovascular disease and stroke, is insulin resistance. The interplay between insulin resistance and obesity leads to the pathogenesis of metabolic syndrome, in which one condition contributes to the other in this complex disease state. Excess free fatty acids increase hepatic glucose production, modify downstream signaling of insulin metabolism, and inhibit insulin effectiveness in decreasing local glucose production. Furthermore, insulin is an important mediator of antilipolysis, which is impaired significantly in insulin resistance. In the setting of increased influx of free fatty acids to the liver, in obese individuals there is an increase in apolipoprotein B-containing, triglyceride-rich very low-density lipoprotein (LDL). Insulin resistance also furthers an increase in triglycerides by promoting hepatic synthesis and by decreasing the concentrations of lipoprotein lipase in the adipose tissues. These lead to additional changes to the lipid profile. In the presence of excess triglycerides, the composition of HDL is modified, and there is an increased clearance of circulating HDL, leading to lower levels of HDL. Similarly, LDL experiences changes to its structure in the presence of elevated levels of triglycerides with greater circulating levels of small, dense LDLs, felt to be more atherogenic than normal circulating LDL. Increasing and prolonged exposure to free fatty acids leads to decreased pancreatic insulin secretion. Insulin resistance also contributes to the development of hypertension—one of the components of metabolic syndrome. The mechanisms by which this occurs are related to the action of insulin as a vasodilator, which is lost in insulin resistance. Insulin also promotes sodium reabsorption and activates the sympathetic nervous system, both of which are still preserved in insulin resistance. Insulin resistance can also contribute to atherogenesis via other mechanisms, including its association with increased uric acid, fibrinogen, PAI-1, asymmetric dimethylarginine, homocysteine, proinflammatory cytokines, microalbuminuria, and obstructive sleep apnea.[5]

OBESITY AND NONOBESE PHENOTYPES

Adipose tissue has various functions in energy homeostasis, including glucose uptake and conversion, lipogenesis, lipolysis, and fatty acid oxidation. Adipocytes may contribute to cardiovascular disease and diabetes via the secretion of lipid and hormonal products termed *adipokines*, and by retaining toxic lipid species. Leptin is an adipokine excreted in proportion to the amount of adipocyte fat content. It acts on the hypothalamus by inhibiting food intake, increasing metabolic rate and energy expenditure, and regulating insulin and glucose homeostasis. Paradoxically, obese individuals have high levels of leptin and, as such, it is postulated that obesity leads to leptin resistance in the brain. Excess leptin decreases vasorelaxation and is linked to endothelial dysfunction.[25] Leptin has been shown to be associated independently with first-ever hemorrhagic stroke, and also with inflammatory markers, procoagulant factors, and insulin resistance.[26,27] Adiponectin, another adipokine, acts as an insulin sensitizer in the liver. It has anti-inflammatory effects and protects cardiac and pancreatic β cells. Its secretion by

adipose tissue decreases in obesity, especially in central obesity. Low adiponectin levels are associated with insulin resistance and hypertension.[25] Low adiponectin levels have been shown to be associated with stroke in case–control studies, but the same has not been observed in prospective cohort studies, although associations with diabetes, hyperglycemia, hypertension, and obesity were noted.[28–30] Adiponectin is associated with increased carotid intima media thickness, but not with carotid plaques, in healthy subjects.[31] Interleukin 6, also secreted by adipocytes, promotes insulin resistance by interfering with insulin receptor signal transduction.[32] Resistin regulates glucose homeostasis and insulin metabolism. It may dysregulate endothelial functioning and is implicated in atherosclerosis via endothelial inflammation. Resistin has been associated with ischemic stroke in postmenopausal women and is a predictor of composite outcomes of cerebral and cardiac events.[33,34]

Despite obesity's contribution to cardiovascular disease, as discussed in the section on metabolic syndrome, there are some circumstances in which it may have protective effects. An "obesity paradox" has been described in which obese subjects with cardiovascular disease may survive longer than nonobese control subjects with cardiovascular disease and stroke. The reasons for such a phenomenon are still unclear, but could be the expression of an epidemiological bias. As an example, obese patients may experience stroke subtypes associated with lower recurrence risk, obese patients may receive more aggressive therapy, or the paradox may reflect a survival bias in which patients who are obese and who have survived until their event have metabolically benign obesity.[35] Conversely, there are nonobese subjects who may have high-risk metabolic derangements. Described as *metabolically obese normal weight*, these subjects have hyperinsulinemia, insulin resistance, and hypertriglyceridemia, and are prone to develop diabetes. They may have a normal BMI but a high body fat content and are similarly subject to coronary disease and cardiovascular mortality.[36,37] Another group of patients termed *sarcopenic obese*, have a high body fat content in addition to low lean body mass, and display reduced cardiorespiratory fitness, physical function, and mobility, and experience premature mortality. With this condition, improved fitness levels lead to better cardiovascular outcomes.[38,39] Hemiparetic stroke may exacerbate the metabolic abnormalities of sarcopenic obesity, not only through reduced physical activity but also via changes in skeletal muscle constitution, leading to increased oxidative injury, inflammation, and insulin resistance. This finding may contribute to the very high prevalence (up to 75%) of insulin resistance and diabetes in stroke survivors.[35]

Stroke Risk

Insulin resistance—one of the underlying mechanisms of diabetes, metabolic syndrome, and obesity—has been shown to be an independent risk factor for stroke. Insulin resistance, as measured by plasma insulin concentrations or steady-state plasma glucose levels, carries a relative risk (RR) of ischemic stroke ranging from 1.5 to 2.1 for subjects without diabetes in the highest 20% to 25% of insulin resistance.[40]

DIABETES

Stroke risk has been shown consistently to be increased in subjects with diabetes. In a large meta-analysis of prospective studies involving nearly 700,000 subjects, the hazard ratio (HR) in persons with diabetes compared with control subjects was 2.24 (95% CI, 1.94–2.59) for ischemic stroke and 1.56 (95% CI, 1.19–2.05) for hemorrhagic stroke after adjusting for various cardiovascular risk factors. HRs were greater for younger subjects (HR = 3.74; 95% CI, 3.06–4.58) age 40 to 59 years, and for women compared with men (HR = 2.83; 95% CI, 2.35–3.40). The diabetes-attributable risk of

stroke was calculated at 12%.[41] The risk of ischemic stroke is higher in blacks compared with whites with diabetes, with the greatest risk occurring in younger blacks age 35 to 44 years.[42] In the Northern Manhattan Stroke Study, diabetes accounted for 10% and 14% of strokes in Hispanics and blacks, respectively.[43] Duration of diabetes is also important in determining ischemic stroke risk, which increases 3%/year and triples after 10 years of diabetes.[44] Interestingly, in the Northern Manhattan Stroke Study, the risk of stroke was increased only in subjects with fasting blood glucose levels of 126 mg/dL or more, thus suggesting that tight glucose control may ameliorate stroke risk.[45] Among persons with diabetes, microalbuminuria—measured using the albumin-to-creatinine ratio (normal range, 1–2.5 mg/mmol)—of more than 2.5 conferred twice the risk of a stroke compared with those without microalbuminuria.[46]

Differences have been noted in the stroke risk for subjects with type 1 diabetes compared to persons with type 2 diabetes. In the Nurses' Health Study, the RR for ischemic stroke in women age 30 to 55 years who were monitored for 24 years was 6.3 (95% CI, 4.0–9.8) for type 1 diabetes and 2.3 (95% CI, 2.0–2.6) for type 2 diabetes. The risk of hemorrhagic stroke was increased for type 1 diabetes (RR = 3.8; 95% CI, 1.2–11.8) but not for type 2 diabetes. Ischemic stroke subtype risks also varied and were greater for thrombotic, large-vessel, and lacunar stroke in type 1 diabetes (RRs= 6.4 [95% CI, 3.9–10.5], 7.2 [95% CI, 3.2–16.2], and 7.2 [95% CI, 3.2–16.1], respectively).[47] Another large epidemiological study noted that, among young ischemic stroke patients, those with diabetes were more likely to have small-vessel strokes compared with subjects without diabetes. Patients with type 1 diabetes had more associated coronary and peripheral arterial disease, whereas patients with type 2 diabetes were more commonly older and male, and had more associated obesity, peripheral arterial disease, transient ischemic attack, and stroke.[48]

Regarding stroke subtype, patients with type 2 diabetes are at greater risk for lacunar stroke. The ARIC study demonstrated this, showing a risk ratio for incident lacunar stroke of 3.23 after adjusting for multiple risk factors. Diabetes carried a population-attributable fraction of 26.3% for lacunar strokes. The same study also showed that the risk of cardioembolic stroke is elevated in persons with diabetes, with a risk ratio of 2.63 and a population-attributable fraction of 20.7% for cardioembolic stroke.[49] Furthermore, the ARIC study also demonstrated that very small lacunes (diameter, <3 mm) were associated with diabetes compared with larger lacunes.[50] Interestingly, an association between diabetes and atrial fibrillation has been observed in many studies, although the cause of this correlation remains unknown. A large meta-analysis involving approximately 1.6 million subjects showed that diabetes is associated with a 34% increased risk of atrial fibrillation, with a population-attributable risk of atrial fibrillation from diabetes of 2.5%.[24]

METABOLIC SYNDROME

Metabolic syndrome is associated with an increased risk for vascular events and stroke, with an HR for stroke ranging from 1.57 to 2.10.[51] Metabolic syndrome confers a greater stroke risk in women than in men (HR = 2.0; 95% CI, 1.3–3.1 vs. HR = 1.1; 95% CI, 0.6–1.9; respectively). This effect is likely the result of greater overall and central obesity in women compared with men.[52] Furthermore, stroke risk is greater in Hispanics (HR = 2.0; 95% CI, 1.2–3.4) compared with blacks and whites, and also in non-Hispanic blacks compared with non-Hispanic whites.[52,53] It is estimated that elimination of metabolic syndrome would result in a 19% reduction in stroke overall, a 30% reduction of stroke in women, and a 35% reduction of stroke among Hispanics.[52] Metabolic syndrome contributes to cardiovascular and stroke risk in an additive fashion, according to the number of its components.[54,55] However, even after adjusting for these individual components, metabolic syndrome itself is an independent risk factor for stroke.[56,57] It is felt that obesity is the key component of this syndrome that confers stroke risk. Considering stroke subtypes, metabolic syndrome appears to be

associated more strongly with intracranial rather than extracranial atherosclerosis.[58] Increased silent brain infarcts and white matter hyperintensities have also been reported in older subjects with metabolic syndrome.[59]

OBESITY

Obesity has been established as a risk factor for stroke. When using BMI for the determination of obesity, men with a BMI of 30 kg/m^2 or more have double the risk of stroke compared with men with a BMI less than 23 kg/m^2. For each unit increase in BMI, there is a 6% increase in stroke risk (RR = 6%; 95% CI, 4–8).[60] Using the waist-to-hip ratio definition of obesity, those in the highest tertile of WHR have a 65% increased risk of stroke compared with those in the lowest tertile. The population-attributable risk of stroke resulting from increased waist-to-hip ratio is 26.5%.[61] In women, each unit increase of waist circumference is associated with a 2% increased stroke risk.[62] Regarding specific stroke subtypes, overweight and obesity are associated with ischemic stroke; in a large meta-analysis, individuals who were overweight and obese had an increased risk for ischemic stroke of 22% and 64%, respectively, compared with normal-weight individuals. This did not differ according to sex or degree of hypertension, but these findings were more significant in Europeans and North Americans than in Asians. Hemorrhagic stroke, however, was associated weakly with overweight status, and approached statistical significance only for obese subjects compared with normal-weight individuals (RR = 1.24; 95% CI, 0.99–1.54; $p = .059$).[63]

Short- and Long-Term Stroke Outcomes

DIABETES

Diabetes contributes to mortality after stroke. Reports vary regarding the timing of mortality in patients with diabetes with stroke, but most studies do not report an increased mortality during the first 3 months after stroke in persons with diabetes compared with others, although persons with diabetes had longer hospital stays. However, mortality is slightly increased 1 year poststroke (HR = 1.2; 95% CI, 1.1–1.2).[64] Over 10 years, both type 1 and type 2 diabetes are strong predictors of all-cause mortality, with cumulative risks of 33.5% (95% CI, 17–50%) and 25.4% (95% CI, 13.1–37.7%), respectively.[48] Stroke patients with diabetes also have worse functional outcomes than patients without; they were less able to ambulate at discharge and were more likely to be discharged to a skilled nursing facility or to inpatient acute rehabilitation. Diabetes was also observed to be an independent risk factor for worse health-related quality of life 1 year poststroke.[64,65]

Diabetes also affects patient outcomes after stroke negatively. It is unclear whether this is a result of diabetes being a marker of systemic illness or the effects of persistent hyperglycemia.[40] Part of the increased morbidity in stroke patients with diabetes may be explained by the effects of diabetes on cognition. In children, early-onset diabetes has been associated with worse cognitive outcomes, which persist through adulthood.[66] This is likely a result of the adverse effects of metabolic abnormalities on the developing brain. Adults who develop type 2 diabetes later in life also have more cognitive impairment compared with adults without diabetes. The cognitive domains involved are mainly psychomotor efficiency, executive function, learning, and memory. The risks for Alzheimer's disease (RR = 1.5–2.0) and vascular dementia (RR = 2.0–2.5) are increased in individuals with diabetes. Thus, diabetes could have an attributable risk for dementia of 7% to 13%.[66] Older adults with diabetes also have more pronounced brain atrophy, lacunar infarcts, and a modest increase in white matter hyperintensity volumes.[66]

Diabetes is a strong predictor of recurrent stroke, with 9.1% (95% CI, –2.0 to 20.2) of recurrences attributable to diabetes.[67] This risk seems to be even greater in patients younger than 50 years old.[48]

METABOLIC SYNDROME

Metabolic syndrome is associated with poor outcome after cardiovascular disease, with increased cardiovascular mortality (RR = 2.40; 95% CI, 1.87–3.08) and all-cause mortality (RR = 1.58; 95% CI, 1.39–1.78).[68] It has also been associated with cognitive impairment and increased risk of dementia, primarily in elderly subjects with high levels of inflammation.[69] Multiple cognitive domains can be affected, including executive function, memory, visuospatial function, processing speed, and global intellectual functioning.[59] Some of the individual components of metabolic syndrome, such as hypertension, have been shown to contribute individually to the risk of mild cognitive impairment and dementia. Furthermore, the longer the exposure to these components of metabolic syndrome, the greater the risk of developing mild cognitive impairment or dementia later in life. There is no clear evidence that treatment of metabolic syndrome yields significant reductions in the risk of cognitive impairment.[70]

OBESITY

Obesity is also an independent predictor of poor outcome after stroke. BMI predicts mortality from stroke with a 40% increased risk of vascular death for each 5-kg/m^2 increase in BMI.[71] Obesity has also been shown to affect cognition even at an early age, with deficits in executive functioning, attention, and intelligence quotient in children who are obese.[59]

Management and Impact on Stroke

DIABETES MELLITUS

Lifestyle Modifications

Persons with diabetes who have potentially modifiable associated cardiovascular risk factors such as smoking, obesity, inactivity, excessive alcohol intake, and unhealthy diet should be counseled on smoking and alcohol cessation, and adherence to a heart-healthy diet and exercise program/weight loss. One study that addressed specifically the issue of risk factor modification in more than 2000 Japanese men and women with type 2 diabetes showed a significantly decreased incidence of stroke when adhering to lifestyle modification recommendations in addition to receiving usual medical care compared with usual medical care alone (HR = 0.62; 95% CI, 0.39–0.98; p = .04).[72] However, conflicting results have come from the Look Action for Health in Diabetes research group. These investigators reported initially that persons with type 2 diabetes receiving intensive lifestyle interventions were able to achieve 5% to 10% weight loss with exercise and caloric-goal diet modification. Compared with the routine care group, the intervention group had significant improvements in cardiovascular disease risk factors after 1 year.[73] However, after a median follow-up of 9.6 years, the Look Action for Health in Diabetes Trial was stopped early on the basis of futility because the primary outcome (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina) was similar in both groups despite sustained greater weight loss and greater reductions in glycated hemoglobin (HbA1c) levels in the intervention group (HR = 0.95; 95% CI, 0.83–1.09; p = .51). There was also no significant reduction in the risk of stroke with the intervention (HR = 1.05; 95% CI, 0.77–1.42; p = .78). The authors postulated that the lack of significant differences in outcomes could be the result of more aggressive management of diabetes in the control group and improved risk factor modification in these patients. In addition, there was reduced use of cardioprotective drugs in the intervention group, and the effect of the intervention on weight loss and all other cardiovascular risk factors decreased after the first few years of the study.[74,75] Further studies may be warranted to verify these findings.

Glucose-Lowering Treatments

Intensive versus standard glucose-lowering therapies in diabetes has been the subject of several trials. The United Kingdom Prospective Diabetes Study (UKPDS) group randomized newly diagnosed patients with type 2 diabetes to conventional diabetic management with dietary restriction alone versus intensive glucose-lowering therapy with sulfonylureas or insulin, or metformin in patients with diabetes who were overweight. After 10 years there were no significant differences in HbA1c levels among groups. However, patients with diabetes on sulfonylurea–insulin or metformin had significant risk reductions for any diabetes-related end point, myocardial infarction, and death from any cause compared with the standard-therapy group. In addition, in the sulfonylurea–insulin group there was a significant reduction in the rate of microvascular disease.[76] Converse results were seen in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which included patients with diabetes with longstanding disease who were at high risk for a cerebrovascular disease-related event and a median HbA1c level of 8.1%. Participants were randomized to intensive glucose-lowering therapy (goal HbA1c level, <6.0%) or standard therapy (target HbA1c level, 7%–7.9%). After 3.5 years, there was no difference in the two groups in the risk of a composite end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, but there was a significantly greater risk of death in the intensive-therapy group (HR = 1.22; 95% CI, 1.01–1.46; $p = .04$). In addition, there were significantly higher rates of hypoglycemia and weight gain in the intensive-therapy group. The intensive therapy was stopped prematurely because of the higher death rate, and participants in that arm were transitioned to the standard-therapy protocol; the other interventions embedded in the glycemia trial were continued to the planned end. Reasons for the higher mortality rate remain unclear. There were no differences in the risk of stroke between groups.[77] A large meta-analysis of studies of intensive glucose-lowering therapies in type 2 diabetes concluded that the benefit-to-risk ratio for preventing macrovascular and microvascular events remained inconclusive, and the harm associated with hypoglycemia could offset the benefits of therapy. There was no reduction in the rates of all strokes or nonfatal strokes with intensive glucose-lowering therapy.[78]

For patients with type 1 diabetes, intensive glucose-lowering therapy (i.e., three or more daily insulin injections or insulin pump, four or more daily measurements for goal glucose levels of 70–120 mg/dL premeal or <180 mg/dL postmeal, and a goal HbA1c level of <6.05%) compared with conventional therapy (management of hypo-/hyperglycemia and one to two daily injections of insulin) had beneficial effects. After 6.5 years of treatment and 17 years of follow-up, intensive therapy reduced the risk of any cardiovascular event by 42% and risk of nonfatal myocardial infarction, stroke, or cardiovascular death by 57% (both, $p = .02$). Reductions in HbA1c values were associated with the positive effects on reduction of cardiovascular disease. There were very few strokes in both groups to draw conclusions regarding therapy and risk of stroke in type 1 patients with diabetes.[79]

Antihypertensive Treatment

Hypertension has a prevalence of 40% to 60% in patients with diabetes. It increases the risk of cardiovascular complications associated with the disease and promotes microalbuminuria and retinopathy. In the UKPDS, treatment of patients with hypertension with diabetes with an angiotensin-converting enzyme inhibitor or a beta blocker with goal BP of less than 150/85 mmHg reduced substantially the risk of death and complications resulting from diabetes and led to a 44% reduction in the risk of stroke (95% CI, 11–65; $p = .013$).[80] In the ACCORD study, an intensive BP therapeutic trial was embedded in the glycemic trial and showed that decreasing BP further in patients with diabetes to the goal systolic BP of less than 120 mmHg compared with less than 140 mmHg was not associated with reduced risk of fatal or nonfatal cardiovascular events, but did confer a significant risk reduction for stroke (HR = 0.59; 95% CI, 0.39–0.89; $p = .01$). However, this was at the expense of a significantly

greater risk of serious adverse events ($p < .001$).[81] A recent meta-analysis concluded that a target systolic BP of 130 to 135 mmHg in patients with type 2 diabetes is acceptable, but that lowering BP further confers no benefit for macrovascular complications other than stroke, and it increases the risk of serious adverse events to 40%.[82] In the LIFE study, losartan was compared with atenolol in patients with diabetes with hypertension and left ventricular hypertrophy. Compared with atenolol, losartan use was associated with a significant decrease in the risk of cardiovascular morbidity and mortality (RR = 0.76; 95% CI, 0.58–0.98; $p = .031$) as well as all-cause mortality, independent of the level of BP control obtained. However, there was no difference in the risk of all-fatal or nonfatal strokes (HR = 0.79; 95% CI, 0.55–1.14; $p = .20$).[83] An alternative approach was sought in the ADVANCE study, in which patients with type 2 diabetes with known cardiovascular disease or cardiovascular risk factors were randomized to combination angiotensin-converting enzyme inhibitor and diuretic (perindopril plus indapamide) or to placebo regardless of baseline BP or use of other antihypertensives. Patients with diabetes on combination therapy had a 9% RR reduction of macrovascular or microvascular complications (HR = 0.91; 95% CI, 0.83–1.00; $p = .04$), and an 18% RR reduction of cardiovascular death (HR = 0.82; 95% CI, 0.68–0.98; $p = .03$). There was no significant effect on the risk of stroke.[84] Unfortunately, the benefits of antihypertensive therapy in patients with type 2 diabetes for reduction of all macrovascular complications, including stroke, were not sustained after 10 years in the UKPDS when between-group differences in BP were lost. Thus, good BP control is necessary to maintain the benefits of antihypertensives in patients with type 2 diabetes.[85]

Lipid-Lowering Therapies

Patients with diabetes commonly have high levels of triglycerides and low levels of HDL, although total cholesterol and LDL levels may not, necessarily, be elevated significantly. The Heart Protection Study aimed to test whether simvastatin could reduce the risk of cardiovascular disease and stroke in patients with diabetes. In this study, 5963 patients with type 1 and type 2 diabetes were allocated randomly to simvastatin 40 mg daily or placebo. Patients receiving simvastatin had a significant 22% rate reduction in cardiovascular events (95% CI, 13–30; $p < .0001$) compared with placebo, and this was present even in the absence of known arterial occlusive disease or with a baseline LDL level of less than 116 mg/dL. Furthermore, the risk of a first fatal or nonfatal stroke was reduced by 24% (95% CI, 6–39; $p = .01$) in the simvastatin group compared with placebo. This reduction was mainly the result of a 28% reduction in ischemic stroke and no difference in hemorrhagic stroke risk. The study authors concluded that statin therapy should be offered to all patients with diabetes at significant risk of cardiovascular disease regardless of their initial lipid profile.[86] Similarly, in the Collaborative Atorvastatin Diabetes Study, atorvastatin 10 mg daily was compared with placebo for primary prevention of cardiovascular disease in patients with diabetes with LDL levels of 75 mg/dL or less, triglyceride levels of 122 mg/dL or less, and hypertension, smoking, or signs of microvascular disease. There was a 37% rate reduction in cardiovascular events (95% CI, −52 to −17; $p = .001$) and a 48% reduction in the rate of stroke (95% CI, −69 to −11; $p = .001$) in the atorvastatin arm compared with placebo.[87] Additional studies explored fibrates, which increase HDL, for the reduction of cardiovascular disease. Compared with placebo, fenofibrate 200 mg daily did not lead to a significant reduction in cardiovascular events in patients with type 2 diabetes with normal total cholesterol and triglyceride levels. There was also no significant reduction in the rate of stroke with fenofibrate therapy.[88] Furthermore, in ACCORD, the combination of fenofibrate and simvastatin did not reduce significantly the rate of cardiovascular disease or stroke when compared with simvastatin plus placebo.[89]

Antithrombotics

The use of antithrombotics for the primary prevention of cardiovascular disease in patients with diabetes has been the subject of a Japanese randomized controlled trial. In that study, the use of aspirin

(ASA) 81 TO 100 mg daily in patients with type 2 diabetes did not reduce the risk of cardiovascular disease, cardiovascular death, transient ischemic attack, fatal stroke, and nonfatal ischemic stroke (HR = 0.93; 95% CI, 0.52–1.66; $p = .80$) after a median 4.4 years of follow-up.[90] A large meta-analysis explored this issue further and also found no benefit for the use of aspirin for primary prevention of stroke in patients with diabetes.[91] In an antithrombotic trialist's collaboration, secondary prevention of cardiovascular events was assessed in patients receiving antithrombotic medication. In patients with diabetes, there was a reduction of cardiovascular events (including ischemic stroke) similar to that observed in patients without diabetes. Despite the relatively low risk reduction obtained, antiplatelets are still recommended for secondary prevention of cardiovascular disease and stroke in patients with diabetes.[92]

Diabetes is also a risk factor for atrial fibrillation. As such, patients with diabetes with atrial fibrillation should be either on full-dose anticoagulation or antiplatelet therapy, according to their CHA_2DS_2-VAS score, for primary or secondary stroke prevention.[93]

Summary Management Recommendations

The American Diabetes Association recommends screening for diabetes in the following situation: age more than 45 years, or earlier in subjects with additional cardiovascular risk factors. Most important, for subjects with sustained BP greater than 135/80 mmHg, screening is advocated for asymptomatic patients because the targets for BP control change after a diagnosis of diabetes is made.[2] American Diabetes Association management guidelines recommend a goal HBA1c of less than 7.0%, a goal BP of less than 130/80 mmHg, and a goal LDL level of less than 100 mg/dL.[94] Similarly, the National Cholesterol Education Program's Adult Treatment Panel III guidelines suggest a goal total cholesterol of less than 200 mg/dL and an LDL level of less than 100 mg/ dL.[95]

OBESITY

Weight loss is recommended for all overweight or obese people with or without diabetes, with the use of low-carbohydrate, low-fat, calorie-restricted, or Mediterranean diets. In addition, given the risk associated with sarcopenic obesity, behavioral management and physical activity are recommended.[96] A lifestyle modification program that aims at diet modification, exercise, and weight loss prevented the development of type 2 diabetes in obese subjects with glucose intolerance over a follow-up period of 3.2 years.[97] A similar study showed that both lifestyle interventions and metformin use are effective in the prevention of type 2 diabetes, with numbers needed to treat of 6.9/3 years and 13.9/3 years, respectively.[98] Unfortunately, there are no studies to date addressing the issue of weight loss and its impact on stroke risk in purely obese subjects. However, given the linear increase in stroke risk with increases in BMI, it is reasonable to aim for a goal BMI of 22 to 25 kg/m^2.[35]

Guidelines usually recommend an initial weight loss of 5% to 10% of body weight. More can be recommended if the patient is willing, especially if there are abnormal cardiovascular parameters. To achieve weight loss, counseling is recommended initially, with best results obtained from multidisciplinary programs with lifestyle coaching, one-on-one programs with physical activity recommendations, and prepared meals.[99,100] Moderate aerobic physical activity at least five times per week is generally recommended for all adults age 18 to 65 years, but it usually does not result in a significant weight loss as does dietary modification.[101] Medications can be given to help promote weight loss as second-line therapy after diet, exercise, and behavioral modification. As a last option, bariatric surgery (adjustable gastric banding or roux-en-Y gastric bypass) has been shown in clinical trials to promote significant weight loss (up to 21% of body mass), remission of diabetes in up to 75% of subjects, reduction in BP and vascular inflammation, and improved quality of life.[35]

METABOLIC SYNDROME

Metabolic syndrome carries a high risk for cardiovascular disease and type 2 diabetes. These risks can be short-term or may occur over the longer term (>10 years). Thus, all subjects with metabolic syndrome should undergo 10-year risk assessment (e.g., with the Framingham Risk Score) for evaluation of their cardiovascular risk and potential need for pharmacotherapy.[5]

The primary goal in the treatment of metabolic syndrome is to address its modifiable risk factors and thus delay the onset of diabetes and complications of atherogenic dyslipidemia. As with obesity, behavioral approaches should be initiated to promote behavioral modifications aimed at weight loss (goal, loss of 7%–10% body mass in 1 year). Dietary modifications should include low intake of saturated fats, transfats, cholesterol, and simple sugars; and an increased intake of fruits, vegetables, and whole grains.[5] Physical inactivity should be addressed as well, because sustained physical activity improves all the risk factors comprising metabolic syndrome. In subjects in whom atherogenic cardiovascular disease or diabetes are present, pharmacological therapy should be initiated to address each of the components of metabolic syndrome, as discussed in the section on therapy for diabetes. In the treatment of atherogenic dyslipidemia, statins should be used initially to reach the goal LDL. Only thereafter should other therapies (fenofibrates, niacin) be added to address low HDL and elevated triglyceride levels. Antithrombotics are also recommended in metabolic syndrome to counter the associated hypercoagulable state.[5,51]

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15

LIFESTYLE FACTORS AND THE RISK OF STROKE

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Introduction

There are several risk factors for stroke that involve our everyday health choices and the environment that surrounds us, and the objective of this chapter is to review several of these lifestyle risk factors for stroke. We briefly highlight data on the effect that factors such as smoking, alcohol consumption, dietary habits, physical activity, obstructive sleep apnea, exposure to air pollution and use of illicit substances may have in increasing or reducing the risk of stroke. Because these relationships are heterogeneous, we attempt to describe how they differ by gender, age groups and stroke subtypes, as well as the potential biological mechanisms explaining these associations.

Smoking

The various adverse health effects of cigarette smoking are well recognized, and one of these is an increased risk of stroke. Consistent results across populations of diverse origins have shown smoking to be an independent risk factor for all types of strokes.

The Framingham Heart Study was one of the first epidemiological studies to explore this link.[1] In their study, Wolf et al. showed not only that smoking was associated independently with the risk of stroke over 26 years of follow-up (with a hazard ratio [HR] = 1.6 in women and HR = 1.4 in men), but also that the risk increased in a dose-dependent manner. Heavy smokers consuming more than 40 cigarettes per day had a twofold increased risk of stroke compared with light smokers consuming less than 10 cigarettes per day. Furthermore, the study estimated that, 5 years after smoking cessation, former smokers experienced the same risk of stroke as nonsmokers.

Multiple studies have since noted similar findings in other populations. In the MONICA Risk, Genetics, Archiving and Monograph Project, which included 18 populations in eight European

countries,[2] it was estimated that smoking doubled the risk of stroke (HR = 2.0 in women and HR = 1.8 in men) during a follow-up of about 13 years. The Strong Heart Study[3] found that current (HR = 2.4) and previous smoking (HR = 1.6) were each related to an increased risk of stroke compared with never-smokers in 4549 participants belonging to 13 Native American tribes. There have also been several large studies conducted in Asian populations. In the Japan Public Health Center—which studied 19,782 men and 21,500 women age 40 to 59 years who were free of prior diagnosis of stroke, coronary heart disease, or cancer and were monitored for up to 11 years—smokers had a 30% greater risk of all strokes compared with nonsmokers, smoking increased the risk for most stroke subtypes (except intracerebral hemorrhage), and a dose-dependent relationship was again noted.[4] Similarly, the risk of stroke increased in a dose-dependent relationship in a representative sample of 169,871 Chinese women and men smoking 1 to 19 cigarettes per day (HR = 1.21) versus more than 20 cigarettes per day (HR = 1.40)[5] when each group was compared with nonsmokers. Last, the Asia Pacific Cohort Studies Collaboration, which included 40 studies from the Asian-Pacific region,[6] estimated the risk of stroke to be 40% greater among current smokers compared with never-smokers, also displaying a dose-dependent relationship association between the number of cigarettes smoked and an increased risk of stroke.

In high-income countries, the recent decrease in stroke mortality noted is, in part, attributed to a lower prevalence of smoking.[7] Worldwide, the number of new smokers is increasing faster in low- and middle-income countries than in high-income countries, and among women compared with men,[8,9] although smokers are still more likely to be men than women. Smoking rates are projected to peak among women from low- to middle-income countries during the next few years,[10, 11] and therefore it is important to assess whether the harmful effects of cigarette smoking might differ between genders as they do for some other cardiovascular risk factors. The excess risk of stroke attributable to cigarette smoking, however, does not seem to differ between women and men. These findings have been summarized in a meta-analysis that pooled results from 81 cohort studies.[12] No differences were found between women and men when comparing the risk of stroke, regardless of stroke subtype, among current smokers versus nonsmokers or never-smokers. Further exploration of the dose-dependent association and the beneficial effects of smoking cessation on the risk of stroke did not differ, either, among the sexes. The only estimate that differed was that of women who currently smoke compared with female nonsmokers, showing a 17% increased risk of total hemorrhagic stroke compared with men, in whom the risk of hemorrhagic stroke was not significantly greater in current smokers compared with nonsmokers.

Concerning stroke subtypes, results from several studies have established the role of cigarette smoking as a risk factor for ischemic stroke and subarachnoid hemorrhage; nevertheless, the findings have been less consistent for intracerebral hemorrhage.[13–15] In the Japan Public Health Center study discussed earlier,[4] multivariate relative risks (RR; 95% confidence intervals [CIs]) for current smokers compared with never-smokers after adjustment for cardiovascular risk factors were 1.27 (95% CI, 1.05–1.54) for total stroke, 1.66 (95% CI, 1.25–2.20) for ischemic stroke, 0.72 (95% CI, 0.49–1.07) for intracerebral hemorrhage, and 3.60 (95% CI, 1.62–8.01) for subarachnoid hemorrhage. The respective multivariate RRs among women were 1.98 (95% CI, 1.42–2.77), 1.57 (95% CI, 0.86–2.87), 1.53 (95% CI, 0.86–4.25), and 2.70 (95% CI, 1.45–5.02).

There are several established biological mechanisms that link smoking and stroke. Exposure to cigarette smoking has been shown to promote arterial wall damage and progression of atherosclerotic disease,[16] increase fibrinogen levels,[17] elevate blood pressure and induce vasoconstriction,[18] all of which can increase the risk of an ischemic stroke. Cigarette smoking has also been shown to be a risk factor for the formation, growth, and rupture of intracranial aneurysms,[19–21] which constitute a primary cause of subarachnoid hemorrhage. Increased blood pressure[18] and vascular wall damage[16] caused by smoking could also contribute to intracerebral hemorrhage.

It should be acknowledged that not only are smokers at an increased risk of stroke, but also those exposed to second-hand smoke experience similar harmful effects. In a pooled analysis including 20 studies from across the United States, Asia, and the United Kingdom, a 25% increased risk of stroke was observed among nonsmokers exposed to second-hand smoke compared with nonexposed individuals. Furthermore, the study showed a dose-dependent relationship, in which individuals exposed to 5, 10, 15, and 40 cigarettes per day had an increased risk of stroke of 16%, 31%, 45%, and 56%, respectively, compared with those not exposed to second-hand smoke.[22]

The reduction in the risk of stroke seen after 5 years of smoking cessation is encouraging, and governments are urged to reinforce public policies to reduce the prevalence of smoking among societies through education, taxation, regulation, and other means; to reinforce preventive strategies targeted at children and young adults (most smokers start smoking in their teens or 20s); and to encourage smokers to stop smoking, including providing them with the incentives and the medical, societal, and psychological support to quit.

Alcohol Consumption

The effects of alcohol consumption on the risk of stroke are less straightforward than those seen for smokers. Heavy drinking has been recognized as a major risk factor for the risk for both ischemic and hemorrhagic stroke; however, the effects of light drinking seem to differ depending on the stroke subtype.

The definition of the amount of alcohol intake varies from one study to the other and according to geographic regions. Broadly, light drinking has been set to a consumption of less than one to two drinks per day (or the equivalent of about 12–24 g/day) whereas heavy drinking is considered to be the intake of more than five drinks per day (or, equivalently, about 60 g/day).[23]

There seems to be a linear, dose-dependent relationship between the amount of alcohol intake and the risk of hemorrhagic stroke.[24] The Honolulu Heart Program was one of the first cohorts to report this association in men, in whom the risk of hemorrhagic stroke doubled in light and moderate drinkers, and tripled in heavy drinkers compared with nondrinkers.[25] A recent meta-analysis suggests, however, that the shape of this relationship might be J shaped for women, in whom light drinking could confer a protective effect for nonfatal hemorrhagic stroke.[26] The aggravating effects of alcohol drinking for hemorrhagic stroke have been attributed to alcohol-induced hypertension,[27] and alterations in homeostatic function leading to impaired fibrinolytic potential[28] that may promote the rupture of aneurysms or small vessels.

As for the risk of ischemic stroke, its association with alcohol intake appears to behave in a J-shaped relationship for both women and men. Compared with nondrinkers, light drinkers have a reduced risk of ischemic stroke whereas heavy drinkers show an increased risk.[24] Interestingly, a potential effect modification by the apolipoprotein E, or *APOE*, gene on the association of alcohol with risk of ischemic stroke has been suggested by the Cardiovascular Health Study,[29] in which the protective effect of light drinking was attenuated in elderly *APOE* ε4 carriers. However, this finding has not been replicated in other populations.[30] The beneficial effects on the cardiovascular system conferred by the light to moderate consumption of alcohol might be mediated by the increase in high-density lipoprotein cholesterol and apolipoprotein A1 levels, as well as a reduction in platelet aggregation and fibrinogen levels.[31] These biological effects might thus confer some protection against ischemic stroke. However, in light of the many detrimental health effects attributable to heavy alcohol use and alcohol abuse, the overall recommendation from the stroke community is for nondrinkers to continue avoidance of alcohol, and for low to moderate consumption by those who already consume alcohol.

Diet

The relation between nutrition and stroke is complex because diet can affect, in different ways, other stroke risk factors such as hypertension, hypercholesterolemia, or diabetes.

A healthy diet may confer protective effects against vascular events. For instance, adherence to a Mediterranean diet has been associated with reduced mortality from cardiovascular diseases.[32] This diet is based on the frequent consumption of plant-based foods (i.e., seasonal fruits and vegetables, breads, cereals, potatoes, beans, nuts, and seeds) and olive oil as the main source of dietary fat; and low to moderate consumption of dairy products (i.e., cheese and yogurt), fish, poultry eggs, and wine; keeping red meat, saturated fats, processed foods, and sweets to a minimum.[33] In the Nurses' Health Study, following a Mediterranean diet was related to a 13% stroke risk reduction among white women, with the greatest adherence after 20 years of follow-up.[34] Another population-based study conducted in a multiethnic population of Hispanic, black, and white persons living in northern Manhattan found that a Mediterranean diet was associated with a 20% risk reduction in the combined end point of ischemic stroke, myocardial infarction, and vascular death after 9 years of follow-up.[35] Other studies have analyzed individual components of diet in relation to stroke. Frequent consumption of fruits, vegetables, grains, and fish has been associated with a reduced risk of stroke. Pooled results from cohort studies conducted in the United States, Japan, and Europe have shown a reduction of 11% in the risk of stroke among individuals consuming three to five portions of fruit and vegetables per day, and a reduction of 26% in the risk of stroke among those consunming more than five portions of fruit and vegetables per day.[36] Results from another meta-analysis suggested a marginally significant reduction of 17% in the risk of stroke in individuals consuming whole grains more frequently.[37] As for fish intake, a meta-analysis including studies from Europe, the United States, Japan, and China found that the consumption of three servings of fish per week was associated with a reduction of 6% in the risk of total stroke and 10% for ischemic as well as hemorrhagic stroke.[38]

The beneficial effects in reducing the risk of stroke are probably mediated by all of the essential vitamins, minerals, fiber, and fats that a varied, healthy diet provides. Results from epidemiological studies often support this concept, although clinical trials do not always confirm these findings. Dietary intake of vitamin C has been related to a reduction in the risk of stroke in prospective cohorts,[39, 40] although these results have not been replicated in clinical trials.[41,42] Greater levels of carotenoids have been associated with a decrease in the risk of stroke in men.[43–45] Results from a meta-analysis of prospective cohorts have shown that a greater intake of flavonols is associated with a reduced risk of stroke.[46] Results for vitamin E are conflicting; clinical trials indicate that vitamin E increases the risk of hemorrhagic stroke by 22% and reduces that of ischemic stroke by 10%.[47] As for vitamin D, results from observational studies have shown that reduced levels are related to an increased risk of stroke.[48,49] Last, greater intake of omega-3 polyunsaturated fatty acids, eicosapentaenoic acid, and docosahexaenoic acid found in fish and certain seeds has been shown to reduce the risk of stroke in women.[50]

In contrast to the Mediterranean diet, the so-called "western diet" has been associated with increased risk of stroke. This dietary pattern seen in industrialized countries is based on the consumption of red and processed meats, refined grains, fried foods, soft drinks, and sweets. After 14 years of follow-up, white women adhering to a western dietary pattern had an increased risk of total (58%) and ischemic (56%) stroke.[51] Another study evaluating racial and regional differences in stroke across the United States found that greater adherence to a southern dietary pattern (close to the western diet, conceptually) was associated with a 30% increased risk of stroke.[52]

Greater consumption of salt is another marker of increased stroke risk, given its widespread and direct relation to hypertension.[53] Indeed, it has been estimated that greater intake of sodium is associated

with a 24% increase in risk of stroke and 63% increase in stroke death.[54] In contrast to sodium, greater potassium intake, found in certain fresh fruits and vegetables, has been shown to decrease blood pressure. A meta-analysis including 10 prospective studies found that for every 1000-mg/day increase in potassium, there was a decrease of 11% in the risk of total and ischemic stroke.[55]

Last, some studies have investigated the intake of common beverages in relation to the risk of stroke. Moderate consumption of coffee (three to four cups per day) has been associated with a reduction of 17% in the risk of stroke,[56] whereas the consumption three or more cups per day of either black or green tea reduced the risk of stroke by 21%.[57] Sugar-sweetened beverages, in contrast, have been related to an increased risk of stroke, and diet sodas appear to have a similar adverse impact. One or more servings of sugar-sweetened or even low-calorie soda per day has been associated with an increased risk of stroke, especially in women.[58]

Physical Activity

Regular physical activity has numerous benefits in reducing all-cause mortality and cardiovascular disease, and improves individual well-being and brain health.[59] Several epidemiological studies have shown the protective effect conferred by physical activity in reducing the risk of stroke.[60] Compared with the more sedentary group, moderately or highly physically active individuals had a 20% to 30% reduction in the risk of stroke.[61] Specifically, the risk of ischemic stroke was reduced by 24% in women and 27% in men; and the risk of hemorrhagic stroke was reduced by 8% in women and 40% in men.[62] Benefits are also evident for occupational physical activity, for which risk reductions of 43% for ischemic, 69% hemorrhagic, and 26% total stroke have been noted in individuals who are active in the workplace compared with persons in inactive occupations.[63] In the Nurses' Health Study, greater physical activity in women was associated with a lower risk of ischemic stroke, with a dose–response effect such that, across quintiles of increasing physical activity, the RRs were 1.00, 0.87, 0.83, 0.76, and 0.52 (p for trend = .003), respectively.[64]

Physical activity is also an important component of the "low-risk lifestyle." In a prospective cohort study involving the participants of the Nurses' and Health Professionals Studies, the combination of modest exercise (≥30 minutes/day), not smoking, maintaining a normal weight (body mass index, <25 kg/m^2), light to modest alcohol consumption, and a healthy diet was associated with a reduced risk of total and ischemic stroke in persons with all five low-risk factors, with RRs of 0.21 (95% CI, 0.12–0.36) and 0.31 (95% CI, 0.19–0.53), respectively, compared with persons who had none of these beneficial factors.[65]

Cardiovascular exercise may even be beneficial in improving outcomes after stroke onset. A pooled analysis of clinical trials found that aerobic exercise improved aerobic capacity, walking speed, and endurance in individuals after mild and moderate stroke.[66]

The mechanisms by which physical activity confers protection are multifactorial. Exercise can have a beneficial impact in reducing other vascular risk factors for stroke such as hypertension, obesity, metabolic syndrome, or diabetes.[67] However, benefits may go beyond the reduction of vascular risk factors, because studies adjusting for them still show significant protective effects. Therefore, physical activity may confer a general improvement of vascular functioning. Results from experimental studies have shown a series of beneficial functional changes such as vascular remodeling through angiogenesis and arteriogenesis, improvement in the regulation of coronary tone and vasodilatory capacity, upregulation of antioxidant defense mechanisms in several tissues (e.g., heart, liver, kidney, skeletal muscle), and downregulation of long-term inflammatory responses—associated strongly with the progression of atherosclerosis.[68] Levels of the brain-derived neurotrophic factor are increased by physical activity, and the brain-derived neurotrophic factor in turn appears to mitigate the adverse effects of ischemia on the brain.

Sleep Apnea

Sleep-related breathing disorders have been related increasingly to cardiovascular diseases.[69] Specifically, results from several studies suggest not only that obstructive sleep apnea (OSA) is frequent in stroke and transient ischemic attack patients,[70] but also that OSA is a risk factor for stroke.

Because OSA is frequently present with comorbidities such as obesity, diabetes, or hypertension,[69] it is important to consider adjustment for vascular risk factors when interpreting results. Epidemiological studies relating OSA and stroke come from retrospective analyses in consecutive patients and population-based studies. In the Wisconsin Sleep Cohort Study, it was found that an apnea–hypopnea index of 20 or more was associated independently with a threefold increase in prevalent stroke.[71] Yaggi et al.[72] investigated the association between OSA and first stroke or all-cause mortality in patients referred to the Yale Center for Sleep Medicine. They showed that, compared with patients without the syndrome, the composite end point almost doubled in patients with OSA after 3.4 years of follow-up, independent of other vascular risk factors.[72] Last, a large, prospective study including 5422 participants of the Sleep Heart Health Study found that men with moderately severe OSA were at an increased risk of ischemic stroke by almost threefold after 8 years of follow-up. This association was not seen in women after adjusting for multiple risk factors.[73]

The mechanisms by which the repetitive reduction or cessation of airflow during sleep may cause stroke are diverse. As mentioned earlier, OSA is associated with other risk factors for stroke, which together may exacerbate the risk of cerebrovascular disease.[69] Additional mechanisms include increased variability in heart rate and blood pressure as a result of a sympathetic hyperactivity[74]; intermittent hypoxemia and changes in cerebral blood flow velocity leading to hypoperfusion and a reduced vasomotor reactivity, which predispose to nocturnal cerebral ischemia[75]; and the activation of proinflammatory responses mediated by oxidative stress that, consequently, may promote endothelial dysfunction and atherogenesis.[76]

Air Pollution

Exposure to outdoor air pollution has been associated with an increased risk of stroke and cardiovascular diseases, especially in individuals at greater risk of developing these conditions and in the elderly.[77] Harmful air pollutants include gases and particulate matter (PM). Airborne PM has been studied most intensively because PM levels of less than 10 μm in aerodynamic diameter (PM_{10}) can penetrate the airways and thus have the most adverse health effects.[78,79]

Several epidemiological studies have found both short- as well as long-term associations with ischemic stroke, although associations with hemorrhagic stroke are less consistent.[80,81] A case–crossover study conducted in Canada found that poor air quality—measured as increased concentrations of ozone, fine PM of less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), and nitrogen dioxide—was associated with more emergency visits for ischemic stroke during the warm-weather months.[82] Another study investigating the short-term effects of air pollution in Boston found a 34% increase in risk of ischemic stroke after 24-hour periods with a moderately high $PM_{2.5}$ compared with periods with good $PM_{2.5}$ levels.[83] Long-term air pollution exposure and risk of stroke was investigated in the Women's Health Initiative. In this prospective cohort, a 10-$\mu g/m^3$ increase in $PM_{2.5}$ levels was associated with a 35% and 83% increased risk of nonfatal and fatal stroke, respectively, after 6 years of follow-up in women.[84] Another study conducted in Japan showed that exposure to traffic-related air pollution up to 3 years earlier, measured by a 10-$\mu g/m^3$ elevation in nitrogen dioxide concentrations, was associated with an increased risk of death from intracerebral hemorrhage (31%) and ischemic stroke (33%).[81]

The pathophysiological pathways by which exposure to air pollutants increases the risk of stroke may involve pulmonary and systemic inflammatory responses, which promote oxidative stress,

endothelial dysfunction, and immune activation, including greater levels of acute-phase reactants and coagulation factors.[85] Results from experimental studies have shown, for example, that ultrafine PM can enter cells and damage organelles such as the mitochondria, generating reactive oxygen species[86,87] and promoting vascular calcification by the activation of inflammatory pathways.[88] Additional exposure to diesel exhaust has been related to increased thrombus formation and platelet activation in healthy men.[89] Another potential mechanism involves the stimulation of the sympathetic nervous system, which induces higher blood pressure, arrhythmias, and vasoconstriction.[90] All these changes might predispose to plaque rupture and thrombosis, increasing the risk of ischemic stroke.[85]

Consumption of Illicit Substances

Because of its illegality, the implementation of epidemiological studies addressing the association between drug use and stroke independent of other risk factors has been challenging. Nevertheless, the use of illicit substances has been suggested as a cause of both ischemic and hemorrhagic stroke, particularly among young adults, from whom most of the evidence comes in descriptive case reports.[91]

Cocaine use has been associated with stroke. It has been reported that hemorrhagic and ischemic stroke are equally frequent in individuals consuming cocaine in its alkaloid form (also known as *crack*), whereas the hemorrhagic subtype was more frequent in those using cocaine in its hydrochloride or inhaled form.[92] In a case–control study using data from the Kaiser Permanente program, it was shown that women consuming cocaine had almost 14 times greater odds of having a stroke.[93] The mechanisms underlying the occurrence of ischemic stroke include elevation of blood pressure, arrhythmia, and cerebral vasospasm in the short term, and endothelial dysfunction and accelerated atherosclerosis may occur in the long term.[94] As for hemorrhagic stroke, possible mechanisms include aneurysm rupture as a consequence of increased blood pressure, vasoconstriction, vasculitis, and poor cerebrovascular regulation.[92,95,96]

Studies assessing the use of cannabis in relation to stroke are inconclusive, because it is often difficult to dissect the impact of this exposure from that of other drugs and risk factors. For instance, results from a study of consecutive patients from New Zealand found that the odds of having an ischemic stroke/transient ischemic attack were almost doubled among cannabis users; however, this association was no longer significant after adjusting for cigarette smoking.[97] However, a recent study using hospital admission data in Texas reported a 76% increase in odds of ischemic stroke among cannabis users after controlling for potential confounders.[98] Putative mechanisms explaining this finding include multifocal intracranial vasoconstriction[99] and impaired regulation of cerebral blood flow.[100]

The consumption of other illicit substances such as amphetamines, ecstasy, heroin, and doping substances used in sports has also been related to an increase risk of stroke,[94] and these associations are discussed in more detail in Chapter 16.

Conclusions

This chapter briefly summarizes the current evidence linking several lifestyle factors with the risk of stroke. Cigarette smoking increases the risk of ischemic stroke and subarachnoid hemorrhage in a dose-dependent manner and has a less consistent adverse impact on the risk of intracerebral hemorrhage. Concerning alcohol use, the risk of stroke depends on the dose and differs by stroke subtype. Alcohol intake is associated linearly with an increased risk of hemorrhagic stroke, whereas the

relationship with ischemic stroke is J-shaped. As for diet, the intake of healthy foods such as those in a Mediterranean diet has been associated with a reduced risk of stroke. In contrast, the consumption of a western-type diet is associated with an increased risk of stroke. Moderate to vigorous physical activity is an important factor that confers protective effects against both ischemic and hemorrhagic stroke. Obstructive sleep apnea and exposure to air pollution have been related increasingly to a greater risk of stroke. Lastly, the consumption of illicit drugs such as cocaine, cannabis, and other psychoactive substances are related to an increased risk of both hemorrhagic and ischemic stroke.

Lifestyle risk factors often cluster in individuals who tend to choose patterns of healthy or unhealthy lifestyles, and thus we see synergistic interactions among the multiple risk factors discussed in this chapter. Although effective behavioral changes might be challenging, modifications in the factors described above represent potential preventive strategies in the fight to lower the burden of stroke across populations.

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16

RISK FACTORS OF STROKE SPECIFIC TO YOUNG ADULTS

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Introduction

Approximately 5% of all ischemic strokes occur in individuals younger than 45 years of age and 10% occur in those younger than 50 years of age. The age cutoff to define young adults in stroke medicine is arbitrary (it varies from 40–55 years in the literature), but has a rationale that is based on differences of stroke etiology and risk factors between young patients and older patients. The major etiologic subgroups of ischemic stroke in the elderly—namely, large-artery atherosclerosis, atrial fibrillation, and small-vessel occlusion—are infrequent among the young, because most major risk factors predisposing to these outcomes (such as hypertension, diabetes, and dyslipidemia) are either less common or less severe, or have not yet caused substantial damage to the cardiovascular system. Thus, stroke risk factors in the young are distinct and need to be examined carefully.

Another feature related to risk factors that distinguishes younger patients from the elderly is that, even after thorough clinical and laboratory examination, many young patients with ischemic stroke remain without a definite etiologic classification. Furthermore, a number of patients remain without a single detected, well-documented risk factor. Many of these individuals harbor, however, less well-documented risk factors for ischemic stroke, such as heavy alcohol consumption, obstructive sleep apnea, or clotting abnormalities.

Risk factors considered rather specific to young adults include genetic and acquired thrombophilia, illicit drug use, migraine with aura, cardiac interatrial abnormalities, heavy drinking, binge drinking, inflammation and infections, sickle cell disease, and, in women, oral contraceptive use, gravidity, and postpartum status. Although many of these risk factors can also predispose to stroke at older ages, the rationale to regard them as age specific include the following: (a) the factor can exist only at young age (e.g., reproductive health-related factors); (b) the factor can exist at all ages, but the association is stronger statistically at younger ages (e.g., patent foramen ovale [PFO], migraine with aura, infections); or (b) the factor is related to modifiable risk behavior in a population that is

more common at younger ages (e.g., illicit drug use, heavy drinking, binge drinking habit, smoking, obesity).

This chapter reviews studies investigating the strength of the association of risk factors particularly in young stroke patients, and overviews the risk factor frequencies with a focus on age-specific differences and gender differences at younger ages. Risk factors considered specific to young adults but not covered elsewhere in this book are discussed in detail here, including cardiac interatrial abnormalities, antiphospholipid antibodies (aPLs), illicit drug use, and chronic and acute infections.

Well-Documented Risk Factors among Young Adults

Strength of Association of Nonmodifiable Risk Factors

A case–control study by MacClellan et al.[1] showed a pronounced aggregation of young-onset stroke in families. Siblings of stroke patients had a fourfold risk for stroke compared with siblings of control subjects.[1] Furthermore, mothers of stroke patients harbored a twofold greater risk for stroke compared with mothers of control subjects. This aggregation was even more profound with decreasing age. For example, odds ratios (ORs) for positive family history for women age 15 to 24 years, 25 to 34 years, and 35 to 49 years were 2.5, 1.6, and 1.5, respectively. Another study including a southeast Asian population showed a statistically strong correlation between stroke family history and stroke in young adults (adjusted OR, 16.15; 95% CI confidence interval [CI] 1.71–151.82),[2] whereas some studies found no such association.[3] In one study, male sex was associated with a greater risk of stroke at a young age.[4]

Even in patients younger than 50 years, increasing age is linked virtually exponentially to increasing risk of ischemic stroke. The risk increases steeply in early midlife and the curve is markedly steeper for males (Figure 16.1).[5] Regarding racial differences among the young, blacks and Hispanics have greater stroke incidence.[6,7]

Strength of Association of Modifiable, Well-Documented Risk Factors

Rather few case–control studies have assessed the strength of association of traditional modifiable risk factors for ischemic stroke in young adults in nonselected patient populations. Several studies involving multiple ethnicities have confirmed the association of hypertension (OR range, 1.6–8.9)[2,4,8–12] and smoking (OR range, 1.6–7.7)[4,8–13] with stroke risk. Love et al.[13] demonstrated a cumulative dose effect with risk of ischemic stroke increasing with each additional pack-year of smoking and no heterogeneity between etiologic subtypes. Fewer studies found an association of diabetes or elevated fasting blood glucose (OR range, 3.3–22.9)[8,9,11,12] or heart disease (OR range, 2.7–3.3)[10–12] with stroke at younger ages. In a study by Rohr et al.,[8] diabetes appeared to be a stronger risk factor for young white men (OR, 22.9) than for young black men (OR, 4.2), whereas smoking and hypertension were more important risk factors among blacks of both genders. In women age 30 to 55 years, the relative risk of ischemic stroke was sixfold for type 1 diabetes and twofold for type 2 diabetes in another study.[14] However, there are scarce data on the risk difference between diabetes subtypes for stroke, particularly at young ages.

We found only one study that investigated the strength of association between physical inactivity and stroke at a young age. In that study, which involved a Thai population age 18 to 45 years, history of no or irregular exercise increased stroke risk eightfold after adjusting for confounders (OR, 8.06; 95% CI, 1.12–57.60), with the odds being a similar magnitude for hypertension in that population.[2]

An association between low high-density lipoprotein cholesterol and ischemic stroke at a young age has been demonstrated.[2,4,9] Furthermore, the presence of three or more components of metabolic syndrome was associated strongly with stroke in an Indian study comparing ischemic stroke patients

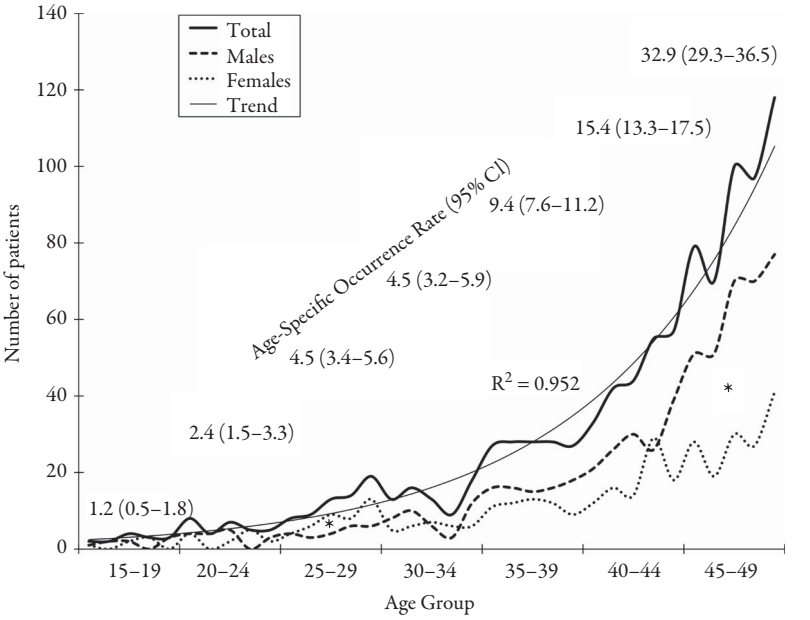

FIGURE 16.1 Incidence of ischemic stroke in patients younger than 50 years stratified according to 5-year age bands in the Helsinki Young Stroke Registry. CI, confidence interval. Number of patients according to age and age-specific occurrence rates per 100 000. R indicates correlation coefficient of the trend line illustrating the exponential increase in occurrence as a function of age. *$P < 0.001$ in comparison of age-specific proportions between genders by Chi-Sq test.

with both community and hospital control subjects (OR, 4.76; 95% CI, 1.93–11.76; OR, 2.09; 95% CI, 1.06–4.13, respectively).[9] Some studies have suggested that lipoprotein(a) concentration increases the risk of ischemic stroke at young age.[15] No such association was found in a study focused on young women only.[16]

The associations of long-term[12] and recent heavy drinking[11,17,18] and ischemic stroke have been confirmed in young adults. Acute heavy drinking or so-called *binge drinking* clearly differentiates young patients from their older counterparts—a risk factor for both ischemic and hemorrhagic stroke considered specific to young adults.[19] There are, however, probably marked cultural variations in drinking habits.

Among a cohort of 6520 Danish men, obesity (body mass index, ≥30 kg/m^2) was associated with a threefold (OR, 3.0; 95% CI, 2.3–4.0) risk of having been diagnosed with any of the following: type 2 diabetes mellitus, hypertension, myocardial infarction, stroke or venous thromboembolism, or death before the age of 55.[20] However, obesity was associated strongly with all individual outcomes as well, except stroke. We found no studies assessing other markers of obesity, dietary habits, or psychosocial stress and the risk of stroke specifically at a young age.

RISK FACTOR PREVALENCE

Table 16.1 summarizes the risk factor frequencies in the three largest data sets to date on ischemic stroke in young adults.[5,21,22] A recent analysis based on pooled data from existing registries in 15 European centers showed that, among patients age 18 to 49 years, the three most frequent risk factors were current smoking (49%), dyslipidemia (46%), and hypertension (36%).[21] The recent, prospective

TABLE 16.1

Comparison of Risk Factor Prevalence in the Three Largest Nonselected Data Sets of Ischemic Cerebrovascular Events at Young Age

	Helsinki Young Stroke Registry (N = 1008)	15 Cities Young Stroke Study (N = 3944[a])	Stroke in Young Fabry Patients (n = 4467[b])
Well-documented, nonmodifiable risk factors			
Mean (SD) or median (IQR) age	41.3 (7.6)	43 (36–46)	47 (40–51)
Male gender	62.3	56.6	59.4
Family history of any stroke	12.7	16.4	17.0
Well-documented, modifiable risk factors			
Dyslipidemia	59.5	45.8	34.9
Cigarette smoking	44.2	48.7	55.5
Hypertension	39.1	35.9	46.6
Obesity (BMI ≥30 kg/m^2)	10.6	NA	22.3
Atrial fibrillation	4.2	3.7	2.4
Cardiovascular disease	10.2	NA	9.2
Coronary heart disease	4.9	6.0	4.2
Heart failure	4.8	3.7	1.2
Myocardial infarction	3.7	NA	3.1
Peripheral arterial disease	1.8	2.7	2.2
Valvular disease	NA	NA	2.3
History of TIA	8.9	8.4	9.3
Diabetes mellitus	10.4	8.0	10.3
Type 1	4.4	NA	NA
Type 2	6.0	NA	NA
Hormone replacement therapy	1.7	NA	NA
Nonmodifiable risk factors			
History of migraine	17.2	NA	26.5
Heavy drinking	14.2	NA	33.0
PFO with or without ASA	10.5	NA	NA
Oral contraceptive use	6.7	NA	NA
Obstructive sleep apnea syndrome	3.8	NA	3.3
Genetic thrombophilia	7.0	NA	NA
Acquired thrombophilia	6.2	NA	NA
Active malignancy	1.6	NA	NA
Recent illicit drug use	1.3	NA	NA
Gravidity or postpartum period	1.0	NA	NA

Note. Data are percentages unless indicated otherwise.
[a]The database includes patients from the Helsinki Young Stroke Registry.
[b]Includes 3396 with ischemic stroke and 1071 with TIA.
ASA, atrial septal aneurysm; BMI, body mass index; IQR, interquartile range; NA, not available; PFO, patent foramen ovale; SD, standard deviation; TIA, transient ischemic attack.

Stroke in Young Fabry Patients study, which included 4467 patients age 18 to 55 years with ischemic stroke or transient ischemic attack, demonstrated that the most frequent, well-documented risk factors were smoking (56%), physical inactivity (48%), arterial hypertension (47%), dyslipidemia (35%), and obesity (22%).[22] Diabetes mellitus was found in 8.0% to 10% of participants in these three studies. Only the Finnish study[22] differentiated between type 1 and type 2 diabetes. Of note, the relative proportions may differ in other countries; the prevalence of type 1 diabetes in Finland is one of the highest in the world.[23]

Demographic differences in risk factor prevalence

In the 15 Cities Young Stroke Study,[21] males were older than females and more often had dyslipidemia or coronary heart disease, or were smokers, than females. In both genders, frequency of family history of stroke, dyslipidemia, smoking, hypertension, diabetes mellitus, coronary heart disease, peripheral arterial disease, and atrial fibrillation correlated positively with age. The study found no difference in the risk factor prevalence among southern, central, and northern European patient populations after adjusting for age and gender.

The Stroke in Young Fabry Patients study demonstrated a clustering of multiple risk factors, particularly in males and with increasing age (Figure 16.2).[22] Specifically, dyslipidemia, smoking, hypertension, cardiovascular disease, diabetes mellitus, and high-risk alcohol consumption accumulated among males. With respect to dyslipidemia and cardiovascular disease, the gender disparity was particularly apparent in the age group of 35 years or older. That study showed increasing prevalence with increasing age of physical inactivity, arterial hypertension, dyslipidemia, obesity, and diabetes mellitus. In contrast, females were more often physically inactive at younger ages (<35 years). Female patients frequently were abdominally obese at the age of 25 years or older. More important, a Danish study including stroke patients across a wide age range showed that lifestyle-related risk factors—smoking, alcohol, and obesity—were indeed more common in younger patients (<60 years), with declining relative importance with increasing age.[24]

Cardiac Interatrial Abnormalities

PFO is a remnant of fetal circulatory bypass of the lungs. The foramen ovale remains patent in approximately 25% of adults, based on autopsy studies.[25] PFO is a slitlike communication between the right and left atrium, which is bounded by two thin membranes—the septum secundum on the right atrial side and the septum primum on the left atrial side—in the cranial part of the fossa ovalis. In most individuals, PFO remains closed most of the time by the positive left-to-right pressure gradient that presses the septal membranes together. In some circumstances, such as during an activity inducing a Valsalva maneuver, right atrial pressure can exceed left atrial pressure and thus cause opening of the PFO and a transient right-to-left shunt. Anatomy of atrial septal abnormalities ranges from an atrial septal defect with spontaneous right-to-left shunt, to large to small PFOs with or without atrial septal aneurysm (ASA). ASA is diagnosed when a fixed displacement or a mobile excursion of the fossa ovalis bulges toward the right or left atrium (or both), exceeding 10 mm from the midline.[26]

PFO has long been linked to ischemic stroke with different postulated mechanisms, of which the so-called *paradoxical embolism* is the most prevailing. This link arose from case descriptions in which a thrombosis from the venous circulation was demonstrated passing through the PFO, as seen during autopsy or via echocardiography.[27,28] Nevertheless, concurrent venous thrombosis in the setting of presumed paradoxical embolism is, in fact, detected only rarely and often is clinically silent.[29] The most typical case in which PFO is thought to play a role is a case in which, after an extensive workup

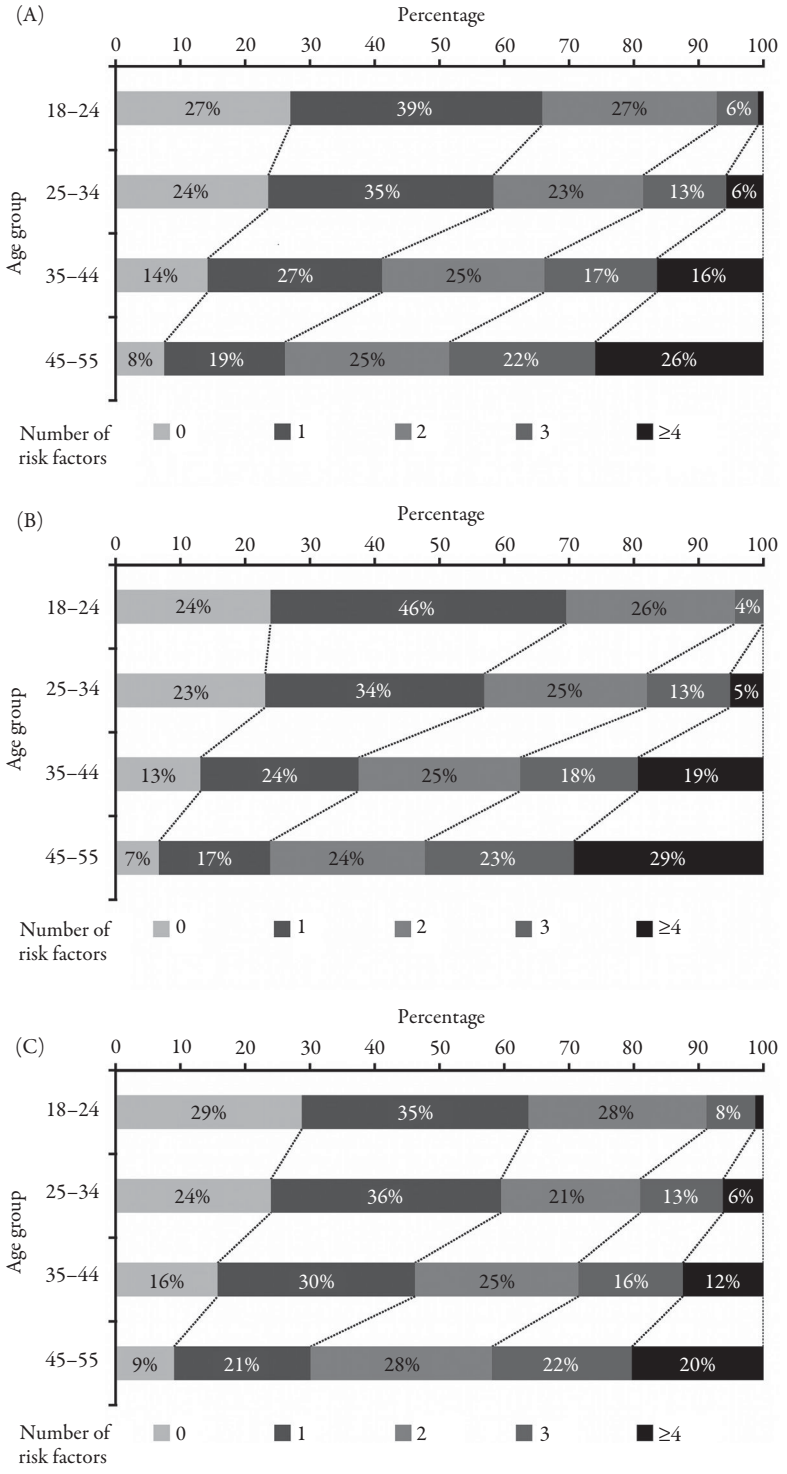

FIGURE 16.2 (A–C) Frequencies of all patients (A), male patients (B), and female patients (C) with none, one, two, three, and four or more well-documented risk factors according to gender.[22]

and the stroke etiology remains unknown, a PFO is demonstrable and, as a result of uncertainty regarding causality, a possible PFO-related stroke is considered a cryptogenic event.

Nevertheless, a meta-analysis has shown an association between PFO, ASA, and PFO with concomitant ASA and ischemic stroke in younger patients.[30] Younger age as a factor clearly increases the odds for these associations. In a recent systematic meta-analysis, Alsheikh-Ali et al.[31] estimated the probability for PFO to be incidental (i.e., not causally related to the stroke) in patients with cryptogenic stroke. They concluded that in studies including stroke patients across a wide age range, the probability that PFO is incidental is 33%, reduced to approximately 20% in younger (<55 years) patients, but is 48% in older patients (≥55 years). These estimates support the view that PFO is an age-dependent risk factor for ischemic stroke, but leave a considerable (at least two-to-five) chance that, even in younger individuals with stroke, it is just an innocent bystander.

PFO characteristics that increase stroke risk include PFO size, length of the PFO tunnel, magnitude of the shunt, and the presence of concomitant ASA.[32] The association of PFO and cryptogenic stroke has been demonstrated in older patients (age ≥55 years) as well. Compared with patients with a known stroke etiology, the OR for having a PFO was 4.7 (95% CI, 1.9–11.7) among younger patients (<55 years) and 2.9 (95% CI, 1.7–5.0) among older patients (≥55 years) with unknown stroke etiology. Similarly, the presence of PFO with ASA in ischemic stroke patients with cryptogenic stroke versus stroke of known etiology was found to be 13.4% versus 2.0% (OR, 7.36; 95% CI, 1.01–326.60; $p = .049$) among younger patients and 15.2% versus 4.4% (OR, 3.88; 95% CI, 1.78–8.46; $p < .001$) among older patients.[33]

Important predisposing factors in PFO-related stroke in which a paradoxical embolism is presumed are concomitant conditions leading to a prothrombotic state, such as inherited thrombophilia,[34,35] and all factors increasing the risk for venous thrombosis.[36] Other possible mechanisms of PFO- or ASA-related stroke include in situ thrombosis in the PFO channel or in the ASA,[28] and predisposition to left atrial dysfunction possibly leading to vulnerability to atrial fibrillation.[37]

The current evidence around PFO as a risk factor for ischemic stroke in the young is supported by meta-analyses of case–control studies, but the mechanisms regarding how this risk increment occurs and how best to prevent recurrent stroke in this setting needs to be investigated more thoroughly. The three recently completed randomized trials on transcatheter PFO closure showed that, in nonselected patients with a nonselected device, the procedure does not reduce the risk for recurrent events compared with best medical treatment.[38] Tools for scoring PFO as potentially pathogenic have been developed recently to guide secondary prevention strategies and to avoid unnecessary closure of PFO.[39]

Antiphospholipid Antibodies

As a result of autoimmune activation, aPLs react against proteins that bind to anionic phospholipids on plasma membranes. Antiphospholipid syndrome (APS) is a condition with at least one clinical event out of (a) arterial, venous, or small-vessel thrombosis in any tissue or organ or (b) pregnancy-related complications such as preeclampsia or miscarriages, associated with two positive blood tests at least 12 weeks apart showing the presence of lupus anticoagulant (LA), anticardiolipin antibodies of immunoglobulin G and/or M isotype in medium or high titer (>40 IgG antiphospholipid units/mL (GPL) or IgM antiphospholipid units/mL (MPL), or more than the 99th percentile), or anti-β_2-glycoprotein I antibodies.[40] In addition, antibodies to plasma protein prothrombin are commonly tested. APS is more prevalent in young women compared with the general population,[41] and can be classified as secondary, if occurring in the setting of systemic lupus erythematosus (SLE) or other collagen vascular disorder, and primary in the absence of SLE.

aPLs can exist in the absence of the criteria for APS. Earlier case–control studies, although with rather small sample sizes, have been able to establish fairly well the role of aPLs as a risk factor for first

ischemic stroke at young age in patients mostly free from SLE.[42–47] In older individuals, the association is far more controversial, with studies showing both positive and negative associations.[48] aPLs also contribute to the risk of cerebral venous thrombosis.[49]

A recent analysis based on a comparison of 175 women younger than 50 years with a first ischemic stroke and 628 healthy control subjects demonstrated an OR for ischemic stroke of 43.1 (95% CI, 12.2–152.0) in women having LA and an OR of 2.3 (95% CI, 1.4–3.7) for women having anti-β_2-glycoprotein I antibodies (cutoff, 90th percentile of control subjects).[50] In this study, the risk of ischemic stroke was not affected by the presence of anticardiolipin or antiprothrombin antibodies, possibly as a result of the rather small number of patients with ischemic stroke harboring these antibodies ($n = 26$ and $n = 38$, respectively).[50] More important, the OR for ischemic stroke increased to 201.0 (95% CI, 22.1–1828.0) in women with LA using oral contraceptives and increased to 87.0 (95% CI, 14.5–523.0) in those who were smokers. The association of anticardiolipin and antiprothrombin antibodies with ischemic stroke remains to be elucidated in a larger study, and investigation of the relevance of aPLs in men is warranted.

It seems that aPLs may necessitate a local trigger or additional systemic risk factors to participate in the thrombotic process.[51] In addition to in situ thrombosis at any arterial site (or in the venous bed, resulting in paradoxical embolism or cerebral venous thrombosis), the mechanisms of how aPLs contribute to stroke risk include accelerated atherosclerosis[52] and cardioembolism resulting from valvular disease (a variety of lesions have been described, with the most classic form being Libman-Sacks endocarditis).[53–55] All these conditions may be aggravated by concomitant chronic comorbidities impairing the endothelium and vascular bed,[50] and the induction of aPL production triggered by transient factors such as infections.[56]

Illicit Drug Use

Illicit drug use refers to recreational use of prohibited substances. Illicit drugs include illegal drugs (e.g., cannabis and cocaine), pharmaceutical drugs when used for nonmedical reasons (e.g., sedatives and opiates), and inappropriate use of other substances (e.g., certain inhalants). Illicit drug use and dependence have important consequences and costs. The U.S. Department of Justice noted, in its 2011 report, that the cost of illicit drug use totaled more than $193 billion in 2007 in the United States alone.[57] In the United States, 9% of individuals age 12 years or older have tried an illicit drug within the past month. Approximately 20 million people worldwide have drug use disorders, with significant geographic differences. Industrialized countries and metropolitan cities are most affected, along with illicit drug-producing regions. The majority of users are young, with approximately one fourth being underage individuals.

Infections are the most common complications of injection drug use, presenting as septicemia, systemic fungal infections, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infections as well as right-side endocarditis. HIV infection among intravenous drug users worldwide has been reported to reach up to 20%. Stroke, in turn, is a rare but serious complication and occurs mainly in the young, and mostly in males, reflecting the age and gender distribution of users. Polysubstance abuse is also found predominantly among men. Illicit drug use epidemics differ from one city or country to another. Some hospital-based series reported that illicit drug use has been implicated causally in as many as 6% of all ischemic strokes[58] and in 15% to 40% of ischemic stroke in young patients.[59] The same researchers reported later that, among 422 ischemic stroke patients age 15 to 44 years, 12.1% had used an illicit drug recently, and the illicit drug was the likely cause in 4.7% of the patients.[60] In contrast, illicit drug use was, very rarely, the underlying cause of ischemic stroke in young ischemic stroke patients from the greater Helsinki region.[5] The link between stroke and illicit drug use is strong for cocaine and amphetamines, but is less

clear for other illicit drugs. Among young abusers, stroke risk was up to 6.5-fold compared with nonusers.[61]

AMPHETAMINES AND RELATED SUBSTANCES

Several amphetaminelike substances (e.g., methamphetamine, methylphenidate, phenylpropanolamine, and ephedrine) are used as central nervous system stimulants, decongestants, and appetite suppressants. A population-based study covering all hospital admissions in Texas between 2000 and 2003 showed that amphetamine abuse was associated with a fivefold increased risk of hemorrhagic stroke, but not with ischemic stroke, and that amphetamine abuse almost tripled hemorrhagic stroke mortality.[62] Amphetamine use was associated with all strokes in young women, with an OR of 3.8 in a population-based study.[63]

Experimental studies in rats and monkeys demonstrated that single or repeated intravenous injections of methamphetamine or methylphenidate led to cerebral vasculiticlike changes.[64] Hemorrhagic strokes after amphetamine use are attributable to acute hypertensive crisis, vasospasm, and drug-induced hemorrhage, sometimes with preexisting arteriovenous malformation or aneurysms. In addition, amphetamine use increases the risk of toxic vasculitis, cardiomyopathy, and heart failure, leading to ischemic stroke.[65]

Methamphetamine is known as crystal, ice, or speed, and can be taken through various routes. It is the most potent of all amphetamines and is the one most frequently abused. It has a similar stroke spectrum as amphetamine. Phenylpropanolamine use in women was associated with increased risk of hemorrhagic stroke, more strongly when used as an appetite suppressant, but also when used as a cough or cold remedy.[66]

Ecstasy (3,4-methylenedioxymethamphetamine), a hallucinogen derivate of amphetamine, was associated with both hemorrhagic and ischemic stroke.[67] Ephedra use showed a trend toward an increased risk of hemorrhagic stroke in a case–control study that led to a ban of its sale and use as a dietary supplement.[68]

COCAINE

Cocaine is the secondmost commonly used illicit drug after marijuana and leads to half of the emergency department visits related to illicit drug abuse. Cocaine can be taken orally, intranasally, or intravenously, whereas crack cocaine is smoked. Cocaine is a local anesthetic, vasoconstrictor, and central nervous system stimulant. In a large population-based study from Texas, cocaine abuse was associated with both hemorrhagic (OR $\cong$ 2.3) and ischemic (OR $\cong$ 2.0) stroke, but not with increased stroke mortality.[62] Cocaine-associated stroke may have several mechanisms, such as acute hypertensive crisis, vasospasm, platelet activation and aggregation with thrombus formation, accelerated atherosclerosis, cardioembolism via arrhythmias and endocarditis, and vasculitis.[65] Cocaine is the most common cause of stroke related to illicit drug use. Arterial constrictions could be demonstrated in cocaine users as early as 20 minutes after intravenous injection, and in a dose-dependent fashion.[69] Several hundred patients with cocaine-related hemorrhagic or ischemic stroke have been reported since 1977.[70] Ischemic and hemorrhagic stroke occurs in roughly equal proportions, and both in anterior and posterior territories.[71]

OPIATES

Heroin, derived from opium, can be snorted, smoked, or injected intravenously or subcutaneously. Hallmarks of heroin overdose are coma, respiratory depression, and pinpoint pupils. Acute

toxic leukoencephalopathy has been described after inhalation of heroin ("chasing the dragon").[72] Cerebral hypoxia may stem from hypoventilation and/or hypotension. Most strokes are ischemic. Cardioembolism in the setting of infective endocarditis is a potential mechanism. Foreign-body embolization with talc and cellulose crystals occurs when oral tablets (e.g., pentazocine) are crushed, suspended in water, and injected intravenously. Vasculitides were also reported in heroin users. Stroke as a consequence of heroin use was first described in 1976 in nine young heroin addicts.[73]

CANNABIS

Cannabis is the most widely used illicit drug worldwide. The *Cannabis sativa* plant produces more than 60 different chemicals called *cannabinoids*, of which the most important is Δ-tetrahydrocannabinol, which is absorbed rapidly when smoked and leads to euphoria, self-confidence, and relaxation. It is still controversial whether cannabis use leads to stroke, although there is a temporal relationship between cannabis use and stroke in case series and population-based studies. Most reported cases are in men with ischemic stroke.[74]

REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME IN THE SETTING OF DRUG ABUSE

Cannabis, cocaine, methylenedioxymethamphetamine, amphetamines, and lysergic acid diethylamide can lead to reversible cerebral vasoconstriction (RCVS). The general feature of RCVS is a sudden, severe headache (thunderclap), with demonstrated widespread cerebral artery vasospasm with alternating areas of arterial constriction and dilatation in multiple vascular beds—so-called *string-and-beads appearance*. Neurological symptoms and signs differ or may be absent. Hypertension is a frequent feature. Most patients are young to middle-age females. Other causes of thunderclap headache (subarachnoid hemorrhage, dissection, or cerebral venous thrombosis) must be ruled out. Beading of cerebral arteries is common and lasts several days to weeks, but disappears usually within 12 weeks. Cerebrospinal fluid examination is almost always normal or near normal and helps in distinguishing RCVS from vasculitis. The course of RCVS is usually benign, but severe neurological syndromes and even death have been reported. In addition to ischemic changes, intracerebral hemorrhage is also frequent, particularly in patients with extreme blood pressures.[75]

Chronic and Acute Infections

Chronic infections may increase the risk of acute ischemic stroke through the following mechanisms: (a) the vascular endothelium can be damaged by increased systemic inflammation; (b) recurrent bacteremia triggers platelet activation and creates a procoagulant state; (c) long-standing infections can have an influence on risk factors, such as serum lipids, toward a more proatherogenic profile; and (c) chronic infections may also be risk factors that act together with conventional risk factors and a genetic predisposition.[76]

Chronic dental infections seem to be associated with ischemic stroke in the young.[77,78] HIV has the potential to cause ischemic stroke, especially in young stroke patients.[79,80] Several studies have found that, as in coronary heart disease, chronic, active *Chlamydia pneumoniae* infection and its elevated antibodies are prevalent in young stroke patients.[81–83] Other pathogens of chronic infection have not been studied systematically in young stroke patients.

A transient increase in the risk of a vascular event is associated with acute preceding infections occurring within 4 weeks, regardless of the patient's age. In ischemic stroke, acute respiratory tract

infections are the most common type of preceding infection.[84–86] In some studies, preceding infections have been linked in particular to large-vessel and cardioembolic ischemic strokes, particularly in patients with no other risk factors.[87,88] A retrospective analysis of 681 patients age 15 to 49 years with ischemic stroke diagnosed within 2 years from symptom onset showed a 10.7% frequency of preceding infections within 4 weeks before stroke.[89] The majority of these infections were upper respiratory tract infections (54%), followed by gastrointestinal (13%), chest (11%), and skin or mucous membrane (11%) infections.

There is a dearth of research on the pathogens causing the acute preceding infection; preceding respiratory infections are mostly of bacterial origin.[85] Viral infections, such as *Varicella zoster* infection, have proved to be potential risk factors for acute ischemic stroke during childhood,[90] but their role is yet to be elucidated in young-adult stroke.

The mechanisms correlating acute infections with stroke involve broadly alterations in immunohematologic mechanisms and systemic manifestations of inflammation, such as elevated anticardiolipin antibody levels, reduced concentrations of circulating antithrombotic proteins, increased concentrations of C-reactive protein, proinflammatory cytokines, or interleukins. These can, in turn, participate, for example, in the initiation of an extrinsic coagulation pathway, can modulate an anticoagulant pathway, or can increase platelet reactivity.[91] Interestingly, even minor acute infections can cause endothelial dysfunction in healthy children.[92] This finding provides evidence that the endothelium and its infection-triggered dysregulation may play a central role in the initiation of thrombotic processes. There also is a significant association between recent infection and cervical artery dissection,[93] which is the most frequent cause of ischemic stroke in young adults. In addition, vessel wall inflammation has been demonstrated by contrast-enhanced high-resolution magnetic resonance imaging and positron emission tomography–computed tomography in patients with cervical artery dissection.[94]

Conclusion

Young patients with ischemic stroke usually have serious and even multiple vascular risk factors and, contrary to customary belief, classic vascular risk factors are commonly present. Identification of these risk factors and implementation of precisely tailored preventive strategies may have a significant impact on long-term prognosis.

Acknowledgments

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17

SEX-SPECIFIC RISK FACTORS FOR STROKE IN WOMEN

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Introduction

The incidence of stroke in women varies over the course of life and increases with advancing age. Factors and situations that occur exclusively in the female sex can confer both protective effects and unique risks with regard to stroke. Estrogen, pregnancy and its complications, the postpartum period, menopause, and exogenous hormones represent some of these sex-specific issues.

Traditional Stroke Risk Factors

Typical risk factors for stroke include hypertension, hyperlipidemia, tobacco abuse, atrial fibrillation, and diabetes mellitus, which may be present in both men and women. However, recent cohort studies have demonstrated a definite difference between men and women regarding specific risk factors for stroke. For example, female stroke patients are more likely to have a history of atrial fibrillation and hypertension.[1–4] Di Carlo et al.[1] found a female predominance for prestroke institutionalization as well. The fact that women typically experience strokes at an older age compared with men may explain the increased prevalence of these risk factors, which tend to develop with advancing age. Men are more likely to have a history of tobacco and alcohol use, as well as a history of myocardial infarction and diabetes mellitus.[1,3] Data from the National Health and Nutrition Examination Survey suggest that cholesterol levels in women increase with each decade of life, but remain the same in men, therefore leading to higher cholesterol levels in women by 55 to 64 years.[5] However, a Canadian study found that women are less likely than men to be treated for hyperlipidemia with statin drugs.[4]

Metabolic syndrome is a cluster of risk factors that have demonstrated increasing importance with regard to cardiovascular and cerebrovascular risk.[6] The presence and implications of various

components of metabolic syndrome vary among men and women. For example, with regard to the diagnosis of metabolic syndrome, waist circumference and low high-density lipoprotein levels were major contributors for the diagnosis in women, whereas hypertension was the major contributor in men.[7] Certain combinations of risk factors have been shown to act synergistically. One such combination is hypertension and low high-density lipoprotein cholesterol, which yields a greater than expected risk of developing atherosclerosis than either condition alone, particularly in women.[8] Furthermore, women with any single metabolic syndrome factor or combination of factors averaged twice the risk of developing atherosclerosis compared with men.[8] Another study[9] assessed for early atherosclerosis by measuring intima media thickness and the extent of plaques in carotid arteries of men and women with metabolic syndrome and found that women had a greater likelihood of developing atherosclerosis compared with men.

Increased body mass index (BMI) has been associated with increased stroke risk in a near-linear fashion.[10] In a Korean study,[10] the trend was associated more strongly with young women (<50 years) and an ischemic-type stroke.[10] Even when correcting for comorbidities such as cholesterol, glucose, and hypertension, the association remained, indicating that BMI is, in fact, an independent stroke risk factor.[10]

Migraine with aura is a stroke risk factor that is more common in women than in men. A history of migraine headache with aura has been associated with a greater risk for subclinical cerebellar posterior circulation infarcts compared with the general population. In addition, women with a history of migraine with aura had more deep white matter lesions than men.[11] The risk of ischemic stroke increases with a frequency of more than 12 migraine (with aura) attacks per year.[12] The mechanisms leading to ischemic stroke are likely a combination of several factors, including vasospasm, endothelial dysfunction, hypercoagulability, oxidative stress, and cortical-spreading depression.[13] Another consideration is the strong association between migraine with aura and a patent foramen ovale, which together confer a greater risk of stroke than migraine alone.[13] The management of patent foramen ovale in the setting of stroke and migraine has been a controversial topic for several years. Routine patent foramen ovale closure for patients with migraine with aura and cryptogenic stroke is not supported by currently available data.[14,15]

Polycystic ovarian syndrome (PCOS) is a female-specific risk factor for cardiovascular disease. PCOS affects 5% to 10% of adolescent girls and young adult women, and is characterized by two of the following three criteria: hyperandrogenism, oligomenorrhea or amenorrhea, and polycystic ovaries.[16] A case–control study reported that women with PCOS evaluated for subclinical risk factors of vascular disease were more likely than control subjects to have classic stroke risk factors, including glucose intolerance, dyslipidemia, and inflammatory markers as well as decreased vasodilation during reactive hyperemia, indicating early atherosclerosis.[17]

The Effect of Estrogen on Stroke Risk

ENDOGENOUS HORMONES

Many observational studies have demonstrated that women have a lower risk of stroke and cardiovascular disease compared with men of the same age until around age 85, when the incidence of stroke increases among women.[18] An analysis from the Framingham Heart Study found that women with natural menopause before age 42 years had twice the risk for ischemic stroke compared with women who experienced natural menopause after the age of 42.[19] These findings suggest that early depletion in levels of circulating estrogens, specifically 17 β-estradiol (E2) leads to a loss of the protective effect against stroke during a woman's premenopausal years. Estrogen has been studied carefully in both animal models and clinical studies, with efforts made to uncover possible mechanisms behind estrogen's cardio- and cerebrovascular protective effects. Even with the vast amount of research in this

area, our knowledge of these mechanisms remains incomplete. A better understanding will enable developments of new therapeutic interventions for the treatment, and prevention of cardiovascular and cerebrovascular disease.[20]

The cerebral circulation is unique in its composition and functionality. It is specialized with tight junctions between endothelial cells, forming the blood–brain barrier and allowing for a very controlled environment. Autoregulatory functions allow for constant blood flow even in response to changing pressures and volume. Estrogen has demonstrated various protective effects on cerebral blood vasculature, including vasodilation, suppression of inflammation, and increased mitochondrial efficiency.

Vasodilation, or decreased vascular tone, is dependent on an intact endothelium. Endothelium-derived relaxing factors, including nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor, are produced by the endothelium to mediate vasodilation. In the cerebral circulation, nitric oxide and prostacyclin are potentiated by estrogen, leading to decreased vascular tone in these specific vascular beds, which can help to prevent vascular injury resulting from shear forces.[21] Nitric oxide is the most potent of the endothelium-derived relaxing factors. Estrogen increases nitric oxide production through stimulation of endothelial nitric oxide synthase (eNOS). This occurs both through immediate effects on the plasma membrane, which enhances eNOS production through eNOS phosphorylation, as well as long-term transcriptional effects, leading to an increase in eNOS messenger RNA and protein levels.[21,22] Cerebrovascular endothelial cells have estrogen receptors (ERs; ERα and ERβ), which mediate these effects. ERα has been shown to be the primary mediator of transcriptional effects because ERα knockout mice do not demonstrate increased eNOS activity with chronic exposure to estrogen.[23] Vasomotor reactivity is dependent on a healthy endothelium that has a balance between the endothelium-derived relaxing factors. Various cardiovascular risk factors including hypertension, diabetes, smoking, and hyperlipidemia cause endothelial dysfunction through decreased bioavailability of vasodilating factors—specifically, nitric oxide. This leads to increased production of vasoconstricting factors such as endothelin, vasoconstricting prostanoids, and angiotensin II.[24] Under these pathologic conditions, endothelium-dependent changes in vascular tone are suspected to indicate early atherosclerosis.

Estrogen levels vary throughout a woman's life and fluctuate during the menstrual cycle, leading to measurable effects on vascular physiology. For example, Diomedi et al.[25] evaluated the vascular reactivity of the right middle cerebral artery to hypercapnia with transcranial Doppler ultrasonography in men and women. There was no difference in vasomotor reactivity in women during their menstrual phase compared with men. However, cerebral vasomotor reactivity was increased significantly in women during their ovulatory phase, when estrogen levels peak.[25]

Estrogen has also demonstrated effects on mitochondrial efficiency and oxidative stress, enabling increased energy production and, at the same time, decreasing reactive oxygen species, a by-product of this process. ERα has been demonstrated in cerebrovascular mitochondria, illustrating the important actions associated with ischemic stroke.[22] Specifically, estrogen increases the level of several mitochondrial proteins, including cytochrome *c*, which results in increased energy production and manganese–superoxide dismutase, a superoxide-converting enzyme. Estrogen increases the degree of vasoprotection through this mechanism during an ischemic stroke, enabling increased energy reserves and decreased reactive oxygen species during reperfusion to maximize preservation of the blood–brain barrier while minimizing edema and influx of inflammatory cells.[22]

Cerebrovascular inflammation after cerebral ischemia or injury is believed to contribute to secondary brain injury through the promotion of leukocyte infiltration into the brain, breakdown of the blood–brain barrier, hyperemia, edema, and increased intracerebral pressures. Estrogen-treated animals have lower levels of cyclooxygenase 2, which is an important enzyme that potentiates this inflammatory cascade.[23] Geary et al.[23] demonstrated a decreased acute cerebrovascular inflammatory

response to experimental stroke in animals treated with estrogen compared with ovariectomized animals, and also showed that these anti-inflammatory effects are ER mediated. Despite these beneficial effects of estrogen (mostly from animal studies), no studies have shown evidence that premenopausal women have better outcome after stroke than men.

A shorter lifetime exposure to estrogen may be associated with an increased risk of ischemic stroke.[26] One Japanese study found that girls with late-onset menarche (>17 years) had a greater risk of mortality from stroke than those who experienced the onset of menarche at younger ages.[27] Another case–control study demonstrated that a shorter estrogenic lifetime (<34 years) was an independent risk factor for stroke, yielding a 51% greater lifetime stroke risk in these individuals.[26] On the other hand, this same study found that a younger age (<13 years) at menarche was also associated with increased risk for stroke.[26] The Adventist Health Study looked specifically at stroke mortality and age at menarche and found that patients with early menarche (<11 years) experienced a greater risk of mortality with stroke.[28] The biological mechanisms surrounding these findings are poorly understood. Some theorize that these findings may be the result of excess levels of estrogen that accumulate over a lifetime and cause detrimental effects, similar to that seen with hormone replacement therapy suggesting a U-shaped association wherein in excess or insufficient estrogen exposure both increase risk of stroke.[26] Another theory suggests that estrogen exposure may be deleterious in a young, physiologically unprepared individual.[26] One population study by Kivimäki et al.[29] suggested that age at menarche is simply a marker of BMI. A greater BMI before menarche was associated with earlier age at menarche and both were associated with a greater BMI in adulthood.[29]

EXOGENOUS HORMONES: ORAL CONTRACEPTION

Exogenous hormones—specifically, oral contraceptive pills—increase the risk of stroke in young women. The hormonal dosage and an individual's preexisting comorbidities modify this risk. The dosage of estrogen seems to be associated directly with the risk of stroke, although progesterone-only birth control medications may also confer a mildly increased risk of stroke.[13] The use of low-dose oral contraception in the absence of other risk factors has not been proved to cause an increased risk of stroke and probably is not associated with an increased risk of stroke in this instance.[13] The overall risk of stroke in users of oral contraceptive pills is two times the risk of nonusers.[30] Because the overall risk of stroke is low in this age group, however, the absolute risk is only about 8 per 100,000 women.[30]

Comorbidities that are associated with a synergistically increased risk of stroke in combination with exogenous hormones include migraine with aura, tobacco abuse, thrombophilias, obesity, and hypertension.[13]

In general, oral contraception is contraindicated in the setting of migraine with aura but should be safe in women who have migraine without aura. Women with migraine with aura who use oral contraception have an eightfold greater risk of stroke than with either risk factor alone, and a 16-fold greater risk of stroke compared to women with neither risk factor.[31] When a woman with migraine also uses tobacco products and oral contraception, a synergistic increase in stroke risk is observed. This combination of factors is associated with an odds ratio (OR) of 34.4 compared with individuals possessing none of these risk factors.[31] Use of low-estrogen-containing or progestin-only oral contraceptive formulations should be considered for women with a history of migraine with aura.[32,33]

Oral contraception alters mechanisms of coagulation, and therefore patients with an underlying thrombophilia are at an increased risk for thrombotic events. This is well documented for venous thrombosis; however, few studies have evaluated the association between stroke and the use of oral contraception in the setting of an underlying prothrombotic condition. The Risk of Arterial Thrombosis in Relation to Oral Contraceptives study evaluated 193 women age 20 to 49 years with ischemic stroke and compared them with 767 control patients. The study found

that patients with factor V Leiden mutation and the MTHFR mutation (677T variant) were 1.8 times more likely to have had a stroke compared with those who lacked these mutations. Carriers of the MTHFR mutation 677T variant who used oral contraceptive pills demonstrated a fivefold increased risk of stroke compared with women with neither risk factor. Carriers of the factor V Leiden mutation who took oral contraception demonstrated an 11-fold increased risk compared with women with neither risk factor.[34]

EXOGENOUS HORMONES: OVARIAN HYPERSTIMULATION SYNDROME

Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication of in vitro fertilization. Severe OHSS results in massive ovarian enlargement, ascites, pleural effusion, oliguria, electrolyte imbalance, hemoconcentration, and thromboembolism.[35] The exact pathophysiology behind OHSS is unknown. The current understanding is that inflammatory mediators including prostaglandins, histamine, the renin–angiotensin system, and vascular endothelial growth factor result in increased vascular permeability. Proteinaceous fluid from the vasculature leaks into extravascular spaces, resulting in pleural, pericardial, and peritoneal effusions.[36] Thromboembolism resulting in either venous or arterial thrombosis is the most serious complication and is hypothesized to result from a combination of factors. Hemoconcentration may result from reduced circulating blood volumes, immobility may result from ascites, and decreased venous return may result from enlarged ovaries.[35] Most thromboses (75%) are of venous origin[35]; the remaining 25% are arterial thromboses and may affect cerebral, mesenteric, or peripheral arteries, resulting in severe morbidity.[35]

EXOGENOUS HORMONES: HORMONE REPLACEMENT THERAPY

The average age of a woman at menopause is 51, with a range in age from 40 to 60 years.[37] Clinical trials evaluating the safety and efficacy of hormone replacement therapy in postmenopausal women demonstrated that 10 years or more after menopause, hormone replacement therapy seems to cause more harm than benefit.[38]

Some studies have suggested that exogenous estrogen exhibits a differential effect on women after menopause, which varies by age—a concept known as the *timing hypothesis* or *window of opportunity hypothesis*.[13] This may actually have more to do with the level of atherosclerosis rather than age (Figure 17.1). In one animal study, no benefit of estrogen was shown in mice deficient in apolipoprotein E with mature atherosclerotic plaques. Treatment with estrogen did not slow or prevent progression of mature plaques.[39] Benefit was seen, however, in mice with less advanced atherosclerosis after treatment with estrogen. These mice demonstrated fewer signs of initial atherosclerosis, such as fatty streaks.[39] This study suggests that, during the early stages of atherosclerosis, endothelial dysfunction can be improved with estrogen replacement. In the setting of more advanced atherosclerotic lesions, however, the prothrombotic and inflammatory effects of exogenous hormones is likely to lead to progression and instability of mature atherosclerotic lesions.

The largest study of hormone replacement therapy for the prevention of cardiovascular disease and stroke was the Women's Health Initiative (WHI), a randomized trial of 16,608 healthy postmenopausal women. It demonstrated that combination estrogen and progestin replacement increased ischemic stroke by 44% (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.09–1.90).[19,40] Another arm of the study assessed 10,739 women after hysterectomy and found that women who used conjugated equine estrogen alone also had an increased risk of stroke compared with placebo (HR, 1.39; 95% CI, 1.10–1.77).[41] Subgroup analyses of these two WHI trials suggested that there was a nonsignificant reduction in the risk of coronary heart disease (CHD) in women less than 10 years postmenopause (HR, 0.76; 95% CI, 0.50–1.16) versus placebo. However, there was an increased risk of

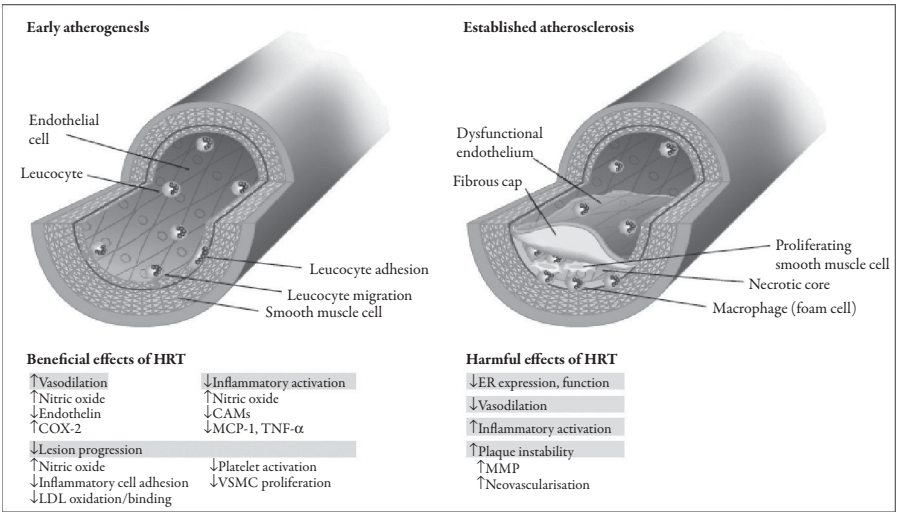

FIGURE 17.1 Hormone replacement therapy use with early versus late atherosclerosis.
Effects of hormone replacement therapy use with early vs late atherosclerosis; reproduced with permission from: Mendelsohn and Karas. Molecular and cellular basis of cardiovascular gender differences. Science 2005; 308:1583-7.

stroke with hormone therapy (HR, 1.77; 95% CI, 1.05–2.98) in women less than 10 years since menopause.[38] In women age 50 to 59 years at the time of randomization, there was no significant benefit for hormone replacement therapy against CHD (HR, 0.93; 95% CI, 0.65–1.33) or stroke (HR, 1.13; 95% CI, 0.73–1.76).[38] The results of the WHI's assessment of the timing hypothesis showed that there may be a trend toward benefit for CHD with hormone therapy early after menopause, but not for stroke.

Another randomized clinical trial, the Heart and Estrogen/Progestin Replacement Study demonstrated that hormone replacement therapy yielded an increased risk of thromboembolic events without benefit with regard to cardiovascular disease prevention.[42] The Women's Estrogen for Stroke Trial looked at estradiol for secondary prevention of stroke and concluded that it did not reduce recurrent nonfatal stroke (relative risk [RR], 1.0; 95% CI, 0.7–1.4) or mortality alone (RR, 1.2; 95% CI, 0.8–1.8).[43] In fact, women randomized to the estradiol group experienced greater mortality secondary to stroke (RR, 2.9; 95% CI, 0.9–9.0) compared with the placebo group. In addition, the estradiol group was noted to have slightly worse outcomes regarding functional and neurological deficits.[43]

The use of exogenous hormones after premature menopause is not recommended by the American Heart Association for the primary prevention of cardiovascular disease or stroke, primarily because of the WHI results.[19] Additional studies, including the Kronos Early Estrogen Prevention Study as well as the Early Versus Late Intervention Trial with Estradiol. may provide insight regarding the timing of exogenous estrogen treatment with regard to menopause.[44,45]

Stroke Risk over a Lifetime

CHILDHOOD

During childhood, the overall risk of stroke is low, regardless of gender. Two large studies assessing gender ratios in childhood stroke found that boys had a greater overall risk ratio of stroke compared with girls (1.29–1.49).[46,47] A California study of childhood stroke demonstrated a higher mortality

rate among boys with ischemic stroke compared with girls, but demonstrated no gender differences with regard to mortality rates for intracerebral hemorrhage or subarachnoid hemorrhage in these groups.[48]

Increased risk of stroke and poorer stroke outcomes in boys have been demonstrated in clinical observational studies as well as in animal models. Hypotheses for these increased risks include hormonal effects, neuroprotective mechanisms in response to cellular injury, and behavioral differences. Regarding hormonal effects, estrogen levels are higher in girls than boys throughout childhood, even in the years preceding puberty.[49] It is well known that estrogen exerts vasodilatory and anti-inflammatory effects on the vascular system; however, the fact that gender differences have been observed in stroke risk and outcome during childhood prompted further research with animal-based models to explore other possible explanations for these innate sexual differences.

Estrogen has been shown to exert a protective effect on brain tissue in the setting of various types of cell injury. For example, astrocytes derived from female neonatal rats were more resistant to oxygen–glucose deprivation compared with astrocytes derived from male rats of the same age.[50] The study was performed in a growth medium that lacked estrogen. Female astrocytes had enhanced aromatase activity, which is the mechanism through which astrocytes produce local estradiol. An aromatase inhibitor resulted in the absence of sex differences in response to oxygen–glucose deprivation, and supplementation with 17 β-estradiol conferred protection from injury in both female and male astrocytes.[50] Another study evaluated male and female rat neurons and their response to various toxins independent of circulating estradiol and found that male neurons were more susceptible to certain types of cytotoxic agents (nitrosative stress and exocytotoxicity) compared with female neurons.[51] This gender difference is secondary theoretically to the inability of XY neurons to maintain reduced glutathione intracellularly. Glutathione plays a role in cell detoxification after various injuries, including those caused by Parkinson's disease, traumatic brain injury, and cerebral ischemia.[51] A third hypothesis regarding gender differences and childhood stroke is behavioral differences—namely, physical activity. This is in light of the strikingly greater rates of stroke resulting from cervical dissection among boys compared with girls. Fullerton et al.[48] demonstrated that boys made up 74% of the total anterior cervical artery dissections (i.e., extra- and intracerebral carotid) and 87% of the posterior cervical artery dissections (i.e., vertebral). Findings from the International Pediatric Stroke Study demonstrated a similar trend.[46] Even after adjusting for dissections resulting from trauma, however, males still demonstrated a significant predominance in the incidence of spontaneous dissection, suggesting that boys may be more susceptible to dissection than girls.[46,48]

PREGNANCY AND STROKE

Epidemiology

Pregnancy and the postpartum period are associated with an increased risk of all stroke, including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Several epidemiological studies have attempted to determine the incidence and RR of stroke during pregnancy and the postpartum period, as well as to identify specific periods when stroke risk is greatest. The incidence of stroke varies, ranging from 4.3 to 18 per 100,000 deliveries for ischemic stroke and 4.6 to 11.6 per 100,000 deliveries for hemorrhagic stroke.[52] One study by Kittner et al.[53] used discharge diagnosis codes from 46 hospitals in the Baltimore–Washington, DC, area and concluded that there is no increased risk of ischemic stroke during pregnancy, but that the risk of all stroke— intracerebral hemorrhage, in particular—was increased in the 6 weeks after delivery. The RR of ischemic stroke was 8.7 during the first 6 weeks postpartum. The RR of intracerebral hemorrhage during pregnancy was 2.5, but increased substantially to 28.3 during the 6 weeks after delivery.[53] This trend—demonstrating only modest increases in the risk of stroke during the early stages of pregnancy, yet substantial

increases in risk surrounding delivery and the postpartum period—has been found in other studies as well (Figure 17.2).[54] A French study, which evaluated the pregnancy period and 2 weeks postpartum, revealed greater risks of all strokes during the postpartum period compared with pregnancy.[55] A separate study of pregnancy-related intracerebral hemorrhage in 423 subjects found that most of the increased risk was attributable to the postpartum period.[56]

Pathophysiology

The exact mechanism for this preponderance of stroke during the postpartum period is not known definitively, but thromboembolic stroke risk is likely associated with the relative hypercoagulable state of pregnancy. This change in hemostasis leads to increased levels of clotting factors and fibrinogen, along with decreased anticoagulants and fibrinolytic activity reaching a peak level of hypercoagulability around delivery and immediately postpartum. Most of the coagulation factors increase throughout the course of pregnancy. Factor VII reaches up to 10 times the levels present in nonpregnant females by the end of pregnancy.[57]. Fibrinogen is present in double the amounts by the end of gestation compared with nonpregnant levels, even when accounting for increased plasma volume.[57] Protein S decreases and activated protein C resistance increases during pregnancy.[57] In addition, the decrease in tissue plasminogen activator along with increased levels of endothelial-derived plasminogen activator inhibitor 1, placenta-derived plasminogen activator inhibitor 2, and thrombin activatable fibrinolysis inhibitor result in an overall decrease in fibrinolysis.[57] These changes gradually return to the nonpregnant state around 4 weeks postpartum.[57] Hemostatic changes are probably related to hormonal changes during pregnancy to protect against fatal hemorrhage at the time of placental separation.[57]

The etiology of intracerebral (excluding subarachnoid and subdural) hemorrhage in pregnant and postpartum females is often related to severe hypertension in the setting of preeclampsia and eclampsia. Hemodynamic changes may also contribute to this increased risk—particularly around delivery, when elevations in venous blood pressure cause increased cardiac output and increased arterial

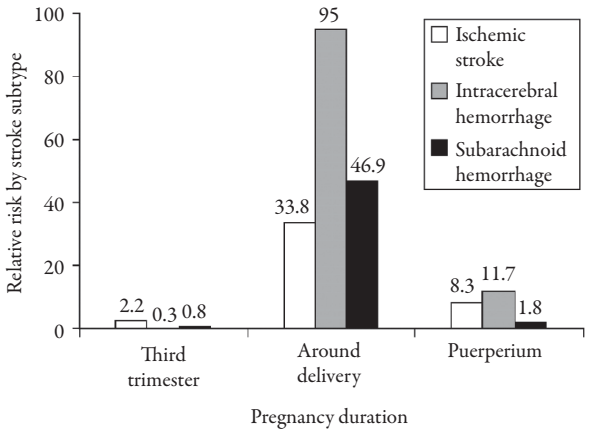

FIGURE 17.2 Risk of stroke in women during the third trimester and the peri- and postpartum periods versus risk of nonpregnant women and women in their first two trimesters.[54]
HRT-hormone-replacement therapy. CAMs-cell adhesion molecules. COX-2-cyclooxygenase-2. MCP-1-monocyte chemotactic protein 1. TNF-α-tumor necrosis factor α. VSMC-vascular smooth muscle cell. LDL-low-density lipoprotein. ER-oestrogen receptor. MMP-matrix metalloproteinase protein. Reproduced from Mendelsohn and Karas,[67] by permission of the American Association for the Advancement of Science.

pressures.[52] These hemodynamic changes return to nonpregnant norms around 2 to 6 weeks postpartum.[52] The increased venous and arterial pressures may increase the risk of hemorrhagic stroke, particularly in the setting of underlying pathology such as a cerebrovascular malformation or an aneurysm.[52]

Mechanisms and Risk Factors

Causes of stroke unique to pregnancy include preeclampsia, eclampsia, peripartum cardiomyopathy, postpartum cerebral angiopathy, amniotic fluid embolism, air embolism, and choriocarcinoma.[52] Postpartum cardiomyopathy is a cause of cardioembolic or watershed stroke specific to pregnancy and is defined as unexplained cardiac failure during the ninth month of gestation or the 5 months after delivery.[58] It is rare in the United States overall, affecting about 1 in 3000 to 4000 pregnancies. Within the United States, black and multiparous women are more commonly affected.[52,58] The incidence of postpartum cardiomyopathy is much more common among Haitians, affecting 1 in 350 to 400 deliveries.[59] The exact pathophysiology of postpartum cardiomyopathy is currently not known, but several studies have identified antibodies against cardiac tissue implicating a possible autoimmune mechanism.[59] The condition is associated with high mortality and recurrence with subsequent pregnancies.[60]

Amniotic fluid and air emboli are rare causes of stroke. An amniotic fluid embolism develops when amniotic fluid is forced into the maternal circulation from uterine veins. Rather than focal ischemic infarction, this results more commonly in an acute hemodynamic collapse and disseminated intravascular coagulation, causing global cerebral hypoperfusion.[52,58] However rarely, an amniotic fluid embolus or air embolus may cause a focal ischemic stroke by crossing from the venous to the arterial system via a patent foramen ovale.[52,58] Air embolus can develop at any point during pregnancy but is more common during delivery, particularly via cesarean section.[52,58]

Choriocarcinoma is an important but rare cause of hemorrhagic stroke, which occurs most commonly in molar pregnancies but also may occur in live births, or ectopic or terminated pregnancies.[58] These tumors are highly vascular and arise from gestational trophoblasts. Choriocarcinoma commonly metastasizes to the lungs, liver, and brain.[58] They tend to bleed as a result of their vascular nature and tend to cause subarachnoid hemorrhage or intraparenchymal hemorrhage.[58] In the brain, the tumor typically metastasizes to the gray–white junction, resulting in an intraparenchymal hemorrhage that may be mistaken easily for hemorrhagic transformation of ischemic stroke.[52]

Preeclampsia and eclampsia not only confer an increased risk of both ischemic and hemorrhagic stroke throughout the course of a pregnancy, but also increase the risk of ischemic stroke remote from pregnancy.[61] Preeclampsia is defined as new-onset hypertension (diastolic blood pressure, ≥90 mmHg) with proteinuria (>300 mg protein in a 24-hour period) after 20 weeks' gestation.[62] Preeclampsia is described as severe when the systolic blood pressure is at least 160 mmHg and/or the diastolic blood pressure is 110 mmHg along with proteinuria of 5 g per day or more.[61] About 1% to 2% of patients with severe preeclampsia will develop generalized tonic clonic seizures, meeting the criteria for eclampsia.[61] In addition to hypertension and proteinuria, preeclampsia may affect multiple organ systems, resulting in hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; disseminated intravascular coagulation; acute pulmonary edema; and acute renal failure.[61] Fetal complications can accompany the maternal effects, resulting in fetal growth restriction, small size for gestational age, reduced amniotic fluid, and placental insufficiency, which may result in fetal hypoxia and hypoperfusion.[62] Aside from ischemic and hemorrhagic stroke, complications of preeclampsia and eclampsia include reversible posterior leukoencephalopathy syndrome or posterior reversible encephalopathy syndrome characterized by vasogenic edema in the occipital or parietal lobes, which can be identified easily on cerebral imaging.[61] Clinical symptoms include seizures, encephalopathy, or visual field deficit resulting from occipital lobe involvement. Reversible cerebral vasoconstriction

syndrome is another syndrome caused by preeclampsia. The unique clinical feature is thunderclap headache with or without focal neurological deficits. Neuroimaging reveals vasoconstriction that affects medium and large arteries that may or may not cause infarction. These vessel abnormalities typically reverse after about 12 weeks.[63]

Women with preeclampsia and eclampsia during pregnancy are four times more likely to develop hypertension after delivery and have a twofold greater risk for both ischemic heart disease and stroke later in life.[61] Some studies have demonstrated earlier onset of menopause in women with preeclampsia compared with those without preeclampsia, as well as greater levels of biomarkers that indicate endothelial dysfunction.[64] Persistent endothelial dysfunction has been demonstrated in women with a history of preeclampsia in studies using brachial artery flow-mediated dilation responses evident 1 year after delivery.[65]

Aspirin for the Prevention of Preeclampsia during Pregnancy

A recent meta-analysis assessed the effectiveness of low-dose aspirin for the prevention of preeclampsia in high-risk women. The criteria used to identify women who were at high risk included previous history of preeclampsia, preexisting hypertension, family history of preeclampsia or vascular disorders, maternal age younger than 20 years or older than 40 years, and gestational diabetes mellitus, as well as those patients who were identified to be at high risk with Doppler ultrasonography, the roll-over test, or the angiotensin II sensitivity test.[66] Overall, these women benefited from low-dose aspirin (<100 mg/day) with a 21% reduction in the risk of preeclampsia (RR, 0.79; 95% CI, 0.65–0.97).[66] In women with low risk for the development of preeclampsia, no risk reduction was observed. One systematic review and meta-analysis of the major randomized controlled trials in this subject found similar results with no benefit in the low-risk group (RR, 0.95; 95% CI, 0.81–1.11), but modest benefit in the high-risk group (RR, 0.87; 95% CI, 0.79–0.96) with low-dose aspirin.[67] Another study found a reduction in preeclampsia (OR, 0.86; 95% CI, 0.76–0.96), perinatal death (OR, 0.79; 95% CI, 0.64–0.96), spontaneous preterm birth (OR, 0.86; 95% CI, 0.79–0.94), and increased mean birth weight without increased risk of placental abruption, fetal hemorrhage, or other neonatal bleeding in patients treated with low-dose aspirin.[68]

Stroke Prevention during Pregnancy

There are scant data available regarding preventative therapies for stroke during pregnancy. Aspirin during pregnancy, particularly during the first trimester, has been associated with an increased risk of congenital anomalies and malformations in both human and animal studies. Because of the limited information available and absence of randomized controlled trials, guidelines vary regarding stroke prevention during pregnancy. The American Heart Association/American Stroke Association recommends consideration of low-molecular weight heparin or unfractionated heparin during the first trimester, followed by a low-dose aspirin in women who would benefit from antiplatelet therapy outside of pregnancy.[69] Guidelines regarding treatment of thrombophilia during pregnancy by the American College of Chest Physicians recommend low-dose aspirin in combination with prophylactic or intermediate-dose unfractionated heparin exclusively for women with antiphospholipid antibody syndrome.[70] They also recommend no prophylaxis for women with inherited thrombophilia or prior miscarriages without antiphospholipid antibody syndorme.[70] Regarding treatment of high-risk thromboembolic conditions, including thrombophilias and mechanical heart valves, the American Heart Association/American Stroke Association recommends low-molecular weight heparin or unfractionated heparin throughout pregnancy.[69] Alternatively, patients may be treated with low-molecular weight heparin or unfractionated heparin during their first trimester, transition to warfarin during the second trimester through the

middle of the third trimester, then convert back to using unfractionated heparin or low-molecular weight heparin until they deliver.[69]

Tissue Plasminogen Activator Use During Pregnancy

Recombinant tissue plasminogen activator is listed as category C regarding its safety in use during pregnancy. It has not demonstrated teratogenicity in animal studies and does not cross the placenta. Although pregnancy is a relative contraindication for administration of recombinant tissue plasminogen activator because of the risk of systemic bleeding, there have been several reports of its successful use during pregnancy. Overall, it appears that thrombolytics generally yield positive results when used during pregnancy; however, the risks and benefits must be weighed carefully in each case.[71] The safety and efficacy of mechanical thrombectomy in pregnancy has not been studied formally; however, case studies have demonstrated positive outcomes in this popuation.[71]

MENOPAUSE AND STROKE RISK

The perimenopausal transitional period is characterized by various endocrine and biological changes, resulting in clinical manifestations and eventually leading to the permanent cessation of menstruation. Menopause is defined formally by the absence of a menstrual period for 1 year and typically affects women ages 40 to 60 years with a mean age of 51 years.[37] During menopause, levels of sex hormones decline. Specifically, estradiol levels decline by about 60%.[37] Levels of testosterone decrease by about 50% between 20 to 40 years of age, but remain stable throughout the perimenopausal period and may even increase after menopause, leading to a relative androgen excess.[72,73] These hormonal changes, characterized by the loss of estrogen and the excess of androgens, likely contribute to other accumulated risk factors for stroke, leading to an overall increased risk of stroke during the postmenopausal years. Although the role of age at menopause is still controversial,[37] two studies suggest this might be an important risk factor for stroke. The first analysis was from the Framingham Heart Study, which showed that women with menopause at age 42 or younger had twice the risk of stroke.[19] A second study comes from the Multi-Ethnic Study of Atherosclerosis, which demonstrated that women with menopause onset at age 46 or younger had a twofold increased risk for both stroke and CHD.[74] More research is needed to understand more completely the reasons for earlier menopausal transitions and how they might be tied to stroke risk.[19]

Primary Prevention and Stroke Therapies

Multiple studies demonstrated that men are more likely to be on antiplatelet therapy before experiencing a stroke.[1,3] This may be a result of their propensity for myocardial infarction before stroke. Among stroke survivors, men older than 85 years were more likely than women to receive aspirin, whereas both genders received similar treatment between the ages of 65 years and 84 years in a Canadian–based study.[3] Regarding primary prevention for stroke, a meta-analysis of studies of men only, women only, and both genders showed that aspirin was associated with a 17% reduction in stroke events with no effect on myocardial infarction in women, whereas men had a 32% reduction in myocardial infarction but no impact on stroke risk.[75]

Several recent studies have demonstrated discrepancies among stroke treatment between genders. Several studies have demonstrated no difference regarding treatment with anticoagulants between the sexes despite the increased frequency of atrial fibrillation among women.[1,3,76,77] Gender differences have also been found with regard to the risk of thromboembolism and bleeding complications.[78] The Canadian Registry of Atrial Fibrillation found that women were older at the time of

presentation, with faster heart rates in atrial fibrillation. They were half as likely to receive anticoagulant therapy but twice as likely to be treated with aspirin. Of the patients who were treated with warfarin, women were 3.4 times more likely to experience a major bleeding complication than men.[78]

Another secondary prevention treatment that is performed more commonly in men than in women is carotid endarterectomy.[4,79,80] One study found that male stroke survivors were more likely to have carotid atherosclerosis. When restricting the analysis to patients with carotid disease, no gender difference was found, indicating that these gender disparities may be the result of fundamental differences in the pathophysiology of stroke among males and females.[79]

Sex Differences in Stroke Outcomes

Overall, the age-adjusted risk for stroke is greater in men compared with women. Throughout the course of an entire lifetime, however, strokes occur more commonly, cause greater disability, and result in greater mortality in women. Studies evaluating disability after stroke revealed that, even after controlling for age, race, education, and marital status, women were more likely to require assistance with their activities of daily living compared with men.[1,18,81] In general, mortality rates are similar in men and women. However, because of longer life spans in women, this population makes up 60% of the total deaths resulting from stroke.[19] These factors underscore the importance of stroke prevention and risk factor modification in women, particularly as they age.

Conclusion

In conclusion, there are several factors unique to women with regard to stroke. Understanding gender differences in stroke pathophysiology as well as stroke risk factors that are unique to women will enable physicians to provide individualized care. Further research is warranted to enable a better understanding of the roles of estrogen and exogenous hormone therapy, pregnancy, and menopause to develop the best prevention strategies for women across their life span.

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18

MIGRAINE AND RISK OF CEREBROVASCULAR DISEASE AND STROKE

Alessandro Pezzini

Introduction

Migraine is a common, chronic, multifactorial neurovascular disease affecting between 10% and 20% of the population. The clinical presentation is heterogeneous and includes recurrent headache attacks, associated symptoms of vegetative disturbance, and hypersensitivity of various functional responses of the nervous system.[1,2] About one third of migraineurs experience additional transient neurological symptoms, mostly involving the visual system before or during a migraine attack, which are known as *migraine aura*.[2] The International Headache Society (IHS) has established gold-standard criteria for the diagnosis of migraine.[3] Although migraine with aura (MA) and migraine without aura (MO) are the most common forms, the IHS also acknowledges, for example, certain forms lacking one diagnostic criterion as probable migraine as well as rare familial monogenetic forms. Neurological aura symptoms (MA) are present in a percentage of patients that varies, according to the ascertainment criteria and the study design, from up to one third in population-based studies to a lower frequency in clinic-based studies.[3–5]

Although migraine attacks may be acutely disabling, the traditional view is that they do not result in long-term consequences to the brain. Contrary to this assumption, new data have emerged that emphasize the high prevalence of migraine among young individuals with stroke as well as a dysfunction of cerebral arteries during migraine attacks and the finding of silent infarctlike brain lesions in migraineurs, thus leading to the hypothesis that a comorbidity between migraine and cerebral ischemia exists.[6] Despite this, a careful evaluation of the existing data on the relation between migraine and stroke raises more questions than provides a clear picture.

Migraine as a Risk Factor for Ischemic Stroke

Apart from historical anecdotal reports pointing toward a unidirectional causal relation,[7] the first epidemiological suggestion that migraine may be an independent risk factor for stroke came from the Collaborative Group for the Study of Stroke in Young Women, published in 1975,[8] which showed a doubling of the relative risk (RR) of stroke in persons with migraine compared with control subjects. Since then, the association of migraine with the risk of stroke has been investigated in a number of clinic-based and population-based studies (Table 18.1) and three meta-analyses,[9–11] the most recent of which included 13 case–control studies and 8 cohort studies.[11] All the 21 observational studies included in this meta-analysis addressed the potential confounding effect of age and sex in effect estimates. Some studies also addressed the potential confounding effects of hypertension (19 studies), smoking (16 studies), oral contraceptive use (10 studies), cholesterol (9 studies), cardiac disease (8 studies), family history of migraine or stroke (3 studies), and postmenopausal hormone therapy (2 studies).

According to this meta-analysis, the pooled, adjusted odds ratio (OR) of ischemic stroke among patients with any type of migraine is 2.04 (95% confidence interval [CI], 1.72–2.43). The ORs for people with MA and MO are 2.25 (95% CI, 1.53–3.33) and 1.24 (95% CI, 0.86–1.79), respectively, whereas the pooled, adjusted OR for ischemic stroke in studies of women migraineurs only versus nonmigraineurs was 2.89 (95% CI, 2.42–3.45). These results are in apparent disagreement with those of the previous study by Etminan et al.,[9] which reported a statistically significant, although less strong than for MA, risk of stroke for MO (pooled RR, 1.83; 95% CI, 1.06–3.15), and instead support the findings of Schurks et al.[10] (Table 18.2).

The discrepancy with the first meta-analysis is likely the result of the differential inclusion of a large study by Stang et al.,[12] which reported a negative association with ischemic stroke in patients with migraine. Overall, based on these findings, it seems at least unlikely that MA and MO are equally associated with ischemic stroke. Currently, because the association is not as robust, whether MO should be considered a stroke risk factor remains unclear. Similarly, because the prevalence of migraine is three times lower in men than in women, the association is more uncertain in men. There are also strong arguments to hypothesize that the risk of brain ischemia is greater for those with a greater frequency of migraine attack[13,14] and for women with MA who smoke cigarettes and use oral contraceptives.[15]

Is this enough to conclude that migraine is a risk factor for stroke? As pointed out by many authors, most of these studies are subject to several limitations.

First, a consistent definition for migraine is often lacking. Accurate diagnosis of migraine is important to avoid nondifferential misclassification of exposure, which would bias the risk estimate toward showing no association. If this is the case, however, we cannot but assume that the increased risk of stroke emerging from the pooled analysis of data from observational studies is rather an underestimation of the effect. As such, it should be retained as an argument in favor of the reported association between migraine and stroke. Furthermore, in case–control studies an interviewer bias and a recall bias can arise as possible consequences of the retrospective design.

Second, potential bias in the selection of patients should be taken into account. At least theoretically, a referral bias may exist if stroke patients with migraine were referred to the recruiting centers more frequently than stroke cases without migraine, or if the investigators were more prone to include stroke patients with migraine than without migraine. A further bias could be the consequence of a stroke–migraine misdiagnosis. Because transient ischemic attacks are sometimes difficult to distinguish from an attack of MA, especially when the aura occurs without headache, and migraine with

TABLE 18.1

In Epidemiological Studies, Risk of Ischemic Stroke According to Type of Migraine

Authors, year	Methodology	Population	Subjects' characteristics	Patients with migraine		Migraine Status		Adjustment for covariates and confounders	Notes
				ischaemic stroke cases (%): controls (%)	Any RR (95% CI)	MA RR (95% CI)	MO RR (95% CI)		
Collaborative Group for the Study of Stroke in Young Woman, 1975	Case-control study	Women aged 14-44yrs	430 stroke cases, 429 hospital control subjects and 451 neighborhood control subjects	48(34.2) : 234(26.5)	2.0 (1.2 to 3.3)*	NS	NS	Age, contraceptives, smoking	* RR calculated for ischemic stroke using neighbor controls for comparison
Henrich, 1989	Case-control study	Men and women aged 15-65 yrs	89 ischemic stroke cases, 178 hospital controls	17(19.1) : 20(11.2)	1.8 (0.9 to 3.6)	2.6 (1.1 to 6.6)	1.3 (0.5 to 3.6)	NS	
Marini et al, 1993	Case-control study	Men and women aged 15-44 yrs	308 ischemic stroke or TIA cases, 308 hospital controls and 308 population controls	46(14.9) : 57(9.2)*	1.91 (1.05 to 3.5)	14.85 (1.8 to 124)	1.6 (0.9 to 3.0)	Diet, obesity, alcohol, smoking, contraceptives, hypertension, diabetes, paroxysmal disorders, hematocrit, cholesterol, triglycerides, HDL, cardiac and carotid abnormalities	* from ischemic stroke and TIA cases
Tzourio et al, 1993	Case-control study	Men and women aged 18-80 yrs	212 ischemic stroke cases, 212 hospital controls	41(19.3) : 34(16)	1.3 (0.8 to 2.3)	1.3 (0.5 to 3.8)	0.8 (0.4 to 1.5)	NS	

Lidegaard, 1995	Case-control study	Women aged 15-44 yrs	497 stroke cases, 1,370 population controls	64(12.9) : 66(4.8)	2.8 *	NS	NS	Hypertension, other predisponsing diseases	* 95% CI not reported; p< 0.01;
Tzourio et al, 1995	Case-control study	Women aged <45yrs	72 ischemic stroke cases, 173 hospital controls	43(59.7) : 52(30)	3.5 (1.8 to 6.4)	6.2 (2.1 to 18)	3.0 (1.5 to 5.8)	Age, smoking, hypertension, contraceptives	
Carolei et al, 1996	Case-control study	Men and women aged 15-44 yrs	308 ischemic stroke or TIA cases, 591 hospital controls and population controls	24(13.9) : 34(10.3)	1.3 (0.7 to 2.4)	1.0 (0.5 to 2.0)	8.6 (1.0 to 75)	Obesity, alcohol, smoking, hypercholesterolaemia, hypertrigliceridaemia, low HDL-cholesterol, age, contraceptives, hypertension, diabetes	
Haapaniemi et al, 1997	Case-control study	Men and women aged 16-60 yrs	506 ischemic stroke cases, 345 hospital controls	86(17) : 42(12.2)	2.1 (1.05 to 2.9)*	NS	NS	Hypertension, cardiac disease, current smoking, diabetes, alcohol, age, body mass index	* RR reported for male subgroup
Chang et al, 1999	Case-control study	Women aged 20-44 yrs	291 ischemic, hemorragic or unclassified arterial stroke cases, 736 hospital controls	26(30.2) : 26(11.8)	3.5 (1.3 to 9.6)	3.81 (1.3 to 11.5)	2.9 (0.7 to 13.5)	Hypertension, smoking, education, family history of migraine, alcohol, social class	
Donaghy et al, 2002	Case-control study	Women aged 20-44 yrs	86 ischemic stroke cases, 214 hospital controls	26(30.2) : 26(12.1)	NS	8.4 (2.3 to 30.1)	2.2 (0.5 to 10.1)	NS	

(*continued*)

TABLE 18.1

Continued

Authors, year	Methodology	Population	Subjects' characteristics	Patients with migraine		Migraine Status		Adjustment for covariates and confounders	Notes
				ischaemic stroke cases (%): controls (%)	Any RR (95% CI)	MA RR (95% CI)	MO RR (95% CI)		
Schwaag et al, 2003	Case-control study	Men and women aged <46 yrs	160 ischemic stroke and TIA cases, 160 hospital controls	37(23.1) : 20(12.5)*	2.1 (1.2 to 3.8)*	NS	NS	NS	* from ischemic stroke and TIA cases
Nightingale et al, 2004	Nested case-control study	Women aged 15-49 yrs	190 ischemic stroke cases, 1,129 population controls	16(8.4) :44(3.9)	2.3 (1.04 to 5.2)	NS	NS	NS	
MacClellan et al, 2007	Case-control study	Women aged 15-49 yrs	386 ischemic stroke cases, 614 population controls	180(47) : 254(42)	NS	1.5 (1.1 to 2.0)	1.0 (0.6 to 1.5)	Age, race, geographic region, study period	
Naess et al, 2004	Case-control study	Men and women aged 15-49 yrs	232 ischemic stroke cases, 217 population controls	187(33) : 217(25)	1.7 (0.9 to 3.2)	NS	NS	NS	
Becker et al, 2007	Cohort study	Poulation from UK/ General Practice Research Database aged 79 yrs or younger	103,376 subjects (51,688 migraine sufferers)	NS	2.85 (1.88 to 4.30)	NS	NS	Age, gender, general practice, calendar time, body mass index, smoking status, diabetes mellitus, hypertension, and dyslipidemia.	

Buring et al, 1995	Cohort study	Male physicians aged 40-84 yrs participants of the Physicians' Health Study	22,071 subjects (1,479 migraine sufferers)	17(1.1) : 154(0.7)	2.0 (1.1 to 3.6)	NS	NS	Age, smoking, elevated cholesterol, diabetes, hystory of angina, body mass index, parental hystory of premature MI, alcohol consumption, excercise, randomized treatment assignment, hypertension	
Merikangas et al, 1997	Cross sectional study	Population-based national probability sample	12,220 subjects (1,109 migraine sufferers)	NS	2.1 (1.5 to 2.9)*	NS	NS	Age, sex, smoking, hypertension, diabetres, cholesterol, heart condition, alcohol	* from all stroke cases
Velentgas et al, 2004	Cohort study	Population from United Health Care	260,822 (13,0411 migraine sufferers)	216(0.16) : 98(0.07)*	1.6 (1.3 to 2.1)*	NS	NS	Age, sex, year of cohort entry, comorbidities in years prior to study entry, oral contraceptive, estrogen replacement therapy	* from all stroke cases
Hall et al, 2004	Cohort study	Popoulations from General Practice Research Database	14,0814 subjects (63,575 migraine sufferers)	71(0.11) : 31(0.04)	2.5 (1.6 to 3.8)	NS	NS	Hypertension, diabetes, cardiac disease, obesity, hypercholesterolemia, oral contraceptive, smoking	

(*continued*)

TABLE 18.1

Continued Authors, year	Methodology	Population	Subjects' characteristics	Patients with migraine		Migraine Status		Adjustment for covariates and confounders	Notes
				ischaemic stroke cases (%): controls (%)	Any RR (95% CI)	MA RR (95% CI)	MO RR (95% CI)		
Kurth et al, 2005	Cohort study	Women aged 45 yrs or older partecipants of the Women's Health Study (WHS)	39,754 subjects (385 ischemic, hemorragic or unclassified stroke cases)	41(13.2) : 5126(13)	1.4 (0.97 to 1.9)*	1.7 (1.1 to 2.7)*	1.1 (0.7 to 1.8)*	Age, hypertension, menopausal status, oral contraceptives use, alcohol consumption, randomized aspirin assignment, exercise, body mass index, smoking status, postmenopausal hormone therapy, diabetes, cholesterol	* calculated as Hazard Ratio (95%CI) for ischemic stroke

Stang et al, 2005	Cohort study	Men and women aged 45-64 yrs participants of the Atherosclerosis Risk in the Communities(ARIC) Study	12,750 subjects (1,015 migraine sufferers)	NS	NS	2.8 (1.6 to 4.9)	0.8 (0.4 to 1.7)	Age, sex, race/ center, hypertension medication use, aspirin use, NSAID use, systolic blood pressure, diabetes, parental hystory of migraines, smoking, pack-years of smoking, cholesterol	
Kurth et al, 2007	Cohort study	Men aged 40-84 yrs participants of the Physicians' Health Study	20,084 subjects (1,449 migraine sufferers)	51(3.5): 699(3.7)	1.1 (0.8 to 1.5)*	NS	NS	Age, hypertension, diabetes, smoking, exercise, body mass index, alcohol, cholesterol, parental hystory of MI before age 60 yrs, randomized treatment assignments	* calculated as Hazard Ratio (95%CI) for ischemic stroke

CI, confidence interval; HDL, high-density lipoprotein; MA, migraine with aura; MI, myocardial infarction; MO, migraine without aura; NS, not specified; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk; TIA, transient ischemic attack.

TABLE 18.2

Summary of the Relative Risk (95% confidence interval) between Migraine and Ischemic Stroke in Three Meta-analyses of Observational Studies

	Etminan et al [9]	Schurks et al [10]	Spector et al [11]
Overall Migraine	2.16 (1.89 – 2.48)	1.73 (1.31 to 2.29)	2.04 (1.72 – 2.43)
Migraine with aura	2.27 (1.61 – 3.19)	2.16 (1.53 – 3.03)	2.25 (1.53 – 3.33)
Migraine without aura	1.83 (1.06 – 3.15)	1.23 (0.90 – 1.69)	1.24 (0.86 – 1.79)

prolonged neurological aura (lasting longer than 24 hours) may mimic stroke, the end results of such misclassifications would be an overestimation of the prevalence of migraine in patients and, therefore, an overestimation of the risk.

Third, in some of the studies the influence of several confounders on the final results was not considered, whereas others were not controlled for. Actually, a number of factors might influence the risk of stroke in people with migraine. For example, migraine has been associated with an increased prevalence of traditional cardiovascular risk factors in several studies,[16–18] although more recent analyses have shown consistently that the increased risk of ischemic stroke in people with MA is seen mainly in those with a favorable vascular risk profile.[15,19–21] Furthermore, the use of medications with a potential effect on stroke risk (i.e., antihypertensive agents) or the presence of risk factors for both migraine and stroke, such as antiphospholipid antibodies, could also be factors affecting the observed association of migraine with stroke.

Fourth, most studies are limited to younger individuals (age 45 years or younger), leaving the association between migraine and stroke among the elderly unclear and ignoring the fact that migraine may start later in life. In these regards, although the available data provide arguments to support the assumption that migraine may have some influence on stroke risk even in older subgroups, effect modification by age appears evident from prospective studies, the risk of stroke in persons with migraine being greater in younger age groups and decreasing over time, with only a modest increase of risk among the elderly (age 60 years or older). Whether this is the consequence of the greater effect of other major risk factors for ischemic stroke with increasing age or of the influence of these factors on the mechanisms by which migraine may lead to stroke remains to be determined.

The association between migraine and increased prevalence of cardiovascular risk factors, and the observation that the vascular dysfunction of migraine may also extend to coronary arteries,[22–24] has led recently to speculation that migraine, especially MA, may not only be associated with increased risk of stroke, but also with other vascular events. To address this specific issue, data from two large-scale prospective cohorts of apparently healthy subjects, one including women age 45 years or older participating in the Women's Health Study (WHS), and the other including men age 40 to 84 years participating in the Physicians' Health Study, were analyzed recently. Data from the 27,840 women included in the WHS indicated an association between overall migraine and major ischemic cardiovascular disease after a mean of 10 years of follow-up. Such an increased risk for any ischemic vascular event was only apparent for women with MA, and turned out to be approximately twofold greater compared with that observed in women who did not report any history of migraine, after adjusting for traditional cardiovascular risk factors. In contrast, no increased risk for any ischemic vascular event was observed in women who reported MO.[23] With regard to men, data from the 20,084 male physicians included in the Physicians' Health Study indicated an association between overall migraine and major cardiovascular disease. Compared with nonmigraineurs, men who reported migraine had an increased risk for major cardiovascular disease, including ischemic

stroke, myocardial infarction, coronary revascularization, angina, and ischemic cardiovascular death. Men who were younger than 55 years of age had increased risk of stroke that was not apparent in the older age group,[25] thus confirming the age-dependent effect of migraine on disease risk. At least theoretically, it cannot be excluded that the relation between migraine and stroke might be just one aspect of a more generalized effect of chronic, nonspecific headache. Actually, the evaluation of cross-sectional data from the first U.S. National Health and Nutrition Examination Survey showed a 1.5-fold increased risk of stroke in both patients with migraine and patients with severe nonspecific headache compared with subjects without these conditions.[26] More recently, in a prospective cohort study derived from the FINRISK study, Jousilahti et al.[27] found a significant association between chronic nonspecific headache and stroke among men. However, because of the diagnostic criteria adopted in the National Health and Nutrition Examination Survey, it is likely that most cases of severe nonspecific headache actually experienced migraine. Similarly, the lack of a precise definition of migraine represents a major limitation for a correct interpretation of the data proposed by Jousilahti et al.[27] These drawbacks, in association with recent data from large, prospective cohorts that show no association between nonmigraine headache and stroke, make the hypothesis of a major effect of any nonspecific headache on the risk of cerebral ischemia very unlikely.

Classification of Migraine-Related Stroke

One of the most relevant drawbacks in unraveling the complex relation between migraine and cerebral ischemia is the lack of consistency in the definition of migraine-related stroke. In the attempt to categorize this entity, four major situations might be considered.[28] First, cerebral ischemia can occur in the course of an attack of MA, causing true migraine-induced infarction. Second, migraine and stroke share a common underlying disorder that increases the risk of both diseases. Third, migraine might cause stroke because of the interactions with other risk factors involved in stroke pathogenesis. Fourth, stroke may mimic migraine.

Migraine-Induced Stroke: The Migrainous Infarction

It has long been recognized that, although a rare event, stroke may occur during the course of a migraine attack with aura. This phenomenon suggests a causal relationship between migraine and stroke. According to the IHS migraine classification, "migrainous infarction" is defined as a stroke occurring during a typical attack of MA.[3] Patients have a history of MA and the neurological deficits occur in the same vascular distribution as the aura, and are associated with an ischemic brain lesion in a suitable territory demonstrated by neuroimaging. A major criterion of this cause of infarction is that other possible causes are excluded by appropriate investigations. However, which investigations should be done and when are not clear, and the absence of causes other than migraine does not necessarily imply that migraine is the cause, given that about half of the ischemic strokes in young adults have no detectable cause. Furthermore, stroke has been reported in people experiencing MO, and in two large series this was more common than infarcts during attacks of MA.[29,30] Criteria for true migraine-induced stroke should include potentially modifying risk factors that might be present and that are critical to understanding the mechanisms. Last, the definition of migrainous stroke, with the stipulation that the current MA attack is typical of previous attacks, is also biased toward infarcts in the posterior cerebral artery territory, because most auras are visual in nature. According to large series, the incidence of migrainous infarction varies between 0.5% to 1.5% of all ischemic strokes, and between 10% to 14% of ischemic strokes in young patients.[26,30–33] The incidence of migraine-related infarction (per 100,000 persons per year) was estimated at 1.44 (95% CI, 0–3.07)

from the Oxfordshire Community Stroke Project prospective registry, and at 1.7 from a retrospective review of Mayo Clinic records from nearly 5000 migraineurs younger than 50 years.[34,35] In series published since the introduction of the IHS criteria, the percentage of stroke in persons younger than 45 years attributed to migrainous infarction ranges from 1.2% to 14%.[31,32,36,37] Clinical features that were described to be associated with migrainous stroke include female sex, mean age in the low to mid 30s, a history of cigarette smoking, and ischemic involvement of the posterior cerebral artery territory.[31] In summary, IHS criteria might be too strict for a correct diagnosis of migrainous infarction. Despite the limitations inherent in the diagnostic criteria and the consequent weakness of the epidemiological studies, it seems reasonable to assume that migrainous infarction does not account for all strokes occurring during migraine attacks, and, overall, it is responsible for only a minority of migraine-related infarcts.

Migraine and stroke share a common cause (symptomatic migraine)

Ischemic stroke and migraine are major clinical features of some specific syndromes, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS), and retinal vasculopathy with cerebral leukodystrophy (RVCL). The coexistence of ischemic stroke and migraine in the context of a syndrome characterized by a peculiar phenotype, proven inherited background, and chronic alterations of the wall of small cerebral arteries suggests a common pathogenic mechanism shared by these two conditions.

CADASIL is an autosomal dominant disease of vascular and smooth muscle cells due to Notch3 mutations,[38] characterized by leukoencephalopathy; small, deep infarcts; and subcortical dementia. MA is usually the first manifestation, presenting about 15 years before stroke and before the appearance of magnetic resonance imaging (MRI) signal abnormalities. MA is present in one third of symptomatic subjects and its frequency can vary greatly within the affected pedigrees. In 40% of families, more than 60% of symptomatic subjects had a history of MA,[39,40] and within some families, MA is the most important clinical aspect of the phenotype. The frequency of attacks of basilar migraine, hemiplegic migraine, migraine with prolonged aura, or isolated aura, according to the IHS diagnostic criteria, is noticeably high.[40,41] The mechanism underlying MA in CADASIL is not clear. Because it occurs before ischemic manifestations, MA is not the consequence of subcortical infarcts. In CADASIL, the absence of difference in the frequency and distribution of white matter abnormalities between patients with and without MA suggests that chronic subcortical hypoperfusion is also unlikely. Another hypothesis is that MA relates directly to dysfunction of smooth muscle cells of meningeal and cortical vessels, triggering cortical-spreading depression (CSD).[42] Furthermore, if the cell signaling abnormalities (resulting from the mutation) extend and reach neurons, the resulting hyperexcitable membrane instability could predispose to CSD.

Retinal vasculopathy with cerebral leukodystrophy is a rare inherited condition characterized by a primary microangiopathy of the brain in combination with vascular retinopathy. Migraine is a clinical finding in some cases, also including progressive visual loss, seizures, focal neurological deficits of sudden onset, cognitive worsening, renal insufficiency, and proteinuria.

Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes is associated to several mutations in mitochondrial DNA. The phenotypic expression is highly variable, ranging from an asymptomatic state to severe childhood multisystem disease with lactic acidosis. Recurrent episodes of headache (mostly migraine) are part of the clinical spectrum.

Migraine is also part of the clinical spectrum of other mitochondrial disorders, such as Leber's hereditary optic neuropathy and myoclonic epilepsy with ragged-red fibers,[43,44] and of hereditary

hemorrhagic telangiectasia (Osler-Weber-Rendu disease), an autosomal dominant vascular dysplasia characterized by a high prevalence of vascular malformations in various organs, including lung, liver, kidney, and brain, as well as by mucocutaneous teleangiectasias.[45]

MA is related classically to cerebral arteriovenous malformations (AVMs). In most cases, MA ceasing after removal of an AVM has been documented, consistent with the definition of symptomatic migraine, but there are also sparse reports of cases unchanged after surgery.[46] The possibility of a causal relation is supported indirectly by the side of aura, contralateral to the AVMs, and the side of headache, ipsilateral to the AVMs, as well as by the coexistence of MA and arteriovenous shunts in leptomeningeal angiomatosis (Sturge-Weber syndrome).[47] Besides these conditions, a number of other local or systemic vascular and blood disorders are associated with both MA and stroke, such as Moyamoya disease,[48] antiphospholipid antibody syndrome,[49] Sneddon syndrome,[50] systemic lupus erythematosus,[51] cardiac myxoma,[52] and other rare diseases[53–55] (Table 18.3).

However, as opposed to CADASIL, MA is often infrequent and sometimes probably coincidental in these disorders, and the mechanism by which they increase brain susceptibility to aura remains to be elucidated.

MIGRAINE MIMIC: MIGRAINE AS A CONSEQUENCE OF ISCHEMIC STROKE

Stroke resulting from acute structural disease is accompanied by headache and neurological signs and symptoms indistinguishable from those of migraine. This entity might be termed a *migraine*

TABLE 18.3

Disorders Associated with Stroke and with Migraine with Aura

Disorders with brain vessel wall abnormalities
CADASIL (NOTCH3 mutations)
Brain arteriovenous malformations98
Leptomeningeal angiomatosis (Sturge-Weber syndrome)
Moyamoya syndrome
Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu disease)
Sneddon syndrome
Mitochondrial disorders (i.e, MEALS)
Disorders related to COL4A1/COL4A2 mutations
Retinal vasculopathy with cerebral leukodystrophy (RVCL)
Cardiac disorders
Patent foramen ovale
Cardiac myxoma
Blood disorders
Antiphospholipid antibody syndrome
Systemic lupus erythematosus
Essential thrombocythaemia
Polycythaemia

mimic. These symptomatic migraine attacks might be more common than migraine-induced ischemic insults.[56] Cerebral infarction can thus present with migraine attacks at onset, which should not be confused with migrainous infarction. The reported frequency of stroke-related headache ranges from 7% to 65%.[57,58] A stronger association was observed among younger female individuals whose ischemic event was located in the vertebrobasilar territory, and with a personal history of migraine. Unfortunately, no precise data are available on the specific frequency of migraine cases caused by cerebral infarction.

COEXISTING ISCHEMIC STROKE AND MIGRAINE

Because of the high frequency of migraine in young adults, the possibility that this condition can coexist with ischemic stroke without contributing to stroke occurrence cannot be ruled out, despite the apparent increased risk of stroke in migraineurs. Because the etiology of these strokes is probably multifactorial, identification and management of other established risk factors should be pursued with particular vigilance in all patients with migraine.

Diffuse White Matter Lesions in Migraineurs

Abnormalities of uncertain clinical significance are frequent findings on brain magnetic resonance images of patients with migraine. The most common abnormality is white matter lesions (WMLs)—typically, multiple, small punctate hyperintensities occurring in the deep or periventricular white matter and often seen on T2-weighted or fluid-attenuated inversion recovery images. Not infrequently, these WMLs may cause uncertainty for physicians and anxiety for patients, and can lead to a variety of diagnostic tests and treatments.[59] In a small minority of cases, the number, distribution, and location of WMLs may lead to the diagnosis of an underlying disease of which migraine may be but one symptomatic manifestation (Table 18.4).

Clinical history, presence or absence of cardiovascular risk factors, family history, physical examination, and specific neuroimaging features assist clinicians in narrowing the differential diagnosis in these cases, whereas, in select circumstances, specific biochemical and genetic testing, and further neuroimaging are necessary. WMLs are common in the general population, occurring in approximately 10% of individuals in the fourth decade of life and up to 80% of individuals in the eighth decade.[60] Several reports suggest that the prevalence and the number of WMLs on brain MRI increase with advancing age, vascular risk factors (diabetes, smoking, hypercholesterolemia, hypertension), cardiovascular disease, stroke, and dementia.[61,62] The prevalence of WMLs in migraine ranges from 6% to 40%.[60,63] Suggested variables that might influence this association are the quality of MRI equipment and the sequences used, patient age, migraine type and frequency, and the presence or absence of vascular risk factors. Results of a recent meta-analysis showed a fourfold increased prevalence of WMLs on MRI in patients with migraine in contrast to nonmigraineur age- and sex-matched control subjects. The risk of WMLs in migraineurs appears to be independent of age and vascular risk factors.[64] The results of the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis study support the observation that some migraineurs are at increased risk for subclinical infarctlike brain lesions. This cross-sectional prevalence study evaluated a population-based sample of Dutch adults age 30 to 60 years. Randomly selected patients with MA or MO, and age- and sex-matched control subjects underwent brain MRI. Overall, there was no significant difference between patients with migraine and control subjects in prevalence of infarctlike lesions (8.1% vs. 5.0%). However, patients with migraine had a greater prevalence of such lesions in the cerebellum

TABLE 18.4

Differential Diagnosis of Multifocal White Matter Lesions

Hypoxic/ischemic

- Acquired
  - Small vessel ischemic disease (hypertension, diabetes)
  - Embolic: cardiac, atheromatous
  - Unknown mechanism: Alzheimer disease, migraine
- Hereditary
  - Cerebral autosomal dominant arteriopathy with subcortical in farcts (CADASIL)
  - Mitochondrial encephalaopathy with lactic acidosis and stroke (MELAS)
  - Fabry's disease
  - Cerebrotendineous xanthomatosis
  - Familial hyperlipidemia
  - Phenylketonuria
  - Adrenoleukodystrophy

Inflammatory

- Multiple sclerosis and variants
- Primary CNS vasculitis
- Secondary CNS vasculitis (lupus, antiphospholipid antibody syndrome, Sjogren syndrome, Bechet syndrome)
- Sarcoidosis
- Susac's syndrome

Infectious/post-infectious

- Viral: HIV, progressive multifocal leucoencephal omyelopathy (PML)
- Spirochetal: Lyme disease, syphilis
- Acute demyelinating encephalmyelopathy (ADEM), subacute sclerosing postinfectious encephalitis (SSPE)
- Granulomatous (tubercolosis)
- Fungal (coccidiomycosis)

Toxic/metabolic

- Central pontine myelinolysis
- Carbon monoxide intoxication
- Radiation-induced
- Inhaled solvents, heroin
- Vitamin B12 deficiency

Neoplastic

- Primary central nervous system malignancy
- Metastatic disease
- Lymphoma

Other

- Prominent Virchow-Robin spaces

than control subjects (5.4% vs. 0.7%, $p = .02$; adjusted OR, 7.1; 95% CI, 0.9–55.0). The adjusted OR was greater for individuals with MA and migraine attack frequency of one or more per month (OR, 15.8; 95% CI, 1.8–140). The study found no association between severity of periventricular WMLs and migraine, regardless of sex, migraine frequency, or migraine subtype. An increased risk for deep WML load was observed in women (OR, 2.1; 95% CI, 1.0–4.1) and in subjects with an attack frequency of one or more per month. Conversely, the prevalence of deep WMLs in male migraineurs did not differ from control subjects.[65] Overall, the study showed that patients with MA have a 12-fold increased risk of cerebellar infarctlike lesions, and that female migraineurs had more supratentorial deep WMLs than nonmigraineurs. The risk of lesions increased with attack frequency, independent of cardiovascular risk factors. Further analyses of the infarctlike lesions observed in the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis study were performed subsequently in which topographic details of these parenchymal defects were characterized systematically to define their pathophysiology more completely.[66,67] In line with these findings, a study from Iceland found that women with migraine in mid life had an increased risk of infarctlike lesions in the cerebellum in late life.[68] In contrast, a recent population-based study of individuals age 65 years and older from France showed an association between MA and infarct lesions located mainly outside the cerebellum and the brainstem.[69]

Overall, the combination of vascular distribution, deep border zone location, shape, size, and imaging characteristics on MRI makes it likely that these lesions are, indeed, brain infarcts. However, because there are no postmortem studies identifying the pathology of these MRI findings, their etiology is unknown. Interestingly, patients with migraine who developed what appeared to be cerebellar infarcts on MRI, but whose lesions vanished on repeat imaging, have been reported,[70] thus questioning the hypothesis of an ischemic origin of these lesions.

Is Migraine a Progressive Disorder?

The evidence of WMLs in migraineurs opens the issue of whether migraine may be a *progressive* disorder in some way, rather than simply an episodic disorder. The natural history of migraine is to decrease in severity and to abate and disappear in later life, suggesting a nonprogressive course. However, in a population sample, Scher et al.[71] showed that, throughout the course of 1 year, 3% of individuals with episodic headache (headache frequency, 2–104 days per year) progressed to chronic daily headache (attack frequency, >80 days per year). This population-based result is compatible with findings from a case–control study and numerous clinic-based observation studies.[72] Imaging findings suggesting progressive brain changes in migraine are particularly interesting in light of these epidemiological results. However, these data should be interpreted cautiously because numerous factors, other than the presumed progressive course of the disease, may contribute to "chronification" of episodic migraine. Among them, one of the most common modifiable factors for transformation, occurring in approximately one third of patients developing chronic daily headache, is analgesic overuse. The evidence that chronic daily headache may revert spontaneously to episodic in some cases is a further argument against the hypothesis of migraine as a progressive disorder.[72] Last, because the migraine–stroke relation seems to be subtype specific, the influence being prominent for MA and negligible for MO, one might speculate that migraine is a progressive disorder only in a specific subgroup of subjects. Therefore, whether migraine causes permanent, progressive brain lesions is not established definitively and there are no data for whether lesions in the brain produce chronic migraine. To complicate this issue further, a recent population-based study in women suggested that MA also increases the risk of hemorrhagic stroke (RR, 2.25; 95% CI, 1.11–4.54),[73] supporting the initial evidence from two case–control studies.[74,75] Contrasted with ischemic stroke, this association seems to be more apparent in the elderly.

How Can Migraine Lead to Ischemic Stroke?

Although the relationship between migraine and stroke remains one of the most perplexing problems for neurologists, a pathogenic relation between these two entities is plausible biologically. So far, no fully convincing evidence has been produced to explain the exact mechanism of the increased risk of stroke in migraine. Numerous hypotheses have been raised, including vasospasm, endothelial dysfunction, congenital thrombophilia, platelet hyperaggregability, and association with cardiac abnormalities, among others.

A first hypothesis is that stroke can occur during the course of MAs. Migraine is considered to be a neurovascular disorder in which arterial constriction and decreased blood flow to the posterior circulation are consequences of a spreading wave of neuronal depression in the cerebral cortex. In this regard, CSD may induce short-lived increases in cerebral blood flow and tissue hyperoxia,[76] followed by a more profound oligemia and consequent increased intraparenchymal vascular resistance.[77] Thus, low flow in major intracerebral vessels may be the result of increased downstream resistance, not major intracranial arterial vasospasm. Essentially, a low cerebral blood flow and neuronally mediated vasodilatation could cause sluggish flow in large intracerebral vessels during the aura of migraine. Spreading oligemia persists for 1 to 2 hours and corresponds to a 20% to 30% reduction in cerebral blood flow, well above the ischemic threshold. CSD can be evoked easily in animals by many acute triggers, such as electrical or mechanical stimulation, hypoxia, ischemia, emboli without ischemia, local changes in ion concentration, and various substances including air bubbles, cholesterol crystals, or endothelin.[78–81] Similarly, in human beings, the aura can be triggered acutely by focal ischemia[82]; small, cortical subarachnoid hemorrhages[83]; cerebral venous thrombosis[84]; focal hypoperfusion without ischemia[85]; and emboli or substances reaching the brain in patients with right-to-left shunts, such as a patent foramen ovale (PFO)[86]; and during the Valsalva maneuver,[86] diving,[87] or sclerosing treatment of varicose veins in the legs.[88] When oligemia is combined with factors predisposing to coagulopathy, such as dehydration, hyperviscosity, or intravascular thrombosis, migraine-induced cerebral infarction could occur, although rarely. Neurogenically mediated inflammatory responses accompanying vasodilation of extraparenchymal vessels caused by release of vasoactive peptides, nitric oxide, activation of cytokines, and upregulation of adhesion molecules also predispose to intravascular thrombosis.[89] This could explain why migraine-induced stroke usually respects intracranial arterial territories whereas aura involves more widespread brain regions. In addition, frequent aura, if a result of CSD, could induce cytotoxic cell damage and gliosis based on glutamate release or excess intracellular calcium accumulation.[90] Thus, a persistent neurological deficit could be the result of selective neuronal necrosis. Last, vasospasm, the result of the release of vasoconstrictive molecules (including endothelin and serotonin) once thought to be the mechanism of migraine aura, has been implicated in migrainous infarction, although documented cases are rare.

Experimental data also point toward activation of the thrombotic cascade during the course of a migraine attack. In fact, platelets and mast cells have been shown to release platelet-activating factor, a potent inducer of platelet activation and aggregation also involved in the release of von Willebrand factor, and are involved indirectly in the activation of the platelet IIb/IIIa receptor, crucial for binding fibrinogen, thus leading to primary hemostasis.[91] Increased plasma levels of these molecules have been observed during the course of migraine attacks compared with those in the interictal phases. Despite their biological validity, these mechanisms hold only for the so-called *migrainous stroke*, which—as defined by IHS criteria—is a rare event and cannot explain the increased risk of stroke in migraine. Furthermore, ischemic strokes occur mostly between migraine attacks.[92,93]

A second hypothesis is that the migraine–ischemic stroke pathway is modulated by the intervention of common risk factors. In this regard, different case–control studies have observed that PFO is significantly more common in patients who experience MAs than in patients without migraine.[94,95] Similarly, in patients with ischemic stroke, MA is twice as prevalent in patients

with PFO than in those without.[96,97] Several observational studies, from both single- and multicenter experiences, suggest that PFO closure could reduce the frequency of migraine attacks. In particular, among migraineurs, this might be proposed for those patients in the MA subgroup and might reduce indirectly the risk of stroke, despite the small stroke-predisposing effect of PFO and some recent findings indicating no stronger association between MA and ischemic stroke among women with PFO compared with women without.[15] However, these reports present some limitations, including retrospective design, which implicates recall bias; absence of a control group; placebo effect, which can result in up to a 70% reduction of attack frequency[98,99]; administration of aspirin after PFO closure; and its potential prophylactic effect.[100] Paradoxical embolism is suggested to be the causal link between migraine and PFO, but insufficient data are available to substantiate the hypothesis that migraine frequency (and, indirectly, ischemic stroke risk) is reduced by PFO closure. The only way to address this issue is by randomization. Currently, only one prospective, randomized, double-blind trial on the therapeutic effect of PFO device closure in MA patients compared with sham has been conducted—the Migraine Intervention with STARFlex Technology (MIST) trial. In the MIST trial, 73 patients underwent a sham operation and 74 patients had their PFO closed. The primary end point of the study, complete elimination of headache, was not achieved; three patients in the treatment group versus three patients in the sham group had complete resolution of migraine. In contrast, one of the preplanned secondary end points of the MIST trial showed that patients who underwent PFO closure had a 37% reduction in median total migraine headache days compared with 26% in the sham group ($p = .027$), apparently suggesting some benefits of treatment.[101] However, correction for multiple comparison was not applied, making such findings unsubstantiated.[102] A more comprehensive analysis of current data is desirable to provide information about how to identify patients who may have an improvement of their migraine, and a large number of patients with longer follow-up is necessary. Based on all these findings, the possibility of a PFO–migraine–ischemic stroke triangular association remains a matter of speculation.

Although unproved, these observations support the hypothesis that migraine might be a predisposing condition for specific pathogenic subtypes of ischemic stroke, particularly in young patients. In past years, some observations have suggested that migraine may predispose to spontaneous cervical artery dissection (sCeAD), the most common cause of stroke in young adults. In a meta-analysis of five case–control studies,[103] migraine in general was twice as common in patients with dissection as in control subjects, with a further increased risk in patients with multiple dissections. A recent case–control analysis from the Cervical Artery Dissection and Ischemic Stroke Patients study confirmed these findings, also showing that the association was stronger for migraine without aura.[104] The mechanism by which migraine may affect the risk of sCeAD is unknown. A common, generalized vascular disorder is hypothesized to be a predisposing condition for both diseases. Recent observations of increased activity of serum elastase, a metallopeptidase that degrades specific elastin-type amino acid sequences, in migraineurs suggest a possible extracellular matrix degradation,[105] which might facilitate sCeAD occurrence. Furthermore, in line with previous observations of altered common carotid artery distensibility in patients with sCeAD,[106] Lucas et al.[107] recently reported that the endothelium-dependent vasodilatation assessed in the brachial artery is impaired significantly in these subjects. Similar vascular changes have been observed in migraine patients during interictal periods[108] and have been replicated in a recent cross-sectional study in migraineurs of recent onset, thus excluding the possibility of bias resulting from a long-standing history of migraine and repeated exposure to vasoconstricting drugs.[109] Last, analysis of a small number of families has shown that the structural abnormalities related to sCeAD might be familial and follow an autosomal dominant pattern of inheritance.[110,111] This implies that genetically determined alterations of the extracellular matrix may play a crucial pathogenic role and that candidate genes involved in the regulation of endothelial and vessel wall function might increase susceptibility to both conditions.[112,113]

A third hypothesis is that a number of predisposing conditions may be operating to increase the risk of ischemic stroke in migraine, particularly in young women. Hormonal status seems to play a pathogenic role in the development of MO, but not of MA, which is associated with a greater ischemic stroke incidence.[114] Inconsistent results have also been found for the various biological or clinical markers of thrombotic risk studied so far,[115,116] such as platelet activation, factor V Leiden mutation,[116] von Willebrand factor,[117] prothrombin factor 1.2,[118] platelet leukocyte aggregation,[119] antiphospholipid antibodies,[49] and livedo reticularis.[120] In contrast, there is mounting evidence that migraine may be a risk factor for endothelial dysfunction, which may represent a link to ischemic stroke and heart disease. Endothelial dysfunction is characterized by a reduction in the bioavailability of a vasodilator (such as nitric oxide), an increase in endothelial-derived contracting factors, and consequent impairment of the reactivity of the microvasculature. It also comprises endothelial activation, characterized by a procoagulant, proinflammatory, and proliferative state, which, in turn, predisposes to ischemia. Endothelial dysfunction is mediated by increased oxidative stress, an important promoter of the inflammatory process,[121] which has been proposed in the pathogenesis of migraine. In fact, compared with migraine-free control subjects, oxidative stress markers have been found to be higher in migraineurs, even during the interictal period, thus yielding support to the association.

A fourth hypothesis is that the migraine–stroke link is caused by the effects of specific medications. Actually, drugs used in migraine, such as triptans and ergot alkaloids, have been investigated as a possible risk factor for ischemic events. Cardiovascular safety of migraine treatments has been brought forward by their vasoconstrictive action and by reported cases of stroke, myocardial infarction, and ischemic heart disease after triptan and ergotamine use.[122,123] Moreover, an increased number of white matter abnormalities[65] and increased mortality[124] have been found in patients taking ergotamine. During past years, large-scale studies have investigated the risk of ischemic events and death in patients with triptan- and ergotamine-treated migraine. Data from General Practice Research Database in the United Kingdom showed that, in general practice, triptan treatment did not increase the risk of ischemic events.[125] This finding was confirmed by a wide retrospective cohort study from a health care provider in the United States.[124] This study also investigated the rates of vascular events in relation to ergotamine use and found no association. Recently, a retrospective, nested case–control study using data from the PHARMO Record Linkage System, conducted in the Netherlands, investigated whether overuse of triptans and ergotamine is associated with an increased risk of ischemic events.[126] Results showed that overuse of triptans did not increase the risk of cerebral, cardiovascular, or peripheral ischemic events, neither in the general populations nor in those using cardiovascular drugs. In contrast, ergotamine overuse was associated with a significantly increased risk of ischemic complications (OR, 2.55; 95% CI, 1.22–5.36), especially in patients using cardiovascular drugs concomitantly (OR, 8.52; 95% CI, 2.57–28.2). Therapeutic doses of either triptans or ergotamines were not associated with an increased risk of ischemic vascular events. Overall, these findings suggest that triptan use and even triptan overuse is safe in general, whereas ergotamine overuse exposes one to an increased risk of ischemic complications, likely in relation to its greater vasoconstrictive properties.

Although none of the reported mechanisms fully explain the migraine–stroke relation, a unifying hypothesis has been put forward of a continuum between MA and cerebral infarction through hypoxic ischemic episodes that would trigger an MA attack when brief, and an infarct when prolonged, in a subset of patients who have hereditary or acquired comorbid vascular disorders that lower the CSD threshold.[81,85]

Genetic Influence on the Migraine–Stroke Relation

Migraine and cerebral ischemia might be linked via genetic pathways. During past years, evidence from twin and family history studies, although not entirely consistent, have supported the notion that genetic predisposition plays a major role in the occurrence of both migraine and ischemic stroke.[127]

MONOGENIC FORMS OF MIGRAINE

Although many chromosomal regions have been reported to be possibly involved in migraine occurrence, the mutations in three genes for familial hemiplegic migraine (FHM) represent the only established monogenic cause of migraine so far. FHM is a subtype of MA characterized by an autosomal dominant pattern of inheritance and at least some degree of weakness (hemiparesis) during the aura. Despite these clinical markers, broad variability is the rule. Age at onset, frequency, duration, and features of attacks may be different from one patient to another, even among affected members from a given family who carry the same mutation in the same gene.[128,129] Less frequent features such as cerebellar ataxia, which occurs in some families, minor head trauma as triggering factor, and severe attacks with impairment of consciousness have been also reported. Furthermore, the majority of patients with FHM also experience attacks of typical MA and MO. Thus, it seems reasonable to assume that FHM represents one side of the spectrum that, at the other end, is marked by the common forms of migraine. Hence, FHM is likely a valid model to study genetic factors for migraine in general as well as the relation between migraine and ischemic stroke. To date, three different genes responsible for different subtypes of FHM have been identified. FHM1 is caused by mutations in the *CACNA1A* gene, located on chromosome 19p13, encoding the pore-forming α_{1A} subunit of $Ca_v2.1$ (P/Q type) voltage-gated neuronal calcium channels.[130] FHM2 is caused by mutations in the *ATP1A2* gene, located on chromosome 1q23,[131] encoding the α_2 subunit of sodium–potassium pump adenosine triphosphatases. FHM3 is caused by mutations in the *SCN1A* gene, located on chromosome 2q24,[132] encoding the α1 subunit of the neuronal voltage-gated sodium channel $Na_v1.1$ that is crucial in the generation and propagation of action potentials.

Overall, the common consequence of FHM1, FHM2, and FHM3 mutations seems to lead to increased levels of glutamate and potassium in the synaptic cleft, causing an increased propensity to CSD. Whether this might also increase the propensity to cerebral ischemia is unknown.

Similarly, the contribution of FHM genes in common forms of migraine (MO and MA) remains unclear. A recent study showed no linkage to the *CACNA1A* and *ATP1A2* genes in families with an apparently autosomal dominant mode of inheritance of MA,[133] whereas a case–control study investigating the role of the *ATP1A2* gene in MA did not find evidence for an association.[134] Transgenic mice that carry a missense mutation in the *CACNA1A* FHM gene appeared to have an increased susceptibility to ischemia, according to a recent report.[135] This supports the hypothesis that the low threshold for CSD that characterizes the brain in MA also lowers the threshold for cerebral ischemia. Despite the obvious biological interest of these observations, however, it should be noted that, in humans, cerebral infarction is extremely rare in FHM.[136,137]

POLYGENIC FORMS OF MIGRAINE

The recent diffusion of robust new technologies of gene analysis along with the possibility to use informatics resources that provide genomewide sequence and variant data have fostered an effective and challenging approach to complex diseases. Among them, genetic association studies are retained as a powerful instrument to identify small RRs. Based on the results of such analyses, several specific genetic variants have been implicated in migraine susceptibility, which can be gathered into three main streams.[138] The first group includes genes involved in the neurotransmitter-related pathway, such as genes encoding for dopamine D2 receptor (DRD2), human serotonin transporter (HSERT), catechol-O-methyltransferase (COMT), and dopamine β-hydroxylase (DBH). The second group includes genes involved in vascular function, such as 5,10-methylene-tetrahydrofolate reductase (MTHFR), angiotensin I-converting enzyme (ACE) and endothelin type A (ETA) receptor. The third group includes genes involved in hormonal function, such as estrogen receptor 1 (ESR1), progesterone receptor (PGR) and androgen receptor (AR).

Several candidate genes for migraine are also good candidates for cerebral ischemia. The C677T polymorphism of the MTHFR gene and the deletion/insertion polymorphism of the ACE gene seem particularly promising because of their potential effect on ischemic stroke risk. Pooled analyses of 13 studies indicated that the MTHFR 677TT genotype is associated with a 48% increased risk for MA (pooled OR, 1.48; 95% CI, 1.02–2.13), but not MO. In contrast, pooled results from nine studies indicated that the ACE II genotype is associated with a reduced risk for MA (pooled OR, 0.71; 95% CI, 0.55–0.93) and MO (pooled OR, 0.84; 95% CI, 0.70–0.99).[139] Although linkage studies and genomewide association studies (GWASs) gave some conflicting results, likely a reflection of the genetic heterogeneity of migraine,[140,141] recent GWASs have led to the identification of multiple, novel risk variants for migraine, which could be robustly replicated.[141–144] Interestingly, the results of a GWAS conducted on subjects included in the Women's Genome Health Study (WGHS), a subpopulation of the WHS with genomewide genetic data, provided some suggestion that five single nucleotide polymorphisms (SNPs) at different loci might be implicated in the relation between migraine and stroke. Two of the SNPs suggested an association with ischemic stroke (rs7698623 in *MEPE*, rs4975709 in *IRX4*), one with major cardiovascular disease (rs2143678 close to *MDF1*) and one with death caused by cardiovascular disease (rs1406961, intergenic) among women with MA. In addition, rs1047964 in *BACE1* appeared to be associated with death caused by cardiovascular disease among women with any migraine. It should be noted, however, that none of the 339,596 SNPs analyzed are associated with cerebrovascular disease events among migraineurs at the genomewide level.[113]

Practical Implications

The identification of susceptibility factors linking migraine to ischemic stroke is still in its early stages and, thus, in the short term, it will be impossible to stratify migraineurs and identify those at greatest risk of stroke occurrence. Currently, available data support the following recommendations:

1. An emphasis on identifying and treating modifiable vascular risk factors, such as smoking, hypertension, diabetes, and hypercholesterolemia, is warranted in migraineurs, especially those with MA.
2. Because of the potential synergistic effect of several migraine-specific drugs with vasoconstrictive action, including triptans, and traditional predisposing conditions in increasing the risk of ischemic stroke, subjects with major cardiovascular risk factors should be encouraged to adopt migraine prophylactic strategies. This approach should also be recommended to those subjects with a personal history of prior ischemic (cerebral and/or myocardial) disease. Drugs that can decrease the risk of stroke (i.e., antihypertensives) are valid pharmacological options in these cases, whereas nonsteroidal anti-inflammatory drugs or combination analgesics should be considered an alternative acute treatment approach. Triptans are also contraindicated in patients with hemiplegic and basilar migraine.
3. Estrogen-containing oral contraceptives should not be prescribed to women with MA, particularly when they have major vascular risk factors or are 35 years old or older.
4. There is no direct evidence that PFO closure is effective for MA prophylaxis and, indirectly, for primary prevention of stroke. As a consequence, this procedure cannot be recommended for MA prophylaxis. Positive results from small observational studies need to be confirmed in the setting of a randomized, unbiased, placebo-controlled study with adequate power. Whether antiplatelet agents might be an effective preventive measure in these subjects remains to be determined.
5. Patients with migrainous stroke should undergo the same diagnostic workup and receive the same pharmacological treatment of any ischemic stroke in the young, both during the acute phase and at follow-up.

6. The possibility that migraine may be conceptualized not just as an episodic disorder but as a chronic–episodic and sometimes chronic–progressive disorder currently remains an attractive hypothesis. If proved, this shift in conceptualization would implicate that the goals of treatment may also shift. Preventing disease progression in migraine has already been added to the traditional goals of relieving pain and restoring patients' ability to function.[145] If the brain lesions of migraineurs have a significant clinical correlate, preventing the accumulation of brain lesions may become an additional goal of treatment. The association of stroke with frequency of migraine attacks suggests that migraine, especially MA, prophylaxis may actually reduce migraine-related stroke risk, and opens the issue of whether prophylactic drugs that decrease such a risk (i.e., antihypertensives) might be the best option in these cases. Currently, data are too limited to recommend the use of antiplatelet drugs to reduce the risk of stroke in migraineurs. Emerging treatment strategies to prevent disease progression, including risk factor modification, preventive therapies, and the early use of acute treatments, will be an important focus for future investigations.[142]

Conclusions

Strong arguments support the hypothesis that the relationship between stroke and migraine is more than coincidental. The link between MA and cerebral ischemia, indicated by epidemiological observations, appears to be stronger among the young, but may persist in the elderly. In contrast, the evidence is very weak for MO. Although recent findings suggest the hypothesis of migraine as a progressive brain disorder, data are still too scarce to draw any conclusion. Identifying the population with migraine at greatest risk of stroke should be the first step toward risk reduction and the goal of future research. Currently, from the available data, the overall absolute risk of stroke among young patients with migraine seems to be fairly low.

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19

ETHNIC, RACIAL, AND GEOGRAPHIC VARIATIONS IN STROKE RISK, AND RISK FACTORS ASSOCIATED WITH STROKE

Herbert A. Manosalva and Thomas Jeerakathil

The Global Burden of Stroke

It is estimated that in 2005 there were 16 million first-ever strokes worldwide, and this number is projected to increase to 18 million by 2015 and 23 million by 2030.[1] It is also estimated that stroke is responsible for 10% of the 59 million deaths that occur yearly around the world. It is particularly concerning that the World Health Organization estimates that of the almost 6 million persons yearly who die of stroke, 87% live in low-income or middle-income countries that can ill-afford the best treatments for stroke.[1]

According to the Global Burden of Disease Study 2010, cerebrovascular disorders are the second leading cause of death and premature death in the world.[2] The same report describes how cerebrovascular disease has moved from being the fifth most important cause of loss of disability-adjusted life years (DALYs) in the world to the third most important cause in the interval between 1990 and 2010.

Variations in Stroke Occurrence and Mortality by Racial Group and Geography

There is substantial variation in stroke occurrence, stroke subtypes, and mortality by country and racial group. With regard to stroke mortality, the difference between countries is striking (Figure 19.1) with eastern European countries experiencing the highest mortality rate worldwide, and with Europe and North America experiencing lower stroke mortality.[3]

However, to assume that the average stroke mortality for a country is representative of the risk of all or even most of its citizens may be misleading. Even within economically advantaged, developed countries such as the United States, there is impressive variability in stroke mortality across different regions. Since the 1940s a region of the southeastern United States has experienced stroke mortality

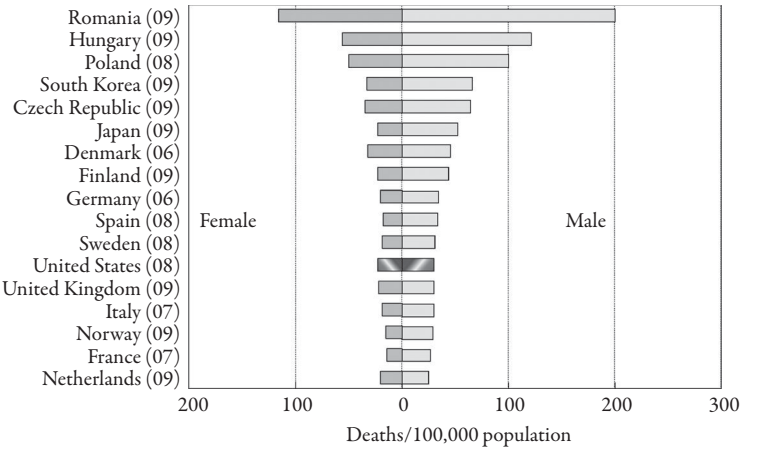

FIGURE 19.1 Variation in Stroke Mortality by Country and Gender in those Aged 35–74. (From 2012 NHLBI Morbidity and Mortality Chart Book, Chart 3-64; with permission)[3]

20% greater than the rest of the nation, and has been labeled the *stroke belt* (Figure 19.2).[4] In more recent years, the central portion of this belt along the coastal plain of North and South Carolina and Georgia has been observed to have even greater stroke mortality (40% greater than the rest of the United States) and has been referred to as the *stroke buckle*. Similar geographic variability has been reported within other countries, such as India (discussed later).

In the United States, there have been consistently greater stroke occurrence rates for non-Hispanic blacks than for whites over time, and recently the Greater Cincinnati/Northern Kentucky Stroke Study reinforced this pattern.[5] Reporting on data from 1993 to 2005, researchers found that the stroke rate for blacks was 1.7-fold greater than for whites, and this ratio was stable over time. An overall decline in stroke occurrence was the result of a statistically significant decline in ischemic stroke occurrence in whites but not blacks. There was no decline in hemorrhagic stroke occurrence in either population.

Stroke mortality has traditionally been higher for non-Hispanic blacks than whites, and this pattern continues to the current day. In the United States, all racial groups have experienced declines in stroke mortality during the past several decades. Although this decline plateaued during the mid to late 1990s, the decline resumed again from the year 2000 onward. Furthermore, although blacks may have experienced a slightly lower annualized decline during the past 10 years than whites (approximately 4.1% compared with 5%, respectively) the trajectory of decline has been similar for blacks and whites (Figure 19.3.[3] Hispanics, North American aboriginals, and Asians appear to be at slightly lower mortality than whites overall, from National Heart, Lung, and Blood Institute data; however, there may be underreporting for the latter two groups (Figure 19.4).[3]

The inaccuracy of stroke mortality reporting for North American aboriginal populations is apparent when studies make more vigorous attempts at case capture. Harwell et al.[6] examined the relative risk for heart disease and stroke for Native Americans compared with whites in Montana and found a 1.5-fold increase in stroke mortality for both men and women compared with whites. It was particularly striking that both the discrepancy in stroke mortality was increasing over time and that most of the excess mortality was in those younger than 65 years (Figure 19.5).[6]

Another population originally thought to have a low rate of stroke is the South Asian population consisting of persons from the Indian subcontinent, including India, Sri Lanka, Pakistan, Nepal, and Bangladesh. The absence of high-quality population-based studies impairs our understanding

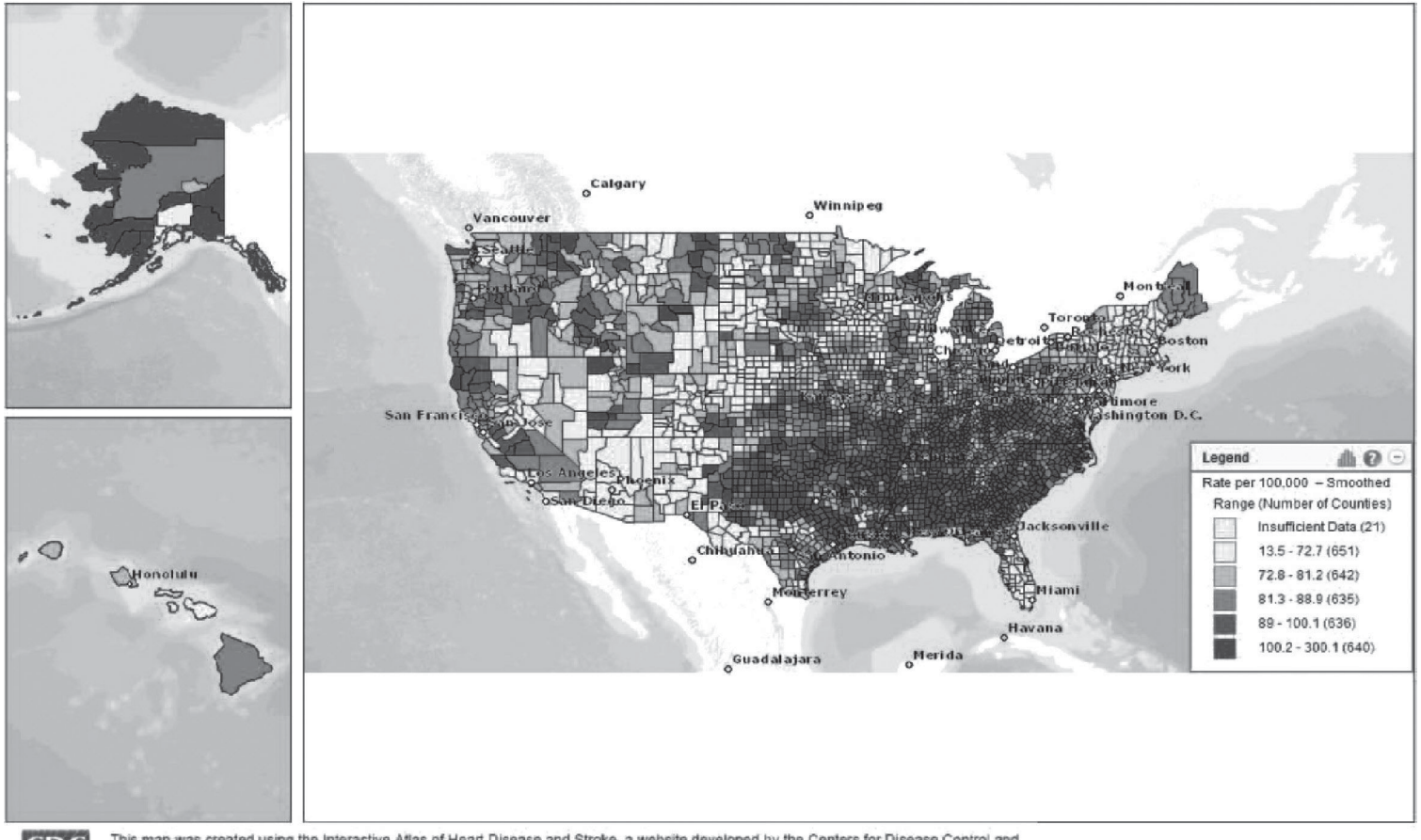

FIGURE 19.2 Stroke Mortality Rates by Region. (From Heart Disease and Stroke Statistics--2014 Update: A Report From the American Heart Association. Chapter 14. Chart 14.7; with permission)[4]

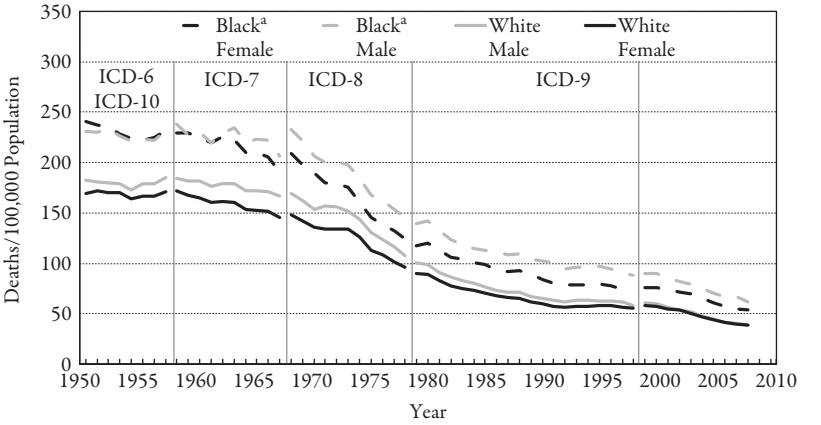

FIGURE 19.3 Age-Adjusted Death Rates for Stroke by Race & Sex, U.S., 1950–2008 (Adapted from from 2012 NHLBI Morbidity and Mortality Chart Book, Chart 3-56; with permission)[3]
[a]Nonwhite from 1950 to 1967. ICD, International Classification of Diseases.

of the true risk for stroke in this population. Early studies examining mostly prevalence rates in India suggested lower prevalence than western industrialized countries.[7] Indeed, the literature is quite inconsistent for South Asians, reporting variably lower and higher rates of stroke compared with western populations and other ethnic groups. However, more rigorous prospective studies performed in recent years in India and incorporating age standardization to the world population demonstrate annual stroke incidence rates that are 50% to 120% higher than western industrialized countries.[7] However, there is evidence of variation within the country of India itself, although studies are hampered by differences in methodology and age strata of the populations sampled. A fairly

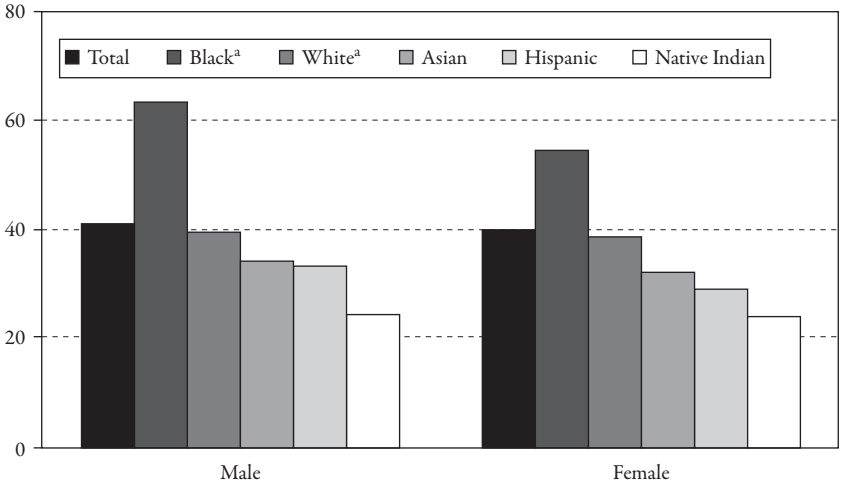

FIGURE 19.4 Age-Adjusted Death Rates for Stroke by Race/Ethnicity and Sex, U.S., 2008 (Adapted from 2012 NHLBI Morbidity and Mortality Chart Book, Chart 3-60; with permission)[3]

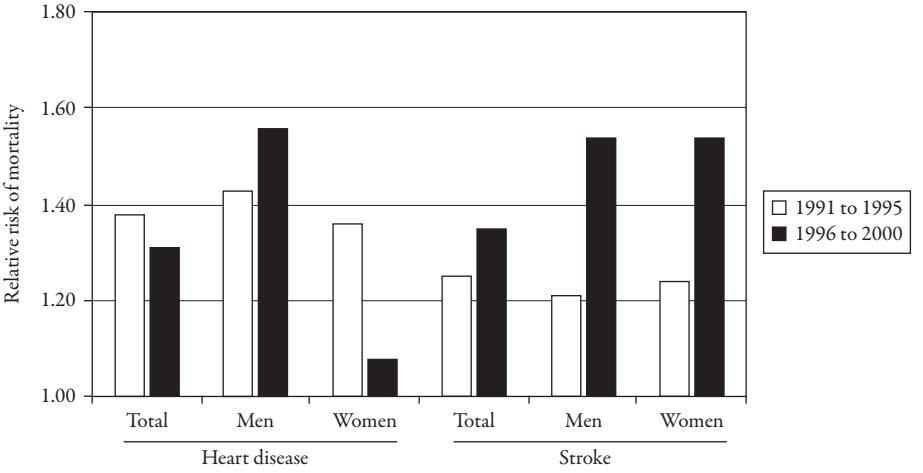

FIGURE 19.5 Relative risk of mortality from heart disease and stroke in American Indians and whites, Montana, 1991 to 1995 and 1996 to 2000. (from Harwell TS, Oser CS, Okon NJ et al. Defining Disparities in Cardiovascular Disease for American Indians: Trends in Heart Disease and Stroke Mortality Among American Indians and Whites in Montana, 1991 to 2000. *Circulation*. 2005;112:2263–2267; originally published online October 3, 2005; doi: 10.1161/CIRCULATIONAHA.105.560607; with permission)[6]

consistent finding is an excess stroke risk in urban and metropolitan populations compared with rural populations.[8]

Although the stroke incidence rates are likely greater for South Asians than for western industrialized populations, the persistent finding of lower stroke prevalence in South Asians requires further explanation. There is evidence for greater stroke case fatality in South Asians than other ethnic groups, which could result in low prevalence as a result of diminished survival. The Kolkata Study took place in a large metropolitan city in India and reported a 30-day case fatality rate for stroke of 42%, which is clearly in excess of that reported for most other countries, with the exception of Eastern Europe.[9] Furthermore, standardized mortality ratios for stroke in migrant South Asian populations in the United Kingdom were 55% greater for males and 41% greater for females compared with the general population.[8] Secular trends in mortality in this population are hard to determine, given the limitations of available data, but suggest either increasing stroke mortality during the past several decades or a substantially lower decline than that observed in western industrialized populations.[7,8]

Race and Stroke Occurrence by Subtypes

Some racial/ethnic groups appear to be more prone to specific subtypes of stroke than others, but a full picture of these discrepancies emerges only when studies of stroke incidence also report stroke classification using a system such as the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification or the Oxfordshire classification.[10,11] The lack of availability of brain imaging with computed tomography or magnetic resonance imaging is a major limitation to understanding stroke subtypes in much of the developing world.

In an effort to identify the main risk factors operating in the different countries of high, medium, and low income and their ethnic groups, and to estimate the associated population-attributable risks (PARs) for the main subtypes of stroke, ischemic or hemorrhagic, an international multicenter

case–control study, the INTERSTROKE study, was developed in 22 countries.[12] Patients having a cerebrovascular event with neurological deficits lasting more than 24 hours were included. The study included neuroimaging (computed tomography or magnetic resonance imaging) and baseline electrocardiography. The patients were classified according to the Oxford Community Stroke Project classification and the study enrolled 6000 participants. In the multiethnic sample overall, the most frequent subtype of stroke was ischemic (78%), with hemorrhagic stroke occurring in 22%, and these proportions establish a reasonable baseline for an "average" global population.[11,12]

An analysis looking at the incidence of the first-ever ischemic stroke in the population examined in the South London Stroke Register study showed that the overall incidence ratio for ischemic stroke (rate ratio, 1.26) was significantly greater among black Caribbeans relative to whites.[13] The rate of small-vessel occlusive stroke was greater for both Caribbean blacks (rate ratio, 1.98) and African blacks (rate ratio, 2.14). Researchers found that both Caribbean and African blacks had a greater proportion of small-vessel occlusion compared with whites (42% for blacks overall compared with 22% for whites).

The Greater Cincinnati/Northern Kentucky Stroke study, which compared first-ever stroke incidence in two different races, showed similar results, with almost twice the incidence of small-vessel strokes and strokes of undetermined etiology in blacks compared with whites.[14] However, the increased incidence of these stroke subtypes parallels the increased incidence of all stroke in American black populations. When stroke subtype is examined as a proportion of total stroke, there are similarities between whites and blacks for small-vessel, large-vessel, and undetermined stroke types. Whites appear to have a slightly greater proportion of cardioembolic strokes (22% vs. 15%).

The Sino–MONICA–Beijing study in China showed a greater incidence of hemorrhagic stroke in Chinese compared with other countries.[15] The most important risk factor explaining the difference is probably the greater incidence of hypertension, but other lifestyle and genetic factors cannot be excluded. A diet producing very low cholesterol levels has been put forward as a potential risk factor for hemorrhagic stroke.

In the United States, a population study at the Mayo Clinic in Rochester, Minnesota, showed that patients from Asia and the Pacific Islands had increased risk of hemorrhagic transformation after intravenous tissue plasminogen activator treatment for ischemic stroke (odds ratio [OR], 2.01; 95% confidence interval [CI], 1.91–2.11) compared with Hispanic, black, and white ethnic groups.[16] One small, uncontrolled trial from Japan has demonstrated reasonable outcomes and an acceptable hemorrhage rate by decreasing the intravenous tissue plasminogen activator dose from 0.9 mg/kg to 0.6 mg/kg, when treating ischemic stroke.[17]

Race, Ethnicity Specific Differences in Impact of Traditional Stroke Risk Factors

HYPERTENSION

Hypertension is the most important risk factor for atherosclerosis and stroke, and a major risk factor for vascular dementia.[18] It is an important risk factor for atherosclerosis. A 10-mmHg increase in arterial pressure may increase the odds for atherosclerosis (ruptured plaque, protruding atheroma) in major vessels, including the aorta, by 43% and, for stroke specifically, by 40%. On the other hand, a 10-mmHg decrease in systolic blood pressure reduces the risk for stroke by 30%. Hypertension is the major risk factor for lacunar ischemic strokes and leukoaraiosis (brain white matter disease). In the INTERSTROKE study, hypertension was the strongest risk factor for hemorrhagic stroke including microbleeds and parenchymal hematomas.[12]

In the provinces of Alberta and British Columbia in Canada, the incidence of hypertension in South Asians (Pakistan, India or Bangladesh origin) is greater compared with whites and Chinese

(East Asians from China, Taiwan, or Hong Kong).[19] This is of particular relevance considering that East Asian populations tend to have a greater incidence of hypertension than the general population in the first place.

The Greater Cincinnati/Northern Kentucky Stroke Study comparing first-ever stroke incidence in two different races showed that hypertension was significantly higher in the black population, and the rate of small-vessel occlusive strokes, which have a particularly strong relationship to hypertension, was almost as twice as high in blacks compared with whites.[14] Along the same lines, the South London Stroke Register study in an urban population in London showed that hypertension was the most frequent risk factor for stroke in black Africans, followed by black Caribbeans, compared with whites.[20]

The Global Burden of Disease 2010 report listed hypertension as the risk factor that has the biggest impact worldwide in regard to DALYs lost.[2] The DALY incorporates both premature mortality and disability, and amounts to years of healthy life lost as a result of a disease or a risk factor. With regard to regional variability, hypertension ranges from being the most important risk factor for stroke in high-income countries in the Asia-Pacific, East Asia (including China and Japan), Central Europe, tropical Latin America, Southeast Asia, Central Asia, North Africa, and the Middle East to ranking as low as the sixth most important risk factor in western Sub-Saharan Africa. Across every geographic region, hypertension exerts substantial influence as a cause of death and disability after stroke.

Smoking

Smoking is a risk factor for all the different subtypes of ischemic stroke (small-vessel occlusion, large-artery atherosclerosis, and cardioembolic stroke) and, unlike many other risk factors, it has the advantage of being completely preventable. In the Greater Cincinnati/Northern Kentucky Stroke Study, current smoking had a significantly greater prevalence in the black population.[14] Black persons smoking more than 1 pack of cigarettes per day were at a four times greater risk for developing an ischemic stroke compared with nonsmokers, and there seems to be little differential effect of smoking as a risk factor across racial groups.[21] The same high prevalence of smoking is true for aboriginal populations in Canada.[22] For Canadian First Nations persons, smoking prevalence ranged from 30% off-reserve to as high as 49% on-reserve, which is considerably greater than the general population of Canada. In a European study in Norway, current smoking was the most important risk factor along with dyslipidemia (OR, 2.06; 95% CI, 1.04–4.08) for the occurrence of small-vessel occlusion.[23]

Smoking was second only to hypertension in importance as a cause of DALYs lost worldwide.[2] The importance of smoking in terms of the proportion of total DALYs lost has been decreasing in the developed world and increasing in the developing world during the past 10 years. Smoking rates vary even between different countries in the developed world, with greater rates on average in western European countries than in North America. Similarly, in the developing world there is substantial variability, with relatively low smoking rates on most of the African continent and very high rates in Asia and Eastern Europe.[24]

Dyslipidemia

Dyslipidemia has a complex relationship with stroke risk, with both low and high levels of lipids conveying some risk for different stroke subtypes. In the multicenter INTERSTROKE study, the ratio of nonhigh-density lipoprotein (non-HDL) cholesterol to HDL cholesterol, increased levels of

apolipoprotein B, and, in particular, the ratio of apolipoprotein B to apolipoprotein A1 were associated strongly with ischemic stroke.[12] Similarly, in a study from Norway, a cholesterol level greater than 193.4 mg/dL and a low-density lipoprotein level greater than 116 mg/dL were the main risk factors for large-artery atherosclerosis and small-vessel occlusive ischemic stroke.[23]

However, in the Multiple-Risk Factor Intervention Trial(MRFIT) research, black men with cholesterol less than 160 mg/dL with a diastolic blood pressure of more than 90 mmHg were found to be at risk for hemorrhagic stroke. [25] The observation of the increased risk for intracerebral hemorrhage from low lipid levels has been replicated in multiple populations, including rural Japanese, whites in the Multiple-Risk Factor Intervention Trial, and Hawaiian Japanese, and the relationship is strongest in those with high diastolic blood pressures.[26,27] In the Rotterdam study, a population-based cohort of community-dwelling elderly persons from the Netherlands, it was demonstrated that it is the triglyceride fraction that, when low, predisposes to intracerebral hemorrhage, and there was no independent relationship between low-density lipoprotein or HDL levels and hemorrhage risk.[28] Researchers have postulated that low lipid levels somehow produce weakening of the blood vessel endothelium, predisposing the vessel to rupture.

Obesity and Diabetes

Obesity, impaired glucose tolerance, and hypertriglyceridemia produce morbidity as individual risk factors but also occur together in a cluster of risk factors referred to as *metabolic syndrome*. Although these three risk factors contribute to death and disability globally, there is disparity across regions and ethnic groups in their relative importance.

The Global Burden of Disease project reports that diabetes has moved from the 21st to the 14th most important disease with regard to years of healthy life lost, and it ranks as one of the top 10 diseases in the world for mortality.[2] High fasting blood sugar is a risk factor that incorporates diabetes as well as impaired glucose tolerance, and ranks as the seventh most important risk factor globally with regard to DALYs lost.[2] With regard to years lived with disability, the same study reports wide variation in the relative importance of diabetes by region of the world. Diabetes is the fourth leading disease that causes years lived with disability in Oceania (Micronesia, Melanesia, Polynesia, and Central and South Pacific), but it drops to the 29th leading cause in Central and Sub-Saharan Africa.

Similarly, obesity or high body mass index (BMI) ranks sixth globally in terms of DALYs lost and is the leading risk factor in Australasia, South and Latin America, and Central and Latin America. High BMI is the second or third leading risk factor in Western Europe, North America, Central Europe, North Africa, and the Middle East, and several other global regions.[29] However, in Southeast Asia and East, Central, and West Sub-Saharan Africa, it is a much less important risk factor, ranking from 14th to 18th in importance. The contrast within Africa itself is striking; obesity ranks third in importance for southern Sub-Saharan Africa.

Obesity is a risk factor for dyslipidemia, hypertension, and diabetes, and in European populations risk increases consistently at a BMI of more than 30 kg/m^2. Although it is recognized that adverse risk factor profiles and cardiovascular disease seem to occur at lower BMIs in populations in East and South Asia, the World Health Organization has been reluctant to support different specific cut points for obesity for different ethnic groups. An important study published in 2007 determined, using factor analysis, the BMI cut points for South Asians, Chinese, Europeans, and aboriginals that were associated with adverse risk profiles for dyslipidemia, hypertension, and hyperglycemia.[30] The investigators found a wide range of cut points for specific risk factors, which varied by group (Table 19.1). However, in general, South Asians, aboriginals, and Chinese had adverse glucose profiles at relatively low BMIs. South Asians also had adverse lipid profiles at low BMIs, suggesting that, even at low BMIs, they are particularly at risk as a result of this "double clustering" of risk factors. Chinese and

TABLE 19.1

A Comparison of BMI Cut Points Related to Adverse Cardiovascular Risk Factor Clusters in a Multiethnic Population

	BMI Cut Point for Specific Risk Factor Clusters		
Ethnic group	Dyslipidemia	Hyperglycemia	Hypertension
European	30	30	30
South Asian	22.5	21.0	28.8
Chinese	25.9	20.6	25.3
Aboriginal	26.1	21.8	NS

Note: Adapted from Razak et al.[30]
BMI, body mass index; NS, not significant.

aboriginal subjects had adverse lipid profiles at intermediate BMIs, but still at much lower BMIs than Europeans. Chinese subjects were at risk for high blood pressure at BMIs greater than 25.3, but this relationship was not as strong for South Asians and was not present for aboriginals.[30]

Cardiac Causes

The Miami Stroke Registry compared the prevalence of vascular risk factors and subtypes of ischemic strokes in blacks, Caribbean blacks, Hispanics, and whites.[31] The prevalence of cardioembolism was greatest in whites (OR, 3.02; 95% CI, 1.42–6.42). Moreover, atrial fibrillation is known as the most frequent cause for cardioembolic stroke and has a greater prevalence in the white population compared with African/Caribbean blacks and South Asians.[32] This was confirmed in the South London Stroke Register study, in which the prevalence of atrial fibrillation was found to be 0.63% overall in 2011 and 1.2% in whites, 0.4% in black African/Caribbeans, and 0.2% in South Asians (India, Pakistan, and Bangladesh origin) (Figure 19.6).[33]

In contrast to atrial fibrillation, which is far more common in the elderly, valvular heart disease from rheumatic fever affects mostly children and young adults. It is estimated that there are more than 16 million persons worldwide burdened by this condition, and the greatest prevalence by far (5.7%) is in Sub-Saharan Africa.[34] Given that valvular heart disease from rheumatic fever is preventable with appropriate treatment, developing countries experience a much higher burden of the disease than developed countries. One exception to this rule is the situation of Australian aborigines who, despite living in an economically advantaged country, have among the highest rates of rheumatic fever in the world. The underlying reasons are not known with certainty, but they may involve routes of infection other than streptococcal pharyngitis.[34]

Nontraditional Risk Factors and Conditions Predisposing to Stroke

Strokes of undetermined cause may occur in as much as 40% of cerebrovascular events in the young population.[35] Some of these individuals may have an underlying genetic disorder, and there is evidence for variability in the occurrence of these conditions across different ethnic groups.

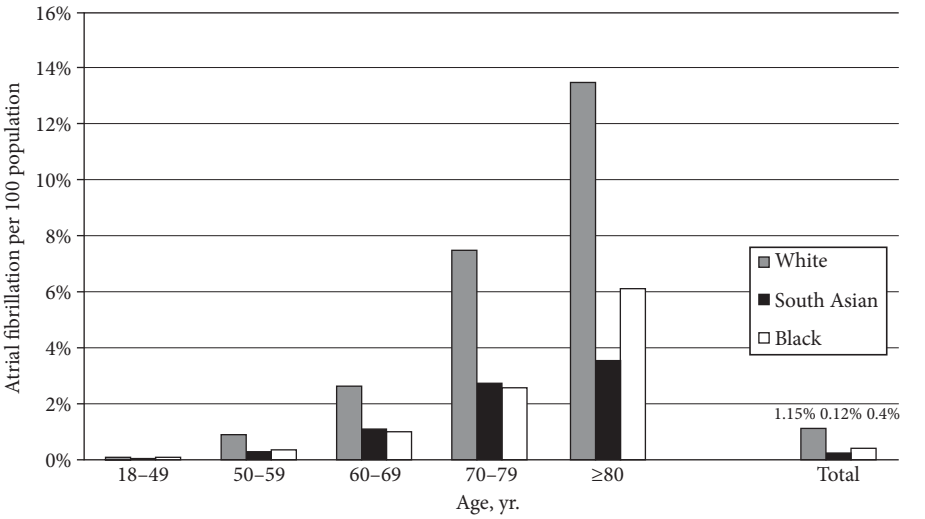

FIGURE 19.6 Prevalence of atrial fibrillation by age and ethnic group. (From Mathur R., Pollara E., Hull S., Schofield P. Ashworth M., et al. Ethnicity and stroke risk in patients with atrial fibrillation. *Heart*. 2013;99:1087–1092; Figure 1; with permission)[33]

CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is an autosomal dominant disorder characterized by migraines with aura, small-vessel occlusion ischemic strokes, leukoencephalopathy, mood disorder, apathy, and dementia by the sixth decade. Both genders can be affected, but mortality may occur 6 years earlier in men.[36] The underlying genetic disorder is a missense mutation in the *NOTCH3* gene. It has been described in Europeans and South Asians.[37] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy has been reported more frequently in Europeans among French, German, and Italian communities.[38] The disease has been identified worldwide, including Arabic families.[39,40]

CEREBRAL AUTOSOMAL RECESSIVE ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOARAIOSIS

Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoaraiosis (CARASIL) is a rare, autosomal recessive disorder characterized by premature baldness, frequent episodes of back pain, migraine, psychiatric disorders such as emotional liability, dementia, and strokes between the third and fourth decade. Patients may develop small-vessel occlusion strokes in the thalamus and basal ganglia, and diffuse white mater disease. This condition is the result of mutations in the *HTRA1* gene. This disorder has been described originally in Japanese and Chinese ethnic groups.[41]

HOMOCYSTINURIA

Homocystinuria was described by McCully[42] in 1969 in autopsies of children who died from a vascular event: cerebrovascular, pulmonary embolism, or ischemic cardiac. Patients develop prematurely severe atherosclerosis of large arteries, such as the carotid arteries, myocardial infarction, or

venous thrombosis. Experimental animal models using vitamin B6 could prevent the development of venous thrombosis, but not the progression of the atherosclerotic plaques. Typically, patients have a marfanoid appearance, with ectopia lentis and mental retardation, and may develop hemidystonia, large-artery atherosclerosis ischemic strokes, and venous thromboembolic disease.[42] This is an autosomal recessive disorder, with deficiency in the enzyme cystathionine β-synthase, which has vitamin B6 as a cofactor, leading to the accumulation of homocysteine (>100 μmol/L) and methionine in plasma, and urine excretion of organic acids. These patients may benefit from vitamin B6 and folic acid. This is an autosomal recessive disorder resulting from mutations in the CBS gene.[43] Allele studies have shown that the frequency of having at least one abnormal allele of this gene is greater in the black population, followed by whites, and is low in East Asians.[44] White patients with homocystinuria homozygous for mutation I278T had a vitamin B6 responsive phenotype, as has been described in Europeans and Americans, whereas black descendants homozygous for mutation T353M had a vitamin B6 nonresponsive phenotype.[45]

HYPERHOMOCYSTEINEMIA

Patients who are homozygous or compound heterozygous for the polymorphism 677 C T, and for whom fasting homocysteine blood levels are greater than 50 μmol/L, may have an increased risk for stroke. This polymorphism is the result of a thermolabile enzyme with 50% reduced activity. It can be seen in 10% of European and 25% of Asian populations. In countries that fortify food with folic acid, the risk turns insignificant.[46]

Homocysteine blood levels can be increased in nutritional vitamin B deficiencies, consumption of animal proteins rich in methionine, increased age, smoking, sedentary lifestyle, postmenopausal state, and decreased renal failure, or provoked by medications such as anticonvulsants, methotrexate, cyclosporine, or cholesterol-lowering medications.[47] Typically, fasting homocysteine levels appear around 15 to 30 μmol/L. The multicenter study VITATOPS, conducted on four continents, showed that supplementation with vitamins in this population was no more effective than placebo in preventing major vascular events.[48]

SICKLE CELL DISEASE

There is a high prevalence of sickle cell disease in the black race. It is an autosomal recessive condition in which there is a mutation in the *HBB* gene, replacing the amino acid glutamic acid for valine in the sixth position of the polypeptide chain. As part of natural selection, people with sickle red blood cells survived the big pandemics of malaria in Africa from the past, because of the inability of the parasite to survive invading a sickle-shaped erythrocyte. The disease begins as hemolytic episodes with vaso-occlusive events in childhood and may affect the brain, eyes, bones, kidney, liver, joints, and spleen. Stroke episodes typically occur during systemic sickle cell crises. These strokelike events may be overlooked in 25% of cases, and the first noticeable neurological symptom may then be cognitive decline, developmental delay, seizures, or abnormal movement disorders such as hemidystonic posturing.[49] In the Northern Manhattan study, the racial/ethnic group at greatest risk for developing stroke resulting from sickle cell disease was, as expected, blacks, followed by Hispanic people—Dominicans in particular.[50] Stroke resulting from sickle cell disease is more common among populations in Africa, the Mediterranean, parts of India, and the Middle East.

MOYAMOYA DISEASE AND FIBROMUSCULAR DYSPLASIA

In Asia, Moyamoya disease can present with steno-occlusive ischemic vascular events, and the first strokes may occur early in childhood. Over time, patients may develop aneurysms and hemorrhagic stroke. Patients typically develop an angiographic picture of a "puff of smoke" (which translates in Japanese to *moyamoya*). The prevalence is higher in Asiatic countries, particularly in Japan and Korea, but is lower in non-Asian populations.[51] A study in California showed that the prevalence of this disease was greatest in Asian Americans (0.28/100,000 person-years), followed by blacks (0.13/100,000 person-years), then whites (0.06/100,000 person-years), and, last, Hispanic Americans (0.03/100,000 person-years).[52] One reason for the ethnic differences may be genetic. Recently, a mutation (4576G>A) in the ring-finger protein 213 gene, *RNF213*, on chromosome 17 was found to be associated with Moyamoya disease, and this variant is more common in Japanese and Koreans compared with Han Chinese.[53]

Fibromuscular dysplasia can be noticeable in adolescence or early youth, predominantly in white women, affecting large-artery blood vessels such as the carotid or renal arteries, with associated stroke, abdominal angina, or vascular claudication. The disease can present frequently later in life, as well, and is a risk factor for cervical artery dissection and subsequent stroke. Occasionally, this condition may be detected in asymptomatic people during routine angiographies, with the typical appearance of a "string of beads."[54]

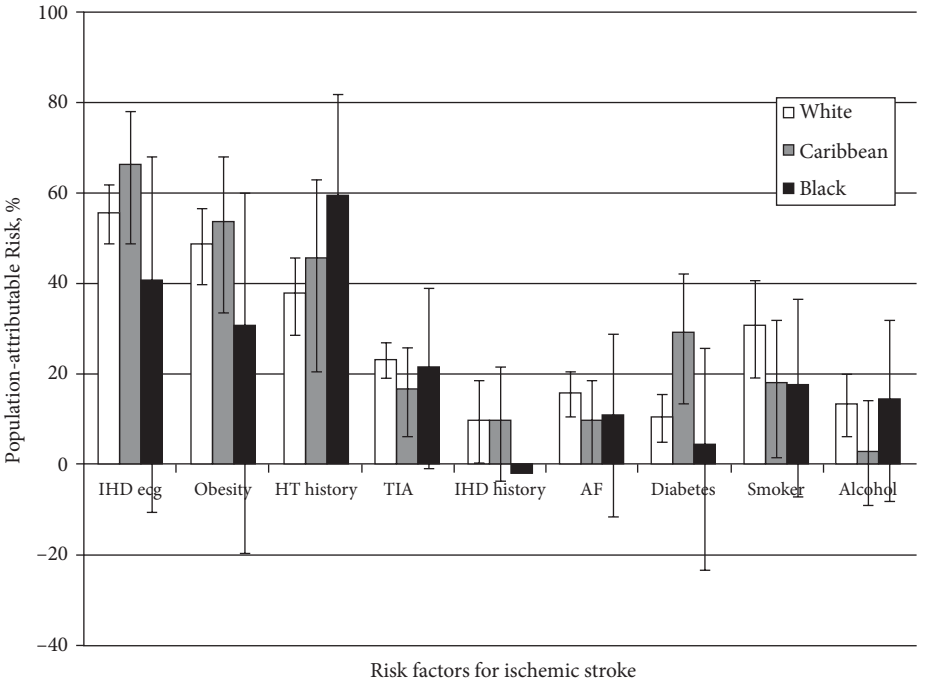

FIGURE 19.7 Population attributable risk for risk factors by ethnic group. (From Hajat C., Tilling K., Stewart J., Lemic-Stojcevic N., Wolfe C. Ethnic differences in risk factors for ischemic stroke: a European case-control study. *Stroke*. 2004;35:1562–1567; Figure; with permission)[20]

AF, atrial fibrillation; HT, hypertension; TIA, transient ischemic attack.

A Summary of the Differences in Risk Factor Profile for Stroke by Racial Group and Geography

The South London Stroke Register study examined the PAR for stroke for a number of risk factors in a multiethnic population (Figure 19.7).[20] In this study white patients had the greatest PAR from ischemic heart disease on electrocardiogram (56%) and from obesity (49%), followed by hypertension (36%) and smoking (31%). Black Caribbean patients had an even greater PAR from ischemic heart disease on electrocardiogram (66%) and from hypertension (46%) and diabetes (29%), but less from smoking, obesity, and atrial fibrillation. African blacks had the greatest PAR for hypertension (59%) and less for obesity, diabetes, and atrial fibrillation than whites.

In general, East Asian populations, such as those in China and Japan, have lower rates of dyslipidemia and obesity than white populations, but they have greater rates of hypertension. These populations also tend to have greater rates of intracranial arterial stenosis as opposed to the extracranial stenosis that occurs in whites, and much greater rates of stroke and lower rates of myocardial infarction than whites.

In contrast, South Asian populations appear to have a high risk of both stroke and myocardial infarction, with both dyslipidemia and abnormal glucose metabolism occurring at a lower BMI than whites. North American aboriginal populations are developing greater rates of obesity and diabetes than the general population, and also have higher rates of smoking.

Risk factors for stroke remain prevalent around the globe, with adverse trends in a number of regions providing some explanation for why stroke has increased in importance between 2000 and 2010 as a cause of death and disability. Both the developing world and the developed world bear the burden of stroke. Health professionals and policymakers involved in stroke prevention need to understand the specific risk profiles of the regions and racial/ethnic groups they serve to focus their interventions to combat the growing threat of stroke.

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IV

Integrative Approach

20

CAROTID DISEASE AS AN INTERMEDIATE MARKER OF STROKE RISK

David Della-Morte and Tatjana Rundek

Physiopathology of Carotid Atherosclerosis Disease

Atherosclerosis is the underlying process that causes most cardiovascular disease (CVD), death, and disability worldwide.[1] It is the cause of myocardial infarction (MI), peripheral artery disease, and stroke. About 10% to 20% of ischemic strokes are the result of large-artery atherosclerosis.[2] The atherosclerotic process leads to luminal stenosis with flow restriction and plaque rupture, causing CVD and stroke.[3] Atherosclerosis is a chronic inflammatory process that involves endothelial injury, activation and recruitment of immunoinflammatory cells, smooth muscle cell proliferation, and the influx of lipoprotein.[4] Various mediators such as chemokines, cytokines, growth factors, proteases, adhesion molecules, and hemostasis regulators, and their interactions are involved in the process of atherosclerosis. Proinflammatory signaling is triggered by oxidized low-density lipoprotein (LDL) or by alterations and remodeling in the extracellular matrix.[5,6] This process leads to different plaque composition and its susceptibility for rupture, with variable vascular risk resulting from artery-to-artery embolization.[7]

Atherosclerosis develops predominantly at specific vascular sites, mainly in areas with altered blood flow, such as carotid bifurcations and areas of vessel curvature. Mass transport and shear stress are two mechanical mechanisms proposed to regulate flow and contribute to atherosclerosis. A low or disturbed blood flow results in an increased uptake of bioactive substances into the vessel wall. Mechanical forces of blood flow on the vessel wall, called *shear stress*, also play an important role in the local development of plaque as well as in protection of endothelium.[6] Atherosclerotic lesions develop mainly in areas of low shear stress. The presence of areas of the arterial tree with different wall shear stress may explain, in part, the different localization of atherosclerotic lesions.

Age, sex, lipid, smoking, blood pressure (BP), diabetes, obesity, and race/ethnicity, among others, are all well-established risk factors for atherosclerosis and CVD.[8] They contribute, with different impacts and mechanisms, to the development of atherosclerosis. There are a number of ways to

determine the future risk of CVD based on levels of these risk factors. The Framingham Risk Score (FRS)[9] is one of the best known and widely used models to predict CVD. Although these scoring systems are useful to predict risk in the populations, their accuracy in predicting cardiovascular risk for individuals varies considerably across populations.[10] Ultrasound methods for quantifying burden of atherosclerosis have been proposed for use in prediction models with a hope to increase the prediction accuracy of CVD beyond traditional vascular risk factors. In a recent study, researchers demonstrated that traditional vascular risk factors explain only 21% of the variance in total carotid plaque (CP) burden.[11] Variation in carotid atherosclerosis is, therefore, largely unexplained by known vascular risk factors, suggesting that other unaccounted factors—both environmental and genetic—play an important role in the determination of carotid atherosclerosis.

Surrogate or Intermediate Markers of Carotid Atherosclerosis

The development of noninvasive ultrasound methods capable of evaluating atherosclerosis quantitatively has improved our ability to design studies of the natural history, progression, and determinants of atherosclerosis, as well as to evaluate the effects of various therapies and preventive measures. According to the National Institutes of Health Definition Working Group, surrogate markers act as a substitute for a clinical end point and should be able to predict the desired clinical benefit and the lack of benefit, or harm, based on epidemiological, therapeutic, pathophysiological, or other scientific evidence.[12] The most validated ultrasound surrogate or intermediate markers of atherosclerosis include carotid intima media thickness (cIMT), CP, and carotid stiffness (STIFF), and are discussed in the following sections.

Carotid Intima Media Thickness

First described by Pignoli et al.[13] in 1986, cIMT is defined as the measured distance between the luminal–intimal interface and the media–adventitial interface of the common carotid artery (CCA). More specifically, the intima media thickness (IMT) is the double-line pattern visualized by B-mode vascular ultrasonography formed by the two parallel lines of (a) the junction of the vessel lumen with the intima and (b) the junction of the media with the adventitia (Figure 20.1).[14]

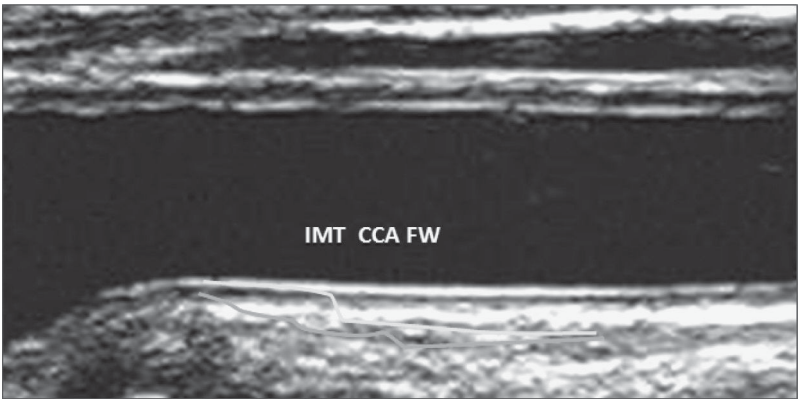

FIGURE 20.1 The double-line pattern of intima media thickness (IMT) in the far wall (FW) of the common carotid artery (CCA). The junction of the lumen (black) and intima is yellow, and that of the media and adventitia is green.

Because of the discrepancies reported in major IMT clinical trials, caused mostly by the use of different scanning and measurement protocols, in 2004 a consensus panel gathered in Mannheim, Germany, to review the cIMT assessment protocols.[15] The large studies reported different associations between cIMT and risk of stroke or MI, depending on whether cIMT was measured in the CCA or in the internal carotid artery (ICA).[16] The Mannheim consensus[17] has recommended that the most reliable cIMT measurements are obtained from the distal 2 cm of the CCA, proximal to the bifurcation, and preferably in a wall region free of plaque. The lower variability of IMT in CCA is one of the advantages of measuring IMT at this level, because the CCA lies close and runs relatively parallel to the skin. Also, plaque formation is less common in the CCA than either the bulb or the ICA, making measurements of IMT easier. The ICA, on the other hand, is less superficial, does not run parallel to the skin of the neck, and is often positioned high in the neck, near the angle of the jaw. These factors make the ICA more difficult to image and leads to a greater variability of IMT in the ICA. Therefore, the incorporation of ICA measurement into the overall cIMT measure produces more variability in the reported IMT results across studies.

For technical aspects, the Mannheim consensus has recommended the use of B-mode transducers with a minimum frequency of 7 MHz, ideally greater than 10 MHz for optimal scanning characteristics. An optimal focus depth of 30 to 40 mm should be used, and frame rates greater than 15 Hz should be obtained. A minimum 10-mm arterial length should be captured within the longitudinal scanning view.[17] Subsequently, other consensus statements for the use of cIMT in assessment of CVD risk in asymptomatic adults have been published by the American Heart Association,[18] the American Society of Echocardiography,[19] the U.S. Preventive Services Task Force,[20] the Society of Atherosclerosis Imaging and Prevention and the International Atherosclerosis Society,[21] and the Society for Vascular Surgery.[22] These professional organizations, in general, agree regarding the use of the standardized and validated IMT protocols for research and call for performing cIMT measurements in certified ultrasound laboratories.

Normal cIMT values in the general populations are reported by several large epidemiology studies.[23–26] The average cIMT varies by age, ranging from 0.50 mm in young individuals to 0.80 mm in the elderly. The upper range of normal is often taken as the 75th percentile of cIMT distribution for a given age, sex, and race/ethnicity of an individual, and values greater than this threshold are indicative of increased cardiovascular risk. By most experts, a cIMT greater than 1.0 mm is considered a value associated with increased vascular risk.

CAROTID PLAQUE

The Mannheim consensus defined CP as a focal extrusion into the arterial lumen of at least 0.5 mm or 50% of the surrounding cIMT value, or a thickness of more than 1.5 mm when measured in the same fashion as cIMT.[15] If CP is identified, the individual is considered to be at risk for future cardiovascular events, and no further cIMT imaging is necessary. Recently, the maximal CP thickness and carotid plaque area (CPA) have been measured by tracing the perimeter of the two-dimensional (2D) longitudinal images of CPs (Figure 20.2). These measures have been associated with a greater risk of stroke and vascular events.[27]

CPA is usually defined as the sum of the 2D areas of all plaques in the carotid arteries.[28] CPA is measured semimanually by tracing the plaque boundaries with electronic cursors or by automated computer-assisted edge detection programs, which are now available commercially (Figure 20.2). Recently, CPA has been demonstrated to be more predictive of stroke than cIMT.[29]

During the early 1990s, Fenster and colleagues began to obtain three-dimensional (3D) images of the carotid arteries[30] and to measure the volume of CP.[31–33] Currently, various, optimized 3D acquisition protocols exist, capturing ~30 slices/s of cross-sectional images of the carotid artery, which are stacked and reconstructed into a 3D image.[27] Although, the current evidence supports the good

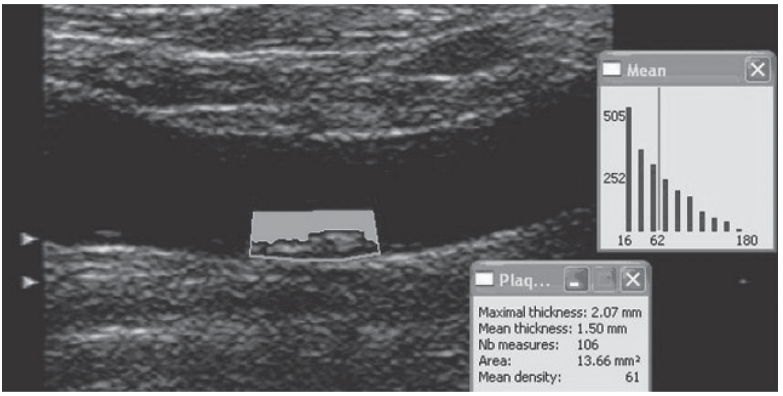

FIGURE 20.2 Carotid plaque (located in grey area) measurements of maximal plaque thickness of 2.07 mm and area of 13.66 mm^2 (bottom legend).

reproducibility of 3D ultrasound for the evaluation of CP volume,[33] there is high heterogeneity between studies. The superiority of 3D over 2D ultrasound in the identification of the vulnerable CP in clinical settings is yet to be established.

CP has been defined as "complicated" if it is associated with ipsilateral neurological symptoms and exhibits common ultrasonic characteristics of being predominately echolucent (soft) or heterogeneous (mixed).[7] In contrast, "uncomplicated" plaques are often asymptomatic, tend to be of uniform consistency, and have no evidence of ulceration.[7] Different classifications of CP ultrasonic appearance have been proposed. CP has been classified as homogenous and heterogeneous. Homogeneous plaques are those with "uniformly bright echoes" that are known as uniformly hyperechoic,[34] as dense and soft,[35] and as echolucent and echogenic based on their overall level of echo characteristics.[36]

The ultrasonographic grayscale densitometry index or grayscale median has been introduced recently as a new parameter to evaluate CP echogenicity. It is calculated as an average (or median) density of the reflecting grayscale signals from the normalized ultrasound image of plaque.[37] The grayscale densitometry index may reflect the content (morphology) of plaque, and therefore may represent a clinically useful marker of vascular risk and a novel tool for monitoring of the effects of antiatherosclerotic therapies.[37]

CAROTID STIFFNESS

STIFF is a measure of the vessel wall's tendency to resist deformation by systolic BP during the cardiac cycle, and is considered a parameter of arterial distensibility (inverse of stiffness).[38] STIFF is greater among people with manifest atherosclerosis, and is considered an early predictor of stroke and CVD.[39] Functional properties of the arterial wall preceding the clinical stage of atherosclerosis have been investigated in peripheral arteries (femoral and brachial) and in the aorta for many years by using different methodologies, such as measurement of pulse wave velocity. Recent development of high-resolution and high-definition ultrasonography has focused new investigations of STIFF on the carotid arteries.

Although an increased STIFF was considered intrinsic to the aging process of the artery,[40] it has been demonstrated that a number of vascular risk factors contribute to the stiffening of the arterial tree.[41] There is no consensus on the gold standard for measuring arterial STIFF. Several methods, including ultrasound, applanation tonometry, and pulse wave velocity, have been recommended by the First International Consensus Conference on the Clinical Applications of Arterial Stiffness[42]

and by the European Network for Noninvasive Investigation of Large Arteries.[43] STIFF can be assessed noninvasively using B- or M-mode imaging, or wall track techniques, by measuring changes in lumen diameter during the cardiac cycle and relating them to the differences in systolic and diastolic blood pressure (BP).[44] In the Northern Manhattan Study (NOMAS), STIFF was a metric calculated as $\frac{In(Systolic\ BP - Diastolic\ BP)}{Strain}$, where Strain is defined as the amount of deformation relative to the unstressed state and is expressed as percent change in the arterial diameter: $\frac{Systolic\ Diameter - Diastolic\ Diameter}{Diastolic\ Diameter}$.[44] New methods, such as noninvasive vascular ultrasound elastography, were introduced recently to assess the mechanical properties (strain or elasticity) of peripheral vessel walls. Noninvasive vascular ultrasound elastography uses the Lagrangian estimator to compute vascular elastograms and was found to be quite accurate and reproducible.[45]

Recently, researchers reported racial/ethnic differences in STIFF and arterial diameter in the NOMAS population,[46] with greater carotid artery diameter and STIFF in Hispanics. These findings may offer a possible explanation for disparities in stroke morbidity and mortality in Hispanics in comparison with blacks and whites.

Markers of Carotid Atherosclerosis and Risk of Stroke in Epidemiological Studies

Carotid Intima Media Thickness and Risk of Stroke

cIMT has been used increasingly as a surrogate end point of vascular outcomes in epidemiological studies and clinical trials aimed at determining the success of interventions that lower risk factors for atherosclerosis and associated vascular disease.[17] The relative risk of high cIMT in comparison with low cIMT in the CCA, adjusted for age and sex, ranged from 2.3 to 3.5 for stroke and 2.3 to 4.0 for total CVD.[47] In a systematic review and meta-analysis, Lorenz et al.[48] reviewed eight observational studies conducted on 37,197 subjects with carotid ultrasound data who were monitored for a mean of 5.5 years. For an absolute cIMT difference of 0.1 mm, the future risk of stroke increased by 13% to 18%.[48] Most studies reported cIMT to be an independent but relatively modest predictor of coronary heart disease (CHD). cIMT may be a better predictor for stroke than for CHD,[47] although this is not reported consistently across studies.

Despite this evidence from epidemiological studies, the enthusiasm for the use of IMT in risk prediction has decreased recently after the results were published of a meta-analysis of 41 trials with 18,307 participants. cIMT regression or slowed progression induced by cardiovascular drug therapies did not translate into the reduction of cerebrovascular events.[49] In addition, prediction of stroke risk varied across the different carotid segments where cIMT was measured. For example, in 1975 participants from the Framingham Offspring Study, cIMT in the ICA, but not in the CCA, was associated with a greater prevalence of magnetic resonance imaging-defined cerebral infarcts.[50] However, a study conducted of 5056 individuals enrolled in the Carotid Atherosclerosis Progression Study demonstrated that cIMT measured in the CCA, bifurcation, and the ICA was highly predictive of stroke even after adjusting for age, sex, and vascular risk factors. Its predictive value was at least as high in younger subjects as in older subjects.[51] In the Atherosclerosis Risk in Communities (ARIC) study, a large population-based study of 13,123 participants with a mean follow-up of 8 years, the absolute annual stroke risk associated with cIMT, measured at the carotid bifurcation, ICA, and CCA, more than 1.0 mm was 0.5% for both men and women.[52] Interestingly, findings from the Progression Intima Media Thickness (PROG-IMT) Study suggested that estimation of cIMT progression may be more useful in predicting CVD than the singular, one-time-point cIMT measurement.[53]

It is important to note that increased cIMT may represent pathological changes of arterial medial hypertrophy or intimal thickening in the absence of atherosclerosis, in which case cIMT is not a real representation of atherosclerosis. However, because the pathological changes and atherosclerosis share common underlying mechanisms, cIMT may be an indicator of the overall vascular risk in an individual.[54]

CP AND RISK OF STROKE

Atherosclerotic plaques that are prone to rupture as a result of their intrinsic composition of a large lipid core, thin fibrous cap, and intraplaque hemorrhage are associated with thromboembolic ischemic events.[55] The presence of stenotic atherosclerotic CP is a well-established risk factor for ischemic stroke.[56]

Small nonstenotic plaque has also been associated with an increased risk of vascular disease. In NOMAS, subclinical CP was a strong predictor of vascular outcomes[57] and beyond the effect of the traditional FRS. In addition, CP with an irregular surface increased the risk of ischemic stroke threefold.[3] The cumulative 5-year ischemic stroke risk among individuals with an irregular plaque surface was more than 8%, whereas those with regular plaque had a stroke risk of less than 3%. These data suggest that plaque surface irregularity, even after adjusting for degree of stenosis and plaque thickness, is an independent predictor of stroke. The data from NOMAS are in agreement with the Rotterdam study,[58] in which the presence of CP increased the risk of stroke and cerebral infarction 1.5-fold, regardless of plaque location.

There is conflicting evidence about the effect of calcified CP on cardiovascular events.[59] Individuals with calcified or echodense plaque are less likely to have symptomatic disease.[60] In contrast, the studies conducted in NOMAS showed that calcified CP was an independent predictor of combined vascular events, defined as ischemic stroke, MI, or vascular death.[61] Moreover, it was demonstrated that people with maximum CP thickness greater than 1.9 mm had a 2.8-fold increased risk of combined vascular events in comparison with subjects without CP.[3] Interestingly, in this study, the amount of atherosclerosis overall was greater among whites and blacks than among Hispanics; but, if CP was present, it had a significant impact on vascular risk only among Hispanics. In fact, in fully adjusted models, the association between CP and vascular events was significant among Hispanics only, suggesting a role of race/ethnicity in the CP-related risk of CVD. Calcified plaque appeared to be a significant predictor of combined vascular outcomes when compared with the absence of plaque and after adjusting for demographics, mean cIMT, education, and risk factors. In agreement with this study, the presence of CP was associated with a twofold increased risk of ischemic stroke in the ARIC study.[62]

New evidence suggests that total CPA is the strongest CVD predictor among the ultrasound phenotypes of subclinical atherosclerosis, including plaque presence, thickness, or cIMT. In the Tromso study, a large population-based study, total CPA was a stronger predictor for incident ischemic stroke than cIMT.[29] In 3240 men and 3444 women, ultrasonographic assessment of plaque area resulted in a significant hazard ratio (HR) of 1.23 in men and 1.19 in women for 1-standard deviation increase in square root-transformed plaque area when adjusted for other cardiovascular risk factors. The multivariable-adjusted HR in the highest quartile of plaque area versus no plaque was 1.73 in men and 1.62 in women.

Taken together, these data support a strong association between the presence of small nonstenotic CP and stroke. However, comparison of the results from various populations must be considered with caution. Differences in demographics and risk factor profiles across different study populations, and use of different measurements of subclinical atherosclerosis may have contributed to varying plaque burden and its associated risk of cerebrovascular events.

STIFF AND RISK OF STROKE

Although study populations, designs, and methods used in different reports have been inconsistent, increased STIFF has been associated with an increased risk of vascular disease. Evidence for a relation of STIFF with future CVD in population-based studies is, however, limited. In a sample of 79 patients with end-stage renal disease patients who were monitored for a mean of 25 months, increased STIFF was associated with a 6.4-fold increased risk of CVD and all-cause mortality, including stroke, independent of other prognostic factors such as diastolic BP and the total cholesterol-to-high-density lipoprotein ratio.[63] In a case–control study conducted in 267 stroke patients, carotid distensibility (inverse of STIFF) was significantly lower in stroke patients than in control subjects even after adjusting for BP, and diastolic carotid diameter and height. Each 1-standard deviation decreased in the carotid distensibility increased the likelihood of stroke independently by 167%.[64] Data from the Second Manifestations of Arterial Disease study confirmed these findings.[65] In 420 participants with carotid stenosis of 50% or greater, the risk of ischemic stroke or transient ischemic attack in the highest quartile of STIFF relative to the lowest quartile was doubled after adjusting for age, sex, systolic BP, minimal diameter of the carotid artery, and degree of carotid artery stenosis.[66]

Several mechanisms may explain the association between increased STIFF and stroke. STIFF may favor the occurrence of CVD through an increase in central pulse pressure that influences arterial remodeling at the sites of both the extracranial and intracranial arteries, increasing the development of carotid artery stenosis and the likelihood of plaque ulceration and rupture. Furthermore, STIFF may be associated with cerebral microvascular processes important in stroke pathogenesis.[39]

In contrast, the Rotterdam study[67] reported no association between carotid distensibility (inverse of STIFF) and stroke. Different populations, methods, and analyses may explain the lack of replication of the study results. Nonetheless, similar to the other markers of subclinical atherosclerosis, the genetic component may play an important role in STIFF.

Table 20.1[68–71] reports some of the principal epidemiological studies that evaluated the impact of subclinical carotid atherosclerosis (cIMT, CP, and STIFF) on the risk of stroke and CVD.

Carotid Plaque (CP) Versus Carotid Intima Media Thickness (cIMT) in the Prediction of CVD

CP is a focal manifestation of atherosclerosis and largely a biologically and genetically different phenotype from cIMT.[27,68] This is not a generally accepted concept, although the supporting evidence that they are distinct markers of vascular disease has been accumulating. cIMT is related mainly to hypertension, resulting in hypertrophy of the media layer of the vessel wall.[15] There is evidence of different genetic contributions to cIMT than to CP, which seems to be influenced more strongly by environmental factors.[72] Traditional vascular risk factors explain only 15% to 17% of the variance in cIMT,[72–74] but account for 52% of the variance in total CPA.[75] Furthermore, although the two processes—cIMT and plaque formation—share some common risk factors, their overlap is partial, and their predictive power for CVD differs. CP seems to be a stronger predictor of CVD than cIMT in large population-based studies (Table 20.2).[76] Nevertheless, the differentiation of early plaque formation from increased cIMT depends on the definition of plaque. Various studies have adopted different plaque definitions, but most include thickness of plaque in the calculation of cIMT.[77]

Atherosclerosis, including plaque formation, represents a dynamic process involving a complex cascade of inflammatory events from lipid deposition to plaque calcification.[78] The combination of cIMT and CP has been shown to improve the prediction of CVD compared with cIMT or CP alone.[79] The comparison of the predictive power of cIMT and CP across various studies, however, is limited as a result of (a) the site of cIMT used (the far wall or the far and near wall combined, the

TABLE 20.1

Principal Epidemiological Studies That Evaluated the Impact of Subclinical Carotid Atherosclerosis on Stroke and Cardiovascular Disease

Study	Subclinical atherosclerosis Measures	*n*	Follow-up, y	Age, y	Combined vascular events[a] hazard ratio (95% CI)	MI hazard ratio (95% CI)	Stroke hazard ratio (95% CI)
NOMAS[3]	CP	2189	6.9	68 ± 10	2.76 (2.10–3.63)	2.87 (1.73–4.78)	1.79 (1.11–2.90)
Tromsø[34]	cIMT and CP	6584	9.6	25–84	NR	NR	cIMT 1.08 (0.95–1.22) in men, 1.24 (1.05–1.48) in women, TCPA 1.73 (1.19–2.52) in men, 1.62 (1.04–2.53) in women
CAPS[53]	cIMT	5056	4.2	50.1	1.45 (1.38–1.52)	1.43 (1.35–1.51)	1.47 (1.35–1.60)
ARIC[52]	cIMT	14,214	7.5	45–64	NR	NR	2.0 (1.20–3.20) in men, 3.3 (1.90–5.80) in women
Rotterdam[58]	CP	4217	5.2	68 ± 8	NR	NR	2.44 (1.42–4.20)
SMART[65]	STIFF and cIMT	570	11.5	59 ± 12	STIFF, HR = 0.23 (0.17–0.27); cIMT, 1.37 (1.15–1.60)	NR	NR
Rotterdam[67]	STIFF	2835	4.1	71 ± 6	2.40 (1.51–3.83)	2.45 (1.29–4.66)	2.28 (1.05–4.96)
Framingham[69]	cIMT and CP	2965	7.2	58 ± 10	cIMT, 1.13 (1.02–1.24); CP, 0.014 (0.003–0.025)	NR	NR
REACH[70]	cIMT	2317	2	68 ± 10	2.09 (1.07–4.10)	1.71 (1.10–2.67)	1.73 (1.31–2.27)
MESA[71]	cIMT	6698	5.3	45–84	1.62 (1.372–1.874)	2.3 (1.5–3.7)	3.5 (1.9–6.6)

[a]MI, stroke, and vascular death.

ARIC, Atherosclerosis Risk in Communities; CAPS, Carotid Atherosclerosis Progression Study; CI, confidence interval; cIMT, carotid intima media thickness; CP, carotid plaque; MESA, Multi-Ethnic Study of Atherosclerosis; MI: myocardial infarction; NOMAS, Northern Manhattan Study; NR, not reported; REACH, Reduction of Atherothrombosis for Continued Health; SMART, Second Manifestations of Arterial Disease; STIFF, carotid stiffness; TCPA, total carotid plaque area.

TABLE 20.2

Plaque Is a "Better" Predictor of CVD than cIMT

Ultrasound measure of subclinical atherosclerosis	Hazard ratio[a]
IMT >1.0 mm	1.5
Plaque presence	1.8
Plaque thickness	2.0
Plaque area	3.0

[a]Approximate average from various studies.
cIMT, carotid intima media thickness; CVD, cardiovascular disease; IMT, intima media thickness.

single CCA or a combined measure of CCA with bifurcation and ICA), (b) the inconstant incorporation of CP in the cIMT measure, (c) the use of mean or maximum cIMT, (d) different CP phenotypes (presence, thickness, area, calcification, ulceration), (e) the arbitrary cutoff point to evaluate cIMT ability to predict risk, and (f) the generalizability of the prognostic value of cIMT, obtained mainly in middle-age and elderly populations, to younger individuals when data are insufficient. Therefore, further studies are needed to clarify more completely the biological and genetic mechanisms underlying cIMT and CP, and their role in CVD in various populations.

Added Value of Intermediate Markers of Carotid Atherosclerosis on Prediction of Stroke by Risk Factors

Subclinical markers of carotid atherosclerosis may provide additional prognostic information to that of traditional risk factors. Besides traditional vascular risk factors such as high BP, diabetes, smoking, stress, obesity, and metabolic syndrome, there is a growing list of less traditional factors such as high LDL or low high-density lipoprotein, C-reactive protein (CRP), lipoprotein(a), homocysteine, LDL particle size, Lp-PLA2, apolipoprotein B/apolipoprotein A.[80] Most of them have been combined with vascular risk scores such as FRS. However, FRS remains the primarily recommended risk prediction tool in preventive guidelines to identify individuals at risk and their targets for preventive therapy.[81]

In the recent analysis from the ARIC study of 13,145 subjects, approximately 23% individuals were reclassified into a different risk category group after adding information on cIMT and CP.[79] Adding cIMT to traditional risk factors provided the most improvement in the area under the receiver–operating characteristic curve, which increased from 0.74 to 0.77. Adding CP to cIMT and traditional risk factors had, however, the best net reclassification index of 10% in the overall population. In the Cardiovascular Health Study,[82] of 5888 participants, an elevated CRP level was associated with increased risk for CVD and stroke only among those individuals who had increased cIMT and plaque detectable on carotid ultrasound. Despite these significant associations with CVD, CRP, cIMT, and plaque improved only modestly the prediction of CVD outcomes, after accounting for the traditional risk factors. Addition of CRP or subclinical carotid atherosclerosis to conventional risk factors resulted in a modest increase in the ability to predict CVD.

In NOMAS, the presence of CP contributed considerably to the better estimation of 10-year FRS.[3] More than a half of the individuals in low and moderate FRS categories were reclassified into the higher risk category if CP was present, and about 30% to 40% were reclassified if the CP thickness was greater than 1.9 mm (bold type in the Table 20.3).

TABLE 20.3

Carotid Plaque Presence and Thickness Reclassifies More Than 30% of Subjects into a Greater FRS Stroke Category in the General Multiethnic Population

	Low FRS		Moderate FRS		High FRS	
Carotid Measures	*N* or *n* (%)	10Year risk, %	*N* or *n* (%)	10-Year risk, %	*N* or *n* (%)	10-Year risk, %
Overall	505 (26)	11.4	920 (47)	15.6	541 (27)	26.0
No plaque	285 (26)	5.8	402 (44)	11.5	178 (33)	27.6
MCPT ≥1.9mm	**62 (12)**	**24.7**	**173 (19)**	**25.1**	157 (29)	30.7
***p* Value**		**.004**		**.002**		.319

Note: Adapted from Rundek et al.[3]
FRS, Framingham Risk Score; MCPT, maximum carotid plaque thickness. Cells in bold indicate participant subgroups wherein carotid data significantly modified risk prediction based on the FRS.

Other studies, such as the Carotid Atherosclerosis Progression Study,[83] the Paroi Artérielle et Risque Cardio-vasculaire (PARC) study,[84] and the Framingham Offspring Study,[69] showed that cIMT measurements may have a favorable impact on selecting and targeting subjects at intermediate FRS risk in primary prevention. Traditional CVD risk prediction schemes need further improvement and assessment of cIMT, and CP may add to risk stratification with a direct implication for intervention in vascular preventive programs.

Clinical Utility of Detecting Carotid Atherosclerosis in Prevention of Stroke: Who Should Be Really Screened?

A major challenge associated with the primary prevention of stroke involves the early and accurate detection of subclinical atherosclerosis in an asymptomatic population at risk. Delay in identifying at-risk individuals may result in a missed opportunity to prevent CVD. Therefore, early detection of subclinical carotid atherosclerosis could help CVD prevention and reduce substantially death and disability attributable to stroke. This goal may be furthered by developing and disseminating the standardized and validated noninvasive ultrasound diagnostic techniques for the identification of individuals at risk in the general population. It has been reported that when subclinical disease develops, the traditional risk factors appear to have a lesser association with the subsequent development of clinical disease, although the traditional risk factors are the primary determinants of subclinical disease.[85] Recently, in NOMAS, researchers demonstrated that traditional vascular risk factors explain only 21% of the variance in the total carotid plaque burden.[11]

With increasing incidence of CVD and stroke, it is important to identify high-risk patients with subclinical manifestation of disease who will benefit from early and aggressive therapy. The Mannheim cIMT consensus states that there is no need to "treat IMT values" nor to monitor IMT values in individual patients apart from a few exceptions.[17] The current American Heart Association guideline for the use of cIMT in the assessment of cardiovascular risk in asymptomatic adults gives cIMT a class IIa rank with a level B for evidence for asymptomatic adults at intermediate risk. It emphasizes the importance of following clear recommendations on the use of appropriate scanning and reading imaging ultrasound methodology.[18] Accordingly, the American Society of Echocardiography recommends that the use of cIMT assessment be reserved for individuals with

Appropriate indications:	Inappropriate:
Intermediate risk patients	Serial testing
Metabolic syndrome	Low risk patients
Older patients	Very high-risk patients

FIGURE 20.3 Appropriate Clinical Use of cIMT.

intermediate cardiovascular risk (e.g., a 6% to 20% 10-year risk of CVD according to FRS). Because some high-risk groups might not be addressed by this approach, there are additional clinical circumstances that should be considered: (a) family history of premature CVD in a first-degree relative (men, <55 years old; women, <65 years old); (b) individuals younger than 60 years with severe abnormalities in a single risk factor (e.g., genetic dyslipidemia) who otherwise would not be candidates for pharmacotherapy, or (c) women younger than 60 years with at least two CVD risk factors.[19]

Appropriate use of measuring cIMT in the clinical setting was examined recently by the Society of Atherosclerosis Imaging and Prevention and the International Atherosclerosis Society.[21] To prevent either under- or overuse of IMT measurements, common clinical scenarios—including risk assessment in the absence of known CHD, risk assessment in patients with known CHD, and serial cIMT imaging for monitoring of CHD risk status—were rated. The conclusion of these professional organizations was that appropriate indications for the use of cIMT should be reserved for individuals without CHD with intermediate risk, older individuals, and individuals with metabolic syndrome. The testing of low-risk or very high-risk individuals with CHD as well as serial cIMT testing is currently considered inappropriate for use in clinical practice (Figure 20.3).

Future Perspectives: Genetics of Subclinical Atherosclerosis and cIMT Progression

GENETICS OF SUBCLINICAL CAROTID ATHEROSCLEROSIS

Genetic and environmental factors underlying subclinical atherosclerosis are of great importance for successful prevention of stroke and CVD, and are in the major focus for future investigations. Genetic contribution also seems to play a pivotal role in the mechanism of cIMT.[86,87] In the Family Study of Stroke Risk and Carotid Atherosclerosis, a high heritability of cIMT was reported in Caribbean Hispanics, and ranged from 0.41 to 0.65 across the different carotid segments. In that study, significant linkage was reported for cIMT on chromosome 7p and 14q.[88,89] Moreover, in a recent cIMT fine-mapping study conducted on the same families, several loci comprising genes strongly related with inflammation were identified.[88] In a candidate gene study conducted in a sample from NOMAS, associations between cIMT and 702 single nucleotide polymorphisms (SNPs) were found for 145 candidate genes involved in the pathophysiology of atherosclerosis,[30] predominantly in hemostasis (PLAT, THBS1), extracellular matrix remodeling (MMP3, MMP12, TGFB2), inflammation (*CXCL12, PTGS2*), antioxidation (*PON1*), endothelium function (*NOS1, SELP*), and the renin–angiotensin system (*SCNN1B, ACE, REN*).[70] In addition, variants in stromelysin 1, interleukin 6, and hepatic lipase genes were associated with cIMT in an earlier study from NOMAS.[90]

Recently in NOMAS, a modest but significant heritability of 0.50 for CP presence and 0.17 for plaque area was reported.[91] The National Heart, Lung, and Blood Institute Family Heart Study[92] reported a heritability of 0.52 for CP, and the San Antonio Family Heart Study[93] showed a heritability of 0.23 for CP. The Diabetes Heart Study[94] found a heritability of 0.40 for calcified CP in white Americans.

In linkage analyses, researchers identified four regions with multipoint LOD scores of 2.00 or more on chromosomes 7q36, 11p15, 14q32, and 15q23 (Figure 20.4). Genetic variants in genes related to inflammation, endothelial function, lipid metabolism, and oxidative stress have been reported to be associated with CP phenotypes.[95,96] These results call for further fine mapping and sequencing of interesting regions, as well as validation in other cohorts.

Other epidemiological studies have taken similar approaches to genetic investigations of subclinical atherosclerosis. Most have reported candidate gene associations, and a few performed linkage analyses and/or fine mapping. In the National Heart, Lung, and Blood Institute Offspring Cohort of the Framingham Heart Study, 11 SNPs with associations at p values less than 10^{-5} were identified for maximum internal cIMT, and five SNPs with associations at p values less than 10^{-5} were identified by family-based association testing for mean common cIMT. In addition, several regions of linkage to internal cIMT were identified on chromosome 12, confirming previous results from the same population.[97]

Recently, the CHARGE consortium[98] reported genomewide association results of cIMT in a sample of 31,211 participants from nine population-based studies and a follow-up analysis that included 11,273 participants from seven independent studies. For common cIMT, they found three independent loci that achieved the genomewide significance threshold ($p < 5 \times 10^{-8}$) in the combined meta-analysis of discovery and follow-up studies. The strongest association was for rs11781551, close to *ZHX2*, and for rs445925, close to *APOC1*. However, scant information exists regarding the function and the proteins encoded by these genes, and their relationships to CVD. No SNP achieved a significance threshold in the follow-up analyses of internal cIMT. For CP, two independent loci achieved the genomewide significance threshold in the combined meta-analysis. The most significant signal was for rs17398575, near *PIK3CG*, which plays an important role in maintaining the structural and functional integrity of endothelium. The second signal was centered at rs1878406, near *EDNRA*, a target for pharmacological treatments to reduce BP. Moreover, SNPs in *EDNRA* were associated with both CP and CHD.

One of the main reasons for the inconsistent results for cIMT and CP may be that multiple genes are likely to influence carotid atherosclerosis, which could account for some of the variation in findings

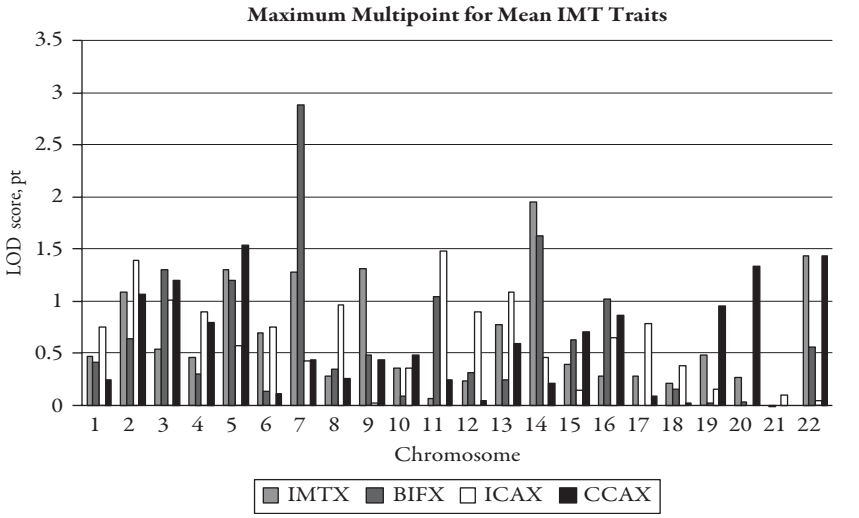

FIGURE 20.4 Maximum multipoint linkage results for mean intima media thickness traits. Multipoint (Logarithm of Odds) LOD scores by chromosome. The most significant results are seen on chromosomes 7 and 14.

IMTX, carotid IMT; BIFX, IMT at carotid bifurcation; ICAX, IMT on internal carotid artery; CCAX, IMT on common carotid artery

among genetic studies. In addition, each segment of carotid artery has its own unique anatomy and hemodynamic environment, and therefore is prone to different pathophysiological mechanisms.[87]. Genetic studies of stroke due to large artery atherosclerosis are discussed in Chapter 5. Collaborative efforts to extend our knowledge of genetic risk factors for subclinical markers of atherosclerosis, and atherosclerosis in relation with stroke, are currently ongoing within various consortia such as CHARGE, the National Institute of Neurological Disorders and Stroke–Ischemic Stroke Genetic Network, the International Stroke Genetic Consortium, and the Genomics and Randomized Trials Network.[99]

Understanding the complexity of the pathogenesis of atherosclerosis will be essential in considering the interaction between genetic and environmental risk factors. Currently, these interactions are poorly understood. Ultimately, the prediction of the disease risk for individuals will be determined by their genotypic and environmental exposures.

PROGRESSION OF CIMT

Recently a collaborative effort has been made by the cIMT Progression Study Group to predict cardiovascular events in the general population (the PROG-IMT collaborative project),[77] a team of international experts in the field of atherosclerosis aiming to test the association between changes in cIMT and cardiovascular risk. In a meta-analysis conducted of 36,984 participants, in whom cIMT progression was derived from two ultrasound visits 2 to 7 years (median, 4 years) apart, the mean cIMT of the baseline as well as of the repeated ultrasound scan was associated positively and robustly with cardiovascular risk, including stroke (HR for the combined end point, 1.16; 95% confidence interval, 1.10–1.22, adjusted for age, sex, mean common cIMT progression, and vascular risk factors).[77] However, cIMT progression calculated from the two visits was not found to be associated significantly with the risk of vascular events. According to the PROG-IMT, the association between cIMT progression assessed from two ultrasound scans and CVD risk in the general population remains unproved. Furthermore, no conclusion can be derived for the use of cIMT progression as a surrogate measure in clinical trials. More frequent cIMT measurements could increase the precision of the assessment of cIMT progression and, therefore, better predict the risk for stroke and CVD. The use of repeated assessment of cIMT in CVD risk assessment still awaits its clinical validation.

Conclusion

In conclusion, subclinical phenotypes of carotid atherosclerosis are significant predictors of vascular events. Ultrasound measures of cIMT, CP, and STIFF are noninvasive, inexpensive tools to detect individuals with increased atherosclerotic burden and risk of CVD and stroke, evaluate the effects of current and novel therapies, and investigate new contributing factors. However, more research is needed to understand more fully the genetic and environmental factors associated with these markers in various populations to develop more efficient and targeted preventive therapies.

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21

MAGNETIC RESONANCE IMAGING-BASED MARKERS OF CEREBROVASCULAR DISEASE AND THE RISK OF STROKE

Svetlana Lorenzano and Natalia S. Rost

Introduction

Magnetic resonance imaging (MRI) plays an essential role in the field of cerebrovascular diseases. The number of MRI techniques that enables a better characterization of brain tissue and vessel status is constantly evolving and becoming extensively available to both clinicians and researchers.

In a nonemergency clinical setting, MRI has become a routine modality of choice, used both for inpatient and outpatient investigations, and as a result, the interpretation of incidental MRI findings such as leukoaraiosis or white matter hyperintensity (WMH), silent brain infarcts (SBIs), and cerebral microbleeds (CMBs) has become necessary to understand their pathophysiology and to define their clinical significance. A number of population-based studies have explored the potential role that the MRI findings play as markers of cerebrovascular disease, including ischemic and hemorrhagic stroke.[1,2] These studies have specifically addressed the MRI-based findings that contribute to the risk of first-ever stroke, and have provided the basis for exploratory research on preventative and therapeutic interventions. In the setting of nonacute trials, in large studies on cerebrovascular disease MRI findings of small-vessel disease (WMH, SBIs, CMBs, brain atrophy)—for example, WMH measured on T2-weighted (T2W) magnetic resonance image—have been used particularly as markers of disease progression and vascular cognitive impairment, or as predictors of treatment response and long-term outcome.[3–9]

In the emergency clinical setting, advanced multimodal MRI techniques enable a reliable, noninvasive clinical diagnosis of ischemic stroke and provide insight with regard to the underlying etiology and more appropriate stroke subtype definition. Current MRI-based evaluation of acute cerebral ischemia delivers detailed information on infarct area characteristics such as age, extent and location, vessel status, and brain tissue dynamics within minutes from the onset of an ischemic event. Furthermore, the fate of the cerebral tissue after an acute ischemic injury can be evaluated through

the degree of cerebral perfusion and estimates of ischemic penumbra.[10,11] In acute hemorrhagic stroke, MRI is not yet used routinely as part of clinical diagnosis, although studies have demonstrated that sensitivity and accuracy of MRI in differentiating intracerebral hemorrhage (ICH) from acute ischemic stroke is high and at least comparable with those of computed tomography (CT).[12,13] Although CT is still considered the preferred acute ICH diagnostic imaging modality, MRI has proved to be superior to CT for identifying subacute and chronic cerebral hemorrhage. Furthermore, in the emergency setting, MRI data can be crucial in guiding clinicians in early patient management options and risk stratification for individualizing acute therapeutic strategies in both ischemic and hemorrhagic stroke. In addition, it can inform the early steps for secondary prevention planning and serves as a potential surrogate marker of stroke recurrence risk and poststroke outcome.[13] In the setting of acute trials, MRI-based findings have been used as part of eligibility criteria for the enrollment of patients with acute ischemic stroke in neuroprotection and pharmacological/interventional recanalization studies, particularly those designed to extend the conventional therapeutic window of the officially approved thrombolytic treatment with recombinant tissue plasminogen activator or to evaluate the response to new thrombolytic agents.[14-21]

In this chapter, we focus on the most frequently used conventional MRI techniques and their applications in detecting all specific gray and white matter changes that have been accepted in the field as markers of cerebrovascular disease, and we evaluate their role in predicting the risk of stroke. Last, we provide insight into novel, advanced MRI techniques that offer great promise in elucidating the pathophysiology of the broad and complex spectrum of cerebrovascular diseases.

Detection of MRI-Based Cerebrovascular Disease Markers

The properties that make MRI the technical modality of choice for the evaluation of neurovascular diseases are noninvasiveness, optimal soft tissue contrast, and the possibility of simultaneous assessment of multiple structural and functional parameters. The most frequently used conventional and advanced MRI techniques in cerebrovascular diseases are those that assess specifically brain structure, including basic T1-weighted (T1W) and T2W imaging, T2 fluid-attenuated inversion recovery (FLAIR), T2*-gradient-recalled echo (GRE), and susceptibility-weighted imaging; and those that evaluate the brain functional aspects such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (Figure 21.1).[22,23]

During the past few decades, these conventional and advanced MRI techniques have contributed definitively to our increasing knowledge on neuroimaging markers of cerebrovascular disease and their role in stroke risk stratification, stroke recurrence risk, and prediction of poststroke outcomes. In this chapter, we review the MRI markers that are the most common and well delineated through their association with the risk of stroke, such as WMHs, CMBs, SBIs, dilated perivascular spaces (DPVSs), microinfarcts (MIs), and superficial siderosis (SS).

White Matter Hyperintensity

WMH is a common, nonspecific term used for the radiographic finding of increased signal intensity of the cerebral white matter detected on T2W or FLAIR MRI that describes a multitude of underlying cerebrovascular conditions presenting as asymptomatic WMH, usually observed in the healthy aging population,[24] isolated or in combination with other small-vessel-related pathologies, such as lacunar infarcts detected in patients with stroke and/or vascular dementia and CMBs.[2,25] The term *leukoaraiosis* used interchangeably with WMH was coined by Hachinski et al.[26] to describe the radiographic appearance of diffuse hypodensity of the periventricular and deep white matter found

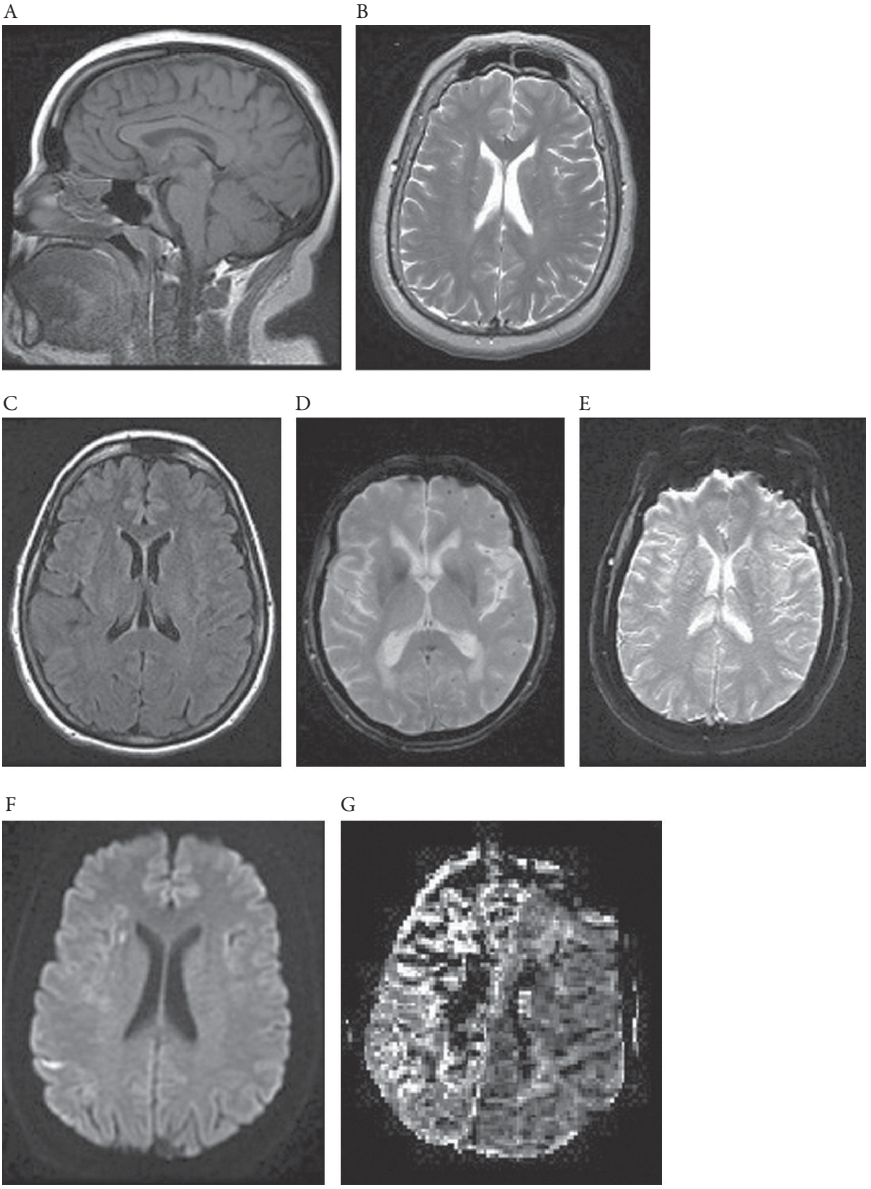

FIGURE 21.1 Magnetic resonance imaging sequences used in study of stroke and cerebrovascular disease. (A) Sagittal T1-weighted image. (B) Axial T2-weighted image. (C) Axial fluid-attenuated inversion recovery image. (D) Axial gradient-recalled echo image. (E) Axial susceptibility weighted image. (F) Axial diffusion-weighted image. (G) Axial perfusion-weighted imaging (mean transit time).

on head CT. Since then, two distinct categories of leukoaraiosis or WMH have been described based on their topography: periventricular WMH (attached and contiguous to the ventricular system) and deep WMH (located in subcortical white matter, apart from the ventricles),[27] giving rise to the ongoing discussion with regard to the potential variability in their respective clinical, histopathological, and pathophysiological correlates.[28]

WMH occurs increasingly with age, and its burden is more severe in the elderly.[29,30] In the general population, WMH prevalence is reported between 11% and 21% in subjects aged 64 years, and is 94% in individuals 82 years old, with the variability explained only in part by different study design, population of interest, and methods adopted for WMH assessment.[1,31–36] The variability in the definitions of WMH as an MRI trait and in its quantification methods have contributed in particular to the heterogeneity of WMH study results reported during the past few decades, and have limited the comparison between individual findings. Early on, semiquantitative visual rating scales became important in the assessment of WMH severity and progression[37,38]; however, the scale and nature of ongoing investigations have demanded a greater precision and high-throughput methodological approaches. Currently, fully automated methods could be considered the gold standard in volumetric assessment of WMH in the context of large, population-based studies.[39] However, semi-automated quantitative methods, which improve measurement specificity and accuracy by using operator-mediated manual correction, have proved to be reliable in ascertaining WMH burden in subjects enrolled in hospital-based studies on acute stroke.[25,40,41] WMH lesion topography detected on MRI, in addition to a total burden of disease, is considered crucial for the potential differentiation of pathophysiology underlying this radiographic trait and in its correlation with the risk of stroke.

MRI APPEARANCE

On T2W MRI, leukoaraiosis is visualized typically as bilateral patchy or confluent areas of hyperintensities, with or without focal, discreet-appearing lesions, distributed in the periventricular, deep, and/or superficial subcortical (juxtacortical) white matter areas. By suppressing the signal from cerebrospinal fluid (CSF) and increasing the signal from white matter changes, FLAIR sequences are conventionally the most sensitive in detecting WMH. As mentioned earlier, WMH also includes subacute and chronic lacunar or nonlacunar infarcts that appear as focal hypointensity on T1W imaging, and hyperintense on FLAIR; but in the case of tissue destruction (e.g., cavities or encephalomalacia), these lesions become hypointense on FLAIR as well and are usually classified as SBIs.

MRI enables one to distinguish different forms and severity of WMHs[42]: (a) periventricular WMH that is usually seen in elderly subjects, including juxtaventricular hyperintensities (i.e., contiguous to the ventricular surface within 3 mm and presenting as thin, hyperintense line—smooth halo) along the lateral ventricles and caps surrounding the horns of the lateral ventricles[43]; (b) irregular periventricular WMH, which is detectable at 3 to 13 mm from the ventricular surface (watershed area)[44–46]; and (c) deep (i.e., subcortical) WMH visualized at approximately 13 mm or farther from the ventricular surface, with multiple punctuate or patchy lesions that may be partially or fully confluent.[47] Last, small WMH lesions located approximately 4 mm apart from the corticomedullary junction can be defined as juxtacortical WMH[42] (Figure 21.2).

HISTOPATHOLOGICAL CORRELATES OF WMH

Histopathological findings corresponding to magnetic resonance-detected WMH can be various based on WMH location (Figures 21.3 and 21.4), possibly reflecting different pathophysiological mechanisms underlying the disease—more specifically, ischemic versus nonischemic (Figure 21.3). In the periventricular caps and smooth halo, areas of demyelination with venous congestion resulting from noninflammatory periventricular venous collagenosis,[48] mild-to-moderate subependymal gliosis, and discontinuity of the ependymal lining that does not have an ischemic origin are observed.[49] No arteriosclerotic vessel changes have been found in these regions.[28] In other cases, areas of irregular periventricular WMH associated with the presence of more severe patchy myelin loss and reactive gliosis of an ischemic nature, including complete microcystic infarcts along with the fibrohyalinotic[50–52] and arteriosclerotic vessels,[50,53] were also observed. Punctuate, early confluent,

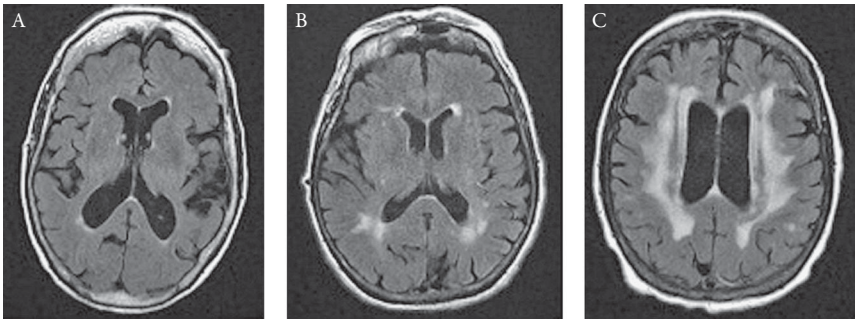

FIGURE 21.2 (A–C) Axial fluid-attenuated inversion recovery (FLAIR) images of mild (A), moderate (B), and severe (C) white matter hyperintensity.

and confluent deep WMH lesions correspond to a degree of progressive tissue changes. In punctuate WMH areas, myelin loss and atrophic neuropil are associated with fibrohyalinotic arterioles and DPVSs. In early confluent deep WMH, myelin sheath rarefaction is combined with loss of axons and astrogliosis. Last, confluent deep WMHs reflect more severe tissue destruction, presenting as loss of

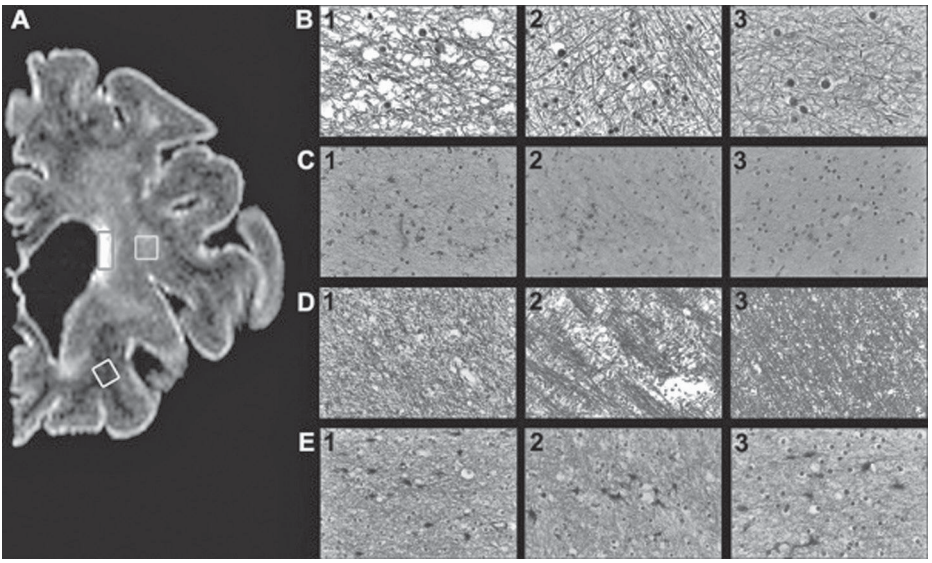

FIGURE 21.3 Histopathological correlates of white matter hyperintensities. (A) Prefrontal coronal fluid-attenuated inversion recovery (FLAIR) image of an 88-year-old woman with Alzheimer's disease. (B–E) Regions of interest represent white matter hyperintensities (WMHs) in the periventricular area (rectangle; B1–E1), WMHs in the deep white matter (upper square; B2–E2), and an area of normal-appearing white matter (NAWM) (lower square, B3–E3). In Bodian Silver-stained sections (B, original magnification ×2003), more lower axonal density was found in WMHs (B1 and B2) than in NAWM (B3). On Human Leukocyte Antigen DR (HLA-DR) immunohistochemical sections (original magnification ×2003), more microglial activation (C) was observed in WMHs (C1 and C2) than in NAWM (C3). In Luxol Fast Blue/Cresyl Violet-stained sections (original magnification ×1003), WMHs also showed more myelin loss (D1 and D2) compared with NAWM (D3). And, in glial fibrillary acidic protein immunostained sections (original magnification ×4003) the severity of astrogliosis (E) was not clearly different between WMHs and NAWM in this patient. (Adapted with permission from Gouw AA et al. *J Neurol Neurosurg Psychiatry* 2011;82:126–135).

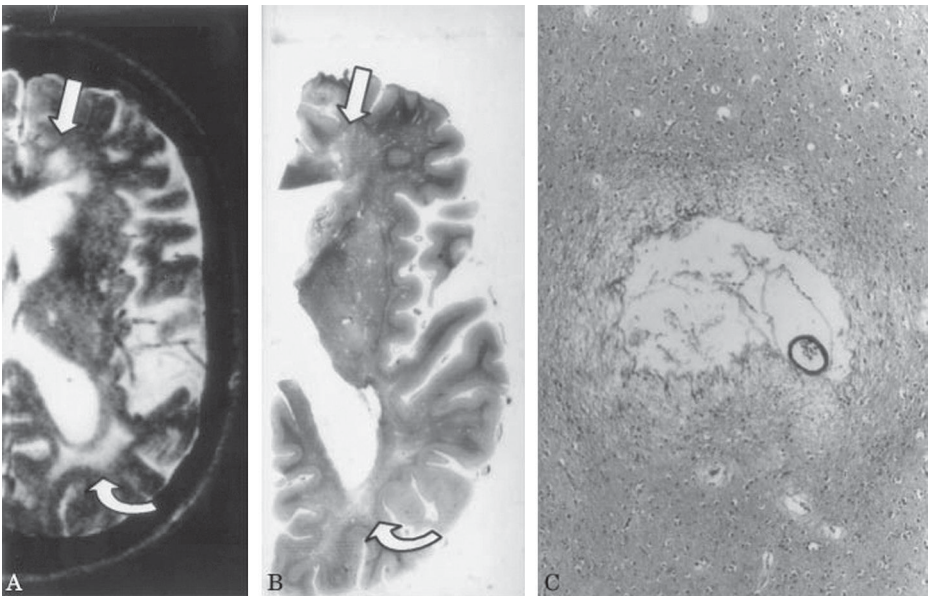

FIGURE 21.4 (A–C) Examples of confluent white matter lesions. Small cavities of tissue destruction are seen within an area of extensive demyelination corresponding to a patchy hyperintensity on premortem (A) and postmortem (B) magnetic resonance imaging (straight arrows in A, B, and magnification of a part of the lesion in C). A large area of myelin pallor is also seen around the posterior horn (curved arrows). (Reprinted with permission in part from Fazekas et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*. 1993;43:1683–1689.)

myelin, axons, and oligodendroglial cells, as well as reactive gliosis associated with DPVSs and areas of complete infarction (Figure 21.4).[28,49,54,55]

PATHOPHYSIOLOGY AND CLINICAL DETERMINANTS OF WMH

Severity and progression of WMH is likely determined by a complex interaction of environmental and genetic factors. WMH has a well-described association with a multitude of cardiovascular risk factors, such as hypertension, diabetes, atherosclerosis, and impaired cerebral blood flow, and it is more common in patients with ischemic stroke and ICH.[31,56–58] WMH is also associated with the development of other important vascular entities such as SBIs[59] and CMBs.[41] However, white matter changes are also a prominent feature in a number of genetic conditions such as mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes caused by mitochondrial DNA mutations[60] and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), an autosomal condition caused by mutations of the *NOTCH 3* gene that might represent a basic model for understanding the pathogenesis of the sporadic white matter changes.[61]

The pathological mechanisms underlying WMH are yet to be fully elucidated; however, the most likely hypothesis emphasizes the vascular ischemic origin supported by findings from population-based studies and pathological–radiographic correlation studies.[49] Given the pattern of white matter vascularization as an arterial border zone or watershed area, susceptibility of white matter to damage as a result of a systemic or focal decrease in cerebral blood flow has been implicated as one of the mechanisms of disease in leukoaraiosis.[54,62] Specifically, the irregular periventricular WMH is thought to be more likely the result of chronic hemodynamic dysfunction, corresponding to an area supplied by

the noncollateralizing ventriculofugal vessels that arise from subependymal arteries.[44–46] Deep white matter areas are supplied by penetrating medullary arteries arising from the cortical branches of the middle cerebral arteries, also supplying the deep gray matter nuclei, and brainstem, which are areas more prone to small-vessel disease. Hence, deep white matter changes can be caused by pathological alterations of these perforating end arteries,[50,63] and this diseased small vasculature may predispose to the occurrence of both small, as lacunar, subcortical areas of infarctions (which, as mentioned earlier, if not cavitated yet, appear as WMH on T2W and FLAIR imaging and are methodologically difficult to discriminate from other WMH subtypes, unless detected on MRI obtained for the evaluation of acute ischemic stroke) and the more extensive patchy or confluent areas of chronic ischemia. Specifically, two different pathophysiological mechanisms have been proposed in the vascular hypothesis on WMH origin: (a) atherosclerosis of larger perforating arteries leading to bigger lacunar infarcts and (b) diffuse arteriopathic alterations with endothelial dysfunction and blood–brain barrier (BBB) changes causing smaller multiple lacunar infarcts associated with patchy/confluent areas of WMH.[54,64–67] Some of the vessel alterations include replacement of the smooth muscle cells by fibrohyaline material with thickening of the wall and narrowing of the vascular lumen, dysregulation of the blood flow to the white matter, repeated episodes of hypoperfusion and ischemic events that may be associated with BBB disruption—another likely important contributor to white matter changes-leakage of macromolecules from plasma into white matter, and consequent astrocyte activation.[54,68,69] Aging, chronic hypertension, and diabetes could contribute to these changes.[70–72] Activated and swollen astrocytes could be responsible for the specific aspects of white matter changes detected by MRI. Cerebral small-vessel disease also appears to be causative of juxtacortical white matter lesions. Juxtacortical white matter is supplied not only by the long penetrating medullary vessels, but also by short vessels, which cross the white matter and the contiguous gray matter, with U-fibers being usually spared from WMH-related changes.

Of notice, other studies have demonstrated that the only WMH subtype of nonischemic origin may be the one observed in the periventricular caps or halos,[49,73] where disruption of ependymal lining may be linked to increased water reabsorption [27] and leakage of CSF[42] associated with abnormal transependymal flow.

The debate in the field whether WMH detected on MRI represents two distinct categories based on its topography and, thus, related mechanism of disease is still ongoing. The authors who propose that periventricular WMH differs from subcortical white matter lesions by separate vascular etiology support their argument by epidemiological and clinicopathological data.[24,43,49,50,51,74–81] Conversely, segmentation maps of WMH on FLAIR images failed to demonstrate that periventricular and deep WMH behave differently enough to support distinct subtypes. Instead, a unique pattern of WMH topography has been reported in which WMH appears to expand smoothly from around CSF spaces to more distal white matter, with the increase of the total volume of WMH, linking it to a compromised watershed area hypothesis.[39]

Clinically, WMH burden is associated with a wide and complex spectrum of symptoms—gait disturbances, urinary incontinence, depression, cognitive impairment, and dementia—all of them possibly linked to the damage caused by chronic hypoperfusion to the associative connections in frontal and subcortical regions.[82] This anatomic hypothesis is supported further by the increasing severity of clinical dysfunction associated with severity of leukoaraiosis.[82]

WMH and the Risk of Stroke

Advances in WMH assessment using qualitative and quantitative methods for MRI analysis set the stage for a comprehensive evaluation of WMH as a potential marker of clinical cerebrovascular disease and, specifically, for its role in stroke risk stratification. Validated in multiple studies, WMH burden has been proposed as a surrogate end point in clinical trials on stroke prevention.[1,4] Furthermore, WMH location, severity, and progression in longitudinal, prospective studies have been associated reliably with an increased risk of first-ever and recurrent stroke (Tables 20.1 and 20.2).

TABLE 21.1

Summary of Studies That Report Associations between MRI Markers of Cerebrovascular Disease and the Risk of First-Ever and Recurrent Stroke

MRI finding	Author, year	Type of study	n	Mean Age, y	Mean Follow-up, y	Measurement methods and marker definitions	Outcome definition	Risk of stroke
WMH	Kobayashi et al.,[89] 1997	Prospective, general population study	933	57.5	NA (1 to >6)	MRI: 0.15 T, 0.2 T; T1, T2, PD WMH: SQ (PV-WMH, 0 – 4)	All strokes: 19 (14 IS, 4 ICH, 1 SAH)	OR, 4.8 (95% CI. 1.1 – 20.6)[a] with focal WMH PV-WMH was not associated with stroke risk
	Wong et al., [84] 2002	ARIC study (prospective, longitudinal, population- based study)	1684	62.3	4.7	MRI: 1.5 T; T1, T2, PD WMH: SQ (0 – 9), dichotomized (≥3 vs. <3)	All strokes: 32 (25 IS, 5 ICH, 2 combined) IS: 25	For WMH ≥3 vs. <3: RR, 3.7 (95% CI, 1.7 – 7.8)[b]; RR, 3.4 (95% CI, 1.5 – 7.7)[a] RR, 3.2 (95% CI, 1.2 – 8.3)[a]
	Vermeer et al,[78] 2003	Rotterdam Study (prospective, longitudinal, population- based study)	1077	72	4.2	MRI: 1.5 T; T1, T2, PD PV-WMH-: SQ (0 – 9) D-WMH-: Q, studied as tertiles and as a continuous variable	All strokes: 57 (42 IS, 6 ICH, 9 unspecified)	HR 4.7 (95% CI, 2.0 – 11.2)[a] with 3rd vs. 1st PV-WMH tertile; HR, 1.36 (95% CI, 1.20 – 1.54)[a] per grade increase of PV-WMH; HR, 3.6 (95% CI, 1.4 – 9.2)[a] with 3rd vs. 1st D-WMH tertile

Kuller et al.,[59] 2004	CHS study (prospective, longitudinal, multicenter, population- based study)	3293	75	7	MRI: 1.5 T except for 1 center using 0.35 T; T1, T2, PD WMH: SQ (0 – 9), 6 classes	All strokes: 278 IS: 226	HR, 3.0 (95% CI, 1.9 – 4.7)[a*] with WMH grade ≤5 HR, 2.9 (95% CI, 1.7 – 4.8) for overall IS with WMH grade ≥5; HR, 4.8 (95% CI, 1.7 – 13.8) for cardioembolic IS; HR, 2.8 (95% CI, 1.4 – 6.0) for unknown IS
Bokura et al.,[85] 2006	Prospective, longitudinal, population- based study	2684	57.8	6.3	MRI: 0.15 T, 0.2 T, 1.5 T; T1, T2, PD, FLAIR WMH: SQ (0 – 4 for PV-WMH, 0 – 3 for D-WMH)	All strokes: 102 (56 IS, 21 ICH, 11 SAH, 11 TIA, 3 unspecified)	OR, 2.08 (95% CI, 1.04 – 4.17)[a] with PV-WMH ≥3 vs. <3; OR, 2.73 (95% CI, 1.32 – 5.63)[a] with D-WMH ≥2 vs.<2
Buyck et al.,[86] 2009	3- City Study (prospective, longitudinal, population- based study)	1643	72.3	4.9	MRI: 1.5 T; T1, T2, PD WMH: Q (automated), studied as quartiles and as a continuous variable	All strokes: 25 (20 IS, 4 ICH, 1 unspecified)	HR, 5.7 (95% CI, 2.0 – 16.4)[a] with quartile 4 vs. quartile 1 + 2 of WMH volume; HR, 6.2 (95% CI, 2.0 – 19.5)* with quartile 4 vs. quartile 1 + 2 of PV-WMH volume; HR, 4.1 (95% CI, 1.5 – 11.3)[a] with quartile 4 vs. quartile 1 + 2 of D-WMH volume

(*continued*)

TABLE 21.1

Continued

MRI finding	Author, year	Type of study	n	Mean Age, y	Mean Follow-up, y	Measurement methods and marker definitions	Outcome definition	Risk of stroke
	Debette et al.,[87] 2010	Framingham Offspring study (prospective, longitudinal, population- based study)	2229	62	5.6	MRI: 1.0 T, 1.5 T; T2 WMH: Q (automated), studied both as a continuous and a dichotomized variable	All strokes: 32 (26 IS, 5 ICH, 1 unspecified)	HR, 1.3 (95% CI, 0.9 – 1.9)[a] with WMH as a continuous variable; HR, 2.3 (95% CI, 1.02 – 5.13)[a] with extensive WMH as a dichotomous variable
	Yamauchi et al.,[98] 2002	Prospective, high- risk population study (subjects with symptomatic lacunar stroke or stroke- free with headache or dizziness)	89	66	4.3	MRI: 0.5 T; T1, T2, PD WMH: SQ, studied as a continuous and a dichotomous (severe vs. mild or absent) variable	All strokes: 7 (5 IS, 2 ICH); proportion of patients with recurrent stroke, NA	RR, 1.6 (95% CI, 1.02 – 2.5)[c] per 1-pt score increase of WMH
	Smith et al.,[101] 2004	Hospital- based study (patients with primary lobar ICH	82	76.3	2.7	CT; MRI: FLAIR WMH: SQ (0 – 9) for PV-WMH, quantitative for D-WMH studied as a continuous variable	Recurrent ICH	HR, 9.0 (95% CI, 1.2 – 67.2)[a] with PV-WMH HR with D-WMH: NA, NS

Appelros et al.,[95] 2005	Hospital- based study (patients with symptomatic lacunar infarct)	81	66.4	5.0	MRI: 1.5 T; T1, T2, PD WMH: SQ, studied as a continuous variable	Recurrent stroke (24): 21 IS (17 lacunar and 4 large-vessel infarcts), 2 ICH, 1 unspecified	HR, 1.7 (95% CI, 1.2 – 2.7)[a]
Fu et al.,[96] 2005	Hospital- based study (patients with acute first- ever stroke)	228	68.3	1.9 (median)	MRI: 1.5 T; T1, T2, FLAIR, DWI WMH: SQ (0 – 3), studied as a continuous variable	Recurrent stroke: 29 (23 IS, 6 ICH)	HR, 4.2 (95% CI, 2.0 – 8.6)[a]
Gerdes et al.,[106] 2006	Hospital- based study (patients with recent [≤6 mo] ischemic stroke, AMI, or peripheral artery disease)	230	62	3.5	MRI: 1.5 T; T1, T2, PD WMH: SQ, studied as dichotomous variable (absence/presence of PV-WMH or D-WMH, and ≥50% vs. <50% of total WMH)	Ischemic stroke: 21 (first ever or recurrent)	HR, 4.4 (95% CI, 1.8 – 11.0) with PV-WMH; HR, 3.2 (95% CI, 1.3 – 8.4)[a] with PV-WMH; HR, 1.5 (95% CI, 0.6 – 3.8) with D-WMH; NS
Naka et al.,[105] 2006	Hospital- based study (patients with stroke)	266	67.2	1.5	MRI: 1 T; T2, T2* WMH: SQ (0 – 3); studied as dichotomous variable (≥2 vs. <2)	All strokes: 26 (16 IS, 10 ICH	HR, 10.7 (95% CI, 2.6 – 43.7)[a] (also adjusted for CMBs) for IS; HR, 0.016 (95% CI, 0.001 – 0.258)[a] (also adjusted for CMBs) for recurrent ICH

(*continued*)

TABLE 21.1

Continued

MRI finding	Author, year	Type of study	n	Mean Age, y	Mean Follow-up, y	Measurement methods and marker definitions	Outcome definition	Risk of stroke
	Longstreth et al.,[115] 2011	CHS study (population- based, substudy in patients with baseline and follow- up MRI)	1741	NA	9.6	MRI: 1.5 T except for 1 center using 0.35 T; T1, T2, PD WMH: SQ (0 – 9)	All stroke	HR 1.39 (95% CI, 1.02 – 1.88)[a] with WMH progression (if WMH ≥1 at follow-up MRI); after adding WMH grade on the initial scan: HR, 1.35 (95% CI, 1.00 – 1.77)[a] NS anymore
	Conijn et al.,[97] 2011	SMART- MR study (high- risk population study with symptomatic/non symptomatic atherosclerotic disease)	1309	58.6	4.5 (median)	MRI: 1.5 T; T1, T2, FLAIR WMH: Q (automated); studied as a continuous and a dichotomous variable (>4.2 mL upper quintile vs. the 4 lower quintiles)	IS	HR, 1.04 (95% CI, 1.01 – 1.07)[b] per milliliter of WMH volume; HR, 1.04 (95% CI, 1.01 – 1.06)[a] per milliliter of WMH volume; HR, 1.02 (95% CI, 0.99 – 1.05)[d] per milliliter of WMH volume; HR, 3.9 (95% CI, 2.1 – 7.6)[b] with upper quintile; HR, 3.6 (95% CI, 1.9 – 6.9)[a] with upper quintile; HR, 2.6 (95% CI, 1.3 – 4.9)[d] with upper quintile

	Folsom et al.,[88] 2012	ARIC and CHS (population- based studies)	4872	NA, 79% aged ≥65	13	MRI: 1.5 T; T1, T2 WMH: SQ (0 – 9) (4 classes)	ICH: 71	HR, 1.68 (95% CI, 0.86 – 3.30)[a] with WMH grade 2; HR, 3.52 (95% CI, 1.80 – 6.89)[a] with WMH grade 3; HR, 3.96 (95% CI, 1.90 – 8.27)[a] with WMH grades 4 – 9; HR, 1.60 (95% CI, 0.81 – 3.14)[c] with WMH grade 2; NS; HR, 3.19 (95% CI, 1.61 – 6.28)[c] with WMH grade 3; HR, 3.28 (95% CI, 1.53 – 7.04)[c] with WMH grades 4 – 9
SBIs	Kobayashi et al.,[89] 1997	Prospective, general population study	933	57.5	NA (1 to >6)	MRI: 0.15 T, 0.2 T; T1, T2, PD SBI: if diameter 3 – 10 mm	All strokes: 19 (14 IS, 4 ICH, 1 SAH)	OR, 10.5 (95% CI, 3.6 – 30.2)[a]
	Bernick et al.,[170] 2001	Prospective, general population study	3324	≈75	4	MRI: 1.5T	All strokes: 159 (131 IS, 23 ICH, 5 unknown)	HR, 1.80 (95% CI, 1.31 – 2.47)[b] HR, 1.52 (95% CI, 1.10 – 2.10)[a]
	Vermeer et al.,[78] 2003	Rotterdam Study (prospective, longitudinal, population- based study)	1077	72	4.2	MRI: 1.5T; T1, T2, PD SBI: if diameter ≥3 mm	All strokes: 57 (42 IS, 6 ICH, 9 unspecified)	HR, 3.9 (95% CI, 2.3 – 6.8)[a]

(*continued*)

TABLE 21.1

Continued

MRI finding	Author, year	Type of study	n	Mean Age, y	Mean Follow-up, y	Measurement methods and marker definitions	Outcome definition	Risk of stroke
	Kuller et al.,[59] 2004	CHS study (prospective, longitudinal, multicenter, population- based study)	3293	75	7	MRI: 1.5 T except for 1 center using 0.35 T; SBI: no size definition	All strokes: 278	HR, 4.2 (95% CI, 2.7 – 6.5)[a] in subjects with SBI and WMH = 3; HR, 4.4 (95% CI, 2.6 – 7.4)[a] in subjects with SBI and WMH = 4; HR, 3.7 (95% CI, 2.1 – 6.5)[a] in subjects with SBI WMH ≥5
	Bokura et al.,[85] 2006	Prospective, longitudinal, population- based study	2684	57.8	6.3	MRI: 0.15 T, 0.2 T, 1.5 T; T1, T2, PD, FLAIR SBI: if diameter ≥3 mm	All strokes: 102 (56 IS, 21 ICH, 11 SAH, 11 TIA, 3 unspecified)	OR, 3.66 (95% CI, 2.28 – 5.89)[a]
	Debette et al.,[87] 2010	Framingham Offspring study (prospective, longitudinal, population- based study)	2229	62	5.6	MRI: 1.0 T, 1.5 T; T1, T2, PD SBI: if diameter ≥3 mm	All strokes: 32 (26 IS, 5 ICH, 1 unspecified) ISs: 26	HR, 3.06 (95% CI, 1.44 – 6.51)[b]; HR, 2.84 (95% CI, 1.32 – 6.10)[a]; HR 2.80 (95% CI, 1.29 – 6.06) after adjustment for WMH volume HR, 3.49 (95% CI, 1.54 – 7.91)[a]

Longstreth et al.,[115] 2011	CHS study (population- based, substudy in patients with baseline and follow- up MRI)	1446	NA	9.6	MRI: 1.5 T except for 1 center using 0.35 T; T1, T2, PD SBI: if diameter ≥3 mm	All stroke	HR, 2.11 (95% CI, 1.48 – 3.02)[a] with ≥1 infarct at follow-up MRI; HR, 2.58 (95% CI, 1.53 – 4.36)[a] in 1312 subjects with ≥1 infarct and WMH progression at follow-up imaging
Kang et al.,[175] 2006	Hospital- based, retrospective study (patients with ischemic stroke)	104	74	19.3 mo	MRI: 1.5 T; DWI, FLAIR, early and late SBI: new lesion on DWI at 5 days and 30 – 90 days, respectively, and not associated with clinical events	IS: 8	OR, 6.55 (95% CI, 1.09 – 39.55) (adjusted for age and cardioembolism) with late SBI
Conijn et al.,[97] 2011	SMART- MR study (high- risk population with symptomatic/ not symptomatic atherosclerotic disease)	1309	58.6	4.5 (median)	MRI: 1.5 T; T1, T2, FLAIR; silent LI and symptomatic LI: ≥3 mm	IS	HR, 3.7 (95% CI, 2.0 – 6.7)[b] both silent and symptomatic LI; HR, 3.2 (95% CI, 1.7 – 5.8)[a] both silent and symptomatic LI; HR, 1.5 (95% CI, 0.8 – 3.0)[d] both silent and symptomatic LI; NS
Weber et al.,[174] 2012	PROFESS Imaging substudy (patients with recent, mild noncardioembolic IS)	1014	66.1	2.5	MRI: 1.0 T, 1.5 T; T1, T2, FLAIR SBI: no size definition	All stroke: 24 IS, 3 ICH	OR, 1.42 (95% CI, 0.79 – 2.56)[b]; NS

(*continued*)

TABLE 21.1

Continued

MRI finding	Author, year	Type of study	n	Mean Age, y	Mean Follow-up, y	Measurement methods and marker definitions	Outcome definition	Risk of stroke
	Folsom et al.,[88] 2012	ARIC and CHS (population- based studies)	4872	NA; 79% aged ≥65	13	MRI: 1.5 T; T1, T2 SBI: if diameter ≥3 mm	ICH: 71	HR, 1.97 (95% CI, 1.10 – 3.54)[a] with 1 SBI; HR, 2.00 (95% CI, 0.83—4.78)[a] with 2 SBIs, NS; HR, 3.12 (95% CI, 1.31 – 7.43)[a] with ≥3 SBIs; HR, 1.72 (95% CI, 0.95 – 3.11)[c] with 1 SBI, NS; HR, 1.49 (95% CI, 0.61 – 3.60)[c] with 2 SBIs, NS; HR, 2.11 (95% CI, 0.87 – 5.14)[c] with ≥3 SBIs, NS
CMBs	Greenberg et al.,[235] 2004	Prospective cohort, hospital- based study of patients with primary lobar ICH	94	47 aged <75, 47 aged ≥75	3	MRI: 1.5 T; GE microhemorrhages: if diameter ≤5 mm; macrohemorrhages: if diameter >5 mm	Symptomatic ICH	HR, 1.5 (95% CI, 1.1 – 2.2) adjusted for vascular risk factors, APOE genotype, and previous ICH
	Soo et al.,[236] 2008	Prospective hospital- based study of patients with IS	908	69.3	26.6 mo	MRI: 1.5 T; T1, T2, T2*-GE, FLAIR CMBs: if diameter 2 – 10 mm	Recurrent stroke (15 ICH, 96 IS)	HR, 5.99 (95% CI, 1.90 – 18.86) adjusted for age; HR, 2.75 (95% CI, 0.50 – 14.99) with 1 CMB, NS; HR, 6.08 (95% CI, 1.35 – 27.42) with 2 – 4 CMBs; HR, 9.81 (95% CI, 2.76 – 34.83) with ≥5 CMBs

Nighoghossian et al.,[247] 2002	Prospective hospital- based study in patients with acute IS	100	60	10 hr	MRI: DWI, T2, T2*-GE CMBs: if diameter 2 – 5 mm	All HTs: 26	OR, 7.2 (95% CI, 1.9 – 28.2)[a] (also adjusted for WMH, lacunes, treatment)
Fiehler et al.,[249] 2007	BRASIL study (international, multicenter, nonrandomized analysis of patients with acute IS treated with IV thrombolysis within 6 hr from symptom onset)	570	69	136 min (median)	MRI: DWI, MRA, T2, T2*-GE CMBs: if diameter <5 mm	Symptomatic ICH (any ICH associated with >2 pt on NIHSS): 37	OR, 2.23 (95% CI, 0.67 – 6.97) for sICH, NS; ARI 3.1 (95% CI – 2.0 to 8.3) for sICH; OR, 1.61 (95% CI, 0.66 – 3.85) for any ICH, NS; OR, 2.2 (95% CI, 0.6 – 8.0) for patients treated ≤3 hr, NS; OR, 0.1 (95% CI, 0.0 – 23.3) for patients treated from 3 – 6 hr, NS; OR, 2.60 (95% CI, 0.57 – 9.11) with >1 CMBs, NS
Imaizumi et al.,[217] 2004	Prospective hospital- based study on patients with deep ICH or lacunar stroke	337	66	22.5 mo	MRI: T1-, T2-, T2*-weighted, FLAIR, DWI CMBs: if diameter up to 7 mm	All recurrent strokes: 20 (13 deep ICH, 7 lacunar infarcts)	HR, 4.36 (95% CI, 1.72 – 11.0)[a] with ≥5 subcortical CMBs

(*continued*)

TABLE 21.1

Continued

MRI finding	Author, year	Type of study	n	Mean Age, y	Mean Follow-up, y	Measurement methods and marker definitions	Outcome definition	Risk of stroke
	Viswanathan et al.,[243] 2006	Retrospective hospital- based study of patients with primary ICH	207	74.5 for lobar ICH, 68.4 for deep ICH	10 for lobar ICH, 4 for deep ICH	MRI: 1.5 T; GRE; CMBs: no size definition	Recurrent lobar and deep ICH in patients under antiplatelet therapy during the follow-up period	HR, 0.8 (95% CI, 0.4 – 3.3) for lobar ICH, NS; HR, 1.2 (95% CI, 0.1 – 14.3) for deep ICH, NS (adjusted for CMBs, CT-defined WMH, and APOE genotype)
	Boulanger et al.,[239] 2006	Prospective hospital- based study of patients with TIA and IS	236	68.9	14 mo	MRI: 3 T; T1, T2, FLAIR, GRE, DWI, PWI; CMBs: no size definition	Recurrent stroke: (6 IS, 1 ICH)	HR, 2.8 (95% CI, 1.1 – 7.3) (mostly IS) adjusted for age, other vascular risk factors, and presence of confluent white matter disease
	Ueno et al.,[244] 2008	Prospective hospital- based study of patients with ICH and IS	87	74.5	NA	MRI: 1.5 T; T2*; CMBs: no size definition	Recurrent warfarin- related ICH	OR, 7.38 (95% CI, 1.05 – 51.83) adjusted for age, other vascular risk factors, and advanced WMH
	Lee et al.,[245]2009	Case – control study of stroke patients with warfarin- related ICH	24	65.0	NA	MRI: 1.5 T; T1, T2, FLAIR, GRE; CMBs: if diameter <5 mm	Recurrent warfarin- related ICH	Adjusted OR, 83.12 (95% CI, 5.96 – 1159.10)

Naka et al.,[105] 2006	Hospital- based study of patients with stroke	266	67.2	1.5	MRI: 1 T; T_2, T_2*; CMBs: no size definition	All strokes: 26 (16 IS, 10 ICH)	HR, 85.63 (95% CI, 6.34 – 1155.65)[a] (also adjusted for advanced WMH) for recurrent ICH
Kim et al.,[237] 2002	Prospective, hospital- based study of patients with acute IS and ICH	91	64.3	16 mo	MRI: 1.5 T; T_2, T_2*-GRE CMBs: if diameter ≤5 mm	All strokes	OR, 2.46 (95% CI, 1.38 – 4.39)[b] (also adjusted for lacunae) for ICH (CMBs plus no or mild WMH); OR, 0.99 (95% CI, 0.94 – 1.04)[a] (also adjusted for lacunae) for ICH (CMBs plus advanced WMH)
Kim et al.,[250] 2006	Hospital- based study of patients with acute IS treated with IV thrombolysis within 6 hr of symptom onset	279	67	1–3 days	MRI: 1.5 T; T_1, T_2, FLAIR, T_2* GRE, DWI, PWI; CMBs: if diameter <5 mm	HT	OR, 1.61 (95% CI, 0.45 – 3.13)[a] NS with CMBs >10
Gregoire et al.,[203] 2010	Case – control study of ICH patients	49	68.7	NA	MRI: 1.5 T; T_2* GRE, T_1, T_2, FLAIR; CMBs: no size definition	Antiplatelet-related ICH	OR, 1.33 (95% CI, 1.06 – 1.66) with the total number of CMBs (adjusted for the presence of leukoaraiosis); OR, 1.42 (95% CI, 1.07 – 1.89) with lobar CMBs (adjusted for the presence of leukoaraiosis); OR, 5.69 (95% CI, 0.95 – 34.22) with deep CMBs (adjusted for leukoaraiosis), NS

(*continued*)

TABLE 21.1

Continued

MRI finding	Author, year	Type of study	n	Mean Age, y	Mean Follow-up, y	Measurement methods and marker definitions	Outcome definition	Risk of stroke
	Thijs et al.,[240] 2010	Prospective, hospital- based study of patients with IS or TIA	487	72	2.2	MRI: 1.5 T or 3 T; T1, T2, FLAIR, GRE CMBs: if diameter ≤5 mm	Recurrent stroke: IS (6.6%) and ICH (0.4%)	OR, 2.4 (95% CI, 1.2 – 5.0) (mostly IS) with lobar or mixed CMBs (adjusted for imbalances in WMH and prior history of stroke)
	Biffi et al.,[242] 2010	Prospective, hospital- based study of patients with lobar ICH with a diagnosis of probable/possible CAA	104	72.5	34.3 mo	MRI: 1.5T; GRE; CMBs: if diameter <5 mm	Recurrent ICH: 29 lobar ICH	HR, 2.93 (95% CI, 1.3 – 4.0)[a] with 2 – 4 CMBs; HR, 4.12 (95% CI, 1.6 – 9.3)[a] with ≥5 CMBs (also adjusted per APOE genotype, previous symptomatic hemorrhage)
	Nishikawa et al.,[232] 2009	Prospective, longitudinal, population- based study in healthy elderly subjects	698	66.7	3.5	MRI: 1.5 T; T2; CMBs: if diameter <10 mm	First-ever stroke: 36	HR, 2.87 (95% CI, 1.27 – 6.48)[a] adjusted for age, sex, and hypertension for all stroke; HR, 2.64 (95% CI, 1.34 – 5.19)[a] also adjusted for antithrombotic therapy for all stroke; HR, 1.48 (95% CI, 0.63 – 3.45)[a] also adjusted for antithrombotic therapy for ICH, NS; HR, 11.77 (95% CI, 2.95 – 46.82)[a] also adjusted for antithrombotic therapy for IS

	Bokura et al.,[233] 2011	Prospective, longitudinal, population- based study in healthy elderly subjects	2012	62.1	3.6	MRI: NA; CMBs: no size definition	First-ever stroke: 44	HR, 50.2 (95% CI, 16.7 – 150.9)[a] (also adjusted for SBIs and WMH) for deep ICH associated with deep CMBs; HR, 4.48 (95% CI, 2.20 – 12.2)[a] (also adjusted for SBIs and WMH) for IS
Microinfarcts	Kang et al.,[288] 2012	Prospective, longitudinal study of patients with acute hypertensive ICH	97	59.1	42 mo (median)	MRI: 1.5 T; DWI and GRE MIs: no clear definition is available, authors reported "all the new ischemic lesions"	Recurrent stroke: 5 IS, 3 ICH	HR, 5.87 (95% CI, 1.004 – 34.31)[a] for IS or ICH; HR, 5.00 (95% CI, 1.15 – 21.86)[a] for IS or vascular death; HR, 5.69 (95% CI, 1.36 – 23.70)[a] for IS and ICH, or vascular death

[a]Adjusted for age, sex, and other risk factors.
[b]Adjusted for age and sex.
[c]Adjusted for age, sex, other vascular risk factors, and multiple lacunar infarcts.
[d]Adjusted for age, sex, other vascular risk factors, and presence of non-LI on MRI or history of clinically evident cerebrovascular disease.
AMI, acute myocardial infarction; APOE, apolipoprotein E; ARIC, Atherosclerotic Risk in Communities; ARI, absolute risk increase; CHS, Cardiovascular Health Study; CI, confidence interval; CMBs, cerebral microbleeds; CT, computed tomography; DWI, diffusion-weighted imaging; D-WMH, deep white matter hyperintensity; FLAIR, fluid-attenuated inversion recovery; ICH, intracerebral hemorrhage; GRE, gradient recalled echo; HR, hazard ratio; IS, ischemic stroke; HT, hemorrhagic transformation; ICH, intracerebral hemorrhage; IS, ischemic stroke; IV, intravenous; LI, lacunar infarct; MIs, microinfarcts; MRI, magnetic resonance imaging; NA, not available; NIHSS, National Institutes of Health Stroke Scale; NS, not significant; OR, odds ratio; PD, proton density; PV-WMH, periventricular white matter hyperintensity; PWI, perfusion-weighted imaging; Q, quantitative; RR, relative risk; SAH, subarachnoid hemorrhage; SBI, silent brain infarct; sICH, symptomatic intracerebral hemorrhage; SQ, semiquantitative; TIA, transient ischemic attack; WMH, white matter hyperintensity.

TABLE 21.2

Summary of Studies That Report Associations between Markers of Cerebrovascular Disease and the Risk of Stroke Based on Marker Topography

MRI finding	Author, year	Lesion location/ distribution	Outcome definition	Risk of stroke
WMH	Kobayashi et al.,[89] 1997	PV diffuse WMH	All strokes	Not associated with stroke risk;
		Focal WMH		OR, 4.8 (95% CI, 1.1–20.6)[a]
	Vermeer et al.,[78] 2003	PV-WMH	All strokes	HR, 4.7 (95% CI, 2.0–11.2) with 3rd vs. 1st PV-WMH tertile[a]; HR, 1.36 (95% CI, 1.20–1.54)[a] per grade increase of PVH[a]
		D-WMH: subcortical (deep) WMH		HR, 3.6 (95% CI, 1.4–9.2)[a] with 3rd vs. 1st D-WMH tertile
	Bokura et al.,[85] 2006	PV-WMH	All strokes	OR, 2.08 (95% CI, 1.04–4.17)[a] with PV-WMH ≥3 vs. <3
		D-WMH: subcortical (deep) WMH		OR, 2.73 (95% CI, 1.32–5.63)[a] with D-WMH ≥2 vs. <2
	Buyck et al.,[86] 2009	PV-WMH	All strokes	HR, 6.2 (95% CI, 2.0–19.5)[a] with quartile 4 vs. quartile 1 + 2 of PV-WMH volume
		D-WMH: subcortical (deep) WMH		HR, 4.1 (95% CI, 1.5–11.3)[a] with quartile 4 vs. quartile 1 + 2 of D-WMH volume
	Smith et al.,[101] 2004	PV-WMH	Recurrent ICH	HR, 9.0 (95% CI, 1.2–67.2)[a]
		D-WMH: subcortical (deep) WMH		HR with D-WMH, NA: NS
	Gerdes et al.,[106] 2006	PV-WMH	First ever or recurrent IS	HR, 4.4 (95% CI, 1.8–11.0) HR, 3.2 (95% CI, 1.3–8.4)[a]
		D-WMH: subcortical (deep) WMH		HR, 1.5 (95% CI, 0.6–3.8); NS

(*continued*)

TABLE 21.2

Continued

MRI finding	Author, year	Lesion location/ distribution	Outcome definition	Risk of stroke
Silent brain infarcts	Bernick et al.,[170] 2001	Cortical	All strokes	HR, 1.36 (95% CI, 0.50–3.72)[b]; NS
		Subcortical		HR, 1.00 (95% CI, 0.37–2.80)[a]; NS
				HR, 1.74 (95% CI, 1.25–2.44)[b]
		Cortical/ subcortical		HR, 1.52 (95% CI, 1.08–2.13)[a]
				HR, 3.18 (95% CI, 1.47–6.88)[b]
				HR, 2.20 (95% CI, 1.00–4.86)[a]
Cerebral microbleeds	Soo et al.,[236] 2008	Mixed cortical–subcortical	Recurrent ICH	HR, 8.87 (95% CI, 3.21–24.52) adjusted for age
	Imaizumi et al.,[217] 2004	Subcortical	Recurrent stroke: deep ICH and lacunar infarcts	HR, 4.36 (95% CI, 1.72–11.0)[a] with ≥5 subcortical CMBs
	Thijs et al.,[240] 2010	Lobar or mixed	Recurrent stroke: IS and ICH	OR, 2.4 (95% CI, 1.2 – 5.0) with lobar or mixed CMBs (adjusted for imbalances in WMH and prior history of stroke)
	Bokura et al.,[233] 2011	Deep	First-ever ICH	HR, 50.2 (95% CI, 16.7 – 150.9)[a] (also adjusted for SBIs and WMH) for deep ICH associated with deep CMBs

[a]Adjusted for age, sex, and other vascular risk factors.
[b]Adjusted for age and sex.
CI, confidence interval; CMBs, cerebral microinfarcts; D, deep; HR, hazard ratio; ICH, intracerebral hemorrhage; IS, ischemic stroke; NA, not available NS, not significant; OR, odds ratio; PV, periventricular; SBIs, silent brain infarcts; WMH, white matter hyperintensity.

WMH and the Risk of First-Ever Stroke

A number of studies have addressed the issue of potential correlation between WMH and the risk of stroke, both in general population and high-risk populations, and in hospital-based cohorts (Table 21.1). This association suggests that WMH may not just be a part of "normal aging" or may be related to generalized, nonspecific vascular changes resulting from an interaction between the broad spectrum of uncontrolled vascular risk factors and age-related changes leading to a symptomatic stroke. But, WMH lesions could serve as a marker for other factors, not yet identified, that could increase the risk of stroke.[1,78] In the general population, the incidence of stroke among healthy, older adults with WMH is increased more than among those without WMH.[83] A number of large prospective, longitudinal, population-based studies[1,59,78,84–86] have demonstrated that WMH, regardless of its location and distribution, is associated independently with

the risk of all clinical strokes (ischemic, hemorrhagic, and combined), after adjusting for age, sex, and other vascular risk factors. These studies ranged from 4.2 to 7 years in their follow-up periods and used both semiquantitative and fully quantitative automated methods for MRI analysis of WMH. The hazards ratio (HR) range for the risk of stroke related to WMH was between 2.3 (95% Confidence Interval [CI], 1.02–5.1)[87] and 5.7 (95% CI, 2.0–16.4),[86] independent of WMH distribution. Considering incident ischemic stroke alone, the risk associated with the presence of WMH is equally high and, apparently, irrespective of specific ischemic stroke subtype.[59] The 5-year cumulative incidence of stroke was estimated to be 4% in individuals with white matter lesions.[84] The relative risk of stroke increases with WMH severity, from 0.6% per year in subjects with mild WMH to 2.8% in subjects with more advanced disease, and it is the highest in the patients with a combination of advanced WMH grade and at least one traditional vascular risk factor.[59] Population-based studies using fully automated WMH volumetric assessment methods, which usually provide more sensitive WMH measurements, have confirmed these results, suggesting that stroke incidence is greater with increasing volumes of WMH, reaching a sevenfold greater risk in those with WMH in the higher quartiles of the volume distribution compared with those in the lower quartile, even after controlling for confounding vascular risk factors.[86] Similar data were observed by MRI-based population studies on the risk of first-ever spontaneous ICH over a mean period of 13 years with 79% of subjects aged ≥65 years.[88] The risk increased progressively with the higher grade of WMH (≥3) (for grade 3: HR, 3.52; 95% CI, 1.80–6.89; for grades 4–9: HR, 3.96; 95% CI, 1.90–8.27).[88] The results were confirmed both in a multivariate model including age and all the other vascular risk factors, and in a second model including the presence of MRI-defined SBIs. Moreover, the combination of more severe WMH with silent infarcts was associated with an almost doubled HR for ICH (HR, 4.27; 95% CI, 2.20–8.28) compared with the combination of SBIs with the lower grade of WMH (HR, 3.19; 95% CI, 1.71–5.96).[88] Other studies demonstrated the association with an increased risk of stroke only when WMH volume was considered as a dichotomous rather than a continuous variable, suggestive of a potential threshold effect, because WMH appeared to be related to a greater risk of stroke only beyond a certain volume.[87]

The distribution and location of the white matter lesions can also have a potential role in predicting the overall stroke risk (Table 21.2). Periventricular and deep WMHs often coexist, because both lesion subtypes could be linked through a common pathogenesis.[85] Although there are few conflicting results,[89] most of studies confirmed that subjects with marked periventricular and subcortical WMH burden have approximately a fivefold and fourfold increase in stroke risk, respectively, compared with individuals in the lowest percentiles of the volumes or grades of white matter lesions.[7,8,85,86] Even stroke-related death prevalence was found to be greater in association with more severe periventricular and deep WMHs[86]; however, the risk estimates for stroke events are greater for periventricular versus subcortical WMH,[86] with marked periventricular WMH being linked more strongly to stroke-related death compared with deep WMH.[85]

Last, a meta-analysis of general population- and high-risk population-based studies confirmed the association of WMH with the risk of ischemic (HR, 3.1; 95% CI, 2.3–4.1, $p < 0.001$; HR, 7.4; 95% CI, 2.4–22.9, $p = 0.001$) and all stroke (HR, 3.5; 95% CI, 2.5–4.9).[1] In combination with the data that link WMH and the risk of stroke in a number of large observational studies on healthy aging adults, high-risk populations, and hospital-based cohorts, this meta-analysis provides convincing evidence that both presence of WMH on brain MRI and its severity represent a validated neuroimaging marker of cerebrovascular disease and a risk factor for stroke.

WMH and the Risk of Recurrent Stroke

In subjects with previous transient ischemic attack (TIA) or stroke, WMH has been linked to the risk of recurrence.[30,54,90–93] A number of early CT-based studies [90–94] demonstrated a twofold

increase in recurrent stroke events in patients with prior stroke or TIA, in particular in those with lacunar infarction or widespread leukoaraiosis on head CT, as well as worse outcomes. Despite the differences in characterization of WMH in CT versus MRI, multiple MRI-based studies confirmed the role of WMH severity as an independent predictor of recurrent stroke specifically in patients with symptomatic lacunar infarcts, with stroke recurrence being associated with worse functional outcome (Table 21.1).[95] There was a fourfold increase in 3-year cumulative incidence of recurrent stroke (43.7% vs. 7.8% and 9.3%, respectively, $p = 0.0001$) and a lower survival rate ($p < 0.007$) in patients with severe WMH compared with those with no or mild WMH.[96] In case of either symptomatic nonlacunar[97] or lacunar infarct,[98] the risk of developing recurrent stroke is increased in the presence of severe WMH. In patients with WMH, lacunar infarction and ICH are the most likely recurrent events, suggesting small-vessel disease as a common etiology, as opposed to cortical territorial infarcts usually associated with large-vessel or cardioembolism.[99]

WMH severity has been linked to a greater risk of hemorrhagic transformation of cerebral infarcts in patients treated with warfarin for secondary prevention,[100] of recurrent lobar ICH,[101] as well as symptomatic ICH after intravenous[102,103] or intra-arterial thrombolysis.[104] However, extensive WMH appears to be a strong predictor of recurrent ischemic stroke rather than recurrent ICH.[105]

Topographic distribution of the white matter lesions appears to affect the risk of stroke recurrence (Table 21.2). For example, periventricular WMH was associated with a greater risk of recurrent ischemic stroke (HR, 3.2; 95% CI, 1.3–8.4) compared with deep WMH (HR, 1.5; 95% CI, 0.6–3.8).[106] Similarly, increased risk of recurrent lobar ICH was strongly related to MRI-based periventricular WMH (HR, 9.0; 95% CI, 1.2–67.2).[101]

Progression of WMH and the Risk of Stroke

Longitudinal cohort studies of WMH progression over 4 to 6 years confirmed age as its main predictor.[2,4] The rate of WMH progression varied in different studies. In healthy individuals aged 50 to 75 years, WMH progressed minimally, with a median WMH volume of 0.01 cm^3 (interquartile range, 0.0–0.3) after 3 years[4] versus 0.1 cm^3 (interquartile range, 0.0–0.7) after 6 years.[107] In older subjects with gait dysfunction, a mean (± standard deviation) increase of 1.1 ± 1.8 cm^3 over 4 years was noted[108]; and in the healthy elderly, a change in median WMH volume from 2.5 cm^3 to 6.0 cm^3 ($p < 0.001$) after 5 years[109] was reported.

In addition to age, baseline lesion volume burden seem to be linked more strongly to a greater degree of progression,[110] as opposed to other proposed risk factors including diabetes, hyperlipidemia, body mass index, smoking, and gender, for which study results are conflicting.[111–113] In fact, when stratified by baseline severity, WMH progression demonstrates similar trends toward an increase of the lesion burden starting from more severe baseline WMH, both in healthy adults[4] and in subjects with hypertension within the placebo group of the MRI substudy of the Perindopril Protection Against Recurrent Stroke Study trial.[7]

In addition, WMH progression has been linked to increased risk of stroke. In MRI-/CT-based follow-up studies, WMH progression has been associated significantly with increased stroke risk in patients with no or mild WMH at baseline (Table 21.1).[98,114] In the Cardiovascular Health Study, worsening of WMH independently increased the risk of first-ever stroke in the elderly (adjusted HR, 1.39; 95% CI, 1.02–1.88), but adjusting for a baseline WMH grade removed the effect of WMH progression on stroke risk in this cohort.[115] In patients with symptomatic carotid artery disease, leukoaraiosis has been reported to progress in 31.5% of cases, with an average rate of progression of 5.2% per year, and patients with progressive leukoaraiosis had a higher occurrence (36.0% vs. 23.5%, $p = 0.01$) of one or multiple subsequent stroke events, particularly lacunar strokes.[114] Hence, uncontrolled vascular risk factors were thought to account for WMH deterioration in patients with clinical cerebrovascular disease.[98]

A recent meta-analysis confirmed the association between WMH and risk of stroke in high-vascular risk populations (HR, 7.4; 95% CI, 2.4–22.9) and in an expanded analysis including healthy adults (HR, 3.5; 95% CI, 2.5–4.9).[1] However, heterogeneity of WMH assessment between the studies serves as a limitation in using these data for estimating the individual risk of stroke.

SUMMARY AND FUTURE IMPLICATIONS

WMH is a significant neuroimaging marker that represents a complex underlying pathophysiological process and that is linked strongly to stroke risk in healthy adults and patients with symptomatic cerebrovascular disease. Based on the current understanding of WMH as a pathological entity, its determinants are likely to be complex and interactive, with a large component in its variability being linked to genetic contribution.[116–118] The increasing prevalence and detection of WMH resulting from the increase in life expectancy and the availability of MRI techniques, and its potential impact on cerebrovascular disease in an individual as well as on the population level warrants intense investigation.

Silent Brain Infarcts

The term *silent brain infarct* indicates single or multiple infarctions that are either completely asymptomatic or associated with neurological signs or symptoms that are not recognized by either patients or physicians as stroke.[119] In population studies, more than 90% of SBIs correspond to lacunar infarcts[120,121]; however, even territorial infarcts can be detected incidentally in neuroimaging without known history of stroke in cases when either neurological symptoms were misinterpreted[122] or clinical symptoms were actually absent.[123] In past decades, the introduction of neuroimaging techniques such as CT[124] and subsequently more sophisticated tools such as MRI confirmed this cerebrovascular entity and increased our ability to detect these lesions as incidental findings in the general population,[125] and especially in the apparently healthy elderly.[120,126] Studies on the epidemiology and pathophysiology of SBIs have radically changed the approach to cerebrovascular disease definitions, particularly because these neuroimaging markers have been linked to the risk of clinically overt cerebrovascular disease.

Data on the prevalence[24,120,121,127–132] and incidence[78,133,134] of SBIs varies across the studies according to the population of interest, definition of SBIs, study design, and neuroimaging modalities used in each individual study. Population-based studies reported an overall SBI prevalence of 8% to 28%, with an incidence of 0.3% to 3% per year that increases progressively with age. The presence of SBIs is a strong predictor of the development of new silent infarcts.[121] In high-risk populations, SBIs are more frequent in patients with cardiovascular disease,[135] stroke,[136,137] and dementia,[138] whereas the likelihood of developing new SBIs is greater among patients with TIA at an annual rate of 19%,[139] and in those undergoing carotid endarterectomy[140–142] or carotid artery stenting,[143–145] with a greater proportion of SBIs detected by using DWI in patients treated with endarterectomy.[146] A high prevalence of stroke symptoms has been reported in the general population without prior official diagnosis of stroke or TIA, meaning there is probably a reasonable proportion of subjects with undiagnosed symptomatic cerebrovascular events that are not screened at all for vascular risk factors and do not receive proper preventive treatments.[147] Hence, MRI interpretation of SBIs should be done by experienced physicians with extensive knowledge in neurology.

MRI APPEARANCE

The MRI diagnostic criteria of SBIs have not been unified and vary across methodologies and parameters adopted within different studies. Developing standardized criteria for the diagnosis of SBIs has a potential to improve interpretation and comparison of data between the studies.[148,149]

MRI appearance of SBIs depends on the stage of the infarct evolution. Combination of T1W and T2W images, particularly FLAIR, enables detecting these lesions with a greater sensitivity, and MRI findings usually correspond to relative histopathological studies (Figure 21.5).[150,151] Novel MRI techniques such as DWI allows the detection of acute, silent small strokes.[152] In general, SBIs appear as focal, irregularly shaped, with a heterogeneous T1 hypointensity, becoming hyperintense on T2W images but hypointense on FLAIR sequences, reflecting tissue destruction and cavitation with irregular rim signals related to morphological changes caused by gliosis (Figure 21.6). Topographically, these lesions are located in "silent" areas of the brain typically including basal ganglia, thalamus, cerebral white matter, but also internal capsule, infratentorial regions such as brainstem, particularly pons, and cerebellum, and they have been also found in the cerebral cortex.[153] Lacunar infarcts that might not cavitate depending on the timing of their detection method, location, and time to follow-up[154,155] may appear as T2 or FLAIR hyperintensities with relative T1 hypointensity on MRI,[153] and might be considered as evolving lacunar infarcts or part of the deep WMHs.[156] Hence, specificity of noncavitated lacunar infarcts is low in the presence of WMH,[149] and different pathophysiological mechanisms might be responsible for disease progression of these distinct entities.[28,67] Conversely, cavitated lesions can be located within areas of diffuse WMH, appearing as black "holes" on FLAIR sequences, and they might be interpreted as silent lacunar infarcts.[157]

With regard to lesion size, no clear consensus exists. Although some studies include only focal lesions that are 3 mm or larger, others refer to a maximum diameter of 15 to 20 mm, according to the classic neuropathological definition of lacunar infarcts,[123] and yet other authors include

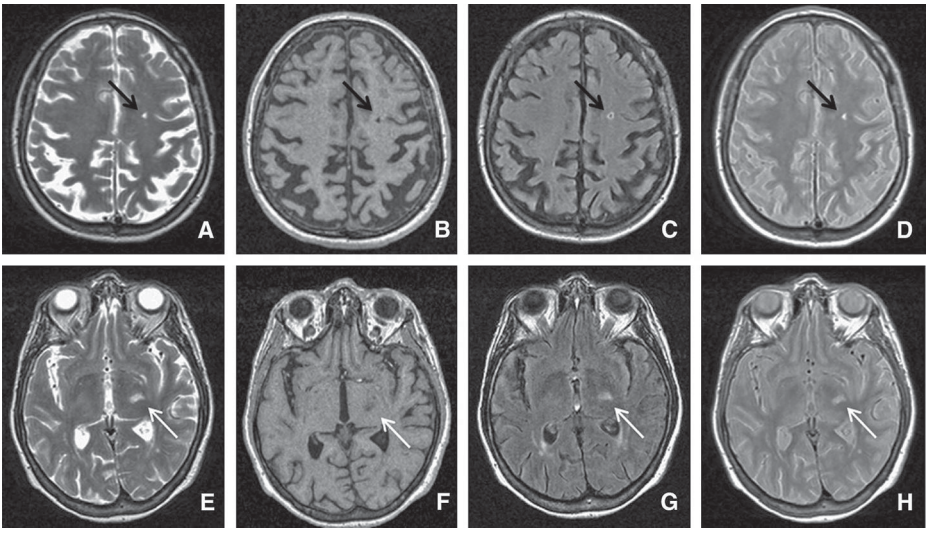

FIGURE 21.5 Main signal characteristics used for defining silent brain infarcts (SBIs) on different magnetic resonance imaging (MRI) sequences. (A–D) A silent brain infarct corresponds to a cerebrospinal fluid (CSF) signal on all MRI sequences (black arrows). (A) Axial T2 weighted (T2W) imaging. (B) Axial T1-weighted (T1W) imaging. (C) Axial fluid-attenuated inversion recovery (FLAIR) imaging. (D) Axial proton density (PD) imaging. (E–H) A hyperintense lesion on T2W images that is moderately hypointense on T1 in the left thalamus (white arrows) is not defined as an SBI in studies defining only cavities containing CSF as infarcts, whereas it is diagnosed as an infarct in studies that simply defined hyperintense T2 and hypointense T1 foci as infarcts. (E) Axial T2W. (F) Axial T1W. (G) Axial FLAIR. (H) Axial PD. (Adapted with permission from Zhu et al. *Stroke.* 2011;42:1140–1145.)

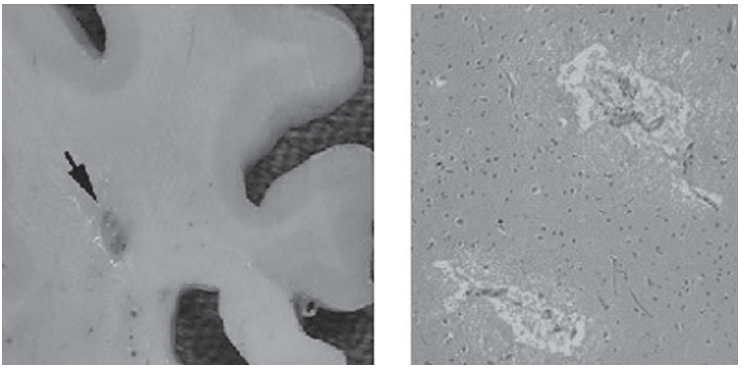

FIGURE 21.6 (A, B) Silent brain infarcts in gross pathology (A) appear as cystic infarcts of 1 cm or less in diameter in the periventricular white matter (arrow), which exhibits softening and discoloration in the surrounding white matter (B). (Adapted with permission from Strozyk et al. *Neurobiol Aging.* 2010;31:1710–1720.)

lesions greater than 25 mm in diameter.[148] Classic MRI studies of healthy individuals reported SBIs as small subcortical infarcts of 3 to 15 mm in diameter[126] and more likely to be located in the basal ganglia.[158] GRE sequences or high-resolution T1W images are particularly helpful in distinguishing SBIs from their mimics, such as DPVSs (état criblé), which are physiological findings surrounding the penetrating arterioles and might be misinterpreted as lacunar infarctions, if enlarged.

HISTOPATHOLOGICAL CORRELATES OF SBIS

Although lacunar infarcts were described for the first time in the 19th century by French neurologists and neuropathologists, Fisher pointed out the common silent nature (up to 77%) of these lesions in clinicopathological studies.[123] The infarcts appear as cystic lesions with ill-defined and irregular margins, the sizes of which are the result of the occluded arterioles. MRI-detected SBIs correspond histologically to irregular cavitations with scattered, fat-laden macrophages and associated surrounding reactive gliosis, myelin, and axonal loss (Figure 21.6).[28,47,123,159,160] With increasing lesion age, the number of macrophages decreases and gliosis becomes more fibrillar,[47,123] whereas other lacunes are found to have selective neuronal loss and relative preservation of glial cells.[123,161]

PATHOPHYSIOLOGY AND CLINICAL DETERMINANTS OF SBIS

SBIs share a similar risk factor profile with symptomatic infarcts, particularly of lacunar subtype, including age; hypertension; diabetes; ischemic heart disease; excessive alcohol consumption; smoking; metabolic syndrome; family history of stroke; symptomatic cerebrovascular diseases; presence of carotid artery stenosis; atrial fibrillation; nocturnal, postprandial, orthostatic hypotension; elevated C-reactive protein; and hyperhomocysteinemia.[119,122,135,153,162,163] In population-based studies, age and hypertension are the strongest predictors of SBIs, whereas other associations remain controversial and may require further validation.[135] To which extent vascular risk factors other than age and hypertension contribute to small-vessel disease and progression to silent lacunar infarction is still unclear.[119,164,165] However, SBIs are associated strongly with WMH,[59,166] and both seem to have synergistic effects[167] on the risk of stroke, suggesting a shared pathophysiology of these distinct MRI entities corresponding to diseased small cerebral vessel state.[54,135]

In younger patients, evidence of SBIs has been associated with type 1 diabetes, obesity, smoking, and increasing age.[168] Genetic factors may also contribute to the risk of SBI development; however, neither the candidate gene association studies (Angiotensin Converting Enzyme [ACE] and endothelial nitric oxide synthase [eNOS] polymorphisms, for example),[153] nor the largest to-date genomewide association studies on MRI-defined brain infarcts in healthy adults[169] have been able to replicate their findings.

SILENT INFARCTS AND THE RISK OF STROKE

The clinical significance of asymptomatic infarcts is still under investigation; nevertheless, prevalence of SBIs will continue to increase as a result of the aging of the population and increased detection, with broader use of advanced neuroimaging. Diagnosis of SBIs may also mark the population that is at high risk for overt cerebrovascular disease (Tables 20.1 and 20.2), as well as recurrent silent infarcts and white matter disease progression, manifesting further risk of brain damage.[167,170,171]

Silent Infarcts and Risk of First-Ever Stroke

In population-based studies, subjects with SBIs have a greater annual incidence of clinical stroke compared with those without (1.8%–2.8% vs. 0.2%–0.9%).[87,89,170] Of these, approximately 74% developed ischemic (mostly lacunar) and 26% hemorrhagic (mostly putaminal hemorrhage) strokes. In extended follow-up, SBIs were associated with a 2- to 10-fold increase in risk of first-ever stroke,[78,89,170] with absolute risk of developing stroke being 11.7% for otherwise healthy adults with SBIs versus 2.3% for those without (adjusted HR, 3.9; 95% CI, 2.3–6.8).[78] In another MRI-based population study of aging adults, not only the risk of first-ever stroke doubled for those persons who had one infarct or more on the follow-up image, but the strength of this association increased when incidence of SBIs was combined with WMH progression.[115] This may explain a recent observation reported in the combined analysis from the Atherosclerosis Risk in Communities study and the Cardiovascular Health Study cohorts that the presence of one or more MRI-defined SBIs, most of them (>80%) lacunar, was associated independently with risk of ICH, and this risk increased progressively with the number of SBIs.[88] Hence, the number of silent infarcts might have a crucial role in modulating the risk of hemorrhagic stroke, as well.[59,78,170] Furthermore, common vascular risk factors such as hypertension may be responsible for variable manifestations of cerebrovascular disease, both silent and symptomatic ischemic and hemorrhagic phenotypes; however, each of these risk factors may demonstrate a different effect size on individual risk of stroke.[78,85,170]

Silent Brain Infarcts and the Risk of Recurrent Stroke

In patients with clinical stroke, SBIs have been linked to stroke recurrence.[172,173] Although there are some conflicting results from small studies,[174] both in CT- and MRI-based studies, patients with TIA or nondisabling symptomatic stroke and evidence of SBI had a greater risk of recurrent atrial fibrillation-related cardioembolism,[173] recurrent acute ischemic stroke predominantly of large-vessel subtype,[175,176] as well as lacunar stroke, or ICH.[97,172,177] SBIs do not seem to account for a greater risk of hemorrhagic transformation in patients treated with intravenous thrombolysis.[176,178] Evidence of SBI after a clinical stroke—either ischemic or hemorrhagic—increases the risk of mortality linked to the index cerebrovascular event (24.3% vs. 10.7%), especially when SBIs are combined with WMH severity.[85]

SUMMARY AND FUTURE IMPLICATIONS

MRI detection of SBIs in the future may reset the current standards of clinical care and ongoing investigations by introducing a sensitive yet reliable approach for cerebrovascular risk assessment.

Although the field may still benefit from standardization of the SBI definition and advancement of neuroimaging techniques to customize an individual image analysis, the use of SBIs, alone or in combination with WMH, may become a centerpiece of stroke risk stratification, targeted treatment approaches, and aggressive prevention strategies in the future.

Cerebral Microbleeds

In addition to silent cerebral ischemia, cerebral small-vessel disease may lead to subclinical hemorrhagic lesions, usually characterized by hemosiderin deposition resulting from blood extravasation from diseased arterioles. These distinct lesions, known as *cerebral microbleeds*, are adjacent to small vessels and are most often asymptomatic; therefore, CMBs are usually detected on MRI as incidental findings.[119,179] First described in the 1990s,[180–182] CMBs are drawing increasing attention both from the clinical and research points of view. Incidental finding of CMBs on the MRIs of apparently healthy individuals as well as patients with stroke depends strongly on the specifics of MRI protocols used. Current data suggest that CMBs are found in up to 6% of the general population, 30% of patients with ischemic stroke, and 60% of patients with primary ICH.[57,183–185] CMBs are associated strongly with age, and CMB incidence ranges between 7% and 23% in various studies.[2,186–190] In the Rotterdam Scan Study, CMBs were found in 18% of individuals aged 60 to 69 years and in 38% of subjects older than 80 years.[190] Based on neuropathological analysis, CMBs in the deep subcortical areas are almost always observed in postmortem brain specimens of subjects aged more than 70 years.[191,192]

MRI APPEARANCE

CMBs can be detected easily using appropriate MRI sequences sensitive to hemoglobin and to its breakdown products,[119] such as T2*-weighted GRE. As a result of the magnetic susceptibility phenomenon exhibited by hemosiderin, CMBs appear as small, homogeneous round or ovoid areas of black signal voids surrounded by brain parenchyma (Figure 21.7.A).[2,188] The adoption of prespecified

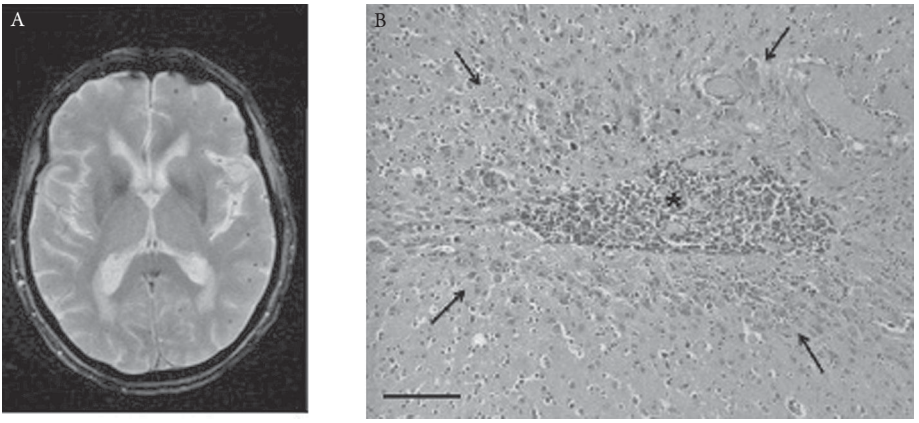

FIGURE 21.7 (A) Axial gradient-recalled echo of microbleeds (A), and histological image of chronic cortical microbleeds using hematoxylin–eosin stain (B). The lesion consists of central hemosiderin accumulation (pigment marked by an asterisk) surrounded by ring-shape astrocytic and microglial proliferation (arrows) with active hemosiderin resorption. Scale bar = 100 μm. Courtesy of Dr. V. Deramecourt. (Figure 7B: Adapted with permission from Cordonnier C et al. *Pract Neurol.* 2010).

MRI parameters such as longer echo time, higher special resolution, lower interslice gap, the use of three-dimensional acquisition, and higher magnetic field can increase the ability to detect CMBs.[193–196]

GRE provides additional information with regard to CMB chronicity as well as their location and overall burden.[122] Cortical CMBs located at the gray–white matter junction and the superficial cortical layers of the parietal, temporal, and occipital lobes are usually associated with cerebral amyloid angiopathy (CAA). The CMBs located in subcortical regions including basal ganglia, thalamus, brainstem, and cerebellum are linked to long-standing arterial hypertension. When multiple CMBs are present, they tend to cluster in the same area.[28,184,197]

Although lesion size cutoffs for CMBs are still debated, a diameter range between 2 mm and 5 to 10 mm is used most frequently.[2,32,185] One proposed diameter cutoff based on bimodal distribution of lesion sizes between micro- and macrohemorrhages was 5.7 mm.[198] However, the more sensitive MRI techniques may increase the number of potentially detectable CMBs,[185,195] as well as possible CMB mimics such as flow voids, cavernous malformations, hemorrhagic transformation of small infarcts, iron deposition, and scattered calcifications that need to be ruled out to improve specificity of CMB detection.[193]

HISTOPATHOLOGICAL CORRELATES OF CMBS

Histological studies correlating brain tissue pathology with neuroimaging confirmed that these hypointense GRE MRI lesions correspond to small hemorrhages, which are usually smaller in size than those apparent on MRI as a result of the blooming effect.[179,199,200] A minority of these lesions may correspond to small lacunes ringed by hemosiderin, vessel wall dissection, or microaneurysm.[200]

On microscopic examination, CMBs correspond to focal hemosiderin deposits containing macrophages in the perivascular space with areas of heme degradation surrounded by inflammatory reaction with activated microglial cells, late complement activation, and apoptosis. Some CMBs are also surrounded by gliosis and ischemic changes. In the walls of the adjacent, ruptured small arterioles, lipohyalinosis-related changes linked to hypertension are usually reported, particularly in CMBs located in basal ganglia, thalamus, and cerebellum.[179] Near CMBs located in the lobar regions, ruptured arteriosclerotic microvessels[201] and CAA-related changes are observed with wall thickening, absence of the muscularis layer, and deposition of β-amyloid (Figure 21.7.B).[179,202]

PATHOPHYSIOLOGY AND CLINICAL DETERMINANTS OF CMBS

As noted earlier, CMBs are detected more frequently in the elderly and are associated strongly with the presence of vascular risk factors such as arterial hypertension,[57,185,193] diabetes mellitus, smoking, or ischemic heart disease, but not with gender.[185] The presence of CMBs and any systolic blood pressure seems to predict the development of new CMBs over a follow-up period of 5.5 years.[203]

CMBs are frequent in patients with CAA, particularly in subjects with hereditary CAA in whom the frequency increases up to 69%.[204] Overall, when compared with healthy subjects and patients with ischemic stroke, prevalence of CMBs has been reported to be greater in patients with both deep and lobar ICH (60.4%–66%).[122,185,188,197] In subjects with primary ICH, age, prior history of stroke, evidence of small-vessel ischemic disease, old hemorrhage on neuroimaging, prior use of antithrombotic drugs, and larger hematoma volume were associated with CMBs.[205,206] Varying reports on prevalence of CMBs in patients with ischemic stroke exist; however, on average, it seems to be approximately 33.5%.[185] CMBs are highly prevalent in patients with lacunar stroke subtype (53.5%–68%),[207] likely reflecting the overlap between cerebral small-vessel disease pathologies. However, CMBs are less common in subjects with atherothrombotic (36%) and cardioembolic (19.4%) stroke subtypes.[185] CMBs have also been associated with other atherosclerosis-related pathological processes, including

peripheral artery disease (13%) and ischemic heart disease (4%).[122] CMBs are noted less frequently in patients with TIAs than in those with ischemic stroke.[185,208] Genetic factors influencing vessel wall integrity, such as apolipoprotein E genotype, may play a role in CMB development,[189,190,209] particularly for lobar CMBs in CAA.[210] Moreover, these lesions are also common in Moyamoya disease[211] and small-vessel genetic disorders such as CADASIL, with a prevalence ranging from 25% to 69%.[185,188,197,212,213]

A strong correlation exists between the presence of CMBs and markers of small-vessel disease, including subclinical lacunar infarcts (with a prevalence up to 62.2% in patients with multiple lacunar infarcts),[185] and WMH and its severity.[57,183,186,188,214] Baseline WMH has also been associated with the development of new CMBs in patients with CAA,[41] suggesting that CMBs and WMHs could represent different manifestations of a progressive microangiopathy in the presence of CAA. The link between CMBs and the markers of chronic, poorly controlled hypertension, such as retinal microvascular lesions[215] and left ventricular hypertrophy,[216] is similarly suggestive of the role of underlying high blood pressure in CMB development and burden.

The number of CMBs could mark severity of the microangiopathy,[217] as in patients with CAA in whom vessel thickness related to amyloid deposits correlates with the number of CMBs[198]; however, there is no conclusive evidence on the etiology and significance of a high CMB burden.[185]

The location of CMBs could be particularly important for understanding the underlying mechanisms of disease that contribute to development and progression of these lesions. Their distribution in cortical, but particularly in subcortical areas of the brain (white matter and deep gray matter, such as basal ganglia, particularly putamen; mainly the posterolateral part of the upper putamen and thalamus—lateral nuclei—and infratentorial regions such as brainstem and cerebellum) matching the distribution of small, deep perforating arteries, can be related to hypertensive vasculopathy affecting these vessels.[216] The Rotterdam Scan Study reported systolic blood pressure, severe hypertension, and presence of lacunar infarcts to be associated with deep or infratentorial CMBs.[190] Similarly, CMB distribution and ICH location correspond, so that subjects with deep ICH tend to have more subcortical CMBs compared with those with lobar ICH,[184,197] suggesting hypertensive microangiopathy as an important underlying mechanisms of subcortical CMBs. CMBs located in the lobar regions, particularly in the posterior regions (temporal and occipital lobe),[218] usually in the cortical–subcortical junctions in the distribution territory of the small and medium leptomeningeal and cortical vessels, are often detected in patients with CAA,[188,219] especially in the presence of normotensive subjects with a history of cognitive impairment and recurrent lobar ICH.[220] The CMB lobar distribution in CAA (i.e., in the posterior region [occipital lobe]) has served as an additional radiological marker to the Boston criteria for probable diagnosis of CAA.[202] Hence, hypertensive small-vessel disease and also CAA seem to be the most important pathological entities found to be associated with CMBs. These findings support the hypothesis of a common small-vessel disease-related pathophysiological mechanism.[221] Furthermore, CMBs can also be found in normal aging brains without evidence of cerebral vessel changes related to hypertension or β-amyloid deposition, suggesting the link to aging vessel pathology.[191] Other causative mechanisms, such as transient, mild BBB disruption with blood extravasation from vascular lumen to the parenchyma may explain the pathological finding of CMBs at the level of capillaries.[191,192]

New insights into the pathogenesis of CMBs came from a study of acute ischemic stroke in which new CMBs were noted to appear outside the index infarcted area in 12.7% of cases on the 7-day follow-up MRI. Furthermore, the newly formed CMBs were predicted independently by the presence of baseline CMBs and severe small-vessel disease, but were not associated with thrombolytic or antithrombotic therapy.[222] These findings may support the hypothesis that CMBs could develop acutely as a direct consequence of pathophysiological events after ischemic stroke, such as endothelial dysfunction, BBB disruption, and inflammation.[221] Similarly, acute SBIs detected on DWI of

patients with CAA-related ICH [177,223] manifest as a link between ischemic and hemorrhagic stroke, sharing a common pathophysiology on the small-vessel level.[221]

Clinically, although CMBs are often considered silent, small hemorrhagic lesions, a number of studies demonstrated a possible direct effect of CMBs on neurological functions, cognition, and outcome in terms of disability and mortality.[193,224] In patients having CMBs with a CAA-related distribution, stereotyped recurrent, focal neurological symptoms responding to anticonvulsants might be related directly to the CMBs and their location, or to cortex irritation caused by blood products.[225] CMBs, and particularly their burden, could play a role in the development of cognitive impairment, with deterioration of specific cognitive functions such as executive abilities,[2] as has been reported in the presence of multiple lacunar infarcts or WMH.[193] Last, CMBs may also contribute in part to the cognitive impairment observed in patients with Alzheimer's disease, in which they have been detected in 15% to 32% of cases.[185,226–229] However, no direct causative effect of CMBs on cognitive impairment has been demonstrated, with these lesions being most likely a marker of the underlying vasculopathy that leads to cognitive deficits.[230]

MICROBLEEDS AND THE RISK OF STROKE

CMBs have become the center of intense investigations during the past decade, reflecting their potential clinical importance, especially their role in predicting the risk of ICH in patients using anticoagulants or antiplatelet agents. However, no conclusive data exist to date on CMBs as a reliable MRI biomarker of increased risk of stroke, or whether they could be used in clinical decision making (Tables 20.1 and 20.2). This uncertainty arises mostly from the limitations of current studies, including study design, varying definitions of CMBs, imaging protocols adopted to detect CMBs, selection of study populations, and outcomes.[185,231]

Microbleeds and the Risk of First-Ever Stroke

Clinical significance of CMBs has been studied extensively in patients with CAA, in whom it serves as an accurate marker of disease progression, CAA-related ICH, and cognitive impairment.[220] However, the significance of CMBs detected in the apparently healthy general population requires further clarification.[188,193] Limited data are available on the association between CMBs and the risk of first-ever stroke (Table 21.1). In a recent longitudinal study, subjects without history of symptomatic stroke and evidence of CMBs were found to have an approximate threefold increase in the risk of first-ever stroke compared with those without CMBs, even after adjustment for age, sex, hypertension, and antithrombotic therapy (HR, 2.64; 95% CI, 1.34–5.19; $p = 0.005$).[232] Furthermore, evidence of CMBs in these subjects predicted ischemic stroke (HR, 11.77; 95% CI, 2.95–46.82; $p < 0.001$) independently but not hemorrhagic stroke (HR, 1.48; 95% CI, 0.63–3.45; $p = 0.36$).[232] However, in another cohort of individuals at high risk of cerebrovascular disease, CMBs were associated strongly with a greater risk of ICH (HR, 50.2; 95% CI, 16.7–150.9as compared with ischemic stroke (HR, 4.48; 95% CI, 2.20–12.2).[233] Overall, CMBs seem to be more prevalent in patients with recurrent stroke compared with those with first-ever stroke, of any subtype.[185,234]

Microbleeds and the Risk of Recurrent Stroke

Prior studies indicate that CMBs may serve as a reliable MRI marker of recurrent stroke.[235,236] The presence of CMBs increases the risk of recurrent ICH,[105,186,237,238] whereas higher rate of recurrent deep ICH and lacunar infarcts is observed among patients with multiple CMBs and small-vessel disease-related stroke, such as ICH and lacunar stroke.[104,216,217,239,240]

In patients with primary lobar ICH, the total number of hemorrhages on baseline T2*-weighted MRI, including the index ICH and micro- and macrobleeds, predicts cumulative risk of recurrent symptomatic ICH over a 3-year follow-up, and increases with the rising burden of hemorrhages and after adjustment for risk factors, apolipoprotein E genotype, and history of previous ICH (HR, 1.5; 95% CI, 1.1–2.2).[235] Recent studies confirmed the significance of the number of CMBs as an independent predictor of recurrent ICH in patients with primary ICH,[241] and particularly of recurrent lobar ICH in patients with probable/possible CAA (2–4 microbleed: HR, 2.93; 95% CI, 1.3–4.0; $p = 0.041$; ≥5 microbleeds: HR, 4.12; 95% CI, 1.6–9.3; $p = 0.001$).[242] Although it is not yet completely clear whether in these patients recurrent ICH tends to develop at the site of CMBs,[241] both the distribution of new CMBs and the location of recurrent lobar ICH have been reported to be associated with distribution of the baseline CMBs.[218]

The role of CMBs in predicting the risk of hemorrhagic complications in those individuals that use antithrombotic agents is currently under investigation. Symptomatic ICH was reported to be more frequent in aspirin users with multiple CMBs versus aspirin users without CMBs (19 of 21 vs. 7 of 21, $p < 0.001$), and in patients with high CMB loads the risk of ICH may outweigh the benefit of aspirin.[203,236] However, the risk of recurrent cerebral hemorrhagic events associated with antiplatelet use in patients with lobar (HR, 0.8; 95% CI, 0.4–3.3; $p = 0.73$) or deep (HR, 1.2; 95% CI, 0.1–14.3; $p = 0.88$) ICH was not altered.[243] With regard to the risk of warfarin-related ICH, CMBs are associated with ICH independent of an increased international normalized ratio (INR) or hypertension (odds ratio [OR], 7.38; 95% CI, 1.05–51.83).[244] Lobar and basal ganglia CMBs are both likely to be associated with a more brain bleeding-prone status in these patients.[245] In other studies, although the number of CMBs was greater in patients on warfarin compared with control subjects, this difference did not reach statistical significance.[246]

Last, the predictive value of CMBs has been explored with regard to the risk of both spontaneous and thrombolysis-related hemorrhagic transformation in patients with acute ischemic stroke. Some studies found CMBs an independent predictor of all hemorrhagic transformations, both spontaneous and pharmacological, within the infarcted area (OR, 7.2; 95% CI, 1.9–28.2) after adjustment for age, sex, vascular risk factors, treatments, WMH, and lacunes.[247] Other small studies suggested a possible relationship between the presence of CMBs and the risk of new hemorrhage from the CMBs themselves after thrombolytic treatment.[248] Overall, current evidence suggests that thrombolytic treatment appears to be relatively safe in the presence of CMBs,[249,250] but large, prospective studies are warranted to examine this.

PRACTICAL CLINICAL AND RESEARCH IMPLICATIONS

Although the specific clinical significance of CMBs with regard to patient diagnosis and treatment remains unclear, CMBs promise to remain an important MRI marker of ongoing cerebrovascular disease. If validated, detection of CMBs on T2*-weighted MRI may have a particular role in the prediction of hemorrhagic risk in thrombolysis for acute ischemic stroke, as well as in secondary prevention therapy with antithrombotic drugs, both antiplatelets and anticoagulants.[248,251–253] Furthermore, CMBs may be relevant in the prediction of ischemic cerebrovascular events, potentially giving an insight into the underlying pathophysiology of various stroke subtypes and TIA.[236] Last, GRE T2* sequence findings may be used in the future as a marker of small-vessel disease severity and/or to stratify patients based on their hemorrhagic risk as part of selection for clinical trials on antithrombotics, thrombolytics, or antihypertensive agents.[188]

Microinfarcts

With the development of advanced MRI techniques during the past few years, new MRI entities such as MIs emerged as markers of cerebrovascular disease. These lesions are usually clinically silent, like

SBIs, and "invisible" to conventional MRI techniques, but a number of recent studies have demonstrated their possible role in cognitive impairment and dementia.[254,255] MIs likely act synergistically with larger SBIs, and they may represent one of the major, although not yet well-defined, pathophysiological "bridges" between cerebral small-vessel disease and cognitive dysfunction.[256]

MRI APPEARANCE

If MIs were visible on conventional MRI, they probably would be hypointense on FLAIR images and hyperintense on T2W images in their cystic stage, and hyperintense both on FLAIR and T_2 in their gliotic stage.[257] The presence of other lesions, particularly those related to small-vessel disease can confound and prevent the detection of MIs, such as WMH, the development toward which MIs may also contribute.[258] MIs could be also confounded with perivascular spaces.[259–261] Increased spatial resolution imaging, such as high-field strength MRI, could detect these microscopic lesions reliably, as shown by a recent postmortem imaging study in patients with CADASIL.[262] In the case of acute MIs, they can be detected with high sensitivity on DWI (Figure 21.8.A).[263,264] As a result of the MRI blooming effect, these lesions may appear larger than they actually are; hence, acute MIs can be classified incorrectly as lacunar infarcts.[256,265]

HISTOPATHOLOGICAL CORRELATES OF MIS

MIs are not visible by the naked eye and on gross macroscopic pathological brain inspection, but they can be detected by light microscopy (Figure 21.8.B).[256,266,267] They appear as microscopic regions of tissue necrosis, which could also be cavitated. The microscopic findings seem to resemble the same pathological characteristics of brain infarcts on a smaller scale; hence, the term *microinfarct*. However,

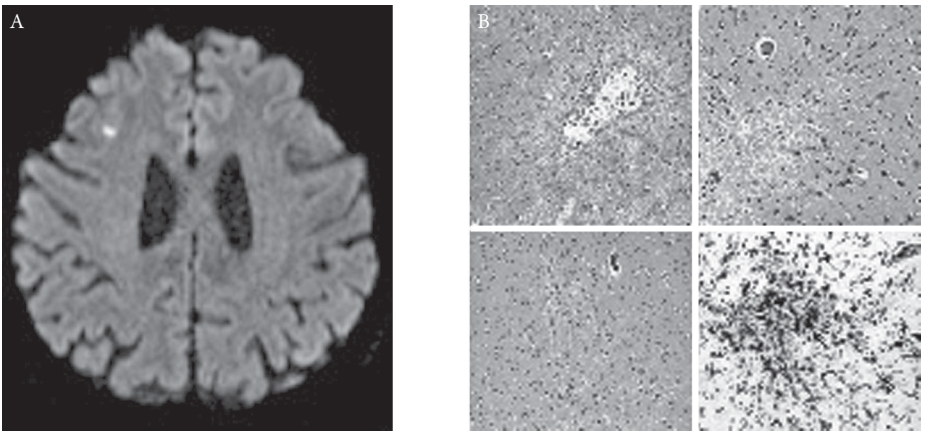

FIGURE 21.8 (A, B) Axial diffusion-weighted imaging of acute microinfarct (A) and histological images of microinfarcts (B). There is a cystic (cavitated) microinfarct (diameter, 600 μm) in the basal ganglia (B, upper left), an incomplete microinfarct without cavitation (diameter, 330 μm) in the midfrontal cortex (B, upper right), a cortical microinfarct with linear scarring (puckering) from the middle temporal cortex (diameter, 120 μm; B, lower left), and immunostaining for major histocompatibility complex II human leukocyte antigen DR3 expression in activated microglia and macrophages in a microinfarct in the basal ganglia (diameter, 320 μm; B, lower right). Images provided by Chunhui Yang (Rush Medical Center, Chicago, IL). (Figure 8B: Adapted with permission from Smith EE et al. *Lancet Neurol.* 2012;11:272–282.)

their pathophysiology is not yet very well defined; thus, areas of incomplete infarction, tissue rarefaction with gliosis, are sometimes erroneously considered MIs.[267–269] The available neuropathological studies, particularly focused on Alzheimer's disease and vascular dementia, are conflicting about the size-based definition of MIs, because some studies have adopted a diameter upper limit of 2 mm,[270] whereas others have an upper limit of 4 mm.[269] Cystic MIs are usually described as larger (up to 5 mm) than noncystic MIs (0.05–0.4 mm).[28,268,271] The mean diameter can have a range from 0.2 to 2.9 mm.[255,272] Another source of variation is represented by the staining methods for the detection of MIs that are not yet standardized.[266] On microscopic examination, MIs appear differently according to their stage. During the acute phase, ischemic red neurons with vacuolization from cytotoxic edema are typically found; during the subacute stage (3–5 days), macrophages surround the infarct area; and later, astrocytosis becomes the prevalent characteristic. Last, during the chronic phase, MIs are reported as having a central area of necrosis or cavitation surrounded by a gliotic reaction.[256] Regarding their location, MIs seem to occur throughout the brain, from cortical to subcortical gray matter and white matter.[257] They are commonly found in the cerebral cortex, at the base or in the superficial layers of gray matter,[268,272] and particularly in the watershed areas of the cerebral cortex.[257] But, their distribution can actually vary from the anterior to posterior white matter, from border zones of major arterial territories [272–274] to the typical location of lacunar infarctions, such as basal ganglia, thalamus, brainstem, and cerebellum, and in this last case they are probably associated with arteriolosclerosis.[256] There are no apparent differences between MIs located in the cortex versus subcortical regions.[257]

PATHOPHYSIOLOGY AND CLINICAL DETERMINANTS OF MIS

Prevalence of MIs on neuropathological examination is extremely heterogeneous, ranging from 3% to 43% in mixed populations with and without dementia, up to 62% in patients with vascular dementia, and up to 78% in patients with dementia and severe CAA.[257] Multiple MIs are present in approximately 6% of subjects without dementia and 31% of patients with dementia[267]—specifically 0 to 4 in patients with different types of dementia,[275] 1 to 37 (with a mean of 6) in patients with severe CAA, 1 to 6 (with a mean of 3) in subjects with mild CAA,[276] and 1 to 4 in each of the watershed zone areas.[274] This variability is mainly a result of the difficulty in detecting these small lesions, which is highly dependent on the thickness of brain tissue slices inspected, favoring semiquantitative methods.[267,270,276,277] In general, among the elderly who died of all causes, MIs are found in 16% to 46%.[256] Because MIs seem to mirror most of the histopathological characteristics of macroscopic infarctions on a smaller scale, they also, in part, share the same risk factor profile. In fact, first of all, these lesions have been associated particularly with markers of small-vessel disease[270] such as lacunar infarcts, leukoaraiosis, ICH,[278,279] CAA,[271,280–283] and CADASIL,[197,284] but also macroinfarcts.[255,278,285,286] However, the underlying pathophysiology of MIs may be more heterogeneous. MIs are commonly observed in the cortical watershed areas, where they may represent the result of intermittent focal ischemic damage from chronic hypoperfusion, particularly in patients with hypertensive microangiopathy or CAA, which is thought to lower the brain's threshold for ischemia.[287] MIs in the brain regions supplied by large arteries may be related to vessel occlusion and thromboembolism.[255,278,285,286] Last, BBB disruption may also contribute to MI development, where the damage is mediated by oxidative stress and inflammation.[256]

Clinically, these lesions are often silent, but it is believed that multiple MIs might play a role in specific clinical syndromes, particularly cognitive impairment, which is likely related to the neuronal loss burden that characterizes these entities, or alterations in neuronal connectivity throughout the brain.[257]

MIS AND THE RISK OF STROKE

Very little evidence exists regarding the link between MIs and risk of stroke (Table 21.1). MIs detected on DWI in patients with acute lacunar infarction or ICH may represent early recurrence

of lesions in patients with severe microangiopathy, or may serve as a predictor of future risk of cerebral small-vessel disease. In a study of patients with ICH who underwent repeated DWI, the frequency of acute ischemic lesions was 7.7% at baseline, but increased up to 25% at 5 days.[288] One long-term follow-up study of acute DWI lesions detected during ICH evaluation demonstrated that they predicted independently risk of ischemic stroke or recurrent ICH (HR, 5.87; 95% CI, 1.004–34.31; $p = 0.049$), ischemic stroke or vascular death (HR, 5.00; 95% CI, 1.15–21.86; $p = 0.032$), or both recurrent ischemic stroke and ICH, or vascular death (HR, 5.69; 95% CI, 1.36–23.70; $p = 0.017$).[288] These findings are similar to previously reported associations between SBIs and stroke risk in population-based studies.[78]

PRACTICAL CLINICAL AND RESEARCH IMPLICATIONS

If the initial findings regarding the role of MIs are confirmed in future studies, they may serve as a valuable marker of the risk of cognitive impairment, especially if combined with other MRI features of small-vessel disease.

Dilated Perivascular Spaces

Virchow-Robin spaces are normal physiological structures that surround the wall of vessels (arteries, arterioles, veins, and venules) as they perforate from the subarachnoid spaces through the brain surface and parenchyma. The basic functional role of perivascular spaces is probably to facilitate solute drainage from the brain through the extracellular spaces, in lieu of lymphatic drainage of the nervous system,[289,290] or possibly to facilitate immunological processes.[290–294] When dilated pathologically, these eventually become DPVSs, which were first described in 1843 by Durand-Fardel as "état criblé," in which a multitude of round holes containing small vessels were observed in the hemispheric white matter, thalamus, and basal ganglia.[2,295] DPVSs appear as punctuate, usually less than 3-mm lesions surrounding perforating arteries in the brain parenchyma and arterioles predominantly in the centrum semiovale, basal ganglia, and hippocampus.

MRI APPEARANCE

Signal intensity of DPVSs on MRI is similar to that of CSF; therefore, they appear hyperintense on T2W images and hypointense on FLAIR. When the signal intensity is measured quantitatively, resulting values are lower than that of CSF,[296] possibly because DPVSs represent interstitial fluid trapped in the subpial or interpial space, and/or because of a partial volume effect.[290] In most studies, FLAIR images have been commonly adopted to differentiate DPVSs from lacunes, based on the absence of a hyperintense rim/halo corresponding to morphological changes caused by gliosis[47,119,150,290]; however, astrocytic gliosis has also been observed surrounding DPVSs in postmortem studies.[161,297] Thus, one of the most reliable MRI sequences for DPVS detection is T1W magnetization prepared rapid gradient echo (MPRAGE) (Figure 21.9.A).

For lesions larger than 3 mm, DPVSs can be interpreted erroneously as lacunar infarcts. With the increased use of gradient echo images, which identify CSF, DPVSs have appeared as filled of CSF and not infarcted tissue.[119] Differential diagnosis of DPVSs from lacunar infarction can be based on size (DPVSs are usually less than 3 mm), location, and symmetry (commonly bilateral, located along perforating arteries), and shape (smooth margins, well-demarcated round, linear, or oval).[148,260,290,298–300]

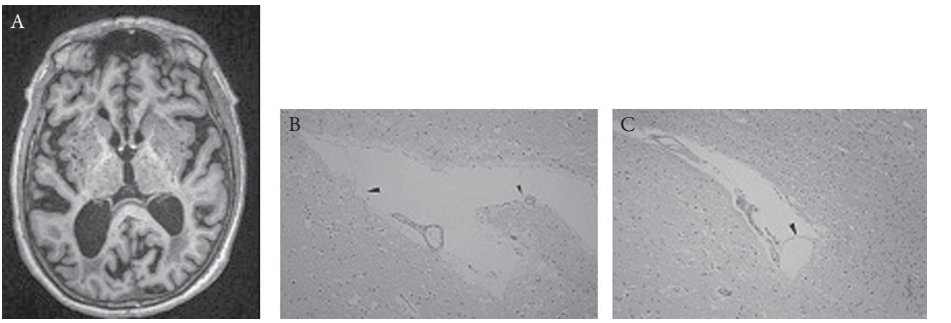

FIGURE 21.9 Dilated perivascular spaces (DPVSs). (A–C) T1-weighted magnetization prepared rapid gradient echo) imaging (MPRAGE) (A) and histological images of DPVSs (B, C), with a photomicrograph showing dilatation of the Virchow-Robin space around an arteriole. A single cell layer (thought to be the inner pial layer) covering the cavity arises at the arteries about 10 mm in diameter (arrowhead) (original magnification ×100). (Figure 9B, C: Adapted with permission from Adachi M et al. *Neuroradiology*. 1998;40:27–31.)

HISTOPATHOLOGICAL CORRELATES OF DPVSS

Pathological studies[299] demonstrate that perivascular spaces do not communicate directly with subarachnoid space,[301–303] but the cortical arteries surrounded by the Virchow-Robin spaces cross from the subarachnoid space through the subpial space into the brain parenchyma (Figure 21.9.B, C).[290] They are bound externally by a layer of pial membrane and internally by the collagen of the arterial adventitia.[302] In contrast, arteries in the basal ganglia are surrounded not by one but by two distinct layers of leptomeninges separated by the Virchow-Robin space.[290]

In histopathological studies, the mean diameter of the arteries incorporated in the DPVSs was 39.0 ± 36.0 μm.[299] The dilation of Virchow-Robin spaces does not seem to be uniform, and some studies reported associated perivascular demyelination, vacuolated myelin sheaths, gliosis,[181,304,305] and arteriolosclerosis.[151]

PATHOPHYSIOLOGY AND CLINICAL DETERMINANTS OF DPVSS

Prevalence of DPVSs depends on the MRI techniques, including field strength and slice thickness adopted for their detection. Overall, DPVS prevalence is low (1.6%–3%) in healthy young individuals,[306,307] but is very common in the aging population.[308]

The pathophysiology of DPVSs is not well understood, but a number of theories have been proposed, including fluid exudation resulting from the increased vessel wall permeability caused by segmental necrotizing angiitis, alterations of interstitial fluid drainage resulting from CSF circulation changes, brain atrophy with a possible ex vacuo phenomenon, perivascular myelin loss, leaking of interstitial fluid from the intracellular compartment to the pial space, fibrosis and obstruction of Virchow-Robin spaces with prevention of fluid drainage, ischemic injury to perivascular tissue, mechanical trauma from pulsation of the CSF, or vascular ectasia resulting from pulsation of elevated blood pressure.[261,290]

MRI-based studies[306] have reported that perivascular spaces are normal anatomic findings in healthy individuals, even if they are dilated. Some studies showed that DPVSs were associated with age, as index of cerebral atrophy, hypertension, and other vascular risk factors, and moreover with cognitive impairment, dementia, and white matter lesions. In some multivariable models, only age remained an independent predictor of DPVSs,[307] whereas others found a significant association

between a number of DPVSs and ambulatory blood pressure.[309] Furthermore, DPVSs have been linked to WMH, vascular dementia, depression in the elderly, retinopathy in diabetics, increased BBB permeability in patients with lacunar stroke, migraine,[306,310,311] CADASIL, and CAA.[312–314] In an MRI-based study of patients with different types of dementia, DPVS number and location were sufficiently specific and sensitive in differentiating between vascular and degenerative dementias.[261]

DPVSs and the Risk of Stroke

Clinical relevance of DPVSs is not yet well defined, because there are no systematic data on the association between DPVSs and risk of stroke. A few studies demonstrated that DPVSs correlate strongly with silent brain ischemic lesions and WMH in patients with first-ever symptomatic lacunar stroke,[310] and that a significant association exists between both total and basal ganglia DPVSs with lacunar stroke subtype (β, 0.38; $p = 0.04$; and OR, 3.16; 95% CI, 1.49–6.70, $p = 0.003$), as well as deep and periventricular WMH, even after adjusting for increasing age and other vascular risk factors.[259] Future large, prospective MRI-based studies are warranted to evaluate the true clinical and prognostic value of DPVSs, and their association with the risk of stroke.

Superficial Siderosis

SS is an uncommon and underdiagnosed disorder characterized by chronic, slow, repeated bleeding in subarachnoid spaces.[315] The resulting hemosiderin deposition may be responsible for central nervous system damage, making SS a possible distinct MRI marker of cerebral small-vessel disease.

MRI Appearance

The advent of MRI techniques sensitive to hemosiderin, such as GRE T2*-weighted imaging and susceptibility-weighted imaging[316] has increased detection and diagnosis of SS. It appears on T2*-weighted MRI as a rim of hypointensity that surrounds the surface of cortical sulci (Figure 21.10.A), particularly in cases with prior lobar ICH or possible CAA, or the surface of brainstem, cerebellum, as well as cranial nerves, spinal cord, and, infrequently, along cerebral ventricles.[317] Intra- or extradural fluid collection is often observed along the spinal cord in patients with SS.[316] In most cases, the initial bleeding site is not identified. Cerebellar atrophy, mainly of the superior vermis and of the anterior cerebellar hemispheres, is a common finding and can explain the gait disturbances in subjects with SS.

Histopathological Correlates

Theoretically, pathological diagnosis of SS requires the presence of specific glia cells commonly found in the cerebellum, which facilitate the conversion of heme to ferritin and hemosiderin, and possibly mediate the brain damage.[318,319] In vivo imaging and pathological correlations confirmed that the hypointense rim surrounding the surface of cortex, brain, cerebellum, and spinal cord corresponds to hemosiderin deposits.[320] Iron is also observed in subependymal and subpial brain, and spinal cord regions, as well as in endothelial and medial cells of the vessels. Neurons and oligodendroglia do not seem to accumulate iron,[321] but gliosis and neuronal loss associated with hemosiderin deposition are usually observed (Figure 21.10.B).[316] Leptomeninges appear fibrotic, thickened, and with hemosiderin-laden macrophages and astrocytes,[321] together with extracellular iron granules in the

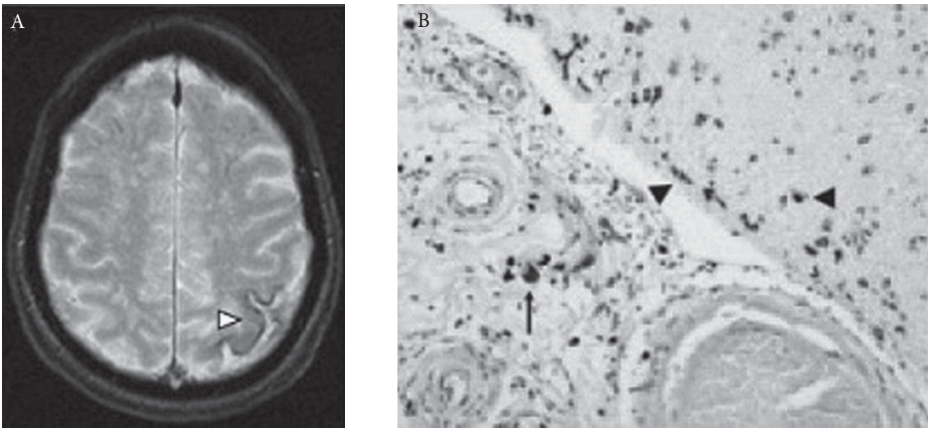

FIGURE 21.10 Superficial siderosis (SS). (A, B) Gradient-recalled echo magnetic resonance imaging of gyriform low signal (arrowheads), corresponding to meningeal siderosis, in the left parietal cortex (A), and a histological image of hemosiderin deposition within macrophages in the subarachnoid space (arrow) and within superficial cortex (arrowheads; B) using Pearl's blue iron staining. (Adapted with permission from Feldman HH et al. *Stroke.* 2008;39:2894–2897.).

subpial brain parenchyma, spinal cord, and cerebellum.[322] Typical histopathological findings of CAA may be associated with SS.[323]

PATHOPHYSIOLOGY AND CLINICAL ASPECTS OF SS

Prevalence of SS on MRI among the general elderly within the Rotterdam Scan Study was 0.7%. Furthermore, SS was found only in subjects with CMBs, particularly lobar ones, supporting the hypothesis of a link with CAA.[324] In patients with definite CAA, SS prevalence was 60.5%.[325]

Most patients with SS have a history of a possible CAA, head or spine injury, ICH, dural pathology, neoplasms, neurosurgical procedures, or have experienced symptoms suggestive of subarachnoid hemorrhage (SAH). In 40% of cases, the source of bleeding remains unknown.[322] Trauma can cause traction of small vessels, which become fragile and prone to rupture, and intradural surgery may cause leakage of blood into the CSF.[317] SS has been also associated with the presence of CSF hypovolemia and craniospinal hypotension, which is usually related to dural defects. The alternate hypothesis of venous hypertension has been proposed given the presence of epidural vein sclerosis resulting from SS.[316] Correlation between SS and CAA might be explained by blood leakage from the superficial CAA-affected vessels from the cerebral parenchyma to the subarachnoid spaces.[326] The association with CMBs can be the result of a clearance disorder of blood product in patients affected by CAA.[324]

SUPERFICIAL SIDEROSIS AND THE RISK OF STROKE

There are a few studies on the association between SS and the risk of stroke, particularly hemorrhagic subtype. SS is a likely marker of CAA-associated focal SAH at the cortical convexity.[323,325–330] Some reports suggested that focal SAH, and hence SS, may predict the risk of future ICH in patients with CAA.[331] Patients with SS and probable or possible CAA followed for a median of 35.3 months demonstrated a high rate of hemorrhagic events (47.1% developed any type of hemorrhage, 35.3% of whom developed ICH; whereas 25.5% developed SAH at the original SS location).[332] Similarly to CMBs, SS might represent the site where vessels are more fragile as a result of a greater deposition of β-amyloid[332,333]; however,

this does not explain ICH occurring remotely from the SAH and SS site.[323,325] Moreover, detection of SS in up to 50% of patients with TIA-like syndrome and CAA[225,334–336] suggests cortical localization.

PRACTICAL CLINICAL AND RESEARCH IMPLICATIONS

Future use of SS as an MRI marker of cerebrovascular disease may have important clinical implications, both in diagnosis of CAA and in the decision-making process for patient management regarding the risk/benefit of antiplatelet or anticoagulant therapy.[332] Future studies are required to confirm the current data on the prognostic value of SS and risk of hemorrhagic stroke.

Summary and Conclusions

As a result of the enormous impact of cerebrovascular diseases on health care, economy, and social systems, there is a growing need to understand more fully the specific role of each vascular risk factor and to identify new markers of the disease. Both current and developing MRI techniques facilitate detection, quantification, and characterization of the markers of widespread cerebrovascular disease. During the past few years, new cutting-edge MRI methods, including diffusion tensor imaging (Figure 21.11), magnetization transfer MRI (Figure 21.12), advanced brain perfusion studies, and high-field MRI (Figure 21.13), have advanced our understanding of the underlying mechanisms of cerebrovascular disease. These MRI tools are now expected to translate the data obtained in the research setting into clinical applications that will validate and develop the diagnostic and prognostic value of the MRI markers of cerebrovascular disease. In the future, a total burden of cerebrovascular disease, including both clinical and "silent" manifestations of neurovascular disorders may prove essential to guide risk stratification, diagnostic workflow, and patient selection for acute interventions as well as stroke prevention strategies. Validated MRI markers of cerebrovascular disease may have a radical effect on the direction of clinical research and the development of novel, targeted therapies for stroke, vascular cognitive impairment, and other cerebrovascular diseases.

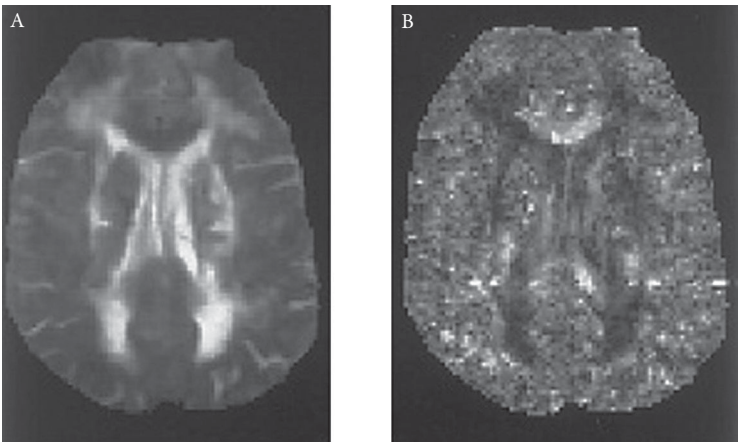

FIGURE 21.11 (A, B) Typical T2-weighted (A) and fractional anisotropy (B) images obtained from a patient. (A) The T2-weighted image shows regions of increased signal intensity adjacent to the horns of the lateral ventricles. (B) The fractional anisotropy image reveals a substantial loss of anisotropy in the regions of leukoaraiosis. (Adapted with permission from Jones DK. *Stroke.* 1999;30:393–397.).

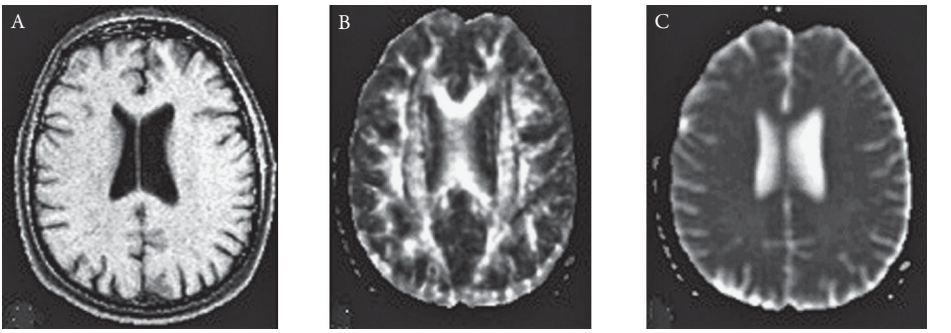

FIGURE 21.12 (A–C) Example of magnetization transfer magnetic resonance imaging (A) compared with fractional anisotropy (B) and mean diffusivity (C). (Adapted with permission from Schiavone F. *J Magn Reson Imag.* 2009;29:23–30.)

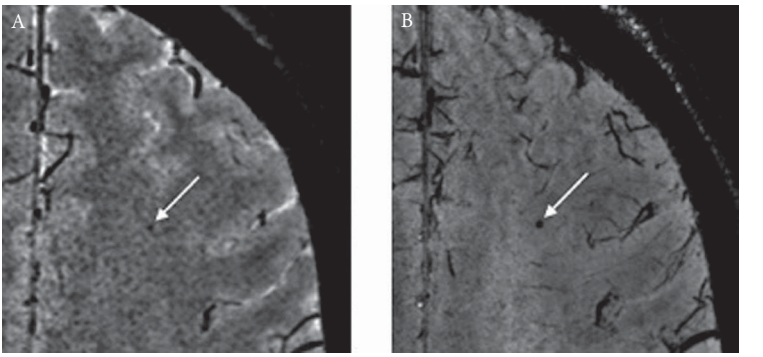

FIGURE 21.13 (A) A 1.5-T magnetic resonance image shows a hypointense lesion (arrow) that was hard to distinguish from noise and was not scored as a microbleed. (B) On 7-T magnetic resonance imaging, this hypointense lesion is visible as a typical microbleed, showing enlargement resulting from the blooming effect. This lesion was scored as a microbleed by two different observers. (Adapted with permission from Conijn MMA. *AJNR Am J Neuroradiol.* 2011;32:1043–1049.)

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22

CIRCULATING BIOMARKERS AND THE RISK OF CEREBROVASCULAR DISEASE AND STROKE

Aleksandra Pikula

Introduction

Cerebrovascular disease is a major public health concern that accounts for a significant proportion of brain aging-related mortality and morbidity. The burden of cerebrovascular disease is attributable largely to well-established vascular risk factors, and genetic and lifestyle differences, but another determinant may be factors that modulate risk and response to ischemic or other vascular brain injury. Therefore, searching for novel biological pathways involved in overt and covert cerebrovascular disease may improve our understanding of disease mechanisms and help facilitate the discovery of new molecular targets for stroke prevention and treatment.

Changes in circulating levels of an increasing number of biological molecules, with varied functions—some specific to the brain and others restricted to the vasculature, liver, blood, or inflammatory pathways—have been associated with an altered risk of stroke.

In this chapter, circulating biomarkers relevant to ischemic cerebrovascular disease are discussed. Based on the plausible biological pathways whereby they might be related to stroke risk, these biomarkers are discussed within pathway-specific categories.

A biomarker has been defined as a characteristic that is measured objectively and evaluated as an indicator of normal biological or pathogenic processes, or of pharmacological responses to a therapeutic intervention. It is thus a marker of a disease "trait, state, or rate." Although biomarkers can include imaging tests and clinical performance characteristics, genetic variants, and cerebrospinal fluid (CSF) levels, in this chapter the term *biomarker* is used to refer to circulating biomarkers only. Biomarkers can have multiple useful functions, permitting more accurate risk prediction, improving prognostication (of recurrence, disability, or mortality after stroke), improving differential diagnosis, and better monitoring of therapeutic interventions.

An ideal biomarker for prediction of vascular risk should be specific and sensitive, but also relatively inexpensive to measure using standardized, precise, reliable, and reproducible assays. Furthermore, it should be independently predictive and additive to already-established vascular risk factors. More important, population-specific normative values should be easily interpretable for clinicians. Biomarkers useful for primary prevention need to have a high specificity to reduce the number of false positives, and need to explain a moderate proportion of disease in the community, in addition to needing evidence that targeting individuals with higher (or lower) levels is superior to conventional risk prevention approaches in preventing stroke. Biomarkers for secondary prevention need to have a high sensitivity to avoid false negatives and are most useful when they influence treatments plans or correlate with disease progression trajectories. Although there are many biomarkers available, markers of endothelial dysfunction and inflammation pathways, such as total homocysteine and high-sensitivity C-reactive protein (CRP), are used more widely in routine clinical practice. All others discussed here are relatively novel biomarkers undergoing validation of their clinical utility in community and clinic-based samples.

Biomarkers of Endothelial Function Pathways

TOTAL HOMOCYSTEINE (THCY)

Homocysteine (tHcy) has been recognized as a marker of endothelial dysfunction and as an independent risk factor for atherosclerosis and cardiovascular disease. The mechanisms by which elevated plasma tHcy concentrations impair vascular function and lead to overt or covert vascular brain injury are not entirely understood. Experimental studies proposed several possible explanations—from endothelial dysfunction leading to an initiation of atherothrombotic mechanisms (oxidation of low-density lipids, activation of monocyte adhesion and inflammatory mechanisms, stimulation of smooth muscle proliferation) to initiation of coagulation cascades with platelet activation, and eventually leading to overt cerebrovascular disease.[1] As an excitatory neurotransmitter, tHcy binds to the N-methyl-D-aspartate (NMDA) receptors resulting in neuronal injury; thus, tHcy is recognized as an important marker of vascular brain injury.[2,3]

Homocysteine is a sulfur-containing amino acid produced by demethylation of the essential amino acid methionine. It is metabolized via two metabolic pathways: (a) remethylation, during which methionine is formed again from a methyl group acquired from methylene tetrahydrofolate or betaine—a process dependent on vitamin B12 and folate—or (b) transsulfuration, during which tHcy is condensed with serine by cystathionine β-synthase to form cystathionine, and this is dependent on vitamin B6. Inherited deficiencies in enzymes necessary for the metabolism of tHcy can result in elevated blood levels of tHcy, as can deficiencies in required cofactors, folate, B12, B6, and betaine.[4]

Blood (plasma or serum) levels of tHcy are measured optimally during the fasting state; serum tHcy concentrations of 5 to 15 μmol/L are considered normal (although for individuals on a folic acid-fortified diet, the upper limit of normal is considered to be 12 μmol/L), and levels more than 15 μmol/L are considered elevated (mildly elevated, 16–30 μmol/L; moderately elevated, 31–100 μmol/L; and severely elevated, >100 μmol/L).[5]

In the general population, deficiency of folic acid, vitamin B12, or vitamin B6 accounts for the majority of persons with elevated tHcy concentrations. Circulating tHcy concentrations increase with age and are elevated in persons with impaired renal function, but are also increased by some medications (carbamazepine, phenytoin, methotrexate), and are elevated in individuals with a gene mutation for methylenetetrahydrofolate reductase.[6]

The "homocysteine hypothesis" of accelerated atherothrombotic vascular disease was proposed in early 1969 by McCully[7] based on his observations of intimal injury, fibrosis, lipid accumulation, and

atherothrombosis of the coronary and cerebrovascular vasculature in children with homocystinuria. Similar observations were reported after inducing acute hyperhomocysteinemia with methionine load in older adults.[8] However, the exact role of elevated tHcy in the pathogenesis of cerebrovascular atherosclerosis remains uncertain. Some evidence suggests stroke subtype-specific increased risk for large-artery and small-artery (lacunar) disease compared with cardioembolic stroke and control subjects, but this observation remains inconsistent across studies.[9] There is a strong association between thrombophilia and venous thrombosis in patients with homocystinuria caused by cystathionine β-synthase deficiency.[10] Homocysteine may also contribute to the development of left atrial thrombus in patients with stroke caused by atrial fibrillation, in which the mean tHcy level was greater in patients with thrombus present on transesophageal echocardiography even when the analysis was adjusted for spontaneous echo contrast and atrial dilation (tHcy >15 μmol/L; adjusted odds ratio [OR], 14.25; 95% confidence interval [CI], 2.7–75.1).[11]

After the introduction of folic acid-fortified diet programs, the Framingham study observed that folate status had improved, with the relative reduction of elevated tHcy levels by almost 50%.[12] Since the introduction of folic acid fortification in 1998, there is limited epidemiological data on the relationship of tHcy to overt cerebrovascular disease. Among 1947 elderly Framingham Study participants (mean age, 70 ± 7 years; mean follow-up, 9.9 years; incident stroke events, 165) after adjusting for traditional stroke risk factors, participants with greater baseline tHcy levels (>14.24 μmol/L) compared with those with lower levels (<10 μmol/L) had an increased risk of stroke, with a relative risk (RR) of 1.82 (95% CI, 1.14–2.91).[13] Similar findings were observed among elderly participants from the Rotterdam Study in which the stroke risk by quintiles of tHcy level was increased significantly only in the group with levels greater than 18.6 μmol/L (upper quintile OR, 2.53; 95% CI, 1.19–5.35).[14] Sacco et al.[15] observed that tHcy levels greater than 15 μmol/L are an independent risk factor for ischemic stroke (hazard ratio [HR], 2.01; 95% CI, 1.00–4.05), whereas mild elevations of tHcy of 10 to 15 μmol/L are less predictive. They also found that the vascular effect of tHcy was greatest among whites and Hispanics (HR, 4.04; 95% CI, 0.92–17.62; and HR, 2.42; 95% CI, 0.87–6.76; respectively), but less among blacks (HR, 0.88; 95% CI, 0.24–3.21).[15] tHcy levels of 7.3 μmol/L or more were associated with an elevated OR for stroke of 1.6 (95% CI, 1.1–2.5)l independent of traditional vascular risk factors, vitamin use, and poverty status among young women (age, 15–44 years) in a biracial women study.[16]

In contrast, the Physicians' Health Study (PHS) and a Finnish population study found nonsignificant or borderline significant associations between tHcy and stroke risk.[17,18] There are several possible explanations for this inconsistency. There was a relatively small number of clinical events in the PHS and the Finnish study, limiting power to detect differences due to the overall low prevalence of hyperhomocysteinemia in the Finnish population, and among physicians who were more likely to take dietary and vitamin supplements compared with non-physicians).

In another longitudinal study of 1039 patients with acute stroke (mean age, 75 years), fasting tHcy was measured within 24 hours after admission with acute ischemic stroke, and patients were monitored for up to 15 months for recurrent events. In adjusted analysis, tHcy was an independent predictor of recurrent stroke (OR, 1.3; 95% CI, 1.1–1.5 for each increase in tHcy of 10 μmol/L).[19]

Several studies have also confirmed an association between tHcy concentrations and subclinical vascular brain injury, such as silent/covert brain infarcts[20,21] and white matter hyperintensities.[21–23] In the Framingham Heart Study, 218 participants had an infarct on brain magnetic resonance imaging (MRI). An elevated initial plasma tHcy level was associated with an increased risk of MRI infarct, and similar observations have been made in other epidemiological cohorts.[21]

Despite the relative strength of the association between homocysteine and vascular risk in observational studies, the benefit of tHcy reduction on vascular disease risk is unclear. A meta-analysis projected a reduction of vascular disease by 30% to 40% with greater folic acid intake.[24] Using clinical trials published before August 2012 ($N = 14$, with 54,913 participants) to measure the association

between B vitamin supplementation and stroke events, B vitamin supplementation for homocysteine reduction was observed to reduce stroke event rates significantly (RR, 0.93; 95% CI, 0.86–1.00; $p = 0.04$). However, this was not true after the analysis was stratified according to concomitant primary or secondary prevention measures used, ischemic versus hemorrhagic stroke, or occurrence of fatal stroke, although the results remained significant in the stratum of subjects not on dietary folate fortification.[25]

Three large, randomized trials investigated tHcy-lowering vitamin supplement therapy for secondary stroke prevention.[26,27] The Vitamins to Prevent Stroke study included 8000 subjects with recent stroke or transischemic attack (TIA) and studied a combined end point of recurrent stroke, myocardial infarction, and vascular death at 2.5 years, comparing persons on a supplement (2 mg folic acid, 500 μg B12, 50 mg B6) with placebo. This study enrolled a total of 8164 patients who were assigned randomly to receive B vitamins ($n = 4089$) or placebo ($n = 4075$) and were monitored for a median duration of 3.4 years (interquartile range, 2.0–5.5); 616 patients (15%) assigned to B vitamins and 678 (17%) assigned to placebo reached the primary end point, but there was only a marginal reduction in risk (RR, 0.91; 95% CI, 0.82–100; $p = 0.05$). There were no unexpected serious adverse reactions and no significant differences in common adverse effects between the treatment groups. Therefore, daily administration of folic acid, vitamin B6, and vitamin B12 to patients with recent stroke or TIA was safe but did not seem to be more effective than placebo in reducing the incidence of major vascular events.[26] In subsequent subgroup analysis, the Vitamins to Prevent Stroke study group has examined several related questions and found that (a) antiplatelet therapy may amplify the benefits of lowering tHcy levels with B vitamin supplementation such that when comparing persons on supplementation with individuals not on antiplatelet therapy, there was a significant beneficial effect on the primary outcome (123 events in the B vitamins group [17%] vs. 153 events in the placebo group [21%]; HR, 0.76; 95% CI, 0.60–0.96)[28]; (b) B vitamin supplementation did not reduce progression of cerebral small-vessel-related brain lesions measured on brain MRI[29]; and (c) daily supplementation with folic acid, vitamin B6, and vitamin B12 in cognitively unimpaired patients with previous stroke or TIA lowered the mean tHcy level but had no effect on the incidence of cognitive impairment or cognitive decline, as measured by the Mini-Mental State Examination, during a median follow-up of 2.8 years.[30]

The Heart Outcomes Prevention Evaluation trial was a randomized, placebo-controlled trial comparing homocysteine-lowering vitamins (2.5 mg folic acid, 50 mg vitamin B6, 2 mg vitamin B12) or placebo in 5522 patients older than 55 years of age with vascular disease or diabetes, regardless of baseline tHcy level. Subjects were monitored for 5 years for the primary composite outcomes (death resulting from cardiovascular causes, myocardial infarction, or stroke). Almost 12% of the population had a TIA or stroke at study entry. Vitamin therapy did not reduce the risk of the primary end point, but there was a lower risk of stroke (4.0% vs. 5.3%; RR, 0.75; 95% CI, 0.59–0.97; $p = 0.03$) in the active therapy group.[31]

The Vitamins in Stroke Prevention study compared the efficacy of high-dose (2.5 mg folic acid, 400 μg B12, 25 mg B6) and low-dose (200 μg folic acid, 6 μg B12, 0.2 mg B6) vitamin supplementation for secondary prevention of stroke or myocardial infarction in 3600 subjects with recent stroke. Two-year stroke rates were 9.2% in the high-dose arm and 8.8% in the low-dose arm. However, moderate reduction of tHcy after nondisabling stroke had no effect on vascular outcomes during the 2 years of follow-up. Although the study was negative, the authors suggested that the short follow-up could have been insufficient to detect a real difference between the two groups.[27] However, in a hypothesis-driven secondary analysis of a subgroup of patients from the Vitamins in Stroke Prevention study, excluding persons least likely to have experienced lowering of tHcy with the study treatment (those with low or very high serum B12, and those with renal failure, $n = 2155$ patients), there was a significant reduction of stroke, coronary events, and death ($p = 0.049$). When the participants were stratified according to the median entry level of B12 (313 pmol/L), those with high serum

B12 at entry who received high-dose vitamins had a 33% reduction of vascular events compared with those with low B12 who received low-dose vitamins.[32]

Thus current recommendations from the American Heart Association (AHA) regarding secondary stroke prevention strategies concur that folate supplementation reduces levels of tHcy and may be considered for patients with ischemic stroke and hyperhomocysteinemia (class IIb, level of evidence B), although there is no convincing evidence that reducing homocysteine levels prevents stroke recurrence.[33]

ASYMMETRIC DIMETHYLARGININE

Although multiple endogenous products contribute to endothelial homeostasis, endothelium-derived nitric oxide (NO) has been recognized as a key mediator of normal endothelial function and is also called the *endogenous antiatherosclerotic molecule*.[34] However, NO synthesis can be selectively inhibited by competitive blockade of the endothelial NO synthesis active site by asymmetric dimethylarginine (ADMA). Hence, ADMA has been identified as a novel biomarker of endothelial dysfunction and preclinical atherosclerosis.[35]

ADMA is an endogenous molecule produced during the degradation of circulating L-arginine; the substrate for endothelial NO synthesis by the enzyme endothelial NO synthesis. Thus, accumulation of ADMA decreases production of NO. Approximately 90% of ADMA is metabolized in the kidneys and liver by dimethylarginine dimethylaminohydrolase (DDAH), which degrades it to citrulline and methylamine. Pharmacological inhibition of DDAH increases ADMA concentration and reduces NO production. It has also been reported that elevated tHcy concentration, high cholesterol levels, and hyperglycemia could inhibit DDAH activity.[35,36]

ADMA is measured by enzyme-linked immunosorbent assay or high-performance liquid chromatography/liquid chromatography–tandem mass spectrometry—methods that achieve the necessary precision and separation of ADMA from other structural isomers. Although efforts are ongoing to define the normal range of ADMA concentrations in healthy humans in different age and sex groups, elevated plasma ADMA concentrations (defined as higher tertiles, quartiles, or quintiles in the study group) have been observed in patients with hypertension, diabetes, left ventricular hypertrophy, smoking, hypercholesterolemia, and high CRP levels; all well-established risk factors for ischemic stroke.[37–39]

Increased ADMA levels have been associated with an increased risk of atherosclerosis, incident cardiovascular disease, cardiovascular mortality, acute coronary events,[40] and an elevated risk of stroke and TIA.[41,42] Of 52 patients with ischemic stroke and 36 healthy control subjects, Yoo and Lee[41] demonstrated significant differences ($p = 0.0001$) in ADMA concentrations between those with recurrent strokes (mean, 2.28 μmol/L), index stroke only (mean, 1.46 μmol/L), and control subjects (mean, 0.93 μmol/L). Moreover, levels greater than the 90th percentile of the control group (≥1.43 μmol/L) increased the overall stroke risk in the elderly population studied (OR, 6.05; 95% CI, 2.77–13.3).[41] In the Population Study of Women in Gothenburg, Leong et al.[43] recruited 880 women with baseline ADMA levels and demonstrated that even small increases in ADMA levels over 24 years of follow-up were associated with a 30% greater risk of myocardial infarction or ischemic stroke. Those participants in the highest quintiles of serum ADMA concentrations (>0.71 μmol/L) carried the greatest risk (RR, 1.75; 95% CI 1.18 –2.59] compared with others.[43]

In stroke-free Framingham offspring participants ($n = 2013$; mean age ± standard deviation [SD], 58 ± 9.5 years; 53% women), baseline plasma ADMA levels were related to subsequent brain MRI measures of subclinical vascular injury such as presence of silent brain infarcts (SBIs). Higher ADMA levels were associated with an increased risk of prevalent SBIs (OR per 1-SD increase in ADMA, 1.16; 95% CI, 1.01–1.33; $p = 0.04$). Participants in the upper age-specific quartiles (Qs) of plasma ADMA values had an increased prevalence of SBIs (OR for Q2–Q4 vs. Q1, 1.43; 95% CI,

1.00–2.04; $p < 0.05$).[44] Increasing its degradation, DDAH may decrease ADMA levels successfully. Recent data demonstrate that some antidiabetic drugs may lower ADMA levels via regulation of DDAH, thus suggesting that new therapeutic agents should not only target ADMA levels directly, but also perhaps DDAH.[45,46]

Currently, there are no formal recommendations on the value of measuring ADMA concentrations and its use in stroke risk stratification in primary and secondary stroke prevention. However, the literature clearly illustrates that ADMA may be a novel stroke risk factor. Therefore, further studies in larger samples are warranted to validate the clinical significance of elevated circulating ADMA concentrations.

Biomarkers of Inflammatory Pathways

Inflammation plays an important role in the progression of atherosclerosis and in the ulcerating of plaques, resulting in clinical disease such as myocardial infarction and ischemic stroke. Several inflammatory markers have been examined in relation to risk of stroke and stroke outcomes, but most attention has been give to high-sensitivity CRP (hsCRP; CRP measured with a high-sensitivity assay) and lipoprotein-associated phospholipase A2 (Lp-PLA2).

C-REACTIVE PROTEIN

CRP is an acute-phase reactant—a marker of systemic inflammation, produced in liver by interleukin 6, an inflammatory cytokine, but also by endothelial and smooth muscle cells, and by adipose tissue.[47] As a marker of atherosclerosis, CRP is an important predictor for cardiovascular events (myocardial infarction, stroke, peripheral vascular disease, and cardiac death) in individuals without a history of heart disease.[47]

Numerous prospective studies have demonstrated that hsCRP is an independent predictor of stroke in both women and men. During a mean follow-up of 12 to 14 years in 1462 Framingham study subjects (591 men and 871 women free of stroke/TIA; mean age, 69.7 years), CRP was a strong independent predictor of first ischemic stroke or TIA ($n = 196$). In multivariable analysis, after adjustment for traditional stroke risk factors, relative risk of stroke/TIA among participants in the highest compared with the lowest CRP quartile was 2.1 (95% CI 1.19–3.83), but only in women.[48]

In a nested case–control analysis from the Physicians' Health Study comparing 543 apparently healthy men in whom myocardial infarction, stroke, or venous thrombosis subsequently developed with 543 study participants who did not report vascular disease, during a follow-up period exceeding 8 years, persons in the highest CRP quartile had double the risk of ischemic stroke (RR, 1.9; 95% CI, 1.1–3.3, $p = 0.002$) compared with those in the lower two quartiles (Q1–2 vs. Q3–4), independent of other lipid-related and nonlipid-related risk factors.[49]

Studies also demonstrated a strong association between hsCRP concentrations and outcomes after stroke.

In a prospective, observational hospital-based study, Muir et al.[50] examined survival time and cause of death for up to 4 years after the index stroke, and investigated whether the stroke outcomes were related to CRP concentration measured within 72 hours of stroke. Survival in those with a CRP level more than 10.1 mg/L was significantly worse compared with those with CRP ≤10.1 mg/L ($p = 0.00009$). Higher CRP concentration was an independent predictor of mortality (HR, 1.23 per additional log unit; 95% CI, 1.13–1.35; $p = 0.02$), whereas older age, stroke severity, and higher CRP concentrations were independent predictors of mortality during the first 3 months after the index event.[50]

Subsequently, Winbeck et al.[51] examined the association of early serial CRP measurements in hyperacute ischemic stroke with long-term outcomes. A total of 127 patients with a first ischemic

stroke (not treated with thrombolysis) were examined within 12 hours after symptom onset and had CRP measurements at admission (CRP 1), within 24 hours (CRP 2), and within 48 hours (CRP 3) after symptom onset. In addition to baseline levels of several vascular risk factors, 1-year outcome and lesion volumes of initial MRI diffusion-weighted images were determined. The CRP concentration increased significantly during the first 48 hours after symptom onset (CRP 1, 0.86 mg/dL [95% CI, 0.69–1.02]; CRP 2, 1.22 mg/dL [95% CI, 0.88–1.55]; CRP 3, 1.75 mg/dL [95% CI, 1.25–2.25]; $p = 0.003$). In multivariable analysis adjusted for vascular risk factors, CRP concentrations obtained within 12 to 48 hours were predictive of an unfavorable outcome (combination of death resulting from any cause and any new nonfatal vascular event such as recurrent stroke, unstable angina, or myocardial infarction [adjusted OR, 3.9; 95% CI, 1.4–10.7; $p = 0.008$]).[51]

Although there is no specific therapy to reduce CRP levels, data from population studies and prospective randomized clinical trials suggest that commonly used agents such as aspirin and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce CRP levels. In the PHS study, aspirin decreased the risk of myocardial infarction significantly, but not stroke among men with high CRP concentrations, although there was no clear effect of aspirin on CRP levels.

Among 472 randomly selected participants in the Cholesterol and Recurrent Events trial, CRP levels were measured at baseline and at 5 years. Patients were assigned randomly to pravastatin versus placebo and were monitored for vascular events. Pravastatin use was shown to decrease the risk of vascular events and stroke, and it also decreased CRP levels significantly during the 5-year follow-up, independent of its effect on low-density lipoprotein–cholesterol (LDL-C), whereas in the patients who were on placebo, CRP levels actually increased over this time.[52]

The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was a double-blind placebo study to investigate whether treatment with rosuvastatin (20 mg daily) versus placebo would decrease the rate of first major cardiovascular events (including any strokes) in patients with normal LDL-C levels but elevated CRP concentrations (>2.0 mg/dL) who also had one additional vascular risk factor for cardiovascular disease. Over a median follow-up of 1.9 years, in participants on rosuvastatin, hsCRP concentrations were decreased by 37% compared with participants on placebo. The JUPITER trial demonstrated a 44% reduction ($p < 0.000001$) of the events in the prespecified primary end point (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, coronary revascularization, or cardiovascular death), with no evidence of heterogeneity across geographic regions, a 48% reduction in the risk for nonfatal stroke, and a 51% reduction in risk for ischemic stroke (HR, 0.49; 95% CI, 0.30–0.81; $p = 0.004$).[53] Unlike results from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial with atorvastatin for secondary stroke prevention, there was no increase in hemorrhagic stroke with treatment, although the total number of hemorrhagic stroke events was small.[54]

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2

Lp-PLA2 is a macrophage-derived enzyme belonging to the phospholipase A2 superfamily, is involved in the metabolism of LDL in arterial walls, and is responsible for the release of inflammatory mediators from the vessel wall. Lp-PLA2 plays a significant role in atherogenesis; its inhibition blocks enzyme activity in plasma and within atherosclerotic plaques, thus reducing progression of atherosclerosis. [55] Epidemiological studies demonstrate that relatively high levels of Lp-PLA2 are associated with an increased risk of incident ischemic stroke, independent of hsCRP levels.[56]

In a prospective case–cohort study of 12,762 apparently healthy, middle-aged men and women in the Atherosclerosis Risk in Communities study, during 6 years of follow-up, 194 persons experienced

an incident ischemic stroke. After adjusting for traditional stroke risk factors, the highest tertile of Lp-PLA2 concentration was associated with an increased risk of stroke (HR, 2.04; 95% CI, 1.23–3.38, $p < 0.01$). Both Lp-PLA2 and CRP levels in the highest category were also associated with increased stroke risk (HR, 1.91; 95% CI, 1.15–3.18; $p = 0.01$; and HR, 1.87; 95% CI, 1.13–3.10; $p = 0.02$, respectively).[56]

In the Northern Manhattan Stroke study, a population-based study of stroke risk factors, of 467 patients with first ischemic stroke, the authors examined whether levels of hsCRP and Lp-PLA2 predict risk of stroke recurrence, other vascular events, and death. Blood was collected at the time of hospital admission within 72 hours of stroke onset in 391 patients (83.7%) and within 6 days in 420 patients (90.0%). hsCRP, but not Lp-PLA2, was associated with stroke severity. After adjusting for traditional stroke risk factors and hsCRP level, compared with the lowest quartile of Lp-PLA2, those in the highest quartile had an increased risk of recurrent stroke (HR, 2.08; 95% CI, 1.04–4.18) whereas persons with an elevated hsCRP level did not.[57] Subsequently, Elkind et al.[58] demonstrated that hsCRP and Lp-PLA2 measurements collected soon after stroke and myocardial infarction were not reflective of prestroke levels and might be less reliable for long-term risk stratification as a result of the diurnal and acute-phase variability of these biomarkers. Nevertheless, in 2005, the Food and Drug Administration approved the use of Lp-PLA2 for long-term risk prognostication in persons with coronary heart disease or stroke.[58,59]

Current recommendations from the AHA on primary stroke prevention recommends that routine assessment of inflammatory markers such as hsCRP or Lp-PLA2 in patients without cerebrovascular disease be considered to identify patients who might be at increased risk of stroke, although their effectiveness (i.e., usefulness in routine clinical practice) is not well established (class IIb, level of evidence B). Although data remain insufficient to recommend routine use of hsCRP and Lp-PLA2 as additional markers to help determine which stroke patients should be started on statins, such decisions could be based on the Centers for Disease Control and Prevention/AHA guidelines until further data are available.[60]

Biomarkers of Coagulation Pathways

FIBRINOGEN

Fibrinogen is an acute-phase reactant involved in hemostasis and maintenance of blood viscosity. There are 40 different assays to measure fibrinogen, and there are unlimited variations in levels between laboratories; thus, standardization of the assays is important and somewhat lacking. [61]

Nevertheless, several prospective epidemiological studies and recently published meta-analyses recognized strong, independent association between elevated fibrinogen levels and the risk of stroke in individuals with or without a history of prior ischemic event.[62–64]

In a meta-analysis of 154,211 participants in 31 prospective studies, during 1.38 million person-years of follow-up, there were 6944 first nonfatal myocardial infarctions or stroke events and 13,210 deaths. The adjusted HR per 1-g/L increase in fibrinogen level for stroke was 1.75 (95% CI, 1.55–1.98). The association of fibrinogen level with stroke in patients without preexisting cardiovascular disease did not change based on sex, smoking, blood pressure, or blood lipid levels.[64] However, a causal relationship of high fibrinogen levels and stroke risk remains unclear. Only two genetic variants that affect the levels of fibrinogen are related to the risk for ischemic stroke, and a recent Mendelian randomization study suggested that elevations in fibrinogen levels may be consequent to and not causal for atherosclerosis, although this does not rule out the possibility of secondary injury from the elevated fibrinogen levels.[65]

The fibrate class of medications could lower fibrinogen levels. In the large cohort of the Data from an Epidemiological Study on the Insulin Resistance Syndrome study, authors examined the change

in fibrinogen concentrations at 3 years of follow-up between individuals who started fibrate (n = 126) or statin (n = 127) treatment during the follow-up and individuals (n = 3906) who were not on treatment during this period. After adjustment for baseline fibrinogen level, age, and sex, and changes in total cholesterol, triglycerides, and alcohol intake, fibrinogen concentration decreased after fibrate treatment, but increased after statin treatment and in those not using lipid-lowering drugs (−0.07 ± 0.54 g/L vs. 0.10 ± 0.54 g/L vs. 0.08 ± 0.52 g/L, respectively; p = 0.01).[66] However, lowering fibrinogen with bezafibrate did not show an effect on reducing stroke risk or even stroke recurrence.[67,68]

Based on these data, use of fibrinogen levels for risk stratification of patients with or without prior cardiovascular disease is not routinely recommended.

Biomarkers of Hemodynamic Stress

BRAIN NATRIURETIC PEPTIDE

B-type or brain natriuretic peptide (BNP) is a natriuretic peptide with strong vasodilatory activities. During hemodynamic stress, BNP is released by cardiomyocytes.[69] As a result of myocardial fibrosis and cardiac hypertrophy, and change in renal function in otherwise healthy elderly persons, BNP levels may be elevated in the older population. BNP levels are used widely in risk stratification of acute coronary syndrome, and are recognized as a strong diagnostic and prognostic marker in patients with chronic congestive heart failure.[70] Elevated levels of BNP are usually observed in individuals with hypertension, left ventricular hypertrophy, diastolic dysfunction, atrial fibrillation, and renal dysfunction.[69] Several population and hospital-based studies observed an association between high BNP levels and the risk of cardioembolic stroke, stroke outcomes, and long-term mortality.

In community-based study of a Japanese population (n = 13,466), during a mean follow-up of 2.8 years, 102 participants (65 males) experienced a first ischemic stroke. In analysis adjusted for traditional stroke risk factors, risk for ischemic stroke was significantly greater in the highest plasma BNP quartile (HR, 2.38; 95% CI, 1.07–5.29), but only for men.[71] In a hospital-based sample of patients (n = 99) with an acute ischemic stroke, after excluding 23 patients with valve disease, heart failure, myocardial infarction, or chronic renal failure, the authors measured BNP levels, ratio of peak early filling velocity to peak atrial systolic velocity, left atrial diameter, and the left atrial appendage flow to examine which of the four measurements was predictive of cardioembolic stroke. Thirty-six patients were diagnosed with cardioembolic stroke. In adjusted analysis, BNP levels and left atrial appendage flow predicted cardioembolic stroke with more than 95% accuracy.[72] Similarly, Montaner et al.[73] examined the diagnostic value of a panel of biochemical markers to differentiate stroke etiologies in acute stroke patients (n = 707). In addition to D-dimer and soluble receptor for advanced glycation end products, high levels of BNP were observed in patients with cardioembolic stroke (p < 0.0001). More important, in addition to atrial fibrillation, a BNP level of more than 76 pg/mL was an independent predictor of cardioembolic stroke, with an OR of 2.3 (95% CI, 1.4–3.7; p = 0.001).[73] Similarly, in patients with cryptogenic stroke, elevated BNP levels (≥360 pg/mL) on admission were highly predictive of development of atrial fibrillation even at 2 years of follow-up (OR, 5.70; 95% CI, 1.11–29.29; p = 0.037), suggesting the initial event may have been cardioembolic.[74]

In a large, prospective hospital-based study, Rost et al.[75] observed that serum levels of BNP were also highly correlated with mortality and long-term functional outcomes (based on the modified Rankin Scale [mRS]) after cardioembolic stroke. Of 569 patients with ischemic stroke (mean age, 67.9 ± 15 years; 46% female), elevated BNP was associated with poor functional outcome (OR, 0.64; 95% CI, 0.41–0.98) and with higher odds of mortality (OR, 1.75; 95% CI, 1.36–2.24). Addition of BNP to multivariate models improved predictive power for functional outcome (p = 0.013) and mortality (p < 0.03) after cardioembolic stroke.

In 3127 stroke-free Framingham offspring (mean age, 59 ± 10 years; 54% female), a panel of eight biomarkers—hsCRP, D-dimer, plasminogen activator inhibitor 1, aldosterone-to-renin ratio, BNP,—tHcy and urinary albumin-to-creatinine ratio were measured and related to risk of stroke/TIA after a median follow-up of 9.2 years. In a backward elimination analysis, higher BNP levels were associated with increased risk of stroke/TIA (HR, 1.39/1-SD increment; $p = 0.002$), and BNP also improved risk prediction when added to a model with the Framingham Stroke Risk Profile alone (Net reclassification index-NRI, 0.109; $p = 0.037$).[76]

Clearly, serum BNP added statistically significant advantage above and beyond the prognostic value of models built using clinical data alone, but further studies are required to validate the value of BNP as a predictor of cardioembolic stroke (vs. other subtypes), functional outcomes, and mortality after stroke.

Biomarkers of Cellular Injury

MATRIX METALLOPROTEINASE 9

Matrix metalloproteinases (MMPs) are a family of zinc- and calcium-dependent endopeptidases involved in the degradation of extracellular matrix proteins, tissue remodeling, inflammation, and angiogenesis. MMPs are regulated by cytokines, chemokines, and growth factors, and are highly destructive when involved in inflammatory processes.[77]

Of all MMPs, plasma levels of MMP-9 have been studied the most in association with acute stroke. Cerebral tissue expression of MMP-9 is normally minimal to undetectable, but plasma levels of MMP-9 are often elevated after acute stroke (ischemic and hemorrhagic) in humans.[78–80] After vascular brain injury, overexpression of MMP-9 and its activity mediates proteolysis and leads to blood–brain barrier leakage and cell death as a result of the destruction of extracellular matrix proteins.[81]

Montaner et al.[79] measured plasma MMP-2 and MMP-9 levels in 39 patients with cardioembolic strokes not treated with tissue plasminogen activator (tPA) to examine the relation of MMPs to infarct volume and risk for hemorrhagic transformation. MMP-9 peaked at admission (<12 hours from onset) and correlated with stroke severity (on the National Institutes of Health Stroke Severity [NIHSS] scale) and infarct volume on computed tomography (CT) at 48 hours. In the same sample, after adjusting for hypertension and lack of vessel recanalization, baseline MMP-9 levels were related to late hemorrhagic transformation (OR, 9; 95% CI, 1.46–55.24; $p = 0.010$).[79]

In 24 patients with acute middle cerebral artery infarction, plasma MMP-9 levels measured on admission/before intravenous tPA therapy were correlated highly with infarct volume as measured with diffusion-weighted MRI ($r = 0.54$, $p = 0.05$). MMP-9 level was also an independent predictor of the lesion growth at 24 hours after thrombolytic therapy (OR, 14; 95% CI, 1.5–131; $p = 0.019$) as assessed on diffusion-weighted MRI.[82]

Serial MMP-2 and MMP-9 measurements obtained in 41 patients with acute stroke who received tPA within 3 hours of stroke onset demonstrated MMP-9 levels to be highest among patients who subsequently developed a parenchymal hematoma when compared with those with or without hemorrhagic infarction. An MMP-9-level threshold of 191.3 ng/mL had a positive predictive value of 67% and a negative predictive value of 100% for subsequent hematoma development. In regression analysis, early (<3 hours) MMP-9 levels were independent predictors of subsequent parenchymal hematoma (OR, 9.62; 95% CI, 1.3–70.3)[83]

Therefore, plasma MMP-9 concentrations measured in an acute stroke setting may predict infarct size and further infarct growth; but, more important, MMP-9 may identify patients who are more likely to develop intracranial hematomas after thrombolytic therapy. Further large-scale research studies are needed to validate utility of MMP-9 as a marker for tPA risk stratification in acute ischemic stroke.

Lipoproteins and Lipid-Related Biomarkers

Numerous studies report inconsistent relationships between lipids and the risk of stroke likely attributable to methodological and sample differences between the studies.[84–94] Several studies found an increased risk of stroke with higher total cholesterol (TC) and lower high-density lipoprotein–cholesterol (HDL-C).[84–88] A large, prospective study from Finland (n = 58,235), during a mean follow-up of 20.1 years, observed 3914 stroke events. In the multivariable-adjusted analysis at different levels of TC (<5 mm/L [reference], 5–5.9 mmol/L, 6–6.9 mmol/L, ≥7.0 mmol/L), HRs were 1.00, 1.05, 1.16, and 1.22 for total stroke (p = 0.036) and 1.00, 1.06, 1.19, and 1.27 for ischemic stroke (p = 0.02) in men. Low levels of HDL-C and a high TC/HDL-C ratio were associated with increased risks of total and ischemic stroke in both men and women, but after further adjustment for body mass index, blood pressure, and history of diabetes, this association diminished for men.[88] The Cardiovascular Health Study found a similar association in men,[92] whereas in the Framingham study, likely as a result of fewer stroke events, only a weak association between HDL-C and stroke was noted.[89] The mechanisms behind this association are complex. Nevertheless, as a strong antiatherogenic lipid molecule with anti-inflammatory properties, HDL-C was established to be more protective for atherosclerotic stroke subtypes.[84–86,95,96]

TC/HDL-C, a ratio between atherogenic and antiatherogenic lipid molecules, is a more potent predictor of cerebrovascular disease than TC, LDL-C, or HDL-C alone,[97,98] but only a few studies have assessed an association between the TC/HDL-C ratio and risk of ischemic stroke.[87,88] In the previously mentioned Finish population, a high TC/HDL-C ratio was associated with increased risk of total and ischemic stroke in both men and women.[88] In the prospective Women's Health Study, of 27,937 U.S. women aged 45 or older, during 11 years of follow-up, 282 ischemic strokes occurred. And in the multivariable-adjusted analysis, HR (95% CI; p value for trend across mean quintile TC/HDL-C ratio values) for ischemic stroke was 1.65 (1.06–2.58; p = 0.02).[87] Therefore, the role of TC/HDL-C definitely deserves further attention in studies evaluating its clinical utility in stratification of patients at risk for ischemic stroke.

Recently, more attention has been give to the relation between nonfasting triglyceride (TG) and risk of ischemic stroke.[94,96] Of 13,956 Copenhagen City Heart Study participants (mean age, 56.5 years), 1529 developed ischemic stroke. Cumulative incidence of ischemic stroke increased with increasing levels of nonfasting TG (log-rank trend, p < 0.001). In multivariate adjusted analysis, men with elevated nonfasting TG levels of 89 to 176 mg/dL had increased risk of stroke, with an HR of 1.3 (95% CI, 0.8–1.9), and for nonfasting TG ≥443 mg/dL, risk was doubled, with an HR of 2.5 (95% CI, 1.3–4.8; 41 events) versus men with nonfasting levels less than 89 mg/dL (HR, 1.0; p < 0.001 for trend). In women, HRs were 1.3 (95% CI, 0.9–1.7) and 3.8 (95% CI, 1.3–11), respectively, versus women with nonfasting TG levels less than 89 mg/dL (HR, 1.0; p < 0.001 for trend). Absolute 10-year risk of ischemic stroke ranged from 2.6% in men younger than 55 years with nonfasting TG levels less than 89 mg/dL to 16.7% in men aged 55 years or older with levels ≥443 mg/dL.[94] The Women's Health Study corroborated the findings of a strong association between elevated nonfasting TG levels and ischemic stroke.[99]

LDL-C, which is highly correlated with TC concentration, is less consistently associated with ischemic stroke.[87,90] Nevertheless, large clinical trials have shown that statin therapy, which through its pleiotropic properties lowers LDL-C levels, also reduced the risk of ischemic stroke in patients with prior stroke/TIA or in high-risk populations.[100] Thus, the underlying mechanism of the previously mentioned associations in primary and secondary stroke prevention remains a subject of great interest for risk stratification in stroke prevention.

New guidelines released by the AHA and the American College of Cardiology have change the standards for who should be taking cholesterol-lowering medications. The panel of experts advises

on assessing the overall risk and not focusing on the lipid marker values. Thus, the new guidelines identify four groups of the primary and secondary prevention patients in whom clinicians should focus on the reduction the clinical events, and—based on the individual risk—make recommendations regarding the appropriate "intensity" of statin therapy to achieve relative reductions in LDL cholesterol.[101]

LIPOPROTEIN(A)

Lipoprotein(a) [Lp(a)] is analogous to LDL and is identified by the presence of an additional highly glycosylated protein called *apolipoprotein(a)* that might enhance or inhibit fibrinolysis. However, plasma Lp(a) levels are poorly associated with lipids or fibrinogen levels. Therefore, the mechanism whereby it exerts an influence on vascular pathology remains uncertain. A recent meta-analysis of 31 observational studies including 56,010 subjects with more than 4609 stroke events examined the association of Lp(a) levels with risk of stroke. Unadjusted mean Lp(a) was greater in stroke patients (OR, 2.39; 95% CI, 1.57–3.63), and Lp(a) levels were also more frequently abnormally elevated (defined as Lp(a) levels ≥30 mg/L).[102]

Sensitivity analysis and meta-regression analysis did not find any influence of study design, stroke subtype, age, and sex to explain the substantial heterogeneity between studies ($I^2 = 83.7\%$, $p < 0.001$).

In prospective cohort studies ($n = 5$, >1645 strokes), patients in the highest tertile of Lp(a) distribution versus the lowest tertile had greater risk of stroke (RR, 1.22; 95% CI, 1.04–1.43). There was no publication bias or heterogeneity in the prospective studies ($I^2 = 0.00\%$, $p = 0.67$). In nested case–control studies ($n = 3364$ strokes) Lp(a) was found not to be a risk factor for incident stroke (OR, 1.04; 95% CI, 0.6–1.8).[102] Despite these interesting findings, further large sample studies are needed to examine the strength and independence of the association between Lp(a) and risk for ischemic stroke, and its value as a clinical biomarker.

Growth Factors and Neurotrophins

BRAIN-DERIVED NEUROTROPHIC FACTOR

Brain-derived neurotrophic factor (BDNF) is a major neurotrophin that facilitates neuronal repair by promoting neurogenesis and angiogenesis. BDNF controls differentiation and survival of neurons by binding to its high-affinity tyrosine kinase receptor B.[103] Both BDNF and tyrosine kinase receptor B are widely distributed throughout the brain, but they have also been expressed in nonneuronal cell types such as vascular endothelial cells, activated lymphocytes, vascular smooth muscle cells, and platelets.[104] BDNF may mediate resistance to ischemic injury (neuroprotection).[105] BDNF crosses the blood–brain barrier, and its circulating concentrations are measurable. In a general population study, mean levels remained constant over much of the adult life span, with a gradual decline after age 80.[106]

Low serum BDNF concentrations have been observed in patients with coronary artery disease, type 2 diabetes mellitus, metabolic syndrome, acute coronary syndrome,[107] and physical inactivity[108]—all risk factors associated with cerebrovascular disease.

In 3440 stroke-/TIA-free Framingham study participants (mean age, 65 ± 11 years; 56% women), lower baseline BDNF concentrations were associated with an increased risk of incident stroke/TIA (adjusted HR comparing BDNF Q1 vs. Q2–Q4, 1.47; 95% CI, 1.09–2.00; $p = 0.012$). More important, in reclassification analyses, BDNF when added to a risk assessment model based on traditional

stroke risk factors alone (as identified by the Framingham Stroke Risk Profile) resulted in significant improvement of stroke/TIA risk prediction.[109]

In a primate model of lacunar stroke, enhanced production of BDNF was observed in activated glial cells in the white matter ipsilateral to the injury that contributed to tissue repair and regeneration.[110] Therefore, increased expression of BDNF occurring in response to ischemic damage might contribute to "spontaneous" recovery of function in that tissue.[105] In experimental studies, atorvastatin and candesartan appear to be associated with better outcomes after cerebral ischemia as well as induction of BDNF expression.[105,111,112] Yanamoto et al.[113] observed relative resistance to stroke for up to 14 days after the direct intracerebral infusion of recombinant BDNF into the neocortex of experimental animals.

Thus far, one population study has suggested some value for BDNF in stroke prediction, and animal studies have established a positive effect of BDNF on infarct size and on long-term potentiation, neuronal remodeling, and functional motor recovery after induction of an ischemic brain lesion. Therefore, BDNF could have an effect on cerebrovascular disease through its neurotrophic effect or its vascular effect. Further studies are required to confirm whether BDNF will be a useful clinical marker of stroke risk or will help in the prognostication of stroke-related outcomes.

VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor (VEGF) is a vascular permeability factor and specific growth and survival factor for endothelial cells. It promotes vasculogenesis and angiogenesis in physiological and pathophysiological states. VEGF stimulates the synthesis of NO, improves vascular permeability, and stimulates cell growth.[114,115] Biological function of VEGF is mediated via its high-affinity tyrosine kinase receptors; and both (VEGF and its receptors) are expressed not only in vascular tissue, but also in capillary-rich areas of neurons and astrocytes.[114] Experimental data have shown that VEGF and its receptors are upregulated in both neurones and blood vessels in the penumbra after transient or permanent occlusion of the middle cerebral artery.[116] A trophic role of VEGF on neurons has been demonstrated in angiogenesis, neurogenesis, cell survival, and neuronal migration. Thus, under hypoxic and ischemic conditions, VEGF may directly (via inhibition of programmed cell death) or indirectly (via stimulation of angiogenesis, enhancement of blood flow and endothelial permeability, and antioxidant activation) mediate neuroprotective and neuroregenerative effects on neurons.[114,117]

Slevin et al.[118] performed serial measurements of serum VEGF levels (measured on days 0, 1, 3, 7, and 14) in 29 patients with acute ischemic stroke and examined their relationship to stroke subtype and lesion volume. The highest expression of VEGF occurred at day 7 (588 ± 121 pg/mL; $p = 0.005$), and the levels remained significantly elevated at 14 days after stroke. Expression of VEGF correlated with infarct volume, clinical disability (Scandinavian Stroke Scale), and peripheral leukocytosis, and was significantly greater in patients with atherothrombotic large-vessel disease ($p < 0.05$).[118] Subsequently, Lee et al.[119] investigated whether serum VEGF levels in patients with acute ischemic stroke ($n = 188$) with small-vessel disease ($n = 89$; mean age, 63 years; 46% men) and with large-vessel disease ($n = 91$; mean age, 61 years; 47% men) would correlate with long-term prognosis based on the NIHSS scale measured at 24 hours after admission and at 3 months of follow-up. Serum VEGF levels measured within 24 hours of stroke onset were significantly greater in patients with large-vessel disease compared with those with small-vessel infarct. In analysis adjusted for vascular risk factors, higher VEGF levels were correlated with infarct volume ($p = 0.047$). Higher serum VEGF levels in the acute stage were also proportional to an improved NIHSS scale score after 3 months (adjusted OR, 1.57; $p = 0.034$).[119] Interestingly, in a small hospital-based study of 44 patients with suspected ischemic stroke, serum VEGF levels measured on admission and daily for six subsequent days demonstrated a significant increase in VEGF level on the day of symptom onset and at all other time points

when compared with healthy control subjects ($p < 0.01$). However, VEGF levels were also elevated in patients with stroke mimics. Therefore, the sensitivity and specificity for diagnosing ischemic stroke with elevated VEGF levels in acute settings was low: 69% and 73%, respectively.[120]

Although circulating VEGF levels are highly heritable,[121] elevated circulating VEGF concentrations were also seen in patients with hypertension, coronary artery disease, type 2 diabetes mellitus, smoking, and obesity.[122] In 3440 stroke-/TIA-free Framingham Heart Study participants (mean age, 65 ± 11 years; 56% women), baseline serum VEGF levels were related to risk of incident stroke/TIA. In analysis adjusted for traditional stroke risk factors, higher serum VEGF levels were associated with an increased risk of stroke/TIA (HR, 1.21/SD increase in VEGF; 95% CI, 1.04–1.40, $p = 0.012$) or stroke alone (HR, 1.23/SD; 95% CI, 1.05–1.46; $p = 0.013$). As mentioned previously for BDNF, the same study observed that BDNF and VEGF levels alone and in combination, when added to a risk assessment model based on traditional stroke risk factors alone (as identified by the Framingham Stroke Risk Profile), resulted in significant improvement of risk prediction (NRI for BDNF Q1 vs. Q2–4, 0.199; 95% CI, 0.023–0.384; NRI for VEGF, 0.234; 95% CI, 0.067–0.401; and NRI for BDNF + VEGF, 0.274; 95% CI, 0.090–0.449).[109] Based on these findings, VEGF along with BDNF represents novel a risk marker that may improve stratification of patients at risk for stroke/TIA; however, further studies are required to support more widespread clinical use of VEGF levels.

Insulin-like Growth Factor 1

Insulin-like growth factor 1 (IGF-1) is a single-chain polypeptide that has structural similarity to proinsulin. It has short-term metabolic and long-term growth factorlike effects on proliferation and differentiation of endothelial cells, neurons, and glial cells during embryonic and postnatal cell development.[123] In plasma and tissue, IGFs are known to associate with specific binding proteins (IGFBPs1–6). The IGFBPs, and in particular IGFBP-3, are known to regulate the bioactivity and release of IGF-1, but also its high affinity to IGF-1 receptor, which is present on practically every cell type.[124] IGF-1 is widely expressed in the brain and it is recognized as a survival factor for both sensory and motor neurons. IGF-1 also modulates brain plasticity by influencing neurite outgrowth, synaptogenesis, neuronal excitability, and neurotransmitter release, and may influence recovery from ischemic brain injury.[125]

Most of the circulating IGF-1 is found in a 150-kDa complex with IGFBP-3. IGF-1 levels in the blood have a wide normal range from 10 to 1000 ng/mL. IGF-1 levels decrease with age, but also with decline in physical functioning, and in persons with atherosclerosis and type 2 diabetes.[126]

Several epidemiological studies have suggested an inverse relationship between plasma IGF-1 levels and risk of stroke. In a prospective, nested case–control study within a Danish follow-up study ("Diet, Cancer, Health") including 57,053 women and men (mean age, 60 years; 61% men), Johnsen et al.[127] examined baseline circulating IGF-1 (mean, 107.1 μg/L) and IGFBP-3 (mean, 3966 μg/L) levels and their association with incident ischemic stroke. During a median follow-up of 3.1 years, there were 266 participants who developed ischemic stroke. When compared with the top two quartiles, participants in the bottom two quartiles of IGF-1 and IGFBP-3 levels were found to have increased risk of ischemic stroke (adjusted OR, 2.06; 95% CI, 1.05–4.03; and OR, 2.29; 95% CI, 1.17–4.49, respectively).[127]

In a case–cohort analysis of older adults (mean age, 73 years) in the Cardiovascular Health Study, during a mean follow-up of 5.6 years, 370 participants experienced incident ischemic stroke, but the authors found no association between circulating levels of IGF-1 and risk of incident ischemic stroke, whereas low IGFBP-3 levels were associated with increased risk of incident coronary events ($p = 0.05$). Although limited by different study designs, it is unclear whether the observed discrepancies in study results could be the result of an effect modification by age of the association between IGF-1 and IGFBP-3 levels and ischemic stroke.[128]

A small case–control study of elderly subjects (mean age, 83 ± 7.4 years; 34% men) admitted with acute ischemic stroke to a geriatric unit found that older subjects with stroke had lower IGF-1 and IGFBP-3 levels then their age- and sex-matched control subjects. The elderly patients with ischemic stroke and lower IGF-1 levels were observed to have poor outcomes (HR for death at 6 months for each 20-ng/mL increase in IGF-1 levels was 0.7; 95% CI, 0.5–0.9).[129]

Recent observations from the Rotterdam study indicated that such associations could be causative. van Rijn et al.[130] examined the relationship between the presence of a 192-bp allele in the IGF-1 promoter region and survival after stroke. They found that noncarriers who also had low plasma IGF-1 levels were at greater mortality risk after stroke compared with gene carriers. Noncarriers had an RR of 0.7 (95% CI, 0.5–1.0) for ischemic stroke, and the RR of death after an ischemic stroke was 1.5 (95% CI, 0.9–2.6).[130]

Interestingly, intravenous tPA treatment in the patients with stroke was shown to increase free serum IGF-1 levels transiently by almost 70%, suggesting that a neuroprotective effect of tPA may be based in part on a neuroprotective effect of IGF-1.[131] Multiple experimental studies of different models of hypoxic or ischemic brain injury have shown a neuroprotective role for IGF-1. Several experimental studies evaluated the effect of exogenous IGF-1 after induction of transient or permanent middle cerebral artery occlusion at 60 minutes or 120 minutes in animal models of stroke. Mode of administration of IGF-1 was different across the studies—from topical IGF-1 applied at the cerebral cortex to intracerebroventricular and intranasal to intravenous. However, all the studies found that, if given within 1 hour or multiple times within 24 hours, the animals receiving IGF-1 had reduced infarct volumes, increased cell survival, improved functional outcomes, and enhanced neurogenesis and neovascularization.[132] Despite such convincing findings on its neuroprotective effect, the role of IGF-1 in humans needs to be further clarified prior to its testing in clinical trials. Clearly, IGF-1 shows a promising role in modifying ischemic stroke pathophysiology, but more studies are needed for a better understanding of the role of IGF-1 in risk stratification and stroke outcomes.

Growth Differentiation Factor 15

Growth differentiation factor 15 (GDF-15) is a novel, distant member of the transforming growth factor-β superfamily that is activated in acute-phase responses through a currently unknown receptor. Experimental studies have demonstrated upregulated expression of GDF-15 in atherosclerosis, and have noted that GDF-15 deletion has beneficial effects in early and later atherosclerosis.[133] GDF-15 is widely distributed in the brain and peripheral nervous system.[134] In a mouse model of cerebral ischemia, GDF-15 was highly upregulated after experimental ischemic brain injury.[135]

Worthmann et al.[136] explored an association between circulating levels of GDF-15 and neurological outcome (measured by the mRS) in patients with acute ischemic stroke or TIA. Serial blood samples were measured between 6 hours and 7 days after symptom onset in 57 consecutive patients with acute ischemic stroke ($n = 51$) or TIA ($n = 6$). Six hours after symptom onset, GDF-15 levels were abnormally high (>1200 ng/L) in 68% of the patients, but over the course of 7 days, the levels declined by 8% ($p < 0.001$). Patients with stroke and an mRS score of more than 1 point at 7 days or 90 days had higher circulating levels of GDF-15 at all time points compared with patients with an mRS score of 0 point or 1 point ($p \leq 0.002$). In adjusted analysis, GDF-15 levels measured between 6 hours and 7 days after symptom onset were associated with the mRS at 7 days and 90 days such that patients with higher levels of GDF-15 had poorer functional outcomes.[136]

In a larger sample of 264 patients with acute ischemic stroke (mean age, 70.3 ± 12.7 years; 55.3% male) serum GDF-15 levels were measured at 6 hours and 24 hours of symptom onset to examine its association with functional outcomes measured by the mRS. In adjusted analysis, serum GDF-15 levels were associated independently with an mRS score of ≥2 points after day 90 (OR, 1.03; 95% CI,

1.01–1.05, $p = 0.011$). GDF-15 levels increased with higher NIHSS tertiles ($p = 0.005$). More important, an addition of GDF-15 levels to stroke severity scores (NIHSS) in predicting functional outcomes at 90 days improved the model with modest effect (NRI, 0.044; $p = 0.541$).[137]

Thus far, GDF-15 is emerging as an important prognostic marker in individuals with and without existing cardiovascular disease. In a study of determinants of GDF-15 concentrations that included participants in the Framingham Offspring Study and participants in the Prospective Investigation of the Vasculature in Uppsala Seniors study, GDF-15 was associated positively with age, smoking, antihypertensive treatment, diabetes, kidney function, and use of nonsteroidal anti-inflammatory drugs, but associated negatively with TC and HDL-C. This study suggested that, apart from cardiovascular risk factors, genetic factors might also play an important role in determining circulating GDF-15 concentrations.[138] So, GDF-15 is a promising novel biomarker, and its role in predicting stroke risk and stroke outcomes requires further study.

Brain Tissue-Specific Biomarkers

GLIAL BIOMARKERS OF STROKE

S-100 Beta Protein

S-100 beta protein (S-100B) is an astroglial calcium-mediated protein present in high concentrations in glial and Schwann cells.[139] S-100B is recognized as a marker of generalized blood–brain barrier dysfunction, but also as a biomarker of primary brain injury, including injury consequent to a stroke.[140] S-100B is released into the CSF after neuronal damage. Its concentration in the CSF is much higher than in serum, but because of its excellent stability, serum S-100B protein levels have been studied in experimental and clinical stroke studies.[139]

In studies of experimental stroke, S-100B protein was found to be an excellent surrogate for estimating stroke volume, stroke severity, and long-term neurological outcome, as well as response to thrombolysis.[141,142] Studies demonstrated that serum S-100B concentrations increased significantly after stroke, with peak concentrations occurring within the first 24 hours after cerebral infarction, and subsequent normalization within 48 hours.[143] Missler et al.[144] measured plasma concentrations of S-100B protein on admission, and on days 3, 4, 7, and 14 in 44 patients with acute stroke (mean age, 65.1 years). S-100B protein was found to be a useful indicator of acute lesion volume on CT scan, as well as a marker of prognosis based on the Glasgow Outcome Scale 6 months after the acute event.[144] The National Institute of Neurological Disorders and Stroke (NINDS) tPA Study Group also confirmed association of higher initial S-100B levels with initial stroke severity and larger CT stroke lesion volumes. Higher 24-hour peak concentrations of S-100B were associated with higher NIHSS scores ($r = 0.263$, $p < 0.0001$) and with larger CT lesion volumes ($r = 0.239$, $p < 0.0001$). However, this group did not find an association with functional outcomes.[145]

Subsequent acute stroke studies observed that S-100B might be a useful surrogate of long-term stroke outcomes.[146,147] Foerch et al. measured S-100B concentrations at hospital admission and at 24, 48, 72, 96, 120, and 144 hours after stroke, and assessed functional outcome 6 months after stroke (using the mRS) in 39 patients (mean age, 69.1 years) with acute nonlacunar middle cerebral artery infarction presenting less than 6 hours after symptom onset. They found that a single S-100B value obtained between 48 hours and 72 hours after stroke onset was the best predictor of infarct volume and subsequent functional outcome.

However, elevated S-100B concentrations in the blood are not specific to cerebral infarcts alone. S-100B is also elevated after traumatic brain injury and in extracranial malignancies. More important, S-100B does not differentiate between ischemic and hemorrhagic stroke, and stroke mimics.[148] Thus, its use in clinical practice, although most promising for prognostication of stroke outcomes, remains to be determined in representative large-scale studies.

Glial Fibrillary Acidic Protein

Glial fibrillary acid protein (GFAP) is a monomeric filament protein specific to the brain astrocytes. Studies demonstrate increased serum GFAP concentrations in ischemic stroke patients versus control subjects, with peak concentrations occurring 2 to 4 days after acute symptom onset.[149,150] Herrmann et al.[150] performed a comparative analysis of serum concentrations of GFAP and protein S-100B in patients with acute stroke ($n = 37$) and suggested that postischemic release patterns of GFAP and S-100B protein may help understand the underlying pathophysiology of acute cerebral infarcts. The release of both astroglia-derived proteins varied between different subtypes of stroke such that GFAP was found to be a more sensitive marker of brain damage in patients with smaller lacunar lesions or minor strokes.[150]

In a pilot study assessing 135 stroke patients admitted within 6 hours after symptom onset, Foerch et al.[151] examined whether serum GFAP might help identify intracerebral hemorrhage (ICH) in patients with acute stroke. GFAP was detectable in the serum of 39 patients (34 of 42 [81%] with ICH, and 5 of 93 [5%] with ischemic stroke]. Serum GFAP was higher in patients with ICH (median, 11 ng/L; range, 0–3096 ng/L) compared with patients with ischemic stroke (median, 0 ng/L; range 0–14 ng/L; $p < 0.001$).[151] In a subsequent study, the authors observed that, for the first 24 hours after stroke, median GFAP values in patients with ischemic stroke remained below the detection limit, whereas between 2 hours and 6 hours of stroke onset, serum GFAP was significantly greater in patients with ICH compared with patients with ischemic stroke ($p < 0.001$). More important, 2 hours after stroke onset, serum GFAP values were correlated significantly with ICH volume ($r = 0.755$, $p = 0.007$).[152] Based on these findings, Foerch et al.[153] examined more recently the diagnostic accuracy of plasma GFAP for differentiating ICH versus ischemic stroke in patients with symptoms of acute stroke when a blood sample was collected within 4.5 hours of symptoms onset. They found that (a) GFAP concentrations were increased in patients with ICH compared with patients with ischemic stroke (median, 1.91 mug/L; interquartile range, 0.41–17.66 vs. median, 0.08 mug/L; interquartile range, 0.02–0.14; $p < 0.001$), (b) diagnostic accuracy of GFAP for differentiating ICH from ischemic stroke and stroke mimic was high (area under the curve, 0.915; 95% CI, 0.847–0.982; $p < 0.001$) and (c) a GFAP cutoff of 0.29 mug/L provided a diagnostic sensitivity of 84.2% and a diagnostic specificity of 96.3% for differentiating ICH from ischemic stroke and stroke mimics.[153,154]

The enzyme immunoassays currently available for GFAP measurements are not standardized. Therefore, more data are needed for this promising biomarker that might have a role in early stroke differential diagnosis.

Miscellaneous Biomarkers

PARK7 and Nucleoside Diphosphate Kinase A

PARK7 (also called *DJ-1*) is a multifunction protein that plays a key role in transcriptional regulation and is a molecular chaperone. PARK7 has antioxidative stress and antiapoptotic properties and is highly expressed in reactive central nervous system astrocytes in persons with chronic neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. Studies have also shown strong immunoreactivity for DJ-1 within reactive astrocytes surrounding incidentally identified infarcts in patients with these neurodegenerative disorders.[155]

Nucleoside diphosphate kinases are ubiquitous and highly conserved enzymes crucial for the cellular homoeostasis of NTPs and nucleoside diphosphates. Nucleoside diphosphate kinase A (NDKA) is expressed in neurons and was found be involved in the ischemic cascade after acute stroke.

Allard et al.[156] recently demonstrated higher plasma PARK7 concentrations in stroke patients compared with control subjects ($p < 0.001$). They used enzyme-linked immunosorbent assay to measure PARK7 and NDKA in plasma in three independent European and North American

retrospective studies with a total of 622 stroke patients and 165 control subjects. Increases in both biomarkers were significant, with sensitivities of 54% to 91% for PARK7 and 70% to 90% for NDKA, and specificities of 80% to 97% for PARK7 and 90% to 97% for NDKA. The concentrations of both biomarkers increased within 3 hours of stroke onset.[156] However, PARK7—alone or in combination with NDKA—could not differentiate patients with ischemic stroke from patients with hemorrhagic stroke. Further studies are needed to replicate these findings and clarify the utility of this biomarker.

NMDA RECEPTOR PEPTIDES AND ANTIBODIES

NMDA receptors are major excitatory neuroreceptors that regulate neuronal electrical signals. These receptors are located on the surface of cerebral microvessels and are upregulated by oxidative stress states.[157] NR2 peptide fragments are cleaved rapidly from the NMDA receptors by thrombin-activated serine proteases in acute cerebral ischemic injury.[158] Released into the bloodstream within minutes of onset of acute ischemia via the compromised blood–brain barrier, NR2 peptides remain detectable in the blood for at least 3 days after an event.[159]

In early clinical studies, of 105 patients with stroke or TIA and 255 control subjects NR2 antibodies were identified in significantly greater quantities in the patients with ischemic stroke and TIA compared with control subjects ($p < 0.0001$). At a cutoff point of 2.0 μg/L, test sensitivities for TIA and stroke were 95% and 97%, respectively, and positive predictive values were 86% and 91% for TIA or stroke within 3 hours of symptom onset. However, the assay could not differentiate between hemorrhagic and ischemic stroke in an acute setting, but only after 3 days.[160] Dambinova et al.[159] explored the value of NR2 antibodies in differentiating ischemic stroke from stroke mimics. A total of 192 patients with suspected stroke who presented within 72 hours of symptom onset were enrolled prospectively; clinical diagnosis of ischemic stroke was made in 101 of 192 persons (53%), with a diagnosis of no stroke in 91 subjects (47%). The comparison of NR2 peptide value changed in patients with acute ischemic stroke, and control groups (healthy individuals and persons with well-controlled vascular risk factors) yielded a statistically significant ($p < 0.0001$) increase of NR2 peptide values in persons with acute ischemic stroke. When the NR2 antibody cutoff was set at 1.0 μg/L, this resulted in a sensitivity of 92% and a specificity of 96% to detect ischemic stroke. However, some healthy individuals showed an increase in their NR2 peptide of 1.10 to 1.15 μg/mL.[159] NMDA receptor assays, especially assays measuring NR2 peptide, which is released early into the blood stream after acute ischemic cerebral injury, may prove to be valuable biomarkers to differentiate acute strokes from stroke mimics, but larger scale prospective studies are needed to determine their clinical value.

Multimarker Models

As demonstrated, the literature suggests that several serum biomarkers may be potential predictors for stroke risk stratification, stroke diagnosis, stroke subtype differentiation, or stroke outcome, but currently there are no known individual biomarkers that can be used routinely in these clinical settings.

Most of these biomarkers add only modestly to already existing predictive models; thus, novel techniques such as multimarker approaches to investigate the utility of existing biomarkers have been proposed for better prognostication. To be efficacious, multimarker panels must offer additive information for clinical diagnosis, must be inexpensive, and must be easy to use. They should improve the predictive accuracy of the best available model (representing the standard of care) that also incorporates several known predictors of disease including standard vascular risk factors and biomarkers.[161]

TABLE 22.1

Serum Biomarkers for Ischemic Stroke

Biomarker	Role in stroke pathogenesis	Studied in screening of patients at risk for stroke	Studied in diagnosing acute stroke	Studied in prognostication of stroke outcomes	Studied in clinical trials
Arterial susceptibility					
Endothelial dysfunction homocysteine ADMA	Endothelial apoptosis Oxidative stress Inflammation Neuronal injury Endothelial dysfunction Oxidative stress Inflammation Atherosclerotic processes	+ +			+
Inflammation C-reactive protein Lp-PLA2	Inflammation Atherosclerotic processes Inflammation	+ +		+	+
Atherosclerotic processes TC HDL-C TC/HDL-C ratio Triglycerides LDL-C Lp(a)	All markers Formation of atherosclerotic plaque	+ + + + + +			+
Cardiac dysfunction BNP	Hemodynamic stress Cardiomyocyte damage	+		+	
Cell destruction MMP-9	Inflammation Degradation of EMPs Angiogenesis		+	+	+
Blood susceptibility					
Hypercoagulability Fibrinogen D-Dimer	Impaired hemostasis Increase blood viscosity	+ +			+
Fibrinolysis Dysfunction PAI-1	Decreased fibrinolysis	+			
Growth factors					
BDNF VEGF IGF-1 GDF-15	Neuroprotection Angiogenesis Neuroprotection Atherosclerosis	+ + + +	+ + +	+ + +	

(*continued*)

TABLE 22.1

Continued

Biomarker	Role in stroke pathogenesis	Studied in screening of patients at risk for stroke	Studied in diagnosing acute stroke	Studied in prognostication of stroke outcomes	Studied in clinical trials
Brain susceptibility					
S-100B	Glial damage	+	+	+	
GFAP	Glial damage		+	+	
Miscellaneous markers					
PARK7	Oxidative stress Apoptosis		+		
NDKA	Cellular homeostasis		+		
NMDA receptors	Cell damage		+		

ADMA, asymmetric dimethylarginine; BDNF, brain-derived neurotrophic factor; BNP, brain natriuretic peptide; EMP, Endothelial Microparticle Levels; GDF-15, growth differentiation factor 15; GFAP, glial fibrillary acid protein; HDL-C, high-density lipoprotein–cholesterol; IGF, insulinlike growth factor; LDL-C, low-density lipoprotein–cholesterol; Lp(a), lipoprotein a; Lp-PLA2, lipoprotein-associated phospholipase A2; MMP-9, matrix metalloproteinase 9; NDKA, nucleoside diphosphate kinase A; NMDA, N-methyl-D-aspartate; PARK7, Parkinson Protein 7; S-100B, S-100 beta protein; TC, total cholesterol; VEGF, vascular endothelial growth factor.

The simultaneous association of a biologically plausible panel of biomarkers with stroke/TIA risk was recently examined among 3127 stroke-free Framingham offspring participants (age, 59 ± 10 years; 54% women) as discussed earlier in the section on BNP. A panel of eight biomarkers assessing inflammation (hsCRP), hemostasis (D-dimer and plasminogen activator inhibitor 1), neurohormonal activity (aldosterone-to-renin ratio, BNP, and NTP natriuretic peptides), and endothelial function (tHcy and urinary albumin-to-creatinine ratio) was measured and, in multivariable regression analysis, was examined against the risk of stroke/TIA. During a median follow-up of 9.2 years, 130 participants experienced incident stroke/TIA. The biomarker panel was associated with incident stroke/TIA ($p < 0.05$). As mentioned earlier, in stepwise backward elimination analyses, higher BNP (HR, 1.39/per 1-SD increment; $p = 0.002$) and urinary albumin-to-creatinine ratio (HR, 1.31/1-SD increment; $p = 0.004$) were associated with increased risk of stroke/TIA; but, more important, both biomarkers improved risk prediction compared with the Framingham Stroke Risk Profile alone (NRI, 0.109; $p = 0.04$).[76] Other statistical techniques such as machine learning are also being applied to identify a parsimonious set of biomarkers that best predict risk of stroke and outcomes after stroke.

Whether serum biomarkers might provide useful information to improve the prediction of outcome after acute ischemic stroke is unclear. Whiteley et al.,[162] in a systematic literature analysis, observed that no study was able to demonstrate that the biomarkers added predictive power to a validated clinical model. Frequent shortcomings of the reviewed studies were small study size, poor selection of the control population, unclear diagnostic cut points, lack of clinical validation of the proposed biomarkers, and choice of reference standard based on inadequate data. Laskowitz et al.,[163] in the Biomarker Rapid Assessment in Ischemic Injury study, examined a panel of biomarkers including D-dimer, CRP, BNP, MMP-9, and S-100B in a total of 1146 patients presenting with neurological symptoms consistent with possible stroke who were enrolled prospectively at 17 different sites. A separate cohort of 343 patients was enrolled independently to validate the multiple biomarker model approach. The multivariate model demonstrated modest discrimination, with an area under the receiver–operating characteristic curve of 0.76 for hemorrhagic stroke and 0.69 for all stroke ($p < 0.001$). When the threshold for the logistic model was set at the first quartile of the markers, this

resulted in a sensitivity of 86% for detecting all stroke and a sensitivity of 94% for detecting hemorrhagic stroke, and a specificity to distinguish between stroke and stroke mimics was 37%. Thus, this set of biomarkers was not an optimal panel.[163]

More recently, the Prospective Epidemiological Study on Myocardial Infarction evaluated 14 biomarkers simultaneously from distinct biological pathways for risk prediction of ischemic stroke, including biomarkers of hemostasis, inflammation, and endothelial activation, chemokines, and adipocytokines. The Prospective Epidemiological Study on Myocardial Infarction had a cohort of 9771 healthy men 50 to 59 years of age who were monitored for 10 years for cardiovascular events. In a nested case–control study, 95 patients with ischemic stroke were matched with 190 control subjects. Of those, the authors evaluated the effect of 14 biomarkers on risk of ischemic stroke. In the multivariable analysis adjusted for traditional risk factors, fibrinogen (OR, 1.53; 95% CI, 1.03–2.28), E-selectin (OR, 1.76; 95% CI, 1.06–2.93), interferon-γ-inducible-protein 10 (OR, 1.72; 95% CI, 1.06–2.78), resistin (OR, 2.86; 95% CI, 1.30–6.27), and total adiponectin (OR, 1.82; 95% CI, 1.04–3.19) were associated significantly with ischemic stroke. However, adding E-selectin and resistin to a traditional risk factor model yielded a significant categorical net reclassification improvement of 29.9% ($p = 0.001$) and 28.4% ($p = 0.002$), respectively. Simultaneous inclusion of E-selectin and resistin to the traditional risk factor model increased the area under the receiver–operating characteristic curve to 0.824 (95% CI, 0.770–0.877) and resulted in a net reclassification improvement of 41.4% ($p < 0.001$).[164]

Although there is considerable potential for a panel of biologically plausible biomarkers within a multimarker panel to improve risk stratification and facilitate the initial triage process in acute stroke care, more work is required before such biomarkers can be introduced into routine clinical practice.

Omics Approach

Translational research in stroke holds promising potential because cerebrovascular disease is a complex disorder that manifests by multiple cell–cell interactions in the brain, but also by multiorgan interactions. An omic approach offers the use of targeted, high-throughput large-scale analysis of biological samples (blood, cells, tissue) with the most developed technologies being applied to genomics and proteomics discoveries in stroke research.[165] Omic approaches that are using genes, proteins, and metabolites as potential biomarkers in risk stratification, prediction, and diagnosis of stroke have been criticized for their poor reproducibility and labor-intense methodology that, as a result of large data sets, could produce "noise."[166] Therefore, the future of the omic approach will likely be based on a more meaningful understanding of gene expression achieved through the characterization of the products of that expression, such as RNAs and their regulation (messenger RNA and microRNA), and their respective proteins, which are the essential biological determinants of disease phenotype. Interestingly, the field of biomarkers has recently been enlarged by the availability of array technology to assess messenger RNA, microRNAs, and other newly discovered RNA species.[165] Several experimental and human studies have reported how altered profiles of RNA expression could explain various stroke pathophysiologies.[167,168] Although RNA is induced in minutes and well before a stroke event could be detected using protein markers, at the same time, RNA is unstable and degrades rapidly unless stabilized. As suggested by Sharp et al., developing point-of-care PCR may resolve this problem, but the omic approach is still far from ready for wide use in clinical practice.

System Biology Approach

A system biology approach to biomarker discovery consists of placing biomarkers from plausible pathways discovered with previous experimental analysis in the context of a network of biological

interactions, such as gene–gene, gene–protein, or protein–protein interactions, followed by different guilt-by-association analyses.[169] The biological networks are designed from previously published interactions or from computational prediction models by a freely available network visualization tool for integrating biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework, such as Cytoscape Web.[170]

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23

SECULAR TRENDS IN STROKE RISK AND RISK FACTORS FOR STROKE

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Introduction

The study of secular trends in stroke and stroke risk factors is important (a) to describe the natural history and to quantify the projected burden of disease; (b) to track the progression of known risk factors and identify high-risk populations[1]; (c) to recognize the effect of multiple influences such as the changing demographic characteristics of populations, the development of improved diagnostic techniques and methods, changes in definitions and classifications of disease, as well as the effectiveness of primary and secondary prevention measures and, to a lesser degree, acute stroke therapies; and (d) to provide a basis for evidence-based healthcare planning and direction to public policy and research funding allocation, which are especially relevant as governments and government agencies struggle with economic and political uncertainties and limited resources.[2] The information gathered from studies looking at trends can determine or guide the optimal allocation of resources and impact the burden of disease to a greater extent than any single therapy.

Despite the known limitations and heterogeneity of epidemiological studies such as differences in methods of ascertainment, demographic and geographic variations, differing starting time points and time frames covered, and varying analyses used, epidemiological studies—including cross-sectional studies, but longitudinal cohort studies in particular—are the best methods to study trends because of their long-term follow-up and ability to capture trends over multiple epochs, and their well-established and standardized methods of follow up. Many large cohort studies[3–5] such as the Framingham Heart Study (FHS), Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), Atherosclerosis Risk in Communities study, Northern Manhattan Study (NOMAS), Cardiovascular Health Study (CHS) in the United States, and the Oxford Vascular Study (OXVASC) in the United Kingdom; registries such as the World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease[6]; and land surveys such as the National Health and

Nutrition Examination Survey (NHANES), among others, have provided and continue to provide important epidemiological information that tracks the incidence, prevalence, severity, mortality, and various other aspects of stroke and stroke risk factors, and provide compelling data that contribute to our understanding of factors influencing the public health burden of stroke and also helps to generate hypotheses, and allows investigation into novel risk factors and assessment of management practices and therapies.

Trends in Prevalence

Given the aging population of the United States and many European industrialized countries, and the improving mortality and 30-day case fatality rates of stroke, particularly ischemic stroke, the prevalence of stroke is expected to increase substantially during the next two decades. Current estimates from the National Health and Nutrition Examination Survey/National Center for Health Statistics (NHANES/NCHS) surveys are that there are 6.8 million Americans with a history of stroke, with an overall prevalence of 2.8%. There is a higher prevalence reported in Native Americans/Alaskans at 5.8%, mixed or other races at 4%, blacks at 3.8%, whites at 3% versus Asian/Pacific Islanders at 1.9% and Hispanics at 1.8% in the Behavioral Risk Factor Surveillance Survey.[5] With the development of better imaging technology, the prevalence of silent ischemic infarcts has also been estimated at 6% to 28% and has been noted to be increasing with age.

A study[7] describing trends in prevalence in the United States between 1973 and 1991 reported an increase in age, race, and sex-adjusted prevalence from 1.41% to 1.87% with an average increase of 7.5% over each 5-year period within these 20 years. However, much of this increase in prevalence was attributable to the aging population. The Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report* describing trends from 2006 to 2010 report an age-adjusted prevalence of stroke of 2.7% in 2006 and 2.6% in 2010. There was a greater prevalence in persons 65 years or older, in Native American and Alaskan natives, and in adults with a lower level of education.[8] Projections to 2030 are that there will be an additional 3.4 million people who will have had a stroke, or an increase of 20.5% in prevalence from 2012.

There was regional variation in prevalence in 2006 ranging from 1.8% in Colorado, Massachusetts, North Dakota, and Vermont to 4.4% in Alabama. In 2010, age-adjusted stroke prevalence ranged from 1.5% in Connecticut to 4.1% in Alabama. From 2006 to 2010, prevalence rates were stable, with only two states having a significant decline: Georgia, from 3.3% to 2.8% (p for trend < 0.01); and South Dakota, from 2.2% to 1.8% (p for trend = 0.04). In 2010, the states with higher stroke prevalence in general were states in the southeastern United States (the so called *stroke belt*, discussed later in the chapter) and Nevada.

A review[9] of nine population-based studies from different countries reports age-standardized prevalence for people aged 65 years or older ranging from 46.1 to 73.3/1000 population. Overall, there was no significant difference in age-standardized prevalence between selected populations in people aged 65 years or more, except in L'Aquila, Italy, and Newcastle, UK, which reported higher prevalences than the other studies.

Analysis of data from the Global Burden of Disease injuries and risk factors study[10] reflect a worldwide prevalence of 33 million in 2010, of which 30% were in those 75 years and older, and of which 52% came from low- to middle-income countries. Prevalence increased significantly with age in all regions, with the most striking increases in prevalence seen in those 75 years old and older, and a steeper increase in prevalence was noted in high-income countries. Stroke prevalence increased significantly (by 27%) in high-income countries but insignificantly (by 8.5%) in low- to middle-income countries from 1990 to 2010.

Prevalence is projected to increase as the demographic characteristics shift to a more elderly population with better survival. Regional and racial differences should concentrate efforts on the southeastern United States and high-risk populations such as blacks, Native Americans, and Hispanics. Global goals should include improving preventive strategies and risk factor prevalence in low- to middle-income countries.

Trends in Incidence

The incidence of stroke increases with age, and one study of populations of European descent found a 9% to 10% increase in relative risk (RR) of stroke with each year in an adult cohort of 93,695 persons aged 19 to 77 years.[11] Age figures prominently in all stroke risk profile scores such as the Framingham Risk Score, and others developed from the CHS, and the Systematic COronary Risk Evaluation (SCORE) risk from the World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease project, and it is the most important nonmodifiable risk factor when determining temporal trends because it is a dynamic risk factor that wields its influence on incidence as populations get older, and needs to be adjusted for.

Current estimates from the 2014 American Heart Association statistical updates report, which are extrapolations of incidence estimates from the FHS, the Atherosclerosis Risk in Communities study, the CHS, and the GCNKSS, indicate that each year 795,000 people experience a new or recurrent stroke, which translates to someone having a stroke every 40 seconds in the United States.[5] Of these, 610,000 are first attacks and 185,000 are recurrent attacks. The distribution of stroke subtypes is 87% ischemic, 10% intracerebral hemorrhage (ICH), and 3% subarachnoid hemorrhage (SAH).[5] These estimates have remained fairly stable during the past decade.

Longer term secular trends, however, show that the age-adjusted incidence of stroke has been declining during the last 30 to 50 years in the United States. In Rochester, Minnesota,[12] between 1945 to 1949 and 1975 to 1979, the average annual incidence of stroke declined by 45%, from 209/100,000 population to 115/100,000. The FHS indicated that stroke incidence declined over time in its predominantly white cohort over three epochs that were chosen to mark the onset of widespread use of computed tomographic scanning and magnetic resonance imaging (MRI). Data from 1950 to 1977, 1978 to 1989, and 1990 to 2004 showed that age-adjusted incidence of first stroke per 1000 person-years during each of the three periods was 7.6, 6.2, and 5.3 in men, and 6.2, 5.8, and 5.1 in women, respectively.[13] Numerous studies from Europe and Asia report similar trends in stroke incidence, including studies from China,[14] Denmark,[15] Australia,[16] Japan,[17–19] Finland,[20,21] England,[22] New Zealand,[23] and France[24] reporting either decreasing or stable incidences that are attributed to better treatment of risk factors. A study[25] from Japan suggested a plateau of decline in incidence from 1990 to 2001. In 2010, the worldwide estimate was that there were 16.9 million cases of incident stroke, of which 69% were seen in low- to middle-income countries.[10] There was also an alarming trend of increasing age-standardized incidence in young adults overall, especially in low- to middle-income countries, although not yet significant. Although the mean age of people with stroke is increasing in all countries, the proportion of people younger than 65 years is substantial and is increasing, particularly in the low- to middle-income countries.[10] The current ongoing epidemic of diabetes and increasing prevalence of certain risk factors in young adults, particularly in low- to middle-income countries, constitutes another area of substantial stroke burden globally in addition to the aging population, and requires close surveillance and aggressive strategies for prevention.

There were significant racial differences in the trends of ischemic stroke incidence. In the national Reasons for Geographic and Racial Differences in Stroke[26] cohort, 27,744 participants were monitored for more than 4.4 years (2003–2010), and the overall sex and age-adjusted black/white incidence

rate ratio was 1.51. For ages 45 to 54 years, it was 4.02. For those older than 85 years, it was 0.86. Similar trends for a decreasing incidence rate ratio with increasing age were seen in the GCNKSS. The most recent GCNKSS data show that, compared with the 1990s, when stroke incidence rates were stable, stroke incidence in 2005 was decreased for whites, but unfortunately not in blacks.[27] This change was driven by a decrease in ischemic strokes in whites, but there were no changes in the incidence of ischemic strokes in blacks, or for hemorrhagic strokes in blacks or whites. There was also a disturbing trend toward increasing stroke incidence at younger ages, with the mean age at stroke decreasing significantly from 71.2 years to 69.2 years, as well as an increasing proportion of all strokes in those younger than 55 years, with an increase from 12.9% in 1993 to 1994 to 18.6% in 2005. Stroke incidence rates in those aged 20 to 54 years were significantly increasing in both blacks and whites.[28]

The Brain Attack Surveillance in Corpus Christi project demonstrated an increase in the incidence of stroke among Mexican Americans compared with non-Hispanic whites. The crude 3-year cumulative incidence (2000–2002) was 16.8/1000 versus 13.6/1000 in whites. Mexican Americans had a higher cumulative incidence for ischemic stroke at younger ages (45–59 years old: RR, 2.04; 60–74 years old: RR, 1.58), but not at older ages (>75 years old: RR, 1.12). Mexican Americans also had a higher incidence of ICH and SAH than non-Hispanic whites adjusted for age.[29]

The age-adjusted incidence of first ischemic stroke per 1000 was 0.88 for whites, 1.91 for blacks, and 1.49 in Hispanics in NOMAS. Among blacks compared with whites, the relative rate of intracranial atherosclerotic stroke was 5.85; of extracranial atherosclerotic stroke was 3.18; lacunar stroke, 3.09; and cardioembolic stroke, 1.58. Among Hispanics compared with whites, the relative rates for the same categories of stroke were 5.00, 1.71. 2.32, and 1.42 respectively.[30]

Of 4507 Native American participants in the Strong Heart Study in 1989 to 1992, the age-adjusted and sex-adjusted incidence of stroke through 2004 was 6.79/100 person-years, with 86% of incident strokes being ischemic.[31] Blacks, Mexican Americans, and Native Americans are at higher risk, because they have a higher age-adjusted incidence as well as younger age at time of first ischemic stroke.

There were significant gender differences in the secular trends of stroke incidence. Women have a lower age-adjusted stroke incidence than men, but this is modified by age. In the FHS, white women aged 45 to 84 years had a lower stroke risk than white men, but in those older than 85 years this was reversed, with women having an increased stroke risk compared with men.[13] A population-based study from Sweden found stroke incidence to be lower for women than men between ages 55 years and 64 years, but at 75 to 85 years the association reversed. Other studies report a persistent excess risk of stroke for men versus women throughout life, with a diminishment—but no reversal—of the RR.

The decreasing trends in stroke incidence are largely attributable to a decreased incidence of ischemic stroke. ICH, which constitutes 10% of all strokes, has not shown the same decrease. A meta-analysis[32] of 36 studies including 8145 subjects from multiple cohorts all over the world, including Europe, Asia, Australia, South America, and the United States, found no decrease in the incidence of ICH between 1980 and 2008, with an overall incidence of 24.6/100,000 years. Like ischemic stroke, there was a significant increase in incidence with age, but there were no gender differences. There were regional differences in trends; studies from the United Kingdom and Australia reported a decrease from the 1980s to 2001. The Oxfordshire study reported a decrease in incidence of hemorrhage associated with hypertension in those younger than 75 years, but an increase in incidence was associated with antithrombotic treatments in those older than 75 years. Studies from France and Finland reported stable incidences from the 1980 to 2000 and 1980s to 1990s, respectively. A study from Hong Kong noted a stable incidence of ICH but an increasing incidence of hemorrhagic stroke in the younger, 35 to 44–year-old age group, and an overall higher incidence of ICH compared with other countries.[33] Hospital admissions for ICH have increased by 18% during the last 10 years according to a review of published studies and data from clinical trials. This was thought to be secondary to the increase in number of elderly with poor blood pressure control and increasing

anticoagulant/antithrombotic use. Mexican, Latin, Native, and black Americans, as well as Chinese and Japanese people have higher incidences than whites. The GCNKSS reported the annual incidence of anticoagulation-associated ICH to be increased from 0.8 to 1.9 to 4.4/100,000 from 1988 to 1993 to 1999. Rates increased from 2.5 to 45.9/100,000 in those older than 80 years.[34]

There are significant differences in incidence between high-income countries versus low-income countries. A systematic review from 2009 analyzed data from population-based studies from 1970 to 2008 and reported a 42% decrease in stroke incidence in high-income countries and a greater than 100% increase in low- to middle-income countries during the past 40 years.[9] Corresponding trends in stroke incidence are observed in younger (<75 years) and older (≥75 years) age groups, although the differences are more pronounced in the older group. In 2000 to 2008, stroke incidence rates in low- to middle-income countries exceeded those in high-income countries by 23%. In high-income countries, there was a greater, albeit nonsignificant, reduction in the incidence of primary ICH compared with ischemic stroke, whereas the incidence of SAH has remained relatively stable during the past four decades. The incidence and proportional frequency of ICH and SAH in low- to middle-income countries are significantly greater than the incidence and frequency in high-income countries.[35] The recent report of the World Health Organization's Global Burden of Disease[10] project confirms that the age-standardized incidence of stroke has declined between 1990 to 2010 by 12% (95% confidence interval [CI], 6–17) in high-income countries, although it increased by 12% (95% CI, −3 to 22) in low-income and middle-income countries, albeit nonsignificantly. Mortality rates decreased significantly in both high income (37%; 95% CI, 31–41) and low-income and middle-income countries (20%; 95% CI, 15–30).

Overall, there has been a decrease in the incidence of stroke driven by a decrease in the incidence of ischemic stroke, which comprises the majority of all strokes, especially among white males. However, there is concern that this declining trend is not as robust in women and has leveled off in blacks. Furthermore, the incidence of hemorrhagic strokes, both cerebral hemorrhage and SAH, has not decreased. Demographic changes in the United States, with an increasing proportion of Hispanics, who have an overall higher risk for stroke, may also adversely affect these trends of declining stroke risk over time. Internationally, the lower income countries have higher and increasing incidences of stroke, and will shape worldwide trends, but we need to establish longitudinal cohort studies for better surveillance of trends in these countries.

Trends in Mortality

There has been a decrease in case fatality and mortality from stroke during the past 50 years. In 1931, stroke ranked second among all causes of death, with a rate of 195/100,000, and this mortality rate was stable until the 1960s. This was followed by a steady decline (−1.2/100,000), which became more rapid in the 1970s to 1980s (−3.3 to −5.6/100,000), but continued, albeit mildly, in the 1990s and moderately into the 2000s (−0.4 to −2.5/100,000). The result is a stroke mortality rate of 40.6/100,000 in 2008, which is an ~75% decrease from the 1930 to 1960 rates.[36] Temporal trends in stroke mortality have either remained stable or declined in most studies from the United States, Europe, Australia, and Japan. The decline in mortality has been attributed to both a decreasing case fatality and a decrease in stroke incidence.[13]

Stroke has now dropped to fourth in rank of all causes of death, behind heart disease, cancer, and chronic lower respiratory disease (CLRD), although part of this is artifactual because of the inclusion of deaths from pneumonia, influenza, and bronchitis as one category in the reclassification of CLRD, which resulted in a dramatic increase in CLRD deaths. The 2011 CDC statistics indicate[37] that, from 1998 to 2008, the annual stroke death rate decreased by 34.8% and the actual number of stroke deaths declined by 19.4%. Despite this decline, stroke continues to be a major cause of mortality, and the

2012 American Heart Association statistical update indicates that every 4 minutes someone dies of a stroke, with stroke accounting for ~1 in every 18 deaths in the United States in 2008. Approximately 54% of stroke deaths occurred outside the hospital in the same year.

Hemorrhagic stroke is more lethal than ischemic stroke. Among persons aged 45 to 64 years, 8% to 12% of ischemic strokes, but more than a third, or 37% to 38%, of hemorrhagic strokes resulted in death within 30 days according to 1987 to 2001 data.[38] In the CHS study from 1989 to 2000 of subjects who were older than 65 years, the 1-month case fatality was 12.6% for all strokes, only 8.1% for ischemic strokes, but 44.6% for hemorrhagic strokes. Hemorrhagic stroke mortality/case fatality has not declined.[39] There is a predilection for greater mortality in women and the elderly. A meta-analysis of 26 study populations reports a median case fatality of 40.4% at 1 month and 54.7% at 1 year, and noted that fatality was higher in women versus men and in those older than 75 years (28.1% vs. 17.8%).[32]

For SAH, the 30-day case fatality did not decline from 1981 to 1986 to 2002 to 2008, but overall mortality from SAH did decline by ~50% in the OXVASC study. After adjusting for age and baseline severity, the authors concluded that patients surviving to the hospital had reduced risk of death and dependency at 12 months during these two decades. A subsequent pooled analysis of 32 studies from 1980 to 2005, seven of which reported temporal trends, observed an unadjusted case fatality decrease of 0.9% per year.[35]

There are significant gender differences in stroke mortality trends, especially at older ages. The 2011 National Health Statistics office reported there were greater declines in stroke death rates in men than in women among people 65 years of age and older than in those who were younger. More women than men die from stroke each year. They accounted for 60.1% of stroke deaths in 2008. In 2002, death certificate data showed that the mean age at stroke death was 79.6 years; however, males had a younger age at stroke death than females, likely because the average age at first stroke is also lower in men.[40] The FHS data did not show a decline in 30-day mortality or case fatality in women—although it did overall—and in men, and this has been reported in other cohort studies from Europe and Japan as well.[13]

There are racial differences in mortality trends that are likely multifactorial in etiology, including a higher incidence of stroke in minorities, and disparities in socioeconomic status and care. These trends are reflected in the geographic disparities in mortality seen in the stroke belt. From 1995 to 1998, age-standardized mortality rates for ischemic stroke, SAH, and ICH were greater among blacks than whites. Among adults 25 to 44 years of age, blacks and Native Americans/Alaskan natives had greater risk ratios than whites for all stroke subtypes. All ethnicities—blacks, Native Americans, Alaskan natives, Asians/Pacific Islanders, and Hispanics—had younger mean ages than whites.[41]

Well-recognized geographic differences have persisted for the past 50 years, with significantly greater stroke death rates seen in the southeastern United States, or the stroke belt, which includes North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Overall stroke mortality is 20% to 40% higher than in the rest of the United States in both whites and blacks. Disparities in incidence are thought to play a substantial role in mortality disparities.[42]

The pattern of changes in stroke incidence rates in high-income and low- to middle-income countries corresponds to those reported in studies of international mortality trends, suggesting that changes in stroke mortality rates are most likely attributable to the corresponding changes in stroke incidence rates. Early stroke case fatality is decreased in both high-income and low- to middle-income countries, and age-standardized mortality decreased by 36% to 38% from 1990 to 2010. However, internationally, disparities continue to exist in many low-income countries, with Sub-Saharan Africa, Central and Latin America, and South Asia continuing to report increasing mortality trends.[10]

Mortality and 30-day case fatality have decreased significantly during the past 50 years overall, and particularly for ischemic stroke. Hemorrhagic stroke mortality continues to be stable, with overall mortality, but not case fatality, improving in SAH. Racial, regional, and gender differences in trends need further investigation and preventive/public health policy formulation. International disparities in stroke mortality are likely related to larger issues of economics, infrastructure, and resources that

limit access to high-quality health care, including acute stroke therapies and rehabilitation, as well as secondary stroke prevention.

Trends in Severity and Morbidity

The severity of stroke has remained stable and unchanged during the past 50 years,[13] and stroke continues to be the leading cause of serious long-term disability in the United States.[5] FHS data of ischemic stroke survivors who were more than 65 years of age indicated the following disabilities 6 months poststroke: 50% had hemiparesis, 30% were unable to walk without assistance, 26% were dependent for activities of daily living, 19% had aphasia, 35% had depression, and 26% were institutionalized in nursing homes.[43]

Blacks had greater limitations in ambulation than whites after adjustment for age, sex, and educational attainment, but not for stroke subtype. Blacks were also noted to be younger, had more hemorrhagic strokes, and were more disabled at admission. Blacks and Hispanics also had a poorer functional status at discharge and had less improvement in functional status per inpatient day, but were more likely to be discharged home.[44]

In most studies, women have greater disability after stroke than men. The CHS study found that women were half as likely to be independent in activities of daily living after stroke, even after controlling for age, race, education, and marital status. Another prospective study in Michigan found that women had a 63% lower probability of achieving independence in activities of daily living 3 months after discharge even after controlling for age, race, subtype, prestroke ambulatory status, and other patient characteristics.[45] Women have more strokes secondary to longer life expectancy, have strokes when they are older, and have a higher prevalence of risk factors such as hypertension, atrial fibrillation (AF), and prestroke disability, but have a lower prevalence of lethal risk factors such as heart disease, peripheral vascular disease, smoking, and alcohol use. They are less likely to receive tissue plasminogen activator treatment and lipid testing, and have poorer functional outcomes, more frequent depression and lower quality of life than men.[46]

Trends in Lifetime Risk

Women have a greater lifetime risk of stroke.[47] In the FHS, lifetime risk of stroke for those aged 55 to 75 years was one in five women (20%–21%) and one in six for men (14%–17%). Trends in lifetime risk were studied and compared across three epochs—1950 to 1977, 1978 to 1989, and 1990 to 2004—for incident stroke at 65 years of age and was noted to decrease in the latest data period compared with the first, from 19.5% to 14 % in men and 18% to 16.1 % in women.[13] However, the decrease in lifetime risk did not reach statistical significance. Given that the age-adjusted incidence and 10-year cumulative incidence are both decreasing, the trend in lifetime risk was thought to be secondary to increasing life expectancy, which may offset the decreases in shorter term risk.

Trends in Risk Factors

TRANSIENT ISCHEMIC ATTACK

Transient ischemic attack (TIA) is not often investigated within cross-sectional or longitudinal cohort studies. Precise estimates of incidence and prevalence are not obtainable because of inconsistent criteria used to define TIA in epidemiological studies and problems with accurate ascertainment. Ascertainment and adjudication are problematic in that many people who have had TIAs may

not recognize them, and hence may not present to the doctor or hospital. Current estimates come from self-reporting of physician-diagnosed TIA by phone surveys, and they estimate a prevalence of 2.3% or ~5 million,[48] but this is likely an underestimation. The OXVASC study reported that up to 70% of patients do not correctly recognize TIA or minor stroke and 30% delay presentation for medical care for more than 24 hours regardless of age, sex, educational level, or socioeconomic status.[49] The incidence of TIA was reported in the Rochester study[50] in the 1980s and in the GCNKSS in the 1990s, and was estimated at 0.68/1000 and 0.83/1000, respectively. The prevalence of TIA increases with age and varies by sex and race. Men, blacks, and Mexican Americans have greater rates of TIA than their female and non-Hispanic white counterparts.[51]

TIAs confer a substantial short-term risk of stroke, hospitalization for any cardiovascular disease events and death. Of 1707 TIA patients evaluated at the emergency services of Kaiser Permanente, 10% had a stroke within 90 days and 5% had a stroke within 2 days. Predictors of stroke included age older than 60 years, diabetes mellitus (DM), focal neurological symptoms of weakness or speech impairment, and TIA lasting more than 10 minutes. Individuals who survive the initial high-risk period have a 10-year stroke risk of 19% and a combined 10-year stroke, myocardial infarction, and vascular death risk of 43%. Within 1 year of TIA, ~12% of patients will die.[52]

Temporal trends in TIA have been reported only in a few population-based studies from Russia[53] and France,[54] and they report a stable, not decreasing, incidence of TIA in their cohorts.

Because of accumulating data from multiple studies and the development and more widespread use of MRI, the American Heart Association/American Stroke Association has issued a scientific statement endorsing a tissue-based definition, as well as recommendations for workup, diagnosis, and management.[55] The current definition of TIA is a transient episode of neurological dysfunction from focal cerebral, spinal cord, or retinal ischemia *without infarction on imaging*, and the recommended acute imaging modality, preferably undertaken within 24 hours of onset of symptoms, is brain MRI with diffusion weighted imaging sequences. Variability in use of MRI has the potential to impact incidence, and one study estimated that it could result in a 30% reduction in TIA incidence and a 7% increase in ischemic stroke incidence. This will undoubtedly alter the epidemiological data for TIA and ischemic stroke going forward, depending on MRI use. A recent study out of Norway[56] using a prospective registry reported that, with an increase in MRI use for TIA, from 65% in 2006 to 2008 to 89% in 2009 to 2011, there was a significant decrease in proportion of TIAs to ischemic stroke from 12.2% to 8.3%.

HYPERTENSION

Blood pressure is the best-established and most powerful risk factor for both ischemic and hemorrhagic stroke. People with a blood pressure less than 120/80 mmHg have half of the lifetime risk of stroke compared with those with hypertension. Numerous studies, including cohort studies and more than 40 randomized trials with more than 188,000 subjects, have determined that the degree of control has a direct dose–response relationship to risk of stroke, such that each 10-mmHg decrease in blood pressure is associated with an ~33% decrease in risk in subjects 60 to 80 years old regardless of sex, region, stroke subtype, or severity.[57] NHANES statistics[58] suggest that one of three adults in the United States has hypertension, that ~8% of adults have undiagnosed hypertension, and ~76 million Americans have hypertension based on 2008 data. NHANES data[59] describe a favorable trend in blood pressure control from 1988 to 1994 to 2007 to 2008, high blood pressure control rates improved from 27.3% to 50.1%, treatment improved from 54.0% to 73.5%, and the control/treated rates improved from 50.6% to 72.3%. The results of another study looking at only randomized trial data indicated that the benefit of tight blood pressure control is mainly in those without established cardiovascular disease.[60] However, projections show that by 2030, an additional 27 million people could have hypertension, a 9.9% increase in prevalence from 2010, largely as a result of the aging of the population, because the proportion of persons with hypertension increases with increasing age.[61]

There is an overall decreasing trend in age-adjusted incidence of hypertension worldwide, with studies from France, such as the Lausanne Stroke Registry[62]; Portugal[63]; Sweden[64]; Japan[65]; and others all reporting a significant decrease in hypertension in their cohorts.

There is, however, a disturbing trend toward an increasing prevalence of hypertension in children and adolescents in the United States and China. NHANES III, which is a cross-sectional cohort study looking at children and adolescents aged 8 to 17 years, studied trends of systolic and diastolic blood pressure levels between 1988 and 1994, and 1999 and 2000, and found mean systolic blood pressure was 106 mmHg, or 1.4 mmHg higher, and diastolic blood pressure was 61.7 mmHg or 3.3 mmHg higher than in 1988 to 1994. Pressures were higher in blacks and Mexican Americans compared with whites, and these ethnic differences were attenuated when correcting for body mass index (BMI) and obesity.[66] In Shandong, China, the overall prevalence of relatively high blood pressure among children and adolescents aged 7 to 17 years increased from 19.29% (boys) and 14.69% (girls) in 2000 to 26.16% (boys) and 19.77% (girls) in 2010. This was also associated with an increase in obesity and overweight children.[67]

Temporal trends in hypertension appear favorable in most adult cohorts in the United States and worldwide, with a decrease in hypertension and greater use of antihypertensive therapy. There is a concern for the children and adolescents who show an increasing trend in blood pressure in association with greater prevalence of obesity.

DIABETES MELLITUS

Impaired glucose tolerance nearly doubles stroke risk, and DM triples the risk of stroke (see Chapter XX). Age-specific incidence rates and rate ratios show that DM increases ischemic stroke risk at all ages, but is most prominent as a risk factor before age 55 years in blacks and before 65 years in whites. FHS[68] trends show a doubling in the incidence of DM during the past 30 years, most prominently during the 1990s. Of adults 40 to 55 years of age, in each decade of the 1970s, 1980s, and 1990s, the age-adjusted 8-year incidence rates of DM were 2.0%, 3.0%, and 3.7% in women and 2.7%, 3.6%, and 5.8% in men, respectively. Compared with the 1970s, the age- and sex-adjusted odds ratio for DM was 1.40 in the 1980s and 2.05 in the 1990s, with most of the increase in incidence of DM occurring in obese individuals (BMI, >30 kg/m^2).

Racial differences occur in DM incidence in adults.[69] Over 5 years of follow-up in 45- to 84-year-olds, 8.2% of the cohort developed DM. The cumulative incidence was highest in Hispanics (11.3%), followed by black (9.5%), Chinese (7.7%), and white (6.3%) participants. The National Inpatient Survey data from 1997 to 2006 showed that, although stroke incidence decreased, there was trend toward increasing proportion of stroke patients with DM such that one in five to one in three were noted to have DM.[70] According to an international survey[71] and epidemiological data from 2.7 million participants, the prevalence of DM in adults increased from 8.3% (in men) and 7.5% (in women) in 1980 to 9.8% (men) and 9.2% (women) in 2008. The number of individuals affected with DM increased from 153 million in 1980 to 347 million in 2008.

Diabetes appears to be increasing in incidence and prevalence in the United States and is a major risk factor that needs to be addressed to curtail a possible increase in stroke, especially given the increasing incidence of obesity in both children and adults, and changing demographic characteristics in the United States.

OBESITY

Obesity is an epidemic in the United States, with 68% of adults overweight or obese (72% of men and 64% of women). Among men, Mexican Americans and whites were more likely to be overweight or obese than blacks (69%). Among women, blacks (78%) and Mexican Americans (77%) were more

likely to be overweight or obese than whites (61%). More than one third (34%) of all adults were obese (32% of men and 36% of women) according to NHANES 2007 to 2008. Among men and women, blacks (37%) and Mexican Americans (36%) were more likely to be obese than whites.[72] Temporal trends as described in the CDC and NHANES data indicate an increasing prevalence of BMI greater than the 95th percentile, at 4% in 1971 to 1974 and increasing to 20% in 2007 to 2008 in children 6 to 11 year olds, and 6% in 1971 to 1974 and increasing to 18% in 2007 to 2008 in adolescents 12 to 19 years old.[73] Compared with 1973 to 1974, the proportion of children 5 to 17 years of age who were obese was five times higher in 2008 to 2009. There was an inverse association with education level, with college graduates having a 20.8% rate of obesity versus those with less than a high school education, of whom 32.9% were obese.

FHS data from 1971 to 2001 showed that among normal-weight white adults between 30 years and 59 years of age, the 4-year rates of becoming overweight varied from 14% to 19% in women and from 26% to 30% in men.[74] The 30-year risk was similar for both sexes, with some variation by age. The age-adjusted prevalence[75] of obesity among adults increased between 1976 to 1980 and between 1988 to 1994, and again between 1988 to 1994 and 1999 to 2000. Obesity prevalence for men was 28% in NHANES 1999 to 2000 (NCHS) and 32% in NHANES 2007 to 2008; for women, obesity prevalence was 33% in 1999 to 2000 and 36% in 2007 to 2008 (Figure 23.1).

Obesity is increasing in children, adolescents, and adults in the United States and other industrialized countries and, like diabetes, needs to be addressed to avoid a costly increase in cardiovascular disease and stroke.

ATRIAL FIBRILLATION

AF is a powerful risk factor for stroke, increasing the risk approximately fivefold independently for all ages. The percentage of strokes secondary to cardioembolism from AF increases steeply from 1.5% at 50 to 59 years to 23.5% at 80 to 89 years.[76] Stroke risk from AF is probably underestimated because AF can often be intermittent and asymptomatic. The prevalence of AF in 2010 ranged from 2.7 million to 6.1 million and is expected to increase as the population ages—to 56 million to 12 million in 40 years. In Olmsted County, Minnesota, the age-adjusted incidence of AF increased by 12.6% from 1980 to 2000. The incidence of AF was greater in men and increased markedly with older age.[77] Blacks, Asians, and Hispanics have a significantly lower adjusted prevalence of AF compared with whites.[78]

HYPERLIPIDEMIA

Hyperlipidemia is a well-accepted risk factor for stroke because of numerous clinical trials and epidemiological data. Current estimates are that there are 31.9. million adults who have hypercholesterolemia, with a prevalence of 13.8%—and possibly 5.6% remain undiagnosed.[5]

The Minnesota Heart Study[79] reported a decline in cholesterol levels from 1980 to 1982 to 2000 to 2002 from an age-adjusted mean total cholesterol of 5.49 mmol/L and 5.38 mmol/L to 5.16 and 5.09 mmol/L. Analyzing NHANES data, there was also a decrease in lipid levels between 1999 to 2000 and 2005 to 2006; the age-adjusted mean total serum cholesterol level decreased from 204 mg/dL to 199 mg/dL and low-density lipoprotein (LDL) cholesterol levels decreased from 129 mg/dL to 123 mg/dL during this period. LDL cholesterol showed a further decrease in 2000 to 2006, from mean levels of 204 mg/dL to 199 mg/dL. The overall prevalence of elevated LDL levels in adults older than 20 years declined by 33% between 1999 to 2006, but this decline was observed mainly for men older than 40 years and for women older than 60 years.[80] There was little change over this time period for other sex/age groups. Lipid-lowering drug use increased significantly for both sexes among those 35 to 74 years of age. Awareness, treatment, and control of hypercholesterolemia have

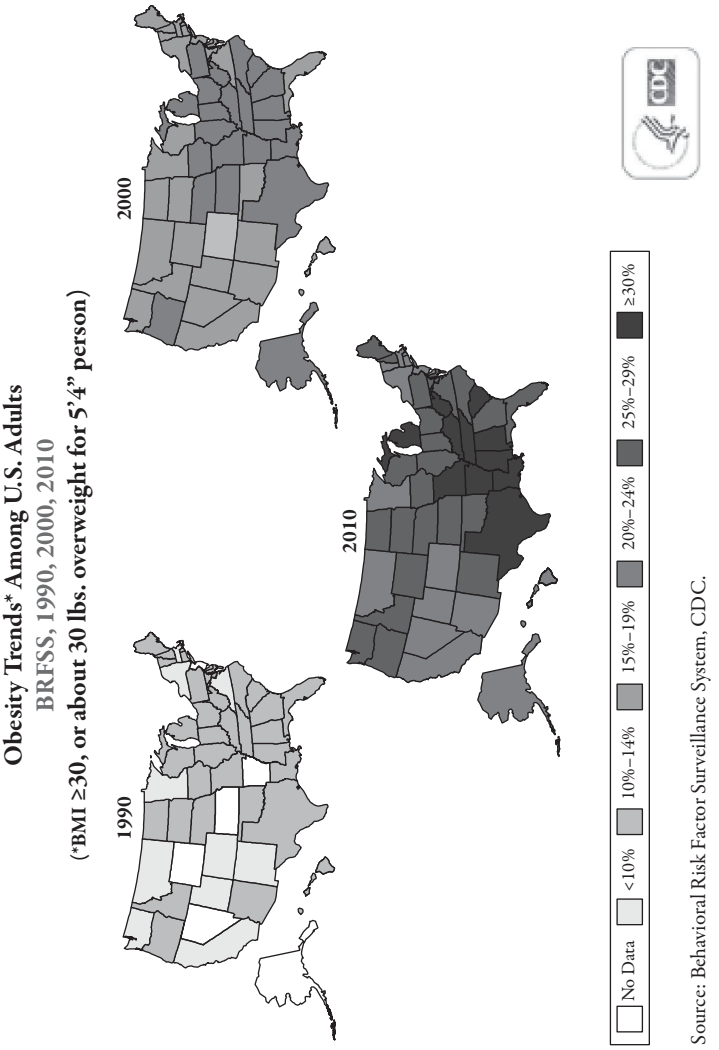

FIGURE 23.1 Obesity trends among U.S. adults over three decades.

increased; however, more than half of those at borderline high risk remain unaware of their condition. Self-reported use of cholesterol-lowering medications increased from 8.2% during 1999 to 2000 to 14.0% during 2005 to 2006.

Cholesterol levels and hyperlipidemia have been decreasing during the past 30 years, and the use of lipid-lowering agents has increased substantially. The improvement in lipid profiles are noted mostly for middle-aged men and women older than 60 years. Future tracking of trends will reveal what kind of impact this improvement in hyperlipidemia will have on stroke.

SMOKING

Cigarette smoking is a well-established, modifiable risk factor for stroke, including ischemic stroke and ICH, and is the most important modifiable risk factor for SAH. Smokers have a two to four times

increased risk of stroke compared with nonsmokers or those who have quit for more than 10 years.[81] Data also support a dose–response relationship across old and young age groups. Discontinuation of smoking has been found to reduce stroke risk across sex, age, and race.

From 1998 to 2010, the percentage of U.S. adults who were current cigarette smokers decreased from 24.1% to 19.3%. In 2010, among Americans adults, 21.2% of men and 17.5% of women were current cigarette smokers. From 1998 to 2007, cigarette smoking prevalence among adults decreased in 44 states and the District of Columbia. Six states had no substantial changes in prevalence after controlling for age, sex, and race/ethnicity.[82] The general trend is a decrease in smoking in adults in most states in the United States.

PHYSICAL INACTIVITY

Baseline physical activity has been studied in numerous cohort and case–control studies. FHS investigators found that medium to high levels of physical activity were protective against stroke in men.[83] The CHS results indicated a 5-year mortality benefit in men and women older than 65 years.[84] A meta-analysis found that high levels of physical activity or moderately intense physical activity, both occupational and leisure time activity, were protective (RR, 0.64–0.85) for all stroke, ischemic and hemorrhagic stroke, compared with inactivity.[85] NOMAS study investigators reported a 35% reduction (adjusted HR, 0.37) in ischemic stroke risk with moderate to vigorous exercise in men monitored for up to 9 years.[86] German and Danish studies suggest that recent activity and the timing of activity in relation to stroke were important.[87]

The prevalence of those who engaged in recommended levels of activity increased slightly from 24.3% in 1990 to 25.4% in 1998, and the prevalence of those reporting insufficient activity increased from 45.0% in 1990 to 45.9% in 1998. Those reporting no physical activity decreased from 30.7% in 1990 to 28.7% in 1998. The components of recommended activity remained relatively stable.[88]

A study[89] looking at trends in occupation-related physical activity using U.S. Bureau of Labor statistics and NHANES data from the 1960s concluded that daily occupation-related energy expenditure had decreased by more than 100 calories during the past 50 years.

A 5-year longitudinal study of adolescents reported unfavorable shifts in activity patterns, such as longitudinal decreases in moderate to vigorous physical activity, coupled with longitudinal and secular increases in leisure time computer use.[90]

There is a significant trend[91] toward less physical activity in both adults and adolescents in the long term, although there was a slight decrease in physical inactivity during the early 1990s.

KIDNEY DISEASE

CHS study results indicated that people with a serum creatinine level of more than 1.5 mg/dL were at increased risk of stroke, with an adjusted HR of 1.77, compared with others. Participants in the Reasons for Geographic and Racial Differences in Stroke study with a reduced glomerular filtration rate were also shown to have an increased risk of incident stroke symptoms. The prevalence of end-stage renal disease (ESRD) was reported by the U.S. Renal Data system[92] to be 547,982 cases in 2008 and is projected to increase to 700,000 by 2020.

Overall, during 1995 to 2005, the age-adjusted incidence of ESRD increased from 260.7 per million to 350.9 per million, even as the rate of increase slowed from 1998 to 2005. In the 2000s, compared with the 1990s, the age-adjusted ESRD incidence continued to increase, but at a slower rate among whites and blacks, and has decreased significantly among Native Americans, Asians, and Hispanics.[93]

Prevalence of diabetic kidney disease in the United States increased from 1988 to 2008 in proportion to the prevalence of diabetes. Among persons with diabetes, prevalence of diabetic kidney disease was stable despite increased use of glucose-lowering medications and renin–angiotensin–aldosterone system inhibitors.[94] There is a trend toward overall increasing prevalence of kidney disease and ESRD.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea was once overlooked but is now a known independent risk factor for stroke. An observational cohort study[95] with 1022 patients, 68% of whom had obstructive sleep apnea, found a significant association with stroke and death (HR, 2.24). After adjusting for age, sex, race, smoking, alcohol consumption, BMI, diabetes, hypertension, AF, and hypertension, the HR was 1.97. Worsening sleep apnea severity is associated with greater stroke risk. Patients with severe sleep apnea have three- to fourfold increased odds of stroke. Continuous positive airway pressure improves a variety of outcomes after stroke. It reduces dramatically the risk of recurrent vascular events among patients with stroke (RR reduction, 81.4%; Number needed to treat-NNT, 3.4). The overall incidence of moderate to severe obstructive sleep apnea for a 5-year period was 11.1% in men and 4.9% in women. Men who had a more than 10-kg weight gain had 5.2-fold odds of increasing their risk of obstructive sleep apnea.[96]

Literature on temporal trends is limited. Given the relationship to weight gain and obesity, the projected trend would be an increase in prevalence.

Summary

Overall, there is a decreasing incidence of stroke, particularly ischemic stroke. Hemorrhagic stroke incidence is stable, and although it comprises a minority of all strokes, it contributes significantly to the mortality and morbidity of stroke. There is a concern that the decreasing trends in stroke incidence and mortality are not as robust in women and blacks. The mortality from stroke has decreased significantly and it now ranks fourth among all causes of death. Mortality from hemorrhagic stroke remains unchanged and has not improved. Severity of stroke is stable, and stroke continues to be the leading neurological cause of long-term morbidity. Women have greater mortality from stroke and poorer recovery, likely a function of having strokes at an older age. Racial and regional differences in mortality exist and need to be addressed with preventive strategies. Lifetime risk of stroke has remained stable despite decreasing stroke incidence and is thought to be secondary to increased life expectancy. Given the aging of the population, decreased mortality, and longer life expectancy, the prevalence of stroke is increasing, and concerns are that it will be a major economic burden to society. Major known risk factors for stroke show divergent trends.[97] Although hypertension, hyperlipidemia, and smoking show decreasing trends in incidence, diabetes, kidney disease, AF, obesity, physical inactivity, and obstructive sleep apnea are increasing, and there are disturbing trends that children and adolescents have increasing blood pressure, obesity, and diabetes. There are composite stroke risk profile scores[98] and American Heart Association recommendations[99] to improve cardiovascular and cerebrovascular health by meeting the metrics: do not smoke; be physically active; have normal blood pressure, blood glucose, and total cholesterol levels; and maintain a healthy weight and eat a healthy diet. These strategies decrease disease and death, but the current success at achieving all these metrics is low. Healthcare planning, policy formulation, and resource allocation should focus on preventive measures, addressed at the population level, for those risk factors that are increasing in prevalence. In addition, investigations of gender, racial, regional, and international differences in care should be instigated.

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Epilogue/Synthesis

STROKE IS A heterogenous entity, but all varieties of stroke share a common etiology of disturbance in the blood supply to the brain. The most common types of ischemic and hemorrhagic stroke share a common substrate of preceding atherosclerotic and arteriosclerotic changes. In this book, genetic variants and a wide range of demographic, lifestyle, and vascular and metabolic characteristics that modify stroke risk have been discussed. We also reviewed circulating biomarkers associated with risk of stroke. Some of these biomarkers likely mediate known associations of lifestyle and vascular risk factors with stroke whereas others appear to point to the involvement of previously unsuspected biological pathways in mediating stroke risk.

Most strokes are predictable and preventable consequences of chronic disease attributable to the impact of risk factors acting over many decades. We can determine the relative impact of addressing various risk factors by estimating a population-attributable risk fraction for each risk factor—a theoretical concept that estimates how much of the disease in a population could be eliminated by the eradication of a specific risk factor—and it depends on both the prevalence of a specific risk factor and the relative risk associated with it. Thus, correcting a common risk factor such as modest elevation in blood pressure would have a greater public health impact than addressing a relatively more rare risk factor such as sickle cell disease, which would reduce risk dramatically for only a few affected persons. Public health strategies to prevent stroke can be categorized as (1) "mass" strategies that focus on health education, legislation, and social, environmental changes, such as cigarette taxes and reducing blood pressure through reduced salt intake; or as (2) "high-risk" strategies that focus on physicians identifying and counseling/treating individual high-risk subjects identified using clinical examination and risk assessment profiles.

The wide range of risk factors discussed in this book do not, of course, act in isolation. Risk factors tend to cluster together, and some of the most frequently observed clusters are recognized as specific conditions with an underlying biological substrate, such as the metabolic syndrome of obesity, hypertension, and dyslipidemia associated with insulin resistance. Moreover, risk factors act synergistically

to increase risk. Risk factors most often affect risk in a continuous, graded fashion, extending into the perceived normal range. At any level of each risk factor, stroke risk varies widely, depending on the number and levels of other accompanying risk factors. The Framingham Stroke Risk Profile (FSRP) was developed nearly 25 years ago as a simple risk prediction algorithm to help identify persons at an increased risk of stroke, based only on information from a medical history and physical examination, plus an electrocardiogram. It integrates the effects of age, sex, and baseline measurements of various modifiable vascular risk factors—systolic blood pressure, use of antihypertensive medications, presence or absence of left ventricular hypertrophy on electrocardiography, presence of diabetes, any cardiovascular disease and atrial fibrillation, and smoking status—to arrive at an estimated 10-year probability of stroke. Thus, for a 70-year-old man with elevated levels of one risk factor, a systolic blood pressure of 160 mm Hg, his stroke risk could vary from 8% in the absence of the six other risk factors considered to 85% in the presence of all six. Other composite stroke risk assessment tools have been developed, but the Framingham risk predictor remains the one used most widely to assess risk and to explore the incremental predictive utility of any novel putative risk marker. It has been endorsed and is used in risk stratification and treatment guidelines published by the American Heart Association, and British and European cardiovascular societies. When applied to countries and race/ethnic samples with different baseline risks of stroke, it has required recalibration to the baseline risk of that sample. However, in a wide variety of settings, the FSRP has proved robust, and few newer biomarkers appear to improve risk prediction further.

Among the most promising "new" markers are indicators of subclinical disease such as carotid stenosis, carotid intimal–medial thickness, and magnetic resonance imaging measures of vascular brain injury. This is because existing stroke risk scores use levels of risk factors at the time of risk prediction (current exposure), although the duration and severity of exposure to a risk factor before the time of risk prediction (remote exposure) also determine risk. Measures of subclinical disease are useful markers of past exposure to risk and preexisting injury, and have been described as "signposts on the highway to disease."

Twenty years ago, it was recognized that an average middle-age person would be concerned about his or her risk of stroke beyond the 10-year period for which the FSRP provided an estimate. The concept of a lifetime risk, already well established for estimating the risk of breast and other cancers, was extended to neurological and cardiovascular diseases, including stroke. The lifetime risk of stroke may be defined as the risk that a person, currently free of stroke, would develop at some time before they died; it is based on estimated life expectancy, and age- and sex-specific risks. The various genetic, vascular, lifestyle, and other risk factors discussed in this book alter short-term as well as lifetime risks. Their impact on lifetime risk is greater if they act congruently on both survival and stroke risk. Most factors that increase stroke risk shorten rather than increase life expectancy, so their impact on lifetime risk of stroke is blunted. However, as survival from cancers and other cardiovascular risk factors improves, the impact of these risk factors on stroke risk could increase. Temporal trends in the risk of stroke and of stroke risk factors are discussed in this book. As a consequence of these temporal trends in risk factor prevalence and treatment, the FSRP overestimates stroke risk for contemporaneous populations in Framingham and elsewhere, and a newer risk profile is being developed and validated. Newer circulating and imaging biomarkers and genetic risk variants associated with stroke risk continue to be identified.

Unfortunately despite all these discoveries, risk prediction remains a very inexact science, and despite stroke prevention efforts worldwide, more than 9 million new strokes will occur this year. We hope you, the reader, will expand the knowledge summarized in this book and accelerate its impact on stroke prevention through your own contributions to stroke research and clinical care.

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