Venkatesh Aiyagari
Philip B. Gorelick *Editors*

Hypertension and Stroke

Pathophysiology and Management

HYPERTENSION AND STROKE

CLINICAL HYPERTENSION AND VASCULAR DISEASES

WILLIAM B. WHITE, MD
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This book is dedicated to the memory of my father.

Venkatesh Aiyagari, MBBS, DM

To my parents, Ruth and Harold Gorelick, dedicated in honor of your sense of family and unwavering support during life's journey.

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Foreword

The importance of hypertension as it relates to cerebrovascular disease and events has been greatly appreciated by physicians and scientists since the results of the earliest Veterans Administration Cooperative Trials in the 1960s and the isolated systolic hypertension trials in the United States (SHEP) and Europe (Syst-Eur) that followed in the 1980s and 1990s. This appreciation of the severity of the complications of this common disorder particularly in advanced age has led to substantial reductions in stroke over the past 50 years. Nevertheless, there is always room for improvement and cognitive decline associated with hypertension and vascular disorders remains an elusive problem in clinical medicine. Drs. Aiyagari and Gorelick's volume on *Stroke and Hypertension* is therefore a most clinically relevant contribution in the area of stroke neurology – this book brings together the basic pathophysiologic, epidemiologic, diagnostic, and therapeutic advances in the evaluation of hypertension in patients with stroke or who are at great risk of stroke.

The editors have nicely organized this volume into sections that cover the general pathophysiology and epidemiology of hypertension, overviews of the epidemiology of stroke and its relationship to hypertension, clinical evaluation that covers a variety of topics such as neuroimaging, diagnostic evaluation, and cognitive assessment, and nonpharmacologic and pharmacologic approaches to the management of high blood pressure in primary and secondary stroke prevention. There are very comprehensive chapters on the evidence supporting various strategies for stroke prevention including blood pressure-lowering therapies, anticoagulation, and management of other cerebrovascular risk factors.

Substantial coverage has been appropriately given to the impact of pharmacologic treatments on stroke prevention based on clinical trials in older hypertensive people in Chapters 10, 11, and 12 of the volume. There are also interesting chapters devoted to special problems in cerebrovascular disorders that highlight problems which are of particular concern in our patients, including progression of white matter disease, cognitive dysfunction, and hypertensive encephalopathy. These sections contribute to the novelty of this book since the chapters are grounded in clinical investigations that have led to enhanced understanding of the evaluation and treatment of hypertension in these special populations. The prevention of dementia in older patients is complex and clinically challenging with advances targeted toward better modalities of early clinical evaluation and improved neuroimaging modalities as outlined in Chapters 14 and 15.

The chapters in *Stroke and Hypertension* have been written by a number of well-known, expert authors who have provided comprehensive, scientifically sound, and clinically appropriate information. As series editor of *Clinical Hypertension and Vascular Diseases*, I am pleased by the publication of this timely, well-organized book and know that *Stroke*

and Hypertension will become a highly utilized textbook for all specialists in neurology and cardiovascular medicine as well as any physician who takes care of older adults.

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Preface

Hypertension and Stroke: Pathophysiology and Management reviews the pathophysiologic relationship between hypertension and cerebrovascular disease and the management of blood pressure in a variety of settings such as primary stroke prevention, acute ischemic and hemorrhagic stroke, secondary stroke prevention, and vascular cognitive impairment. Hypertension is one of the most important global public health challenges, and there is a close linkage between hypertension and cerebrovascular disease. Hypertension is the most significant modifiable risk factor for cerebrovascular disease. The importance of adequately treating elevated blood pressure in the primary prevention of stroke and management of cerebrovascular disease is widely accepted. It is estimated that about 25% and up to 50% of strokes could be prevented by blood pressure control. In the course of clinical practice, however, questions arise about the management of blood pressure in the acute, subacute, and chronic phases of stroke. For example, when is it safe to initiate blood pressure-lowering therapy after acute ischemic stroke? Is it dangerous to lower blood pressure in elderly persons who have had a stroke? What is the blood pressure-lowering target after a stroke has occurred to maximize recurrent stroke prevention? Which blood pressure-lowering agents are most efficacious and safe for persons who have had a stroke or for those in the general population to prevent a first stroke? In this book we explore answers to these and many more important aspects of hypertension and stroke. In recent years, several large clinical trials which address blood pressure management for cerebrovascular disease have been published. In this book we have attempted to collate and synthesize this rapidly expanding knowledge base in a form that can be easily accessed and utilized by treating physicians.

Hypertension and Stroke provides a broad approach to the understanding of this topic from the perspectives of leading experts in the fields of vascular neurology, preventive medicine, nephrology and other cardiovascular diseases, epidemiology, pharmacology, neuropsychology and cognitive function, brain imaging, and nursing. In addition, we have recruited international experts who are well-versed in the area of stroke management, and who provide a unique clinical and epidemiological viewpoint from geographic regions where stroke risk is high.

The book consists of five sections and corresponding chapters which provide insights about the following: (1) epidemiology of blood pressure and hypertension in relation to measurement, definition, diagnosis, and observational epidemiological studies and clinical trials in relation to stroke; (2) mechanisms of hypertension and how hypertension may cause stroke; (3) acute management of blood pressure after hemorrhagic and ischemic stroke, hypertensive encephalopathy, management of blood pressure to prevent recurrent stroke, non-blood-pressure-lowering effects of some antihypertensive agents, and a guide to overall cardiovascular risk factor assessment and management for prevention of recurrent stroke; (4) importance of blood pressure in cognitive function, newer brain imaging modalities

to elucidate brain structure and function in hypertension, and the role of cerebral amyloid angiopathy and brain microhemorrhages on cognitive function; and (5) organization of stroke care to improve blood pressure control and overall stroke prevention.

We believe that this text will provide the most up-to-date and expert information on a myriad of important aspects relating to hypertension and stroke. We anticipate that primary care physicians, neurologists, physician extenders, residents and medical students, and epidemiologists, stroke and other cardiovascular researchers, and public health specialists will benefit from this treatise. The global public health challenge of elevated blood pressure will continue to increase. *Hypertension and Stroke* is designed to help meet these challenges.

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Contents

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I

Blood Pressure and Hypertension as Antecedents of Stroke

1

Blood Pressure: Definition, Diagnosis, and Management

Raymond R. Townsend, MD
and Susan P. Steigerwalt, MD, FASH

DEFINITION OF "HYPERTENSION"

As with many cardiovascular risk factors, a definition of what constitutes "normal" vs. "abnormal" in relation to blood pressure level is challenging as it may be with glucose, cholesterol, and other biomarkers associated with atherosclerotic end-organ disease. Based largely upon actuarial data accrued in the first half of the twentieth century, a convenient definition of blood pressure emerged with levels of 140 mmHg systolic and 90 mmHg diastolic constituting threshold values of high blood pressure. In landmark research of the natural history of untreated hypertension, Perera studied 500 untreated hypertensives, showing that the typical life span of a person diagnosed with blood pressures exceeding a value of 140/90 mmHg was less than 20 years *(1)*. In the past, most studies showing the benefit of drug therapy in reducing blood pressure-related consequences used diastolic blood pressure (DBP) entry criteria (90–100 mmHg) to consistently show that there is substantial cardiovascular benefit of reducing blood pressure with medication *(2)*. The Joint National Committee (JNC), the European Hypertension Societies, as well as most guideline writing bodies now generally agree on definitions of blood pressure as shown in Table 1 *(3)*.

A considerable number of patients have comorbidities which either precede or occur in conjunction with hypertension. A growing body of evidence indicates that in the case of several selected comorbidities (dubbed "compelling indications" by the JNC), there is additional benefit to the reduction of blood pressure below the threshold target values of 140/90 mmHg *(3)*. In a population, increased cardiovascular risk begins at blood pressures as low as 115/75 mmHg. "Optimum" blood pressure is defined as less than 120/80 mmHg and "prehypertension" as a blood pressure of 120–139/80–89 mmHg by JNC 7, based on

Table 1
Classification of Hypertension *(3)*

Blood pressure (mmHg)	Classification of hypertension
120/80	Normal
120–139/80–89	Prehypertension
140–159/90–99	Stage 1 hypertension
≥160/100	Stage 2 hypertension

an increased lifetime risk of developing hypertension in the USA which is estimated to be 80% (JNC 7). However, we lack interventional trials showing cardiovascular protection for treatment of initial blood pressures <140/90 mmHg although the strict "definition" of hypertension in these comorbid states is still 140/90 mmHg. Most practitioners nonetheless initiate treatment when blood pressure exceeds treatment goal (e.g., 130/80 mmHg in diabetics). The discrepancy in blood pressure diagnosis and treatment goal is likely to be addressed in the JNC 8 guidelines.

Finally, with respect to the definition of hypertension, it should be considered within the framework of global cardiovascular risk *(4)*. In such a schema, the level of blood pressure warranting intervention by drug treatment may depend on the presence and severity of other cardiovascular risk factors and the presence of target organ damage.

DIAGNOSIS OF HYPERTENSION

Evaluation Goals

Evaluation of the patient with sustained elevation of blood pressure aims to determine whether it is:

- Secondary to a possible curable cause
- Accompanied by other cardiovascular risk factors
- Accompanied by target organ damage

These considerations influence treatment decisions and provide clues to the optimal management of blood pressure and associated risk factors. Common errors in blood pressure measurement technique tend to falsely increase the readings leading to an overestimate of blood pressure level.

How to Measure Blood Pressure

Ideally, the patient should be placed in the sitting position. This is based on the Framingham Heart Study *(5)* as well as most randomized clinical trials which utilized this position for diagnosis and management of blood pressure *(6,7)*. A correct-sized cuff is applied and calibrated equipment is used with good inflation and deflation technique in a patient seated comfortably with the back supported, feet on the floor, and arm at heart level. The urinary bladder should be empty. The American Heart Association recommends 5 min

of rest prior to measurement and abstention from caffeine and cigarettes for 30 min prior to measurement. This yields the most reproducible blood pressure determination. Blood pressure should be measured in both arms at the first visit, and the arm with the higher blood pressure used thereafter for all measurements. Despite good technique, the average blood pressure varies significantly day to day. Therefore, a running average of at least three measures provides the clearest office estimate of blood pressure

A sizable number of patients use home blood pressure cuffs. The AHA Call to Action provides a description of how to use such home-based results in hypertension diagnosis and management and stresses the need for attention to proper technique *(8)*.

Evaluation of the Hypertension: Addressing Three Key Questions

There are three key questions to address in the diagnosis of hypertension. These are asked to determine: (1) Does the patient have a secondary form of hypertension? (2) Are there associated cardiovascular risks or predisposition to such risks? and (3) Is there any target organ damage? Recognizing the presence of a secondary form of hypertension may direct curative therapy (e.g., removal of an aldosterone-producing adenoma) or provide insight into mechanisms which may help guide therapy (e.g., renal artery stenosis and the use of medications with block renin–angiotensin system blockade activity or endovascular intervention to correct renal artery stenosis).

Identification of the presence and severity of other cardiovascular risk factors is important for two reasons. First, we may wish to avoid using medications which can cause or worsen a risk factor (e.g., the use of beta-blocking drugs in patients with a low HDL cholesterol level which could lower HDL further or thiazide diuretic-induced glucose intolerance or diabetes mellitus) *(9)*. Second, the presence of other risk factors (e.g., components of the metabolic syndrome) may heighten the risk of hypertension and warrant consideration of additional and more intensive therapy.

Finally, the presence of target organ damage is important to detect because it moves the treatment goal from *primary* prevention to *secondary* prevention. For example, a patient with a history of stroke has a risk of another stroke within the next 5 years which may be 30% or higher, a value which far exceeds the average hypertensive patient's risk without such a history. Guidelines suggest the use of a diuretic and angiotensin-converting enzyme inhibitor for recurrent stroke prevention.

General Principles of Diagnosis of Hypertension: Medical History

Patients with elevated blood pressure should have a thorough general history and physical examination and selected investigations (*see* Tables 2 and 3). The evaluation of a patient with elevated blood pressure begins with a complete medical history. The history should query the duration (when known) and severity of high blood pressure. Clues such as the sudden onset of severe blood pressure elevation when blood pressure was previously known to be normal raise suspicion for a secondary cause of hypertension. Knowledge of concomitant medical conditions and associated cardiovascular comorbidities and responses to various treatments should also be obtained. Information about dietary habits, alcohol consumption, tobacco use, level of physical activity, and sleep duration (which predicts both hypertension and CV events *(10)*) should be determined since there may be allied

<div align="center">

Table 2
Medical History in the Patient with Elevated Blood Pressure

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Item	*Evaluation*
Age at onset and duration of elevated blood pressure	Onset in younger patients (e.g., <30 years) may indicate a secondary cause; when blood pressure at onset is severe (e.g., stage 2 hypertension), this may also be a clue to a secondary cause
Lifestyle factors	High salt intake, physical inactivity, psychosocial stress, and sleep-disordered breathing (e.g., sleep apnea) may contribute to elevated blood pressure
Concurrent medications	Consider nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, corticosteroids, licorice, cough/cold/weight-loss pills, and sympathomimetics
Risk factors for cardiovascular disease	Family history of premature cardiovascular disease especially in a first-degree relative (parent or sibling), diabetes, smoking, and elevated cholesterol
Symptoms or history which suggest possible secondary cause	Episodic sweating, heart racing/palpitations, and headache (e.g., pheochromocytoma); muscle weakness and increased urine volume (e.g., hyperaldosteronemia); family history of kidney disease (hereditary forms such as polycystic kidney disease); protein or blood in urine and/or ankle swelling (various types of renal disease); daytime somnolence, snoring/gasping during sleep (e.g., sleep-disordered breathing); prior stroke, heart attack, or peripheral arterial disease (e.g., renal artery stenosis); leg discomfort and claudication in young patient (e.g., coarctation of aorta); and heat intolerance and weight loss (e.g., hyperthyroidism)
Target organ damage	Chest pain or chest discomfort or known prior myocardial infarction (coronary artery disease); neurologic symptoms consistent with stroke or transient ischemic attack (cerebrovascular disease); dyspnea and easy fatigue (possible heart failure); claudication (peripheral arterial disease)

areas of lifestyle or other intervention. A family history of hypertension, renal disease, cardiovascular disease, and diabetes mellitus should be noted. Sleep-disordered breathing which is common in hypertension may be uncovered by queries about daytime sleepiness, snoring/gasping, and nocturnal arousals with breathless symptoms. A screening tool such as the Epworth Sleepiness Scale[TM] *(11)* may be helpful.

In addition, it is important to obtain details of past medication use with particular attention to side effects and effectiveness in controlling blood pressure. Current medications, including over-the-counter preparations, should be reviewed. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the efficacy of antihypertensive drugs, presumably through mechanisms that inhibit the vasodilatory and natriuretic prostaglandin

Table 3
Physical Examination in the Patient with Elevated Blood Pressure

Item	Routine evaluation
General appearance, skin lesions, distribution of body fat	Waist circumference (may fit criteria for metabolic syndrome; adds to diabetic and CV risk); signs of prior stroke from gait/station, motor, and cognition exams; uncommonly secondary forms are evident as striae (Cushing's syndrome) or mucosal fibromas (multiple endocrine neoplasia type 2)
Fundus	Retinal arteriole caliber changes and presence of other retinal pathology reflects severity of hypertension
Neck (thyroid) and carotid arteries	Multinodular diffuse goiter (Graves' disease); presence of carotid bruits may be a clue to elevated stroke risk
Heart and lungs	Presence of rales and/or gallops (target organ damage), interscapular murmur (coarctation of the aorta); displacement of apex beat (point of maximal impulse suggestive of heart enlargement)
Abdomen	Palpable kidneys (polycystic kidney disease); midepigastric bruits (renal arterial disease); striae (Cushing's syndrome)
Neurologic examination	Reduced grip strength or other muscle weakness, hyperreflexia, spasticity, Babinski sign, gait disturbance, or cognitive impairment (previous stroke)
Pulse examination	Delayed/absent femoral pulses (coarctation of the aorta or atherosclerosis); loss of pedal pulses (atherosclerosis, particularly in smokers)

effects and the potentiation of angiotensin-II effects *(12)* (*see* Table 4 for medications affecting blood pressure). It is important to assess the use of alternative medications and supplements, as individuals often do not consider or report these as "medications," and they may contain potent pressor substances such as sympathomimetics or European black licorice. A useful website for further information on complementary and alternative medicine is www.tangcenter.uchicago.edu.

General Principles of Diagnosis of Hypertension: Physical Examination

The physical examination of the patient begins with measurement of height and weight, waist circumference, and blood pressure in *both* arms. The blood pressure is recorded according to the arm with the higher blood pressure measurement. It is sometimes necessary to measure blood pressure in the leg in instances when coarctation of the aorta is suspected. Although blood pressure measurements with the patient supine, sitting, and standing are usually undertaken in a hypertension specialty clinic, in a primary care setting where time constraints are germane, a seated blood pressure is carried out three times and averaged. In patients older than 60 years it is important to determine a standing blood pressure level as well. This helps identify orthostatic hypotension, a predictor of falls in the elderly, and possible intolerance to blood pressure lowering *(13)*.

Table 4
Drugs Associated with Development of or Worsening of Elevated Blood Pressure

Drug class or drug	Proposed mechanism of action
Nonsteroidal anti-inflammatory agents (48)	Prostaglandin inhibition causing renal sodium retention and decrease in GFR
High-dose corticosteroids (49)	Mineralocorticoid receptor (MR) stimulation (sodium retention) and sodium–potassium ATPase inhibition (vasoconstriction)
Oral contraceptives (50)	Unknown, usually trivial elevations of blood pressure
Prescribed Sympathomimetics (Meridia™, Ritalin, Provigil™, etc.) (51, 52)	Vasoconstriction and sodium retention
Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SSNIs) (53, 54)	Increase of serotonin or norepinephrine via reuptake inhibition
Erythrocyte-stimulating agents (55)	Vasoconstriction
Tacrolimus, cyclosporine (56)	Vasoconstriction, sodium retention, decrease in GFR
Highly active anti-retroviral therapy (HAART) (57)	Unknown
European black licorice (often contained in alternative medications and chewing tobacco) (58)	Indirectly causes activation of MR, sodium retention, and enhanced vascular reactivity
Cocaine, ecstacy, methamphetamines and other recreational drugs (59, 60)	Sympathetic activation/vasoconstriction
VEGF inhibitors (61, 62)	Unknown

VEGF, vascular endothelial growth factor; GFR, glomerular filtration rate

Key features of the general physical examination of the patient with elevated blood pressure are listed in Table 3 and below:

- Retina (to assess vascular impact of blood pressure)
- Pulses and vessels (searching for carotid bruits for known or subclinical stenosis; abdomen/midepigastric bruits for renovascular disease; femoral bruits for atherosclerosis; poor or delayed femoral pulses suspicious for aortic coarctation; and pedal pulses for peripheral arterial disease, particularly in smokers)
- Heart for gallop sounds and enlargement
- Lungs (rales; unusual in the early phase of hypertension)
- Legs for edema
- Abbreviated neurologic exam for strength, gait, and cognition

Cardiac examination may show a displaced apical impulse, reflecting left ventricular enlargement. When sustained, the apical impulse may indicate left ventricular hypertrophy. Auscultation of an S_4 gallop may document an early physical findings of hypertension.

Table 5
Follow-Up Recommendations for Subsequent Blood Pressure Monitoring *(3)*

Initial BP		
SBP	*DBP*	*Follow-up recommendation*
<120	<80	Recheck in 2 years
120–139	80–89	Recheck in 1 year
140–159	90–99	Confirm within 2 months
≥160	≥100	Evaluate within 1 month; for those with higher blood pressures (e.g., ≥180/110 mmHg), evaluate and treat immediately or within 1 week depending on clinical situation and complications

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BP* blood pressure

Frequency of Blood Pressure Monitoring After the Initial Examination

After the initial examination, blood pressure monitoring is recommended at specified intervals. We recommend subsequent blood pressure monitoring according to the Joint National Committee 7 guidelines as shown in Table 5 *(3)*.

Laboratory Studies in the Evaluation of the Patient with Hypertension or Elevated Blood Pressure

A number of select laboratory tests are recommended for routine evaluation of the patient with elevated blood pressure. At a minimum these should include the following diagnostic studies: hemoglobin or hematocrit, urinalysis with microscopic examination, serum creatinine and electrolytes, serum glucose, a fasting lipid profile, and a 12-lead electrocardiogram (ECG). Other studies such as thyroid hormone concentrations are guided by a history suggesting thyroid excess or the discovery of a thyroid nodule on examination of the neck. The urine studies and the electrolytes/creatinine determinations (and calculated MDRD eGFR) may reflect target organ damage to the kidney. The glucose and the lipid profile may reveal the presence of other cardiovascular risk factors. The 12-lead ECG may show left ventricular hypertrophy (LVH) or the presence of a prior myocardial infarction, both of which represent valuable information in planning a treatment regimen.

The use of spot urine albumin/creatinine (ACR) in diabetic patients is well established *(14)*. In nondiabetic patients, early morning spot urine ACR may be a marker for increased cardiovascular risk, systemic inflammation, and renal failure *(15)*. Both population-based studies such as PREVEND *(16)* and clinical trials such as HOPE *(17)* show increased cardiovascular event rates associated with presence of increased ACR. We recommend screening for ACR in patients with hypertension, repeating it twice to confirm the abnormality. Elevated ACR requires special attention to control of blood pressure, lipids, and evidence of systemic inflammation.

Evaluation for Secondary Causes of Hypertension or Elevated Blood Pressure

In some instances medical history, physical examination, or the initial diagnostic testing leads one to suspect a secondary cause of hypertension. Table 3 includes findings that may lead one to suspect a secondary cause of hypertension. The reader is referred to several authoritative reviews of secondary causes of hypertension which cover this topic in detail *(18,19)*.

Obstructive sleep apnea (OSA) is probably the most common cause of secondary hypertension. It occurs more frequently in men (9% of men and 4% of women in the US population) and is often associated with obesity *(20)*. In patients with hypertension, 30–80% have at least moderate grades of sleep apnea *(20)*. In population studies, OSA is associated with congestive heart failure, stroke, coronary artery disease, and sudden cardiac death. Post stroke, 43–91% of patients may have OSA *(21)*. In uncontrolled hypertensives, treatment of OSA has been shown to decrease blood pressure on average by 5/3 mmHg *(22)*. Bradley and Floras have said: "OSA appears to increase the risk of cardiovascular disease, and its treatment has the potential to decrease risk. Prospective clinical trials are needed." Their review of the topic is informative *(23)*.

Summary: Evaluation of Elevated Blood Pressure

For proper diagnosis of hypertension or elevated blood pressure, multiple blood pressure readings should be taken at various times to confirm the diagnosis. The accurate measurement of blood pressure is made with the correct cuff size, patient position, and technique. The medical history, physical exam, and initial diagnostic test strategy should address three key questions: (1) Is increased blood pressure primary or secondary? (2) Are other cardiovascular risk factors present? and (3) Is there any evidence of target organ damage?

MANAGEMENT OF HYPERTENSION AND ELEVATED BLOOD PRESSURE

The first steps in the management of hypertension or elevated blood pressure are to establish a goal or target blood pressure and to provide the patient with a balance of lifestyle modification advice in conjunction with medication when drug therapy is warranted. More than 40 years have passed since the publication of the first trial establishing the benefit of treatment of primary or essential hypertension *(24)*. Since then, many clinical trials have been performed enrolling thousands of patients treated for an average of 4–6 years. In the following sections of this chapter we detail the method of establishing a goal or target blood pressure and review lifestyle modification and antihypertensive medication for blood pressure control.

Establishing a Goal Blood Pressure for Blood Pressure Control

In the absence of a comorbidity, the goal blood pressure is currently set at achieving levels of *both* <140 mmHg systyolic and <90 mmHg diastolic. Clinical trial amd office-based experience suggest that, in the best of circumstances, the majority of patients (>80%) achieve diastolic blood pressure goals, and about 60% of the time patients achieve systolic blood pressure goals *(25)*. Those who are not controlled are considered "resistant" or difficult to control, and careful evaluation for adherence and secondary causes of hypertension should be considered *(26)*.

When diabetes (any type), chronic kidney disease, or coronary artery disease (CAD) and CAD equivalents (stroke, heart failure, peripheral arterial disease) are present, the current blood pressure goals are set at 1, taken from the most recent version of the report, the Seventh Report of the Joint National Committee *(3*, *27)*. In case of large amounts of proteinuria (more than 1 g/day), the goal recommended by the National Kidney Foundation is <125 mmHg systolic and <75 mmHg diastolic *(28)*.

Home Blood Pressure Monitoring

Prospective studies show that home blood pressure predicts outcomes better than office readings. The American Heart Association recommends use of a validated oscillometric upper arm device. A recently published, authoritative monograph on blood pressure monitoring is available free of charge at myamericanheart.org. A 1-week, twice daily blood pressure measurement protocol with the patient seated and arm with the higher blood pressure recorded, for diagnosis and management of essential hypertension is recommended. Information concerning validation of particular home blood pressure devices can be obtained at the dableducational.org website.

Current recommendations for goals of home blood pressures for treated hypertensives are <135/85 mmHg in the morning and evening. Blood pressure levels <130/80 mmHg are suggested for patients with chronic kidney disease (CKD), based on studies with relatively small sample sizes *(29)*. Currently, no clear recommendations are available for diabetic patients, but a home target of 130/80 mmHg or lower is reasonable.

Lifestyle Measures

Although a large variety of lifestyle modifications have been proposed over the years to manage hypertension, lifestyle measures continue to be recommended for all hypertensive patients *(3)*. These include weight loss for the overweight, reduction of salt intake, increase of physical activity, and restriction of alcohol intake.

In overweight or obese patients, weight loss is one of the most effective lifestyle measures to reduce blood pressure. On average, a 2-pound weight loss reduces SBP by about 1 mmHg *(3)*. Therefore, a 20-pound weight loss yields an approximate 10 mmHg SBP reduction. Although there are limits to the beneficial effect of weight loss on blood pressure reduction, weight loss is a useful adjunct to antihypertensive treatment.

The American Heart Association recommends reduction of sodium intake to 2,400 mg/day. This can be accomplished by simple and practical advice. Preparation of your own meals (e.g., dining at home or making a "brown bag" lunch) allows one to control sodium added to the meal portion. Meals prepared in a restaurant, for example, may contain extra-added sodium. Furthermore, putting the salt shaker away is a second logical step. Finally, since most of the exposure to salt comes from processed foods, scrutinizing food labels for sodium content may be a valuable strategy.

One diet which has undergone rigorous testing, albeit as a feeding study, is the DASH (dietary approaches to stop hypertension) *(30)*. DASH consists of four to five servings of fruits and vegetables, three servings of low-fat dairy, and an emphasis on whole grains. Sodium intake is reduced because of the preponderance of fresh, nonprocessed foods. In the original feeding study, DASH decreased blood pressure by 12/8 mmHg in patients with

hypertension. However, wider utilization of this diet may be hampered by the lack of access to fresh fruits and vegetables and the temptations of a fast food.

An increase in physical activity may have several beneficial effects on cardiovascular risk including weight loss, blood pressure lowering, and improvement of other cardiovascular factors such as glucose intolerance and lipid levels (e.g., triglycerides and HDL cholesterol levels). Patients should be encouraged to carry out aerobic exercise 30 min five to six times per week. One method to assist in achieving this recommendation is to walk about 1.5 miles a day above one's current activity level. Purchase of a pedometer may be useful as it provides feedback to a patient to help him or her reach the exercise goal.

Finally, control of alcohol consumption may be important. Existent data suggest a "U"-shaped relationship between cardiovascular disease incidence and alcohol intake. Therefore, modest or moderate alcohol intake may be protective or do no harm, but too much alcohol consumption is associated with risk of major cardiovascular events. Currently, 2 mixed drinks or less, two 12-ounce cans of beer, or two 4-ounce glasses of wine daily for men and about half this much for nonpregnant women are recommended *(3)*.

Antihypertensive Medication

Thiazide diuretics were introduced into clinical medicine in 1957, making it possible to treat hypertension effectively for a long period of time with a well-tolerated oral agent *(31)*. This led to the first randomized clinical trials of hypertension therapy initiated in the early 1960s *(24)*. With an increasing number of antihypertensive agents and classes to treat high blood pressure, the first attempt in the USA to organize an approach to management of high blood pressure appeared in 1977 in a report titled the "Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study" *(32)*. A summary of the current approach to hypertension management with medication is shown in Fig. 1, taken from the most recent version of the report, the "Seventh Report of the Joint National Committee" *(3)*.

A great deal has been written about the approach to hypertension management with drug therapy. Key summary points include:

- Reduction of blood pressure with medication reduces mortality and decreases target organ damage.
- Decrease in incidence of target organ damage is most evident for new onset heart failure and stroke.
- Most medication regimens work better when a diuretic is included. Although a very recent study, ACCOMPLISH *(33)* showed superior outcomes with the combination of ACEI/CCB as compared to ACEI/diuretic. The diuretic was low-dose hydrochlorothiazide and not chlorthalidone. However, as noted below, chlorthalidone lowers 24-h blood pressure more effectively than hydrochlorothiazide and has a greater evidence base for improving cardiovascular morbidity and mortality than other agents. The ACCOMPLISH trial shows that the combination of benazepril and amlodipine is superior to benazepril and hydrochlorothiazide in older, high-risk hypertensives (average age 68). The difference in outcome in ACCOMPLISH was not due to differences in nocturnal blood pressure (Jamerson et al., May 2009, abstract presentation at American Society of Hypertension).
- When there are associated comorbidities, better outcomes may occur when specific classes of antihypertensive drugs are administered (*see* "Compelling indications" in Table 6).
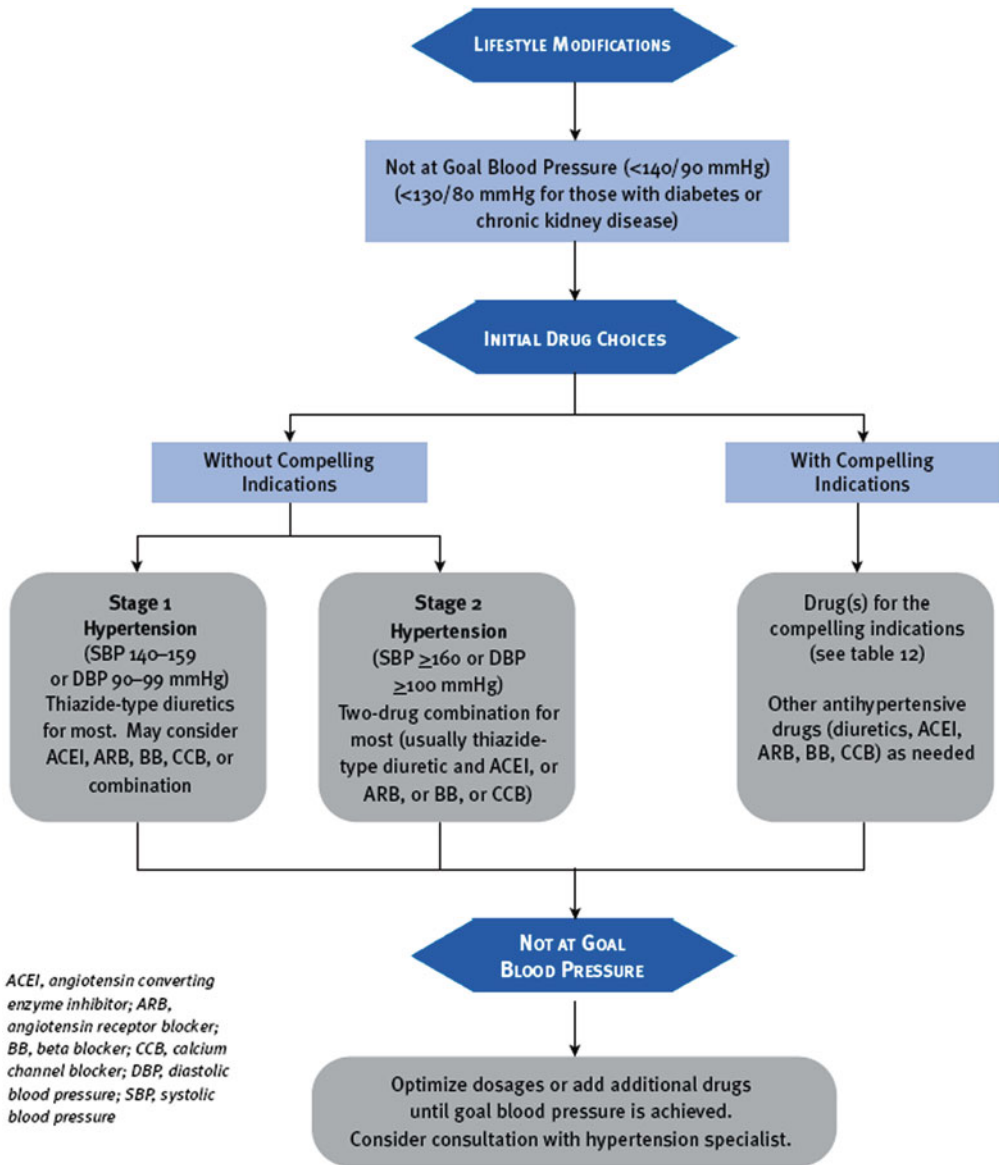
Fig. 1. Algorithm for treatment of hypertension. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ACEI* angiotensin-converting enzyme inhibitor, *CCB* calcium channel inhibitor *BB* beta blocker.

- When >20 mmHg of SBP and 10 mmHg of DBP reduction is needed, initiating therapy with two blood pressure-lowering drugs is advisable.
- When using multiple antihypertensive agents, administer agents with complementary (i.e., across blood pressure-related mechanisms) rather than overlapping (i.e., within blood pressure-related mechanisms) effects on blood pressure.

In the following paragraphs we review commonly used classes of antihypertensive medications. It is not our intent to review every randomized clinical trial of blood pressure

Table 6
Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes *(3)*

			Recommended drugs			
Compelling indication	*Diuretic*	*Beta-blocker*	*Angiotensin-converting enzyme inhibitor (ACEI)*	*Angiotensin receptor blocker (ARB)*	*Calcium channel blocker (CCB)*	*Aldosterone antagonist*
Heart failure	●	●	●	●		●
Postmyocardial infarction		●	●			●
High coronary disease risk	●	●	●		●	
Diabetes	●	●	●	●	●	
Chronic kidney disease			●	●		
Recurrent stroke prevention	●		●			

treatment with drugs as this has been done by others *(3, 34)*. Rather, our goal is to point out what we consider as the salient features and benefits of each drug class.

DIURETICS: CHLORTHALIDONE AND CHLOROTHIAZIDE, INTRODUCTORY YEAR: 1957 (US)

The Merck Renal team was responsible for the synthesis of the first thiazide diuretic (chlorothiazide) *(31)*. The congener hydrochlorothiazide was introduced a few years later and was incorporated into the first randomized clinical trial of hypertension, performed under the auspices of the US Veteran's Administration *(24)*. This pivotal study established the benefit of drug therapy in reducing what would now be considered as stage 2 hypertension. In the intervening years the dosing of the thiazide diuretic class has undergone change. Furthermore, the literature is replete with discussions of whether chlorthalidone (which is longer acting and appears to be a more effective agent for 24-h blood pressure control *(35)*) is superior to hydrochlorothiazide. Many guideline groups, including the Joint National Committee in its Seventh Report, emphasize use of thiazide diuretics because they are inexpensive, effective, and widely available. The mechanism of action for diuretic therapy is likely complex and includes sodium depletion, thus rendering the vessel less responsive to the constricting effects of endogenous compounds like norepinephrine *(36, 37)*. Diuretics are used in hypertensives of all ages. They may be particularly efficacious in the elderly and in African American hypertensives.

BETA-BLOCKERS: PROPRANOLOL, INTRODUCTORY YEAR: 1964 (UK)

Although introduced for treatment of angina, beta-blockade was also noted to reduce blood pressure. Despite more than 40 years of clinical usage, a precise mechanism by which

beta-blockers reduce blood pressure has not been identified. They lower renin activity and typically diminish the force of cardiac contraction. In recent years this class has come under scrutiny principally because atenolol, one of the most widely used beta-blockers, has repeatedly not performed as well as comparators in randomized clinical trials *(38)*. Currently, beta-blocker treatment for hypertension is more commonly used when coronary artery disease is present in young hypertensives, in those with faster heart rates (e.g., more than 80 beats/min), and in pregnant hypertensives. Beta-blocker use, particularly in the elderly, is less supported by evidence, and other classes (such as diuretics and calcium channel blockers) appear to be more protective of target organ damage in these older hypertensives.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS: CAPTOPRIL, INTRODUCTORY YEAR: 1981 (US)

The first orally active ACE inhibitor was the result of carefully designed pharmacologic blockade of what was known to be the active site of ACE. The effectiveness of blocking ACE was predicated on clinical experience with saralesin which blocks angiotensin-II effects, (but also had modest angiotensin-II agonism) and teprotide which blocked ACE but was available only as an intravenous infusion. Initial enthusiasm for the use of captopril was tempered by the package insert which limited its use to three-drug-resistant hypertension, and by clinical concerns over adverse events such as rash, taste disturbances, agranulocytosis, kidney disease, and hyperkalemia which are all far less common now since the currently prescribed doses (typically up to 150 mg daily) are less than the 400 mg to 1 g doses used in the early 1980s.

ACE inhibitors lower blood pressure directly through reduction in the generation of angiotensin-II from ACE and potentiation of bradykinin concentrations and indirectly through reductions in aldosterone production and release, prostaglandin stimulation, and by reducing sympathetic nervous system activity. ACE inhibitor therapy has indications for the management of type 1 diabetes with dipstick-positive proteinuria, in patients with heart failure, chronic kidney disease, and high cardiovascular risk *(39, 40)*.

CALCIUM CHANNEL BLOCKERS: VERAPIMIL/DILTIAZEM/NIFEDIPINE, INTRODUCTORY YEAR: 1981 (US)

Although introduced in 1981, the initial indication for calcium channel blockers was not for hypertension, but rather for angina (particularly Prinzmetal's variant). In the intervening years, they were used for lowering blood pressure, but their short duration of action (most were administered four times daily) and propensity for increase in heart rate (e.g., nifedipine) practically limited their usefulness. The introduction of a long-acting form of verapamil led to the first formal FDA approval for this class of drugs for hypertension. A long-acting form of diltiazem also received approval by the FDA for treatment of hypertension. The introduction of a long-acting nifedipine and ultimately of amlodipine increased greatly the popularity of this class of drugs for hypertension control. In 1995, a report from the Northwest Group Health Cooperative *(41)* suggested that calcium channel blockers might actually increase the risk of coronary artery disease mortality, and these findings dampened enthusiasm for calcium channel blocker treatment. However, several additional studies appeared in subsequent years showing that calcium channel blockade with long-acting formulations was effective for hypertension treatment and did preserve target organs,

particularly in the case of cerebrovascular disease *(42)*. Therefore, calcium channel blocker treatment is considered effective in most types of hypertensives.

Angiotensin Receptor Blockers: Losartan, Introductory Year: 1995 (US)

A large gap in time occurred between the introduction of calcium channel blockers and angiotensin receptor blockers (ARBs). Predicated on the popularity of blocking the renin–angiotensin system, ARBs offered similar blockade without the cough noted with ACE inhibitors and with a highly safe side effect profile. ARBs lower blood pressure through displacement of angiotensin-II binding to the AT_1 receptor, and possibly by stimulation of the (unblocked) vasodilatory AT_2 receptor. ARBs are indicated for the management of type 2 diabetes with dipstick-positive proteinuria, in hypertensive patients with left ventricular hypertrophy and in patients with heart failure *(43–45)*.

Other Blood Pressure-Lowering Agents

In addition to the above, there are several other classes of antihypertensive drug therapy which may be useful in select circumstances. Alpha$_1$-adrenergic receptor blockers (prazosin, doxazosin, terazosin) may be administered to older male patients with lower urinary tract symptoms from prostate enlargement. They are not typically used early in hypertension management since they fail to provide as much target organ protection as other agents, despite similar levels of blood pressure reduction. Alpha$_2$-agonists (clonidine, methyl-DOPA, guanfacine, guanabenz) lower blood pressure by reducing sympathetic outflow. They have a relative high adverse effect profile and are often used as third-line agents. They are useful in those with beta-blocker intolerance, and when given at nighttime their side effects of somnolence may be leveraged advantageously. Direct-acting vasodilators (minoxidil, hydralazine) reduce blood pressure through direct vasorelaxant effects on vascular smooth muscle. They are often associated with increased heart rate and sodium retention. The increase in heart rate can be problematic for hypertensive patients with symptomatic coronary artery disease.

Aldosterone (mineralocorticoid) antagonists have recently gained popularity. Spironolactone (Introductory Year: 1960) and eplerenone are currently available agents whose mechanism of blood pressure reduction is through blockade of aldosterone action. They have been shown to be effective in the treatment of heart failure and are useful adjuncts in the management of drug-resistant hypertension. They also appear to be particularly effective in overweight and obese patients.

Devices and Other Methods for Blood Pressure Lowering

In addition to lifestyle measures and drug therapy, there are several devices available which have been employed to lower blood pressure, as well as a growing number of "mind–body" therapies such as yoga and tai-chi. Overall, there is a lack of large-scale outcome trials to document possible benefit of such measures for target organ preservation *(46,47)*.

Summation: What is the benefit of treating blood pressure with drug therapy?

The use of drug therapy, compared with placebo, is associated with the following benefits *(3)*:

- A 50% reduction in new-onset heart failure
- A 35–45% reduction in stroke
- A 25% reduction in myocardial infarction
- Approximately a 50% reduction in the loss of kidney function over time from high blood pressure in persons with diabetic nephropathy

Blood pressure reduction saves lives and preserves the function of target organs in hypertensive patients. Most drugs used to treat high blood pressure are available in once-daily formulations which make patient adherence moreI likely. Although rates of blood pressure control are generally improving, the most difficult circumstances are the management of hypertension in dyslipidemics and diabetics. When these comorbidities are present, greater effort is needed to maximally reduce global cardiovascular risk.

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2

The Link Between Hypertension and Stroke: Summary of Observational Epidemiological Studies

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CONTENTS

Stroke is the leading cause of disability in the USA and the sixth most common cause of reduced disability-adjusted life years (DALYs) globally *(1)*. Among modifiable risk factors for ischemic and hemorrhagic stroke, hypertension is the most robust one across age, gender, and race *(2,3)*. Hypertension is also a highly prevalent health condition. As many as 65 million adult Americans (one in three US adults) have hypertension defined as elevated blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) or taking antihypertensive medicine or being told at least twice by a physician or other health professional that one has high blood pressure *(4,5)*. The prevalence of hypertension increases rapidly above the age of 65 years. The age-adjusted prevalence of hypertension in 2003–2006 was 75% for women and 65% for men over 65 years of age *(6)*. The prevalence of hypertension also varies by race and is highest amongst non-Hispanic Blacks (Table 1). The lifetime risk for developing hypertension is 90% among individuals who are normotensive at 55 years of age *(7)*.

HYPERTENSION AS A RISK FACTOR FOR STROKE

There is compelling evidence from observational and interventional studies, suggesting that hypertension is a significant and strong risk factor for stroke. It has been estimated that about 54% of strokes worldwide are attributable to high blood pressure (BP) *(8)*. The Framingham Heart Study in 1970 observed a significant relationship between the risk of stroke and blood pressure ≥160/95 mmHg in both sexes and at all ages *(9)*. Recent data

Table 1
Age-Adjusted Prevalence of Hypertension Among Persons 20 Years of
Age and Over in the USA (2003–2006)

	Male	*Female*
Non-Hispanic White	31% (28.4–33.7)	28.5% (26.8–30.2)
Non-Hispanic Black	41.8% (38.4–45.3)	43.3% (40.9–45.8)
Mexican American	24.1% (20.9–27.7)	27.9% (24.4–31.8)

Source: NHANES, 2003–2006 (www.cdc.gov/nchs/hdi.htm).

from this study found that participants with a normal BP (<120/80 mmHg) had approximately half the life time risk of stroke compared to those with high BP (≥140/90 mmHg) *(10)*.

Detailed analyses of large cohort studies have shown that the relationship between BP and risk of stroke is continuous, consistent, and independent of other risk factors. Earlier epidemiological studies used diastolic pressure as a measurement rather than systolic pressure and consistently showed its association with the risk of stroke *(11,12)*. In a meta-analysis of nine prospective observational studies published between 1958 and 1990, MacMahon et al. concluded that as BP decreased so did the risk of stroke. A decrease in diastolic BP by 5, 7.5, and 10 mmHg was associated with a decreased risk of stroke at least by 34, 46, and 56%, respectively (Table 2) *(11)*. The Eastern Stroke and Coronary Heart Disease Collaborative Research Group, a subset of Asia Pacific Cohort Studies Collaboration, also showed a positive relationship between diastolic BP and the risk of stroke. Overall, individuals in the group with the highest diastolic BP (DBP ≥ 110) had a risk of stroke about 13 times greater than those in the group with the lowest diastolic BP (DBP ≤ 79). For each 5 mm decrease in diastolic BP, the risk was almost halved for both ischemic strokes (odds ratio (OR) 0.61, 95% confidence interval (CI): 0.57–0.66) and hemorrhagic strokes (OR 0.54, 95% CI: 0.50–0.58) *(13)*. Systolic BP gained attention around the 1990s after several epidemiological studies suggested that systolic BP might represent a stronger risk factor for stroke than diastolic BP. Moreover, systolic BP increases with advancing age, whereas diastolic BP levels off at approximately age 50 years and decreases after age of 60 years. Systolic BP has been shown to be a better predictor of coronary heart disease after age of 50 years *(14)*. Systolic BP was more strongly correlated with 12-year risk of stroke mortality than diastolic BP in the Framingham Heart Study *(15)*. Also, the prospective population-based Copenhagen City Heart study reported that systolic BP is a better predictor of stroke than diastolic BP *(16)*. The Asia Pacific Cohort Studies Collaboration, which analyzed 37 cohort studies conducted in the Asia Pacific region, reported a continuous, log-linear association between systolic BP and risk of stroke down to at least 115 mmHg. After standardizing for age, a 10 mmHg decrease in systolic BP was associated with a 41% (95% CI: 40–42%) lower risk of stroke in Asia and a 30% (95% CI: 22–37%) lower risk of stroke in Australasia *(17)*. In an analysis of 61 prospective cohort studies by the Prospective Study Collaboration (PSC), a greater than twofold reduction in stroke mortality with

20 mmHg decrease in systolic BP was reported for ages 40–69 years (*see* Table 2) *(18)*. An important finding from the above studies is that the association between BP and risk of stroke is continuous and log linear at all ages, and there is no evidence of a threshold below which levels of BP are no longer associated with lower risk of stroke, down to approximately 115 mmHg for systolic BP or 75 mmHg for diastolic BP *(19)*. This finding suggests that whether blood pressure meets the usual definition of hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) or falls within the range of what is typically considered normal, a lower level of blood pressure has a lower risk of stroke. This steady increase in risk of stroke with increasing systolic BP is also reflected in the stroke risk appraisal score developed by the Framingham Heart study *(20,21)*.

Age is an important cofactor of the stroke and hypertension relationship. The positive relationship between elevated BP and risk of stroke is weaker in older age compared to middle-aged individuals. The Asia Pacific Cohort Studies Collaboration (APCSC) reported that in the age groups <60, 60–69, and ≥70 years, a 10 mmHg decrease in systolic BP was associated with a 54, 36, and 25% lower risk of stroke, respectively (Table 2) *(17)*. A similar trend was observed in the PSC and in the nested case–control study from Rochester Epidemiology Project (Fig. 1, Table 2) *(18,22)*. Although there is a decreased association between risk of stroke and hypertension among older populations, reducing BP is still beneficial due to the high incidence of stroke and high morbidity/mortality rates seen in this group *(19)*.

Racial differences in hypertension and risk of stroke have been reported from a few observational studies in the United States. The Northern Manhattan Stroke Study showed that hypertension was an independent risk factor for ischemic stroke in whites (OR 1.8), blacks (OR 2.0), and Caribbean Hispanics (OR 1.2) *(23)*. The Baltimore–Washington Cooperative Young Stroke Study, another population-based case–control study (patients aged 18–44 years), observed a positive association between hypertension and risk of ischemic stroke in whites and blacks for both men and women. Age-adjusted ORs (95% CI) for ischemic stroke for a history of hypertension for white men, white women, black men, and black women were 1.6 (0.7–3.2), 2.5 (1.1–5.9), 3.8 (1.8–7.9), and 4.2 (2.4–7.5), respectively *(24)*.

Treating hypertension is an important therapeutic target in the prevention of stroke that has been supported by several studies *(25–28)*. Since stroke is more dependent on blood pressure than coronary heart disease, the relationship between absolute risk of events and number of events prevented is stronger for stroke than coronary heat disease *(29)*. A long-term decrease of 5–6 mmHg in diastolic BP after 2–3 years of continuous treatment was associated with about 35–40% less stroke *(30)*. In the Hypertension Detection and Follow-up Program study, patients with hypertension receiving standardized antihypertensive therapy had a 5-year incidence of stroke of 1.9 per 100 persons compared to 2.9 per 100 persons among those receiving routine community care *(31)*. In the Systolic Hypertension in the Elderly Program, the 5-year incidence of all strokes was 5.2 per 100 with antihypertensive treatment versus 8.2 per 100 with placebo treatment *(32)*. A recent report from the Hypertension in the Very Elderly Trial suggests that patients with hypertension who are 80 years of age or older could also benefit from antihypertensive treatment to prevent stroke *(33)*.

Table 2
Overview of Risk of Stroke Associated with Hypertension

	MacMahon et al. (11)	*APCSC (17)*	*PSC (18)*	*Rochester Epidemiology Project (22)*
Study type	Meta-analysis of nine prospective cohort studies published between 1963 and 1989	Meta-analysis of 37 prospective cohort studies conducted between 1961 and 1992	Meta-analysis of 61 prospective cohort studies conducted between 1958 and 1990	Nested case–control study
Number of participants	418,343	425,325	958,074	1,862 (931 cases)
Cases of stroke	843 strokes of all type	5,178 strokes of all type	11,960 strokes of all type	931 ischemic strokes
Age at baseline	25–84	20–107	NR	Age-matched controls
Follow-up period (mean)	6–25 years (10 years)	2–27 years (7 years)	4–25 years (12 years)	15 years[a]
Sex	Male 96%	Male 57%	NR	Sex-matched controls
Study population	USA, Europe, Puerto Rico	China, Japan, Hong Kong, Taiwan, Singapore, South Korea, New Zealand, Australia	Europe, USA, Japan, China, Australia	USA

Table 2
(Continued)

	MacMahon et al. (11)	APCSC (17)		PSC (18)		Rochester Epidemiology Project (22)	
Results		*Age*	*10 mmHg ↓ SBP*	*Age*	*20 mmHg ↓ SBP*	*Age*	*OR (cases versus controls)*
	5 mmHg ↓ DBP 34% ↓ risk	<60	54% ↓ stroke risk	40–49	64% ↓ risk	50	4.8
	7.5 mmHg ↓ DBP 46% ↓ risk	60–69	36% ↓ stroke risk	50–59	62% ↓ risk	60	3.2
	10 mmHg ↓ DBP 56% ↓ risk	≥70	25% ↓ stroke risk	60–69	57% ↓ risk	70	2.2
				70–79	50% ↓ risk	80	1.5
				80–89	33% ↓ risk	90	1.0
				Age	*10 mmHg ↓ DBP*		
				40–49	65% ↓ risk		
				50–59	66% ↓ risk		
				60–69	60% ↓ risk		
				70–79	52% ↓ risk		
				80–89	37% ↓ risk		

APCSC Asia Pacific Cohort Studies Collaboration, *PSC* Prospective Studies Collaboration, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *OR* odds ratio, *NR* not reported

[a]Ischemic strokes identified from 15 years follow-up of Rochester Epidemiology Project.

Fig. 1. Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade. Rates are plotted on a floating absolute scale, and each square has area inversely proportional to the effective variance of the log mortality rate. From Lewington et al. *(18)*, with permission.

HYPERTENSION AS A RISK OF STROKE BY STROKE SUBTYPE

Stroke is usually classified into two major categories: ischemic stroke and hemorrhagic stroke. Hemorrhagic stroke can be further divided into strokes caused by an intracerebral hemorrhage (ICH) or a subarachnoid hemorrhage (SAH). Approximately 80% of strokes are ischemic, 15% are ICH and 5% are SAH *(34)*.

Hypertension and Ischemic Stroke

Various schemes have been developed to classify ischemic strokes into further subtypes according to its etiology *(35,36)*. Among these stroke subtypes, differences in incidence, recurrence rate, long-term survival, and race have been reported *(37,38)*. Several epidemiological studies have also addressed the relationship between risk factors and different stroke subtypes *(39–42)*. Differences in the strength of association between hypertension and risk of stroke among stroke subtypes, especially lacunar versus nonlacunar infarction (or small-vessel disease versus large-vessel disease), has drawn attention. By using the Stroke Data Bank of the National Institute of Neurological and Communicative Disorders and Stroke, Mast el al. determined that lacunar infarcts, especially multiple ones, were strongly related to hypertension (OR 2.5, 95% CI: 1.1–6.0) *(43)*. Hsu et al. compared the risk factors of

lacunar infarct with those of other stroke subtypes among 240 patients admitted to a stroke unit and noted that lacunar patients were more likely to have hypertension *(44)*. Among the 5,017 patients enrolled in the German Stroke Data Bank, hypertension was significantly more common in microangiopathy (79.4%) than in macroangiopathy (70.0%) *(45)*. However, recent studies and a systematic review appear to contradict these results. Schulz et al. observed no differences between stroke subtypes in regards to the association of hypertension and risk of stroke among hospitalized and nonhospitalized ischemic stroke patients *(42)*. Ohira et al. reported that the impact of baseline hypertension on the incidence of ischemic stroke did not vary according to ischemic stroke subtype in the Atherosclerosis Risk in Communities (ARIC) study data *(46)*. Similarly, a recent study by Lai et al. showed that while hypertension was the most common risk factor in first-time or recurrent stroke patients, the history of hypertension was not statistically different by stroke subtypes *(47)*. A systematic review of 28 studies comparing risk factors in patients with lacunar versus nonlacunar infarction showed that the association between hypertension and lacunar infarction is only marginally greater than that of nonlacunar infarction when subtypes were defined independently of risk factors *(36)*.

Hemorrhagic Stroke

Intracerebral Hemorrhage

Evidence from several epidemiological studies demonstrates a strong relationship between ICH and hypertension *(48–56)*. A case–control study of 331 consecutive primary ICH cases by the Melbourne Risk Factor Study (MERFS) Group reported a twofold increased risk of ICH with elevated BP *(57)*. Another case–control study by Feldmann et al. observed that hypertension is an independent risk factor that confers a sixfold higher risk (OR 5.71, 95% CI: 3.61–9.05) of ICH among men and women aged 18–49 years (Table 3) *(58)*. A systematic review of 11 case–control and 3 cohort studies on risk factors for ICH in the general population showed a positive association between hypertension and ICH with an overall OR of 3.68 in case–control studies. Among cohort studies, all studies showed a positive association between hypertension and ICH, and two studies showed an increasing risk of ICH with an increasing degree of hypertension (Table 3) *(59)*. This increase in risk of ICH with increase in degree of hypertension has been seen in other epidemiological studies as well. A pooled analysis of the ARIC and the Cardiovascular Health Study (CHS) data also reported this trend. Compared to normal–high normal BP, relative risk (RR) (95% CI) of ICH was 1.43 (0.90–2.26) for BP 140–159/90–99 mmHg, 2.71(1.58–4.67) for BP 160–179/100–109 mmHg, and 5.55 (3.07–10.03) for BP ≥160/110 mmHg (Table 3) *(60)*. A prospective cohort study carried out within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study also found a similar trend. The RR (95% CI) of ICH was 2.20 (2.28–6.25) for systolic BP 140–159 mmHg and 3.78 (2.28–6.25) for systolic BP ≥160 mmHg, compared to systolic BP ≤139 mmHg. RR was 2.10 (1.34–3.31) for diastolic BP 90–99 mmHg and 4.17 (2.58–6.74) for diastolic BP ≥100 mmHg, compared to diastolic BP ≤89 mmHg (Table 3) *(40)*. Sue et al. and others found a similar association in Asians (Table 3) *(61–63)*. Additionally, the risk of ICH increases with hypertension, in persons who are not compliant with antihypertensive medication, are 55 years of age or younger, or are smokers *(64)*. Improved control of hypertension appears to reduce the incidence of ICH *(65)*.

Table 3
Overview of Risk of Intracerebral Hemorrhage Associated with Hypertension

	Ariesen et al. (59)	*Sturgeon et al. (60)*	*Suh et al. (61)*	*Leppälä et al. (40)*	*Feldmann et al. (58)*
Study type	Systematic review of 11 case–control and 3 cohort studies from 1966 to 2001	Pooled analysis of ARIC and CHS	Prospective cohort study	Prospective cohort study	Case–control study
Number of participants	*Case–control studies* 72–662 *Cohort studies* 28,519–114,793	21,680 (15,792 ARIC; 5,888 CHS)	114,793	28,519	636[a]
Cases of ICH	*Case–control studies* 24–331 *Cohort studies* 112–386	135 (61 ARIC; 74 CHS)	372	112	217
Study population		USA	South Korea	Finland	USA
Age	Age matched on most of case–control studies	Mean age 54 (ARIC) Mean age 73 (CHS)	35–59	50–69	18–49
Sex	Sex matched on most of case–control studies	44.8% male (ARIC) 42.4% male (CHS)	Male only	Male only	56% male

Table 3
(Continued)

	Ariesen et al. (59)	Sturgeon et al. (60)	Suh et al. (61)	Leppälä et al. (40)	Feldmann et al. (58)
Results	*Case–control studies*	*BP* / RR	*BP* / RR	*SBP* / RR	*Adjusted OR*
	Overall crude OR 3.68	SBP <140/DBP <90 — 1.0	SBP <130/DBP <85 — 1.0	≤139 — 1.0	5.71
		SBP 140–159/DBP 90–99 — 1.43	SBP 130–139/DBP 85–89 — 2.16	140–159 — 2.20	
	Cohort studies	SBP 160–179/DBP 100–109 — 2.71	SBP 140–159/DBP 90–99 — 5.32	≥160 — 3.78	
	Adjusted RR 1.14–33 by	SBP ≥160/DBP ≥110 — 5.55	SBP 160–179/DBP 100–109 — 10.44		
	different levels of blood		SBP ≥180/DBP ≥110 — 33.32	*DBP* / RR	
	pressure	BP as continuous measure		≤89 — 1.0	
		10 mmHg ↑ SBP: 25% ↑ risk		90–99 — 2.10	
		10 mmHg ↑ DBP: 47% ↑ risk		≥100 — 4.17	

ICH Intracerebral hemorrhage, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BP* blood pressure, *OR* odds ratio, *RR* relative risk, *ARIC* Atherosclerosis Risk in Communities Study, *CHS* Cardiovascular Health Study

[a]Cases and controls matched on race, age, and gender.

Patients receiving long-term oral anticoagulation medication are also at increased risk for ICH *(66)*. Several risk factors of anticoagulation-associated bleeding have been investigated: advanced age, history of myocardial infarction or ischemic heart disease, diabetes, cerebrovascular disease, concomitant use of antiplatelet agents, intensity of anticoagulation, and hypertension *(67–71)*. A retrospective study by Wintzen et al. found that hypertension was present in 80% of the anticoagulant-associated ICH patients and was the most important predisposing condition *(72)*. Launbjerg et al. found that hypertension was an independent risk factor for anticoagulation-related bleeding in a multivariate analysis of 551 anticoagulated patients in 1,010 treatment years of follow-up *(73)*. Analysis of pooled data from five randomized trials indicates that the patients who had an ICH while taking warfarin had higher systolic and diastolic BPs at study entry than those warfarin-treated patients who did not have ICH *(74)*. On the other hand, a case–control study, comparing 170 patients who developed ICH during warfarin therapy and 1,020 matched anticoagulated patients who did not have ICH, found no statistical difference in the prevalence of diagnosed hypertension *(75)*. The effect of hypertension on mortality in anticoagulation-associated ICH has also been investigated. A retrospective study by Fric-Shamji et al. reported that higher initial mean arterial pressure was correlated with the propensity of hematoma to expand after initial imaging and might partially explain the effect on mortality *(76)*.

Subarachnoid Hemorrhage

Smoking, hypertension, and excessive alcohol are the most important modifiable risk factors for SAH *(77)*. An overview of all observational studies of risk factors for SAH published in English from 1966 through March 2005 reported a positive relationship between hypertension and SAH in both cohort (RR 2.5, 95% CI: 2.0–3.1) and case–control studies (OR 2.6, 95% CI: 2.0–3.1) (Table 4) *(77)*. A reanalysis of patient data in the Asia Pacific Cohort Studies Collaboration demonstrated that hypertension was an independent risk factor for SAH (hazard ratio (HR) 2.0, 95%CI: 1.5–2.7) (refer Table 4). The risk of SAH increases sharply with the increase in systolic BP *(78)*. This trend was also seen in a large cohort study among Asian populations for both men and women (Table 4) *(62)*. Since most subarachnoid hemorrhages are caused by the rupture of a cerebral aneurysm, several studies have attempted to identify risk factors for the rupture/growth of an aneurysm. Family history, age and modifiable risk factors, including cigarette smoking, and hypertension have been thought to increase the risk of rupture *(79–82)*. Among patients with small aneurysms (≤7 mm), hypertension, relatively young age, and posterior circulation location have been reported as significant risk factors for rupture *(83)*. However, a few studies, using magnetic resonance angiography or computed tomography angiography to assess aneurysm growth, did not find any relation between aneurysmal growth and hypertension *(84–86)*.

HYPERTENSION AND STROKE RECURRENCE

Ischemic Stroke Recurrence

Since lowering BP might worsen cerebral perfusion if autoregulation is impaired or if a severe carotid artery stenosis is present, lowering BP during the acute phase of ischemic stroke has been debated. However, several trials have confirmed that long-term BP control can reduce stroke recurrence *(19,25)*. A meta-analysis by Gueyffier et al. reported a

Table 4
Overview of Risk of Subarachnoid Hemorrhage Associated with Hypertension

	KMIC Study (62)	Feigin et al. (77)	Asia Pacific Cohort Studies Collaboration (78)
Study type	Prospective cohort study	Systematic review of 14 cohort and 23 case–control studies published between1966 and 2005	Meta-analysis of 26 cohort studies
Cases of SAH	308	3,936 (cohort 892; case–control 3,044)	236
Study population	South Korea	*Cohort studies* USA, Japan, UK, South Korea, Finland *Case–control studies* Finland, UK, USA, NZ, Portugal, Norway, Japan, Australia, Germany, WHO(Africa/Asia/Europe/Latin America)	Japan, China, Taiwan, South Korea, Singapore, Australia, NZ

(Continued)

Table 4
(Continued)

	KMIC Study (62)	Feigin et al. (77)	Asia Pacific Cohort Studies Collaboration (78)
Results	*Male*	*Cohort studies*	
	BP — *RR*	*Sex* — *RR*	*BP* — *HR*
	SBP <120/DBP <80 — 1.0	Female — 3.3	SBP <140 — 1.0
	SBP 120–129/DBP 80–84 — 1.46	Male — 2.3	SBP ≥140 — 2.0
	SBP 130–139/DBP 85–89 — 2.41	Total — 2.5	
	SBP 140–159/DBP 90–99 — 2.92		
	SBP 160–179/DBP 100–109 — 3.66		
	SBP ≥160/DBP ≥110 — 5.12		
	Female	*Case–control studies*	
	BP — *RR*	*Sex* — *OR*	
	SBP <120/DBP <80 — 1.0	Female — 3.3	10 mmHg ↑ SBP: 31% ↑ risk
	SBP 120–129/DBP 80–84 — 1.77	Male — 2.1	
	SBP 130–139/DBP 85–89 — 2.60	Total — 2.6	
	SBP 140–159/DBP 90–99 — 3.82		
	SBP 160–179/DBP 100–109 — 9.06		
	SBP ≥160/DBP ≥110 — 20.49		

KMIC Korea Medical Insurance Corporation, *SAH* subarachnoid hemorrhage, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BP* blood pressure, *RR* relative risk, *OR* odds ratio, *HR* hazard ratio

28% reduction in the risk of stroke recurrence without any significant adverse effect with antihypertensive drug treatment in hypertensive stroke patients *(87)*. The United Kingdom Transient Ischemic Attack Collaborative Group, which followed patients with a recent history of transient ischemic attack, amaurosis fugax, or minor stroke for average of 4 years, reported a direct and continuous relationship of both diastolic and systolic pressure with recurrence of stroke. Each 5 mmHg reduction in diastolic pressure and each 10 mmHg reduction in systolic pressure were associated with 34 and 28% fewer strokes, respectively *(88)*. A systematic review of seven randomized control trials reported a 24% (95% CI: 8–37) reduction in recurrent strokes in patients with prior ischemic or hemorrhagic stroke or transient ischemic attack with lowering blood pressure or treating hypertension with a variety of antihypertensive agents *(89)*. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), antihypertensive treatment resulted in a 43% (95% CI: 30–54) reduction in stroke recurrence in hypertensive and nonhypertensive patients with history of stroke or transient ischemic attack *(90)*.

Hemorrhagic Stroke Recurrence

Both European and Asian studies have suggested that hypertension is a risk factor for recurrence of ICH *(91–95)*. Yen et al. reported a high prevalence of hypertension among recurrent ICH patients in the Taiwanese population (88.2%) *(96)*. Poor control of arterial hypertension was detected in 7% of hypertensive patients without rebleeding and in 47% of hypertensive patients with rebleeding in a cohort of 112 survivors of a first primary ICH in an average 84.1 months of follow-up *(97)*. After a review of 43 recurrent ICH patients admitted to their hospital, Bae et al. reported an increased risk of recurrent hemorrhage among patients who had antihypertensive therapy of less than 3 months after the initial ICH compared to those with long-term therapy *(98)*. This finding suggests that long-term control of hypertension is necessary to prevent a recurrence of hemorrhage.

In this section, we have discussed hypertension as a risk of stroke recurrence on ischemic and hemorrhagic stroke separately. However, hypertension has also been reported as an independent risk factor of ICH among ischemic stroke patients (SBP ≥ 140 HR 2.07, 95% CI: 1.23–3.83) *(99)*.

IMPORTANCE OF SYSTOLIC BLOOD PRESSURE IN ELDERLY

Aging is associated with an increase in systolic BP and, consequently, isolated systolic hypertension (ISH) (systolic BP ≥140 mmHg and diastolic BP <90 mmHg) is the most common subtype of hypertension in elderly populations. As the elderly population of most developed countries is projected to increase *(100)*, ISH will continue to gain attention. The rise in systolic BP in ISH is mainly due to a decreased elasticity of the large arteries and is not necessarily accompanied by a rise in mean arterial blood pressure or in peripheral resistance *(101)*. Epidemiological studies have indicated that ISH is an independent risk factor for stroke and a potent modifiable target for reducing the risk for stroke. In the Framingham Heart study, individuals with ISH had an increased incidence of stroke independent of age and arterial rigidity *(15)*. In the Honolulu Heart program, the RR of stroke from ISH in Japanese-American men aged 45–54 years and men aged 55–68 years was 4.8 and 1.2, respectively *(102)*. In the NHANES long-term follow-up study, stroke risk was significantly higher in individuals with ISH (RR 2.7, 95% CI: 2.0–3.4) *(103)*. Meta-analysis

of eight clinical trials including 15,693 patients with ISH showed that the HR for stroke associated with a 10 mmHg higher initial systolic BP was 1.22 and active treatment of hypertension reduced stroke by 30% *(104)*.

CONCLUSION

In this chapter, current data pertinent to hypertension and its risk of stroke are reviewed. The prevention and management of hypertension are major public health challenges *(105)*. Despite the availability of therapies, it has been reported that even in developed countries, many patients with hypertension remain undetected or untreated *(106)*. The 2005–2006 data from NHANES/NCHS showed that 78.7% of adult Americans with hypertension were aware of their condition, 69.1% were under current treatment, and 45.4% had it under control (NCHS and National Heart, Lung, and Blood Institute (NHLBI)) *(5)*. Data from the Framingham Heart study show that control rates of BP in men <60, 60–79, and ≥80 years of age were 38, 36, and 38%, respectively. For women in the same age groups, they were 38, 28, and 23, respectively *(5)*. It is not surprising that nontreatment or nonoptimal treatment of hypertension is associated with an excess risk of stroke. Compared with treated and controlled hypertensives, the RR of stroke for treated and uncontrolled hypertensives and for untreated hypertensives who needed treatment was 1.30 (95% CI: 0.70–2.44) and 1.76 (95% CI: 1.05–2.94), respectively *(107)*. It has been reported that there is a lack of blood pressure control ,particularly in the early morning hours in patients receiving seemingly effective antihypertensive therapy *(108,109)*. This so-called "morning blood pressure surge" is reported to coincide with a higher prevalence of multiple silent infarcts on magnetic resonance imaging and an increased risk for stroke *(110)*. Elliott et al performed a meta-analysis of 31 publications and reported a 79% (95% CI: 72–87%) increase in stroke of all types between 6:00 a.m. and noon compared to the other 18 h of the day *(111)*. Current evidence suggests that ambulatory blood pressure monitoring may provide a more sensitive means of detecting patients at risk and monitoring therapeutic effect *(112)*. More studies on how to effectively control hypertension are needed to prevent stroke.

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3 Blood Pressure Control and Primary Prevention of Stroke: Summary of Clinical Trial Data

William J. Elliott, MD, PhD

CONTENTS

INTRODUCTION

Hypertension, or high blood pressure (BP), is the most important modifiable risk factor for stroke *(1–3)*, accounting for 54% of the population-attributable risk worldwide in a recent global health model *(4)*. Stroke is the second leading cause of death worldwide (although third to cancer in the USA) and ranks very highly as a cause of adult disability in all countries. As developing nations overcome problems related to sanitation and infant mortality, hypertension is expected to become the most important risk factor worldwide for premature mortality and morbidity among adults. The purpose of this chapter is to review the existing clinical trial evidence supporting the use of antihypertensive drug therapy to prevent a first stroke. Unfortunately, many such clinical trials enrolled individuals with a history of a prior stroke (who are typically at three to four times the risk of stroke as people without such a history) and reported only the aggregated results. Some investigators have attempted to retrieve the numbers of such subjects (and the numbers who suffered a recurrent stroke) from some of the earlier clinical trials *(5)*. Two trials (e.g., the Heart Outcomes Prevention Evaluation and the Study on Cognition and Prognosis in the Elderly) have reported sufficient data in different publications to be able to calculate these parameters *(6–9)*. Since the results of many recent and large trials have not disclosed their results in this fashion, we are forced to examine the small set of clinical trials for which we have data about primary strokes (i.e., those studies that excluded subjects with a history of a prior

stroke), but the results of the analyses differ little from the overall conclusions (which are based on all studies that reported both primary and recurrent strokes in the aggregate).

CLINICAL TRIALS INVOLVING PLACEBO OR NO TREATMENT

There are 33 trials that observed strokes and involved comparisons of placebo or no treatment (hereinafter called "Placebo") with active antihypertensive agents (Table 1). The importance of the link between BP lowering and stroke can be illustrated by the fact that many of these important clinical trials used "incident fatal or nonfatal stroke" as their prespecified primary endpoint, and based their power calculation on an estimate of the efficacy of BP-lowering drugs in preventing stroke *(17,21,22,26,27,32,36,39)*. Many of these trials were performed during the last millennium, when placebo or no treatment was still ethical in outcomes studies. Most recent trials have compared outcomes in subjects whose established antihypertensive medication regimen was augmented by the addition of a placebo or one or more active antihypertensive agents, as an attempt to control BP was considered mandatory. It is likely, therefore, that the early studies (in which placebo-treated patients were typically allowed to receive "rescue" active antihypertensive drug therapy only if the BP exceeded thresholds) showed a larger impact of antihypertensive drugs on primary stroke prevention than more recent studies, because efforts to control BP were made in both randomized groups. The other major *caveat* about these results is that, in all trials, some subjects chose to discontinue their assigned treatment. Thus, in each arm this decision "biases the result of the trial toward the null." As a consequence, the estimates of the effectiveness of antihypertensive drug therapy are typically biased in a pessimistic direction, i.e., the results obtained in general medical practice with patients who follow their healthcare providers' recommendations are likely to be even *better* than those shown here.

A good example of these challenges is the earliest, multicenter, placebo-controlled long-term trial of antihypertensive drug treatment that recorded stroke outcomes, the Veterans Administration's Cooperative Study Group on Antihypertensive Agents *(10)*. In the 143 subjects with diastolic BPs between 115 and 129 mmHg (after 7 days of hospitalization, bedrest, and a low-sodium diet), there were 11 with a prior thrombotic stroke. It has not been revealed if the five strokes observed before the study's early termination (at 18 months) occurred in individuals with a prior history of stroke. Among those randomized to placebo, seven experienced "treatment failure" necessitating termination of participation (at an average of 17 months), and active antihypertensive drugs were given.

The results of these trials can be summarized in many different ways (Fig. 1), but the results are quite similar. If one restricts the meta-analysis to the nine studies that randomized subjects to *initial* therapy with either placebo or antihypertensive drug therapy, *and* included only subjects with no prior history of stroke *(8,9,12–17,19,22)*, there is no significant inhomogeneity across studies [P (homogeneity) = 0.28], and the combined relative risk for a first stroke is 0.69 (95% confidence interval: 0.60–0.79, $P < 0.0001$). If one then adds the trial that used no treatment (rather than placebo) in the control group *(20)*, there is little change (combined relative risk = 0.68, 95% CI: 0.60–0.77). After adding data from a study that simply added an ACE inhibitor or placebo to whatever other antihypertensive therapy was required *(6,7)*, the combined relative risk for *all* 11 studies that reported only

Table 1
Placebo-Controlled Trials of Primary Stroke Prevention Involving Antihypertensive Drugs

Trial Acronym, Year	Years of Follow-Up	Subjects with HTN (%)	Δ SBP (mmHg)	Active Arm		Control Arm		Comments (Number with Prior Strokes)
				Agent	Number of First Strokes/ Number of Subjects	Agent	Number of First Strokes/ Number of Subjects	
VA I (10), 1967	1.5	100	30	Diuretic + other	1/73	Placebo + "rescue"	3/70	(6/5)
VA II (11), 1970	3.3	100	31.4	Diuretic + other	5/186	Placebo + "rescue"	20/194	(NR/NR)
USPHS (12), 1977	7	100	16	Diuretic + other	1/193	Placebo	6/196	(0/0)
Oslo (13), 1980	5.5	100	17	Diuretic	0/406	No treatment	5/379	(0/0)
ANBP-1 (14), 1980	3	100	NR	Diuretic	13/1721	Placebo	22/1706	(0/0)
Kuramoto (15), 1981	4	100	20	Diuretic	3/44	Placebo	4/47	(0/0)
HDFP[a] (16), 1982	5	100	10	Diuretic	87/5364	Placebo	142/5333	(N/A)
EWPHE[a] (17), 1985	4.6	100	21	Diuretic	16/386	Placebo	22/405	(N/A)
MRC-1 (18), 1985	5.5	100	~13 / ~9.5	Diuretic or β-blocker	18/4297 / 42/4203	Placebo	109/8654	(32 or 31/61)
IPPPSH (19), 1985	4	100	3.8	β-Blocker	45/3185	Placebo	46/3172	(0/0)
Coope & Warrender[a] (20), 1986	4.4	100	18.0	β-Blocker	18/410	No treatment	38/460	(N/A)
SHEP Pilot (21), 1989	2.8	100	15	Diuretic	11/443	Placebo + "rescue"	6/108	(8)

(Continued)

Table 1
(Continued)

Trial Acronym, Year	Years of Follow-Up	Subjects with HTN (%)	Δ SBP (mmHg)	Active Arm		Control Arm		Comments (Number of Subjects with Prior Strokes)
				Agent	Number of First Strokes/ Number of Subjects	Agent	Number of First Strokes/ Number of Subjects	
SHEP[a] (22), 1991	4.5	100	11.1	Diuretic	95/2314	Placebo + "rescue"	152/2338	(N/A)
STOP-1 (23), 1991	2.1	100	19.5	Diuretic or β-blocker	28/782	Placebo	49/784	(32/36)
MRC-E (24), 1992	5.7	100	15 15	Diuretic or β-blocker	45/1081 56/1102	Placebo	134/2213	(NR or NR/NR)
STONE (25), 1996	2.5	100	9.5	CCB	16/817	Placebo	36/815	(NR/NR); not randomized
Syst-EUR (26), 1997	2.5	100	10.7	CCB + other	49/2398	Placebo + other	80/2297	(103)
Syst-China (27), 1998	2.8	100	8.0	CCB + other	45/1253	Placebo + other	59/1141	(45); not randomized
HOPE[a] (6,7), 2000	4.5	46	3	Other + ACE-I	113/4188	Other + placebo	175/4190	Add-on (N/A)
PART2 (28), 2000	4.7	Unknown	6.0	Other + ACE-I	7/308	Other + placebo	4/309	Add-on (34/28)
IDNT (29), 2001	2.6	100	3 4	(ARB or CCB) + other	28/579 15/567	Placebo + other	26/569	(NR/NR)

Table 1
(Continued)

Trial Acronym, Year	Years of Follow-Up	Subjects with HTN (%)	Δ SBP (mmHg)	Active Arm		Control Arm		Comments (Number of Subjects with Prior Strokes)
				Agent	Number of First Strokes/ Number of Subjects	Agent	Number of First Strokes/ Number of Subjects	
RENAAL (30), 2001	3.4	100	2	ARB + other	47/751	Placebo + other	50/762	(0/1)
EUROPA (31), 2003	4.2	27? (BP > 160/95)	5.0	Other + ACE-I	98/6110	Other + placebo	102/6108	Add-on (210/199)
HY-VET Pilot (32), 2003	1.1	100	23.0 23.0	ACE-I or diuretic	6/426 12/431	Placebo + rescue	18/426	(18 or 18/22)
SCOPE^a (8,9), 2003	3.5	100	3.2	ARB + other	83/2386	Placebo + other	100/2378	(N/A)
DIAB-HYCAR (33), 2004	3.3	55	1.3	Other + ACE-I	118/2443	Other + placebo	116/2469	Add-on (107/100)
PEACE (34), 2004	4.8	45	3.0	Other + ACE-I	71/4158	Other + placebo	92/4132	Add-on (291/248)
ACTION (35), 2005	4.9	100	6.6	Other + CCB	50/1975	Other + placebo	75/2002	Add-on (NR/NR)
FEVER (36), 2005	3.3	100	3.5	Diuretic + CCB	177/4841	Diuretic + placebo	251/4870	Second-line (685/753)

(Continued)

Table 1
(Continued)

Trial Acronym, Year	Years of Follow-Up	Subjects with HTN (%)	ΔSBP (mmHg)	Active Arm Agent	Number of First Strokes/ Number of Subjects	Control Arm Agent	Number of First Strokes/ Number of Subjects	Comments (Number of Subjects with Prior Strokes)
ADVANCE (37), 2007	4.3	68	5.6	Other + diuretic + ACE-I	215/5569	Other + placebo	218/5571	Combination (502/520)
Jikei (38), 2007	3.1	88	1.0	Other + ARB	25/1541	Other	43/1540	Add-on (NR/NR)
HYVET (39), 2008	1.8	100	15.0	Diuretic	51/1933	Placebo	69/1912	(130/131)
TRANSCEND (40), 2008	4.7	76	4.0	Other + ARB	112/2842	Other + placebo	136/2836	Add-on (648/654)

[a]Denotes study for which the number of observed primary (as opposed to both primary and secondary) strokes can be calculated. (N/A) indicates that the number of subjects with prior stroke has been reported and subtracted from the total number of subjects in the trial.

HTN hypertension, *SBP* systolic blood pressure, *VA I* First Veterans Administration Cooperative Study Group on Antihypertensive Agents, *VA II* Veterans Administration Cooperative Study Group on Antihypertensive Agents, *USPHS* United States Public Health Service trial, *ANBP-1* First Australian National Blood Pressure trial, *HDFP* Hypertension Detection and Follow-up Program, *EWPHE* European Working Party on Hypertension in the Elderly, *MRC-1* First Medical Research Council trial, *IPPPSH* International Prospective Primary Prevention Study in Hypertension, *SHEP* Systolic Hypertension in the Elderly Program, *STOP-1* First Swedish Trial in Old Patients with Hypertension, *MRC-E* Medical Research Council trial (in elderly hypertensives), *STONE* Shanghai Trial Of Nifedipine in the Elderly trial, *Syst-EUR* Systolic Hypertension in Europe trial, *Syst-China* Systolic Hypertension in China trial, *HOPE* Heart Outcomes Prevention Evaluation, *PART2* Prevention of Atherosclerosis with Ramipril study Number 2, *IDNT* Irbesartan Diabetic Nephropathy Trial, *RENAAL* Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan, *EUROPA* EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease, *HYVET* Hypertension in the Very Elderly Trial, *SCOPE* Study on Cognition and Prognosis in the Elderly trial, *DIAB-HYCAR* non-insulin-dependent DIABetes, HYpertension, microalbuminuria or proteinuria, Cardiovascular events And Rampril study, *PEACE* Prevention of Events with Angiotensin-Converting Enzyme inhibition trial, *ACTION* A Coronary disease Trial Investigating Outcome with Nifedipine GITS trial, *FEVER* Felodipine EVEnt Reduction study, *ADVANCE* Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation, *TRANSCEND* Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease trial, *CCB* calcium channel blocker, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BP* blood pressure, *NR* not reported

initial strokes is therefore 0.67 (95% CI: 0.60–0.75), with the *P* (homogeneity) = 0.37 (data not shown in Fig. 1).

This conclusion is relatively robust to adding the results of clinical trials that included subjects with a history of prior strokes, but for which the numbers of subjects with recurrent strokes have not been revealed. Below the thick horizontal line in Fig. 1 are included, in sequence, the placebo-controlled studies that used initial therapy *(10,11,18,21,23,24,26,29,30,32,39)*, the two nonrandomized studies *(25,26)*, the trial that randomized hypertensive subjects to placebo or a calcium antagonist as second-line therapy *(36)*, and the trial that added either placebo or a calcium antagonist to whatever other antihypertensive drugs were already being taken *(35)*. The combined relative risk for stroke for these trials is 0.66 (95% CI: 0.62–0.71), with a *P* (homogeneity) = 0.32. Finally, one can add the results of trials in which "add-on" placebo or antihypertensive drug was given, but the subjects were not all hypertensive *(28,31,33,34,37,38,40)*. Many object to this, however, because the study populations become much less homogeneous. This may be the reason for the significant inhomogeneity (*P* = 0.0011) in the fixed-effects meta-analysis of these data. Nonetheless, using a random-effects model, the pooled relative risk for stroke across all 33 trials involving placebo or no treatment (whether primary or mixed primary/secondary stroke prevention) is 0.71 (95% CI: 0.65–0.78, *P* < 0.0001).

One of the most important conclusions from this dataset can be illustrated in Fig. 2. Across all trials, the number of strokes prevented (per 1,000 subject-years) is directly proportional to the absolute risk of stroke (per 1,000 subject-years in the placebo-treated group). The corollaries to this are: "It may be difficult, if not impossible, to prevent a stroke in a person who has a very low risk of a stroke," and conversely, "The higher the baseline risk of stroke, the greater the number of people who will benefit from treatment." The relationship is strengthened even further if placebo-controlled trials of secondary stroke prevention (e.g., the Perindopril pROtection aGainst REcurrent Stroke Study) are added.

CLINICAL TRIALS COMPARING TWO OR MORE ACTIVE ANTIHYPERTENSIVE DRUGS

Thirty-one clinical trials that reported strokes compared two or more active antihypertensive drugs in primarily hypertensive patients (Table 2). Note that three trials included a placebo arm (and are therefore also listed in Table 1) *(18,24,32)*, and that all except ONTARGET had hypertension as an inclusion criterion. Only five of these studies were planned as primary prevention trials *(41,42,46,47,49)*. The other 26 have enrolled at least one subject with a prior stroke, and none have reported the numbers of subjects that suffered a first vs. second stroke.

The lack of solid data about primary stroke prevention in hypertension trials can be illustrated by the results of a network meta-analysis of the data (nine placebo-controlled trials and six actively controlled trials). Unfortunately, the number of trials reporting observed first strokes is zero with an angiotensin receptor blocker (ARB), and only two each for a calcium antagonist or an angiotensin-converting enzyme (ACE) inhibitor. This leads to a high degree of "incoherence" (ω = 0.136) in the model, and nonsignificant point estimates for regimens beginning with anything by a diuretic or β-blocker (data not shown).
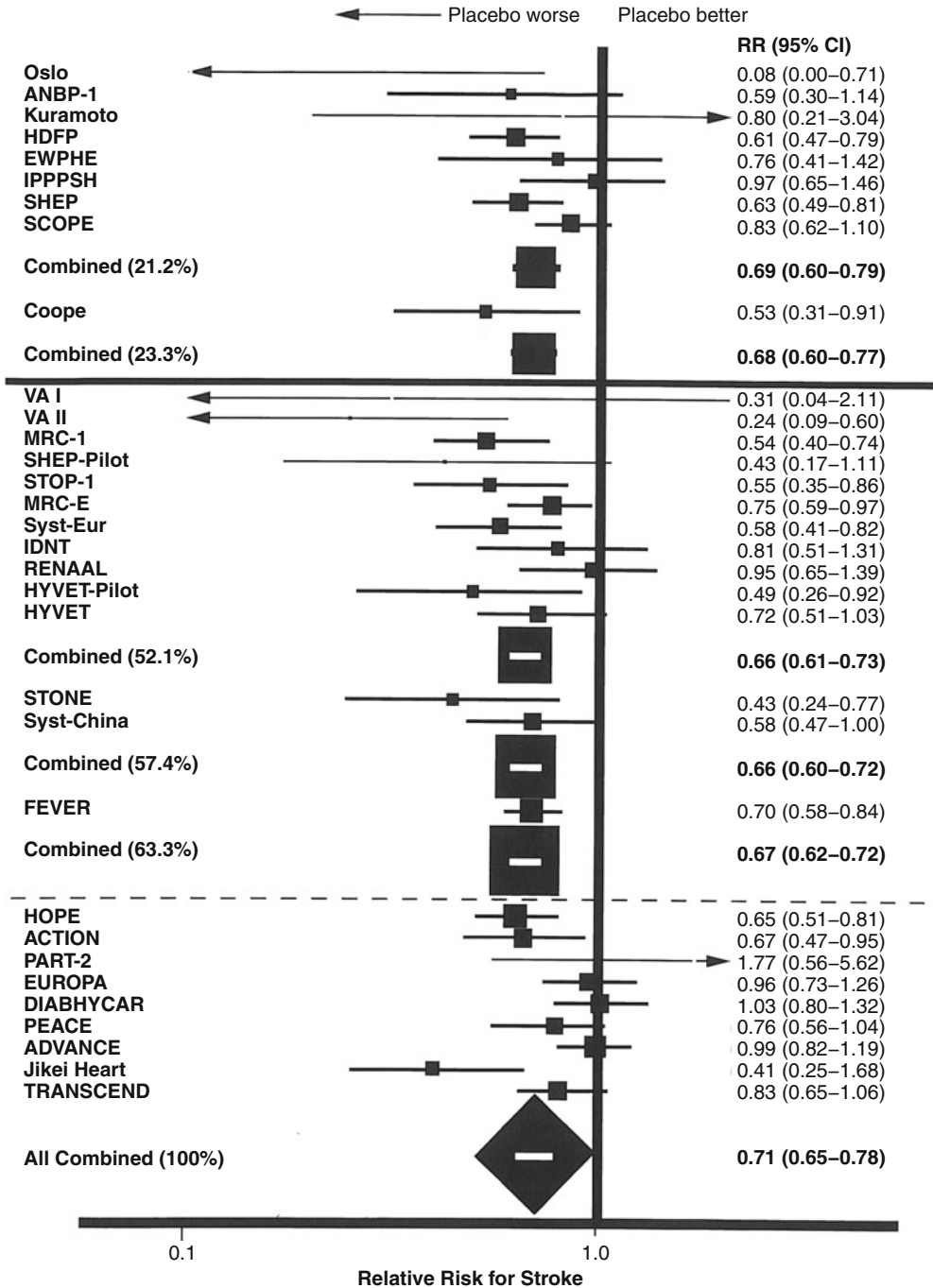
Fig. 1. Meta-analysis of placebo-controlled clinical trials of antihypertensive drugs that reported either first or first and recurrent strokes. The trials above the *broad horizontal line* include only hypertensive subjects suffering a first stroke. The distinctions between groups of trials are discussed in the text. The *boxes* (representing the point estimates of relative risk, RR) are drawn in proportion to the number of strokes, and the *horizontal lines* represent the 95% confidence intervals for each trial. The meta-analytic results (drawn in the figure as *squares*) above the *dashed horizontal line* (above "HOPE") showed no significant inhomogeneity in fixed-effects models. When trials that included nonhypertensive subjects
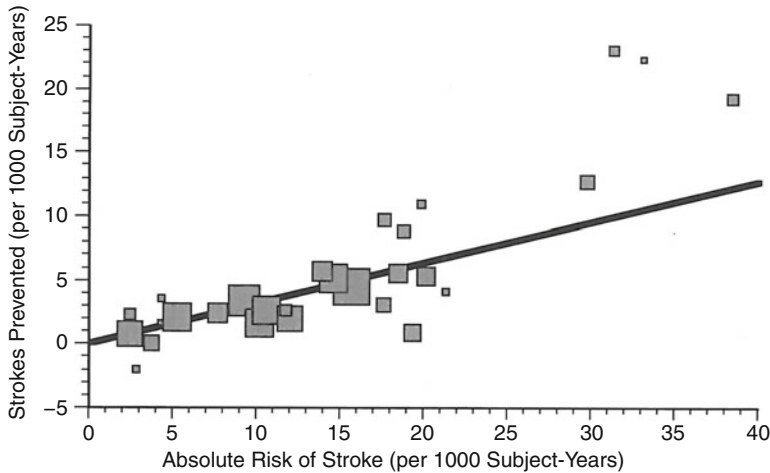
Fig. 2. Relationship of the absolute risk of stroke (calculated as strokes per 1,000 subject-years in the placebo-treated group) and the number of strokes prevented by treatment (per 1,000 subject-years). Data from individual trials are plotted as *squares*, with the area of each *square* proportional to the number of strokes reported for each trial. The correlation coefficients for this relationship were 0.86, *P* < 0.001 for unweighted data, and 0.89, *P* < 0.001 for weighted data.

These results stand in sharp contrast to those obtained from those derived from "the preponderance of the evidence," i.e., trials comparing placebo and/or antihypertensive drugs in hypertensive subjects (Fig. 3). For this much extensive network (involving 51 trials, 67 comparisons, 10,252 strokes, and 278,962 subjects), the incoherence value is very small ($\omega = 0.0000163$), suggesting a high degree of internal consistency. All five classes of antihypertensive drugs significantly (all *P* < 0.00001) prevent stroke, better than placebo (Fig. 3). If the referent agent is arbitrarily changed to "diuretic," the incoherence does not change, and all comparisons (except the calcium antagonist) are again significant, indicating that placebo (odds ratio 1.60, 95% confidence interval: 1.44–1.78, *P* < 0.0001), β-blocker (odds ratio: 1.23, 95% CI: 1.10–1.37, *P* < 0.0003), ACE inhibitor (odds ratio: 1.16, 95% CI: 1.04–1.29, *P* < 0.008), and ARB (odds ratio: 1.18, 95% CI: 1.01–1.38, *P* < 0.04) are significantly inferior to a diuretic in preventing stroke. The difference between the diuretic and calcium antagonist (odds ratio 1.02, 95% CI: 0.93–1.12, *P* = 0.69) is not significant. These conclusions were robust to a wide range of changes in the dataset (e.g., omit ACCOMPLISH, as it studied initial combinations of agents; allocate the results of Scandinavian trials *(23,48,50,52)*, which used the physician's choice of either an initial β-blocker or an initial diuretic as "conventional therapy") to β-blocker, diuretic, or a 60:40 attribution of risk, similar to the reported distribution of initial treatments (data not shown).

Fig. 1. *(Continued)* were added (below the *dashed horizontal line*; see text for details), the random-effects model showed a similar overall result (drawn as a *rhombus*) as the prior meta-analyses, despite significant inhomogeneity in the fixed-effects model. These data suggest that the point estimates and confidence limits for these meta-analyses are robust to many alterations in the dataset (and the rigor with which trials are included or excluded). For expansions of acronyms of trials, *see* Tables 1 and 2.

Table 2
Actively Controlled Trials of Primary Stroke Prevention Involving Initial Antihypertensive Drugs

Trial Acronym, Year	Years of Follow-Up	Subjects with HTN (%)	Δ SBP (mmHg)	Active Arm Agent	Number of First Strokes/ Number of Subjects	Control Arm Agent	Number of First Strokes/ Number of Subjects	Comments (Number of Subjects with Prior Strokes)
MRC-1 (*18*), 1985	5.5	100	4.5	Diuretic	18/4297	β-Blocker	42/4203	(32/31)
HAPPHY (*41*), 1987	3.8	100	0	D	41/3297	β-Blocker	32/3276	(0/0)
MAPHY (*42*), 1988	5.0	100	0.3	D	25/1625	β-Blocker	23/1609	(0/0)
MRC-E (*24*), 1992	5.7	100	0	Diuretic	45/1081	β-Blocker	56/1102	(NR/NR)
MIDAS (*43*), 1996	3.0	100	3.5	Diuretic	3/441	CCB	6/442	(NR/NR)
VHAS (*44*), 1997	2.0	100	1.0	Diuretic	4/707	CCB	5/707	(NR/NR)
ABCD (*45*), 1998	5.0	100	0	ACE-I	7/235	CCB	11/235	(2/3)
FACET (*46*), 1998	2.5	100	–4	ACE-I	4/189	CCB	10/191	(0/0)
UKPDS (*47*), 1998	8.4	100	–1	β-Blocker	17/358	ACE-I	21/400	(0/0)
CAPPP (*48*), 1999	6.1	100	2	β-Blocker/ diuretic	148/5493	ACE-I	189/5492	(39/50)
NICH-ES (*49*), 1999	4.2	100	0	Diuretic	8/215	CCB	8/214	(0/0)
STOP-2 (*50*), 1999	5.0	100	1 1	β-Blocker/ diuretic	237/2213	ACE-I or CCB	215/2205 207/2196	(86/86) (or 83)
INSIGHT (*51*), 2000	3.5	100	0	Diuretic	74/3164	CCB	67/3157	(NR/NR)
NORDIL (*52*), 2000	4.5	100	–3	β-Blocker/ diuretic	196/5471	CCB	159/5410	(88/74)
AASK (*53,54*), 2001, 2002	4.4 or 3.6	100	0 2	β-Blocker	23/441	ACE-I or CCB	23/436 9/217	(NR/NR)

Table 2
(Continued)

Trial Acronym, Year	Years of Follow-Up	Subjects with HTN (%)	Δ SBP (mmHg)	Active Arm		Control Arm		Comments (Number of Subjects with Prior Strokes)
				Agent	Number of First Strokes/ Number of Subjects	Agent	Number of First Strokes/ Number of Subjects	
IDNT (29), 2001	2.6	100	1	CCB	28/579	ARB	15/567	(NR/NR)
LIFE (55), 2002	4.7	100	–1.1	β-Blocker	309/4588	ARB	232/4605	(359/369)
ELSA (56), 2002	3.8	100	–0.2	β-Blocker	14/1157	CCB	9/1177	(NR/NR)
ALLHAT (57), 2002	4.9	100	2 1	Diuretic	675/15255	ACE-I or CCB	457/9054 377/9048	(NR/NR) (or NR)
ANBP-2 (58), 2003	4.1	100	1	Diuretic	107/3039	ACE-I	112/3044	(~152/~122)
CONVINCE (59), 2003	3.0	100	0.1	Diuretic or β-blocker	58/3831 60/4466	CCB	79/3986 54/4393	(393/370)
SHELL (60), 2003	3.6	100	–1.6	Diuretic	38/940	CCB	37/942	(NR/NR)
INVEST (61), 2003	2.7	100	0.3	β-Blocker	201/11309	CCB	176/11267	(567/595)
HYVET-Pilot (32), 2003	1.1	100	0	Diuretic	6/426	ACE-I	12/431	(18/18)
JMIC-B (62), 2004	3.0	100	–2	ACE-I	16/822	CCB	16/828	(NR/NR)
VALUE (63), 2004	4.2	100	2.23	CCB	281/7596	ARB	322/7649	(1501/1513)

(Continued)

Table 2
(Continued)

Trial Acronym, Year	Years of Follow-Up	Subjects with HTN (%)	Δ SBP (mmHg)	Active Arm		Control Arm		Comments (Number of Subjects with Prior Strokes)
				Agent	Number of First Strokes/Number of Subjects	Agent	Number of First Strokes/Number of Subjects	
DETAIL (64), 2004	5.0	100	−4	ACE-I	6/130	ARB	6/120	(NR/NR)
ASCOT (65), 2005	5.5	100	1.6	β-Blocker	422/9618	CCB	327/9639	(1063/1050)
CASE-J (66), 2008	3.2	100	1.7	CCB	50/2349	ARB	61/2354	(225/248)
ONTARGET (67), 2008	4.7	69	0.9	ACE-I	405/8576	ARB	369/8642	(1805/1758)
ACCOMPLISH (68), 2008	3.0	100	0.9	ACE-I + diuretic	133/5762	ACE-I + CCB	112/5744	(736/762)

HTN hypertension, *SBP* systolic blood pressure, *MRC-1* Medical Research Council trial (in "mild" hypertensives), *HAPPHY* Heart Attack Primary Prevention in Hypertensives study, *MAPHY* Metoprolol Atherosclerosis Prevention in Hypertensives trial, *NR* not reported, *MRC-E* Medical Research Council trial (in elderly hypertensives), *MIDAS* Multicenter Isradipine Diuretic Atherosclerosis Study, *VHAS* Verapamil Hypertension Atherosclerosis Study, *ABCD* Appropriate Blood pressure Control in Diabetes study, *FACET* Fosinopril Amlodipine Cardiac Events randomized Trial, *UKPDS* United Kingdom Prospective Diabetes Study, *CAPPP* CAPtopril Primary Prevention Project, *NICH-ES* National Intervention Cooperative Study in Elderly Hypertensives, *STOP-2* Second Swedish Trial in Old Patients with hypertension, *INSIGHT* International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment, *NORDIL* NORdic DILtiazem study, *AASK* African American Study on Kidney disease and hypertension trial, *IDNT* Irbesartan Diabetic Nephropathy Trial, *LIFE* Losartan Intervention For Endpoint reduction trial, *ELSA* European Lacidipine Study on Atherosclerosis, *ALLHAT* Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial, *ANBP-2* Second Australian National Blood Pressure trial, *CONVINCE* Controlled-ONset Verapamil INvestigation of Cardiovascular Endpoints trial, *SHELL* Systolic Hypertension in the Elderly: Lacidipine Long-term study, *INVEST* INternational VErapamil-trandolapril STudy, *HYVET* Hypertension in the Very Elderly trial, *JMIC-B* Japan Multicenter Investigation for Cardiovascular Diseases-B study, *VALUE* Valsartan Antihypertensive Long-term Use Evaluation, *DETAIL* Diabetics Exposed to Telmisartan And enalaprIL study, *ASCOT* Anglo-Scandinavian Cardiac Outcomes Trial, *CASE-J* Candesartan Antihypertensive Survival Evaluation in Japan study, *ONTARGET* Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial, *ACCOMPLISH* Avoiding Cardiovascular events with COMbination therapy in People LIving with Systolic Hypertension, *CCB* calcium channel blocker, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker
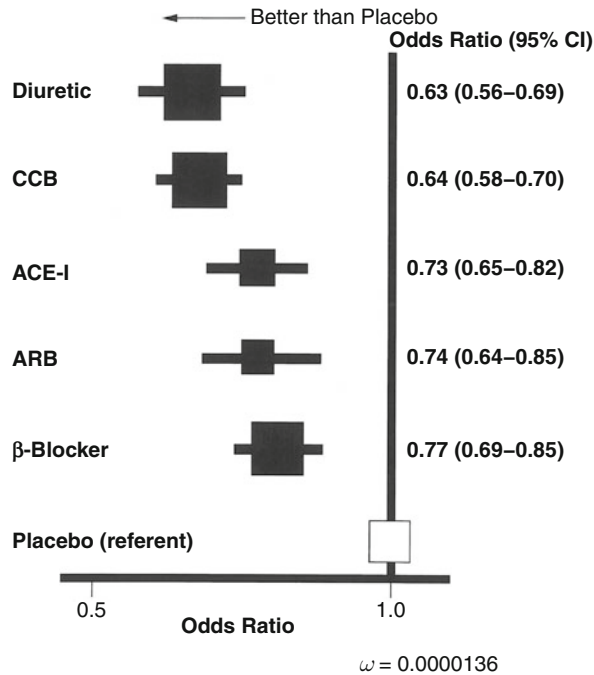
Fig. 3. Results of network meta-analysis of 51 clinical trials in 278,962 hypertensive subjects comparing placebo (or no treatment) and/or active antihypertensive drugs for prevention of stroke. When available, the numbers of subjects at risk for and suffering first strokes were used; othe rwise the total numbers of subjects at risk for and suffering a first or recurrent stroke were used. The *box* corresponding to the point estimate of the effect size (relative to placebo) is drawn in proportion to the number of strokes observed with that class of antihypertensive drugs across all trials; the *horizontal lines* through the *boxes* correspond to the 95% confidence intervals for each point estimate. Note that this model has a high degree of internal consistency (as the incoherence value, $\omega = 0.0000136$). CI = confidence interval, CCB = calcium channel blocker, ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

If one broadens the criteria for entry into the network meta-analysis, and includes any and all trials reporting first strokes (i.e., all trials in Tables 1 and 2, and including trials that included nonhypertensive subjects *(6,7,28,31,33,34,37,38,40,68)*), the model deteriorates, much as with the fixed-effects meta-analysis of all placebo-controlled trials, discussed above. The overall conclusions remain stable. Specifically, all classes of antihypertensive drugs are significantly superior to placebo, with the same rank ordering, but the incoherence increases ($\omega = 0.023$; data not shown). Intuitively, this result makes sense (and is consistent with Fig. 2), because giving antihypertensive drugs to individuals who do not have elevated BPs, and/or are unlikely to lower their BPs very much with these drugs, should be less likely to prevent strokes than giving the same drugs to hypertensive individuals.

BLOOD PRESSURE LOWERING: RELATIONSHIP TO PRIMARY STROKE PREVENTION

The traditional way to try to interrelate BP lowering and stroke prevention is a meta-regression analysis, plotting the difference in achieved (systolic) BP (as the independent
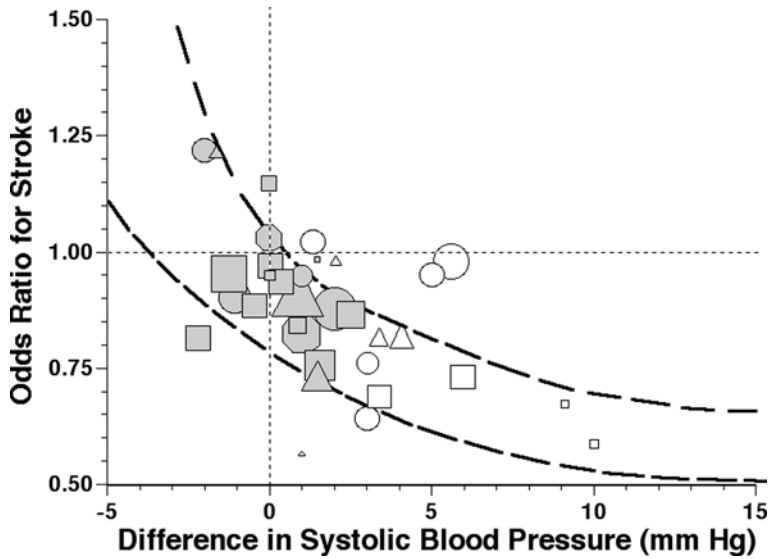
Fig. 4. Meta-regression plot of the relationship between the difference in achieved systolic blood pressure between randomized arms and the odds ratio for stroke for the larger trials in Tables 1 and 2. Note that trials with fewer than 58 strokes (5% of those observed in the chlorthalidone–lisinopril comparison in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) are not shown, as their *symbols* are below the resolution of the figure. Trials involving an angiotensin receptor blocker are denoted by a *triangle*, calcium antagonists by *squares*, ACE inhibitors by *circles*, and both of the latter by an *octagon*. *Open symbols* denote placebo-controlled trials. The area of each *symbol* is proportional to the number of strokes observed in each trial. The identity of each *symbol* can be ascertained by reference to Tables 1 and 2. Note that 91% of the area for all symbols falls within the *dark, curved, dotted lines*, representing the upper and lower 95% confidence limits for the significant ($P < 0.0001$) meta-regression analysis that was based on the results of placebo-controlled trials of diuretic and/or β-blocker reported before the year 2000. From Staessen JA, Wang J-G, Thijs L. *(69)*.

variable) and the odds ratio for stroke (as the dependent variable; *see* Fig. 4 for an example). The reason for using systolic, rather than diastolic, BP is that many of the studies in older patients enrolled subjects with near-normal diastolic BPs, and therefore the differences in diastolic BPs are not nearly as impressive as the differences in systolic BP. If one includes enough comparisons, there is a significant curvilinear relationship: trials having a larger difference in achieved (systolic) BP show lower odds ratios for stroke *(69–71)*. Recent analyses suggest that the use of estimated central aortic pressure differences for each comparison leads to a nearly linear relationship, but central aortic pressure was actually directly estimated in hypertensive subjects in a substudy of a single trial *(65)*.

Some investigators have claimed that calcium antagonists significantly prevent stroke, independent of their BP-lowering effects *(71)*. Most, however, would agree with the 2007 conclusion of the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology: "Comparative randomized trials show that for similar blood pressure reductions, differences in the incidence of cardiovascular morbidity and mortality between different drug classes are small, thus strengthening the conclusion that their benefit depends largely on blood pressure lowering per se" *(72)*. This international panel of experts estimates the "BP-independent effect"

of calcium antagonists on stroke or ACE inhibitors on CHD as 5–10% of the "dominant protective effect exerted by blood pressure lowering" *(72)*. Nonetheless, a meta-analysis and meta-regression analysis of 22 trials that measured changes in carotid intima-media thickness indicated a significantly lower rate of carotid intima-media thickening in trials involving calcium antagonists, which was apparently independent of their BP-lowering effects *(73)*. While this information is consistent with (and may provide a pathophysiological explanation for) the idea that calcium antagonists have a "BP-independent effect" on preventing stroke, it does not prove that the phenomenon is true.

There has also been much discussion in the recent literature that angiotensin receptor blockers might be particularly protective against stroke, especially a second stroke *(74,75)*. In primary stroke prevention, the Losartan Intervention For Endpoint reduction (LIFE) trial showed a significant lowering of stroke (with very little long-term BP difference) *(55)*, and other studies involving angiotensin receptor blockers showed a nonsignificant trend suggesting benefit on stroke *(8,9)*. More recent data, however, including much larger studies of ARBs for primary or secondary stroke prevention, have failed to verify these earlier observations *(40,76)*. Yet the data from each of these large trials fall quite within the expected ranges in the meta-regression plots of differences in observed systolic BP vs. odds ratio for stroke.

So far, only one trial has directly tested the hypothesis that greater BP lowering (using identical drug regimens) would result in a different risk of stroke *(77)*. Some believe that there must be a BP below which further BP lowering should be harmful, as few people survive long with systolic BPs <60 mmHg. However, when 17,980 hypertensive subjects were randomized to diastolic BP targets of ≤80, ≤85, or ≤90 mmHg, treated intensively with multiple drug regimens (calcium antagonist initially, followed by an ACE inhibitor), and then followed prospectively in an open-label fashion for 3.8 years, there were no significant differences in stroke across the three groups ($P = 0.74$). Although the *actual* differences in diastolic BPs across the groups were much less than originally planned (~2 vs. 5 mmHg), the clear conclusion was that lowering BP further than what is currently recommended (which was <140/90 mmHg at the time the Hypertension Optimal Treatment Study was designed) is neither helpful nor harmful with respect to stroke for the general hypertensive population. In contrast, the HOT study clearly showed the benefits of the lower-than-usual BP for diabetics, as those randomized to the lowest target (diastolic BP ≤ 80 mmHg) enjoyed a significant 51% reduction in cardiovascular events, compared to those treated with the "conventional" target (diastolic BP ≤ 90 mmHg) *(77)*. These data are only part of the impressive database that suggests that attempting to lower BP below current targets is unlikely to be effective in preventing stroke, and likely to waste scarce healthcare resources (including antihypertensive drugs and healthcare providers' time and energy).

CONCLUSIONS

Although *first* strokes have been reported in only 9 of the 32 placebo-controlled clinical trials (and constitute only 23% of the number of strokes), the conclusion that antihypertensive drug therapy prevents about 31% of strokes in these 9 trials falls within the 95% confidence limits for the result of the meta-analysis across all 32 placebo-controlled trials (22–35%). In network meta-analysis of all 51 trials involving 278,962 subjects (all

of whom had hypertension), 67 pair-wise comparisons, and 10,252 strokes, all antihypertensive drug classes showed significant prevention of stroke, compared to placebo or no treatment, with an initial diuretic or calcium antagonist being more effective than other drug classes. Nearly all of the trials have shown better stroke prevention in the arm(s) that achieved a lower systolic BP, although some suggest that calcium antagonists have a small (but significant) BP-independent effect on stroke prevention. Since elevated BP is the most common population-based remediable risk factor for stroke, more attention to achieving and maintaining BP targets (at least <140/90 mmHg in everyone, and <130/80 mmHg in those with diabetes, chronic kidney disease, or established heart disease) should be a high-priority public health goal.

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II Mechanisms of Hypertension and Hypertension-Related Stroke

4

Mechanisms Underlying Essential Hypertension: Neurogenic and Nonneurogenic Contributors

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CONTENTS

OVERVIEW

Stroke is the third leading cause of death in the USA and a leading cause of incapacitation, often leaving individuals permanently impaired and unable to work or live independent lives. One of the leading risk factors for stroke is hypertension, and the risk of stroke is directly proportional to the elevation and duration of high blood pressure *(1–3)*. Furthermore, hypertension also contributes significantly to cardiovascular disease, which itself increases the risk of stroke. Despite the prevalence of hypertension, its significant negative impacts on health, and nearly a century of research, the mechanisms underlying the chronic increase in arterial pressure in most hypertensive individuals remain elusive. As initially elucidated by Guyton and others, renal factors are a prominent contributor to hypertension in many individuals, but an increasing amount of research indicates that the sympathetic nervous system and its interactions with vasoactive hormones and intracellularly generated substances also contribute to the pathogenesis of hypertension. This chapter reviews the evidence, suggesting that a neurogenic mechanism can chronically elevate peripheral resistance and arterial pressure, and interactions between the sympathetic nervous system and the hormones (e.g., angiotensin and nitric oxide) act synergistically to increase blood pressure. Finally, it reviews the role of intraneuronal reactive oxygen species in the modulation of sympathetic activity and the evidence for a role of the eicosanoid 20-hydroxyeicosatetraenoic acid (20-HETE) in vascular smooth muscle regulation in both hypertension and stroke-induced vasospasm.

The Sympathetic Nervous System and Hypertension

Over the past 40 years, clinical studies and animal research have strongly suggested that sympathetic nervous system overactivity contributes to several forms of essential hypertension *(4)*. However, what leads to this elevated sympathetic activity is unclear. The rostral ventrolateral medulla (RVLM) is the final nucleus in the brain that drives sympathetic nervous system activity. The RVLM neurons spontaneously discharge at a frequency that corresponds to basal sympathetic nervous system activity *(5)*, and this basal discharge appears to reflect an autorhythmic pacemaker-like activity. Several studies indicate that in neurogenic hypertension, RVLM neurons display abnormally increased discharge frequency, leading to increased sympathetic nervous system activity, augmenting vasoconstriction and thus elevating arterial pressure. The elevated neuronal discharge rate in these cases may reflect an altered autorhythmicity and/or a change in neural inputs that increase the RVLM neuronal discharge rate (Fig. 1). The RVLM neurons are extrinsically controlled by excitatory inputs from several regions, including the caudal pressor area in the brain stem *(6,7)*, the hypothalamus and chemoreceptor input *(8)*, and the inhibitory inputs from baroreceptors and other CNS sites. Work by Dampney and others suggest that modulation
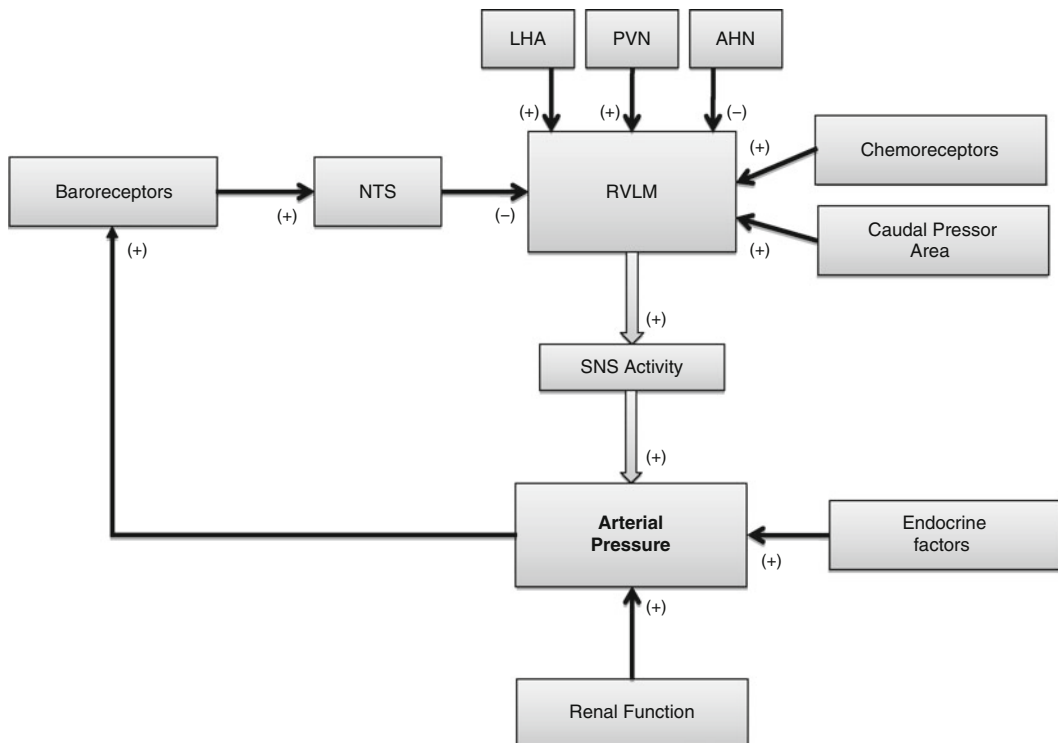
Fig. 1. Arterial pressure is a function of sympathetic nervous system (SNS) activity, circulating endocrine factors, and renal function. SNS activity is regulated by the spontaneous discharge of neurons in the rostral ventrolateral medulla (RVLM), which are regulated by baroreceptor and chemoreceptor input to the nucleus of the solitary tract (NTS) and innervation from the caudal pressor area of the medulla and from hypothalamic regions, e.g., the paraventricular (PVN), lateral hypothalamic area (LHA), and anterior hypothalamic (AHN) nuclei.

of these inputs by increased excitation and/or reduced inhibition enhances the discharge rate of RVLM neurons *(5,9–11)*.

Sympathetic nervous system activity may also be elevated because of an impairment of neurohumeral reflexes. Feedback from arterial baroreceptors (which respond to changes in arterial pressure), cardiopulmonary receptors (which detect changes in blood volume), and chemoreceptors (which respond to changes in blood gas levels and pH) all strongly regulate sympathetic nervous system activity and blood pressure in response to acute changes in those parameters. The net effect of these feedback systems is to alter autonomic nervous system activity to maintain a normal arterial pressure (Fig. 1).

While impaired sensory feedback can cause acute large elevations in arterial pressure, whether such alterations play a role in chronic hypertension remains the subject of considerable debate. Bristow et al. *(12)* were the first to suggest that arterial baroreceptor imbalance could chronically alter arterial pressure regulation; however, extensive work by Cowley and Guyton demonstrated that in dogs, the elimination of baroreflex feedback increased the lability of blood pressure but did not increase the average arterial pressure *(13)*. Subsequent studies demonstrated that in response to sustained increases in arterial pressure, baroreceptors rapidly reset to a new set point and, thereafter, adjusted autonomic nervous system activity to defend the new arterial pressure set point. These findings led to the hypothesis that baroreceptors are only short-term regulators of autonomic activity and are not involved in chronic, neurogenic hypertension [reviewed in Cowley *(14)*].

In contrast to this common wisdom of earlier decades, a number of recent studies suggest that baroreceptors have a more chronic role in the regulation of autonomic nervous system activity and, therefore, may contribute to elevated sympathetic outflow and sustained hypertension in some individuals. Studies by Thrasher suggest that baroreceptors can exert chronic inhibitory feedback on sympathetic nervous system regulators and that imbalances in these reflexes can lead to sustained hypertension *(15)*. Other studies have shown that while baroreceptor control of heart rate appears to reset to higher pressure, renal sympathetic nerve activity and renal function do not reset *(16,17)*. This suggests that sympathetic output to specific regions may be differentially regulated—an idea supported by work by Malpas and colleagues, who identified differential control of renal and lumbar sympathetic nerve activity *(18)*. Blockade of nitric oxide production in rabbits resulted in a greater decrease in renal (compared to lumbar) sympathetic activity, while volume expansion decreased only renal nerve activity. In contrast, hypoxia changed both lumbar and renal nerve activity similarly. Thus, activation of baroreceptors may lead to differential regional control of sympathetic nerve activity and thus the sympathetic outflow may nonuniformly reset following sustained changes in arterial pressure. Differential changes in regulation of these distinct sympathetic pathways may lead to imbalances that underlie a chronic role for baroreflexes in hypertension.

HIGHER NERVOUS SYSTEM REGULATORS OF BLOOD PRESSURE

While the RVLM has been extensively studied because of its role as the brain's tonic sympathetic nervous system drive and a dominant acute arterial pressure regulator, higher brain areas coordinate the activity of RVLM and other sympathetic nervous system regulatory neurons. The hypothalamus has emerged as one of the major regulators of this coordinated output to the autonomic nervous system (Fig. 1).

Among the areas of the hypothalamus that appear to be important in this regulation are lateral posterior hypothalamus, paraventricular hypothalamic nucleus (PVN), and anterior hypothalamic area nuclei. The lateral hypothalamic area predominantly contains sympathoexcitatory neurons, whereas the anterior and preoptic regions tend to be sympathoinhibitory. In rats made hypertensive by administration of the steroid deoxycorticosterone acetate and a high salt diet, stimulation of the posterior or lateral hypothalamus increases arterial pressure and heart rate, whereas lesions of the posterior hypothalamus reduce arterial pressure [19]. Furthermore, the lateral hypothalamic area responds to circulating leptin levels and increases sympathetic activity and blood pressure, and is proposed to be responsible, at least in part, to hypertension that accompanies obesity [20].

In PVN, magnocellular neurons synthesize and release vasopressin into the circulation, while parvocellular neurons project to several CNS cardiovascular control nuclei, including the RVLM, area postrema, NTS, and the intermediolateral nucleus of the spinal cord. Through these connections the parvocellular neurons alter cardiovascular function. The extensive projections of the PVN to these regions indicate that the PVN plays a significant role in modulating RVLM activity and sympathetic outflow. The PVN receives input from a large number of regions in the brain, including those associated with osmotic control (the subfornical and median preoptic nuclei), appetite and energy metabolism (lateral hypothalamic), stress and other areas that exert effects on blood pressure [21]. Thus, it is clear that the role of the PVN is to integrate inputs from a variety of sources and modify RVLM activity accordingly.

The anterior hypothalamic region contains several areas that are important in cardiovascular control, including the anteroventral third ventricle, which can contribute to hypertension in several animal models. The median preoptic nucleus appears to underlie many of these cardiovascular effects (*see*, e.g., [22,23]). Other preoptic nuclei regulate vasopressin release and water balance and contribute, at least indirectly, to arterial pressure control. The anterior hypothalamic nucleus, along with the preoptic area, provides important sympathoinhibitory influences, most of which are mediated by projections to sympathoexcitatory nuclei in the diencephalon and brain stem. An example of their importance is seen in spontaneously hypertensive rats (SHRs), in which diets high in salt exacerbate hypertension, at least in part, by reducing sympathoinhibitory drive from the anterior hypothalamic nucleus [24].

Several cortical regions of the brain appear to influence blood pressure, especially in relation to emotional situations. These include the anterior cingulate and insular cortices and the amygdala.

The Renin–Angiotensin System and Hypertension

Circulating endocrine factors contribute significantly to arterial pressure regulation via peripherally mediated actions and may serve as causative factors in hypertension. Of these, the renin–angiotensin–aldosterone system (RAAS) is probably the most thoroughly studied circulating hormone, largely because angiotensin II (AII) exerts potent vasoconstrictor effects and is a powerful regulator of blood volume. Of the current arsenal of antihypertensive drugs, angiotensin-related pharmaceuticals have emerged as one of the most effective antihypertensives for a majority of patients. Furthermore, several rodent models of hypertension display a strong linkage to circulating AII, including SHRs, TGR mRen2 rats, Dahl
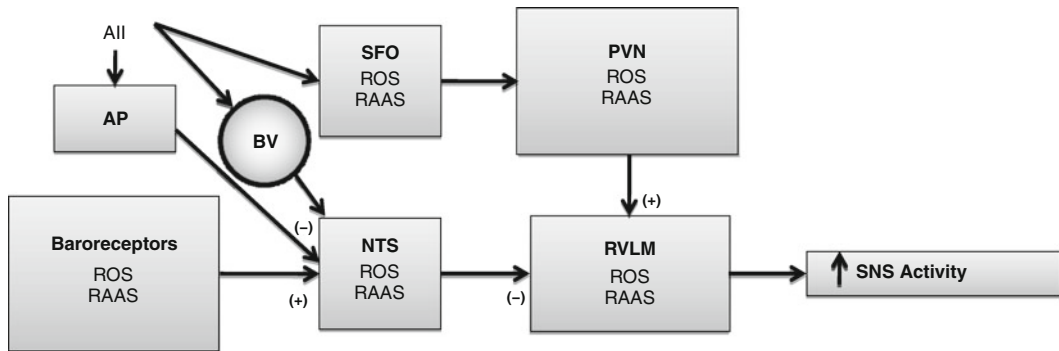
Fig. 2. Circulating angiotensin (AII) can bind to circumventricular organs (e.g., the area postrema (AP) or subfornical organ (SFO)), increasing neuronal activity of sympathoexcitatory nuclei or modulating baroreceptor sensitivity. Alternatively, AII stimulation can lead to activation of the intraneuronal renin–angiotensin–aldosterone system (RAAS) and subsequent generation of AII and related metabolites and/or generation of reactive oxygen species (ROS), both of which may alter the neuronal firing rate of cardiovascular regulatory nuclei and increase sympathetic nervous system activity. AII activation of receptors in the blood vessels (BVs) of the brain stem can also alter neuronal activity in the NTS and RVLM through generation of second messengers that cross the blood–brain barrier (e.g., NO and superoxide).

salt-sensitive rats, DOCA-salt rats, and renal hypertensive rats *(25)*. While AII appears to raise arterial pressure in these models, at least in part, through inappropriate volume retention or increased vascular resistance, these models are also characterized by elevated sympathetic activity. This has led researchers to hypothesize that an overactive RAAS may elevate arterial pressure both through its peripheral actions and by directly augmenting sympathetic nervous system activity.

One central action by which AII may modify autonomic outflow is by inhibition of baroreceptor function (Fig. 2). Several studies have demonstrated that baroreceptor control of arterial pressure is significantly blunted following AII infusion *(26)*, and this can be blocked by administration of an AII type 1 (AT$_1$) receptor blocker *(27)*. This effect extends to many hypertensive rat models, including SHR *(27)*, the high renin TGR(mREN2)27 *(28)*, two-kidney one-clip *(29,30)*, and the Lyon *(31)*. Conversely, angiotensinogen transgenic rats [TGR (ASrAOGEN)], which are characterized by low levels of AII, demonstrate an enhanced baroreflex response compared to nontransgenic controls, and infusion with AII decreases baroreceptor sensitivity in this model *(32)*.

The observation that circulating AII inhibits baroreflex activity suggests that AII must access sites within the CNS to exert this effect. However, AII cannot cross the intact blood–brain barrier; thus, in most cases, circulating AII must bind to receptors in circumventricular nuclei that lack a blood–brain barrier, allowing its neurons to respond to circulating endocrine factors, or AII may bind to cerebrovascular receptors that secondarily transmit a signal to the brain *(33)*. The area postrema is likely a circumventricular site for such interactions. It is adjacent to the nucleus tractus solitarius, which is the location of baroreceptor input to the medulla, and it expresses AII receptors *(25)*. A number of observations support a role for the area postrema in mediating AII-induced inhibition of baroreflexes. Microinjection of angiotensin into the area postrema blunts baroreceptor sensitivity, and microinjection of an ACE inhibitor into the area postrema blocks this effect

(34). Ablation of area postrema abolishes AII-induced desensitization of baroreflex in rabbits *(26)* and eliminates AII-induced hypertension in rats *(35)*. Furthermore, removal of the area postrema prevents the antihypertensive effects of AII receptor blockade on baroreceptor function in SHR *(36)*. The subfornical organ provides another circumventricular site at which peripheral AII binds to CNS receptors and can alter brain activity.

Research into the role of the RAAS in hypertension has long focused on peripheral actions of AII (for instance, as an enhancer of norepinephrine release) or its central circumventricular-mediated effects. However, over the past 30 years, a growing body of research demonstrates that neurons and glial cells within the CNS contain all RAAS components, including angiotensinogen, renin, angiotensin-converting enzyme, and all angiotensin receptors *(25,37)*. This discovery suggested that angiotensin may act as a paracrine neuromodulator or be released as a neurotransmitter. AII receptors are distributed in almost all brain nuclei involved in cardiovascular regulation *(37)*, including PVN, parabrachial nucleus, RVLM, and the NTS *(25)*.

These studies have provided detailed localization of an intrinsic renin–angiotensin system in the central nervous system, but its role is only beginning to be understood. Probably, the most studied region containing an endogenous renin–angiotensin system is the subfornical organ (SFO) where circulating angiotensin binds to neuronal receptors leading to alterations in drinking and vasopressin release (from the PVN). The SFO neurons not only respond to angiotensin II, but also use the peptide to transmit signals to CNS neurons, as illustrated by Sigmund and Davisson, using transgenic mice that express human renin and/or angiotensin genes or have deleted angiotensin system genes in selected areas of the brain *(38–41)*. They demonstrated that expression of the human renin (hREN) or human angiotensinogen (hAGT) induced hypertension in these mice, and intraventricular administration of an AT_1 antagonist blunted this response. Furthermore, their studies using conditional transgenic mice demonstrate that neurons in the CNS utilize angiotensin as a neurotransmitter that regulates blood pressure and other functions. More recently, they modified their double-transgenic strain so that it had a neuronal-specific promoter, ensuring expression only in neural tissue *(41)*. Compared to nontransgenic mice, these mice display higher arterial pressure.

One of the major targets of the SFO is PVN, which is a major source of afferents to RVLM. This projection appears to employ angiotensin II to modulate RVLM activity *(42)*. These results suggest that excitatory synaptic inputs from the PVN to the RVLM are mediated, at least in part, by angiotensin receptors in the RVLM. Together with studies by Chen et al. *(43)* and others, these results indicate that angiotensin decreases GABAergic inhibition of PVN neurons, thereby increasing their firing rate and leading to excitation of RVLM neurons (Fig. 2).

Nitric Oxide and Hypertension

Nitric oxide (NO) is a second circulating agent that has been strongly implicated as a modulator of sympathetic nervous system activity and blood pressure control. NO, which is produced from the amino acid precursor arginine by nitric oxide synthase (NOS), is a potent vasodilator and thus tends to reduce blood pressure when generated in blood vessels, or when its precursor is administered exogenously. Impaired NO-mediated vasorelaxation is observed in most animal and human models of aging and also occurs in age-associated

conditions such as hypertension *(44)*. Chronic inhibition of NOS by L-NAME induces hypertension associated with an increase in peripheral vascular resistance and an enhanced vascular responsiveness to adrenergic stimuli *(45)*. Furthermore, when a NO donor is coadministered with L-NAME, the hypertension is prevented *(45)*. Interestingly, L-NAME-induced hypertension appears to involve both the renin–angiotensin system and the sympathetic nervous system *(45)*. Treatment of rats with an angiotensin-converting enzyme (ACE) inhibitor prevents the development of hypertension in L-NAME-treated rats *(45,46)*, at least in part, by reducing sympathetic nervous system activity *(45,47)*. These studies suggest that NO may act within the brain to elevate sympathetic nervous system activity.

Although the mechanisms by which central NO modulates neuronal activity are unclear, research suggests that NO may alter neuronal responses to dendritic input from innervating neurons and paracrine factors. One region of interest in this regard is NTS, which is the relay between baroreceptor input and RVLM. Microinjection of glutamate into RVLM simulates a baroreceptor-mediated signal, indicating a transient increase in arterial pressure. This normally elicits a reflex decrease in heart rate and renal sympathetic nerve activity that decreases arterial pressure *(9)*. Mifflin and colleagues have shown that an RVLM microinjection of the NOS antagonist L-NAME prior to the glutamate injection greatly reduces the reflex response of arterial pressure, heart rate, and renal nerve activity that are normally elicited by the glutamate injection. These results support the hypothesis that within the RVLM, NO facilitates glutamine-mediated feedback from baroreceptors and cardiopulmonary receptors.

Reactive Oxygen Species and Hypertension

While NO and angiotensin play generally opposite roles in the regulation of the sympathetic nervous system in hypertension, both can be responsible for the generation of reactive oxygen species (ROS) and thereby elevate arterial pressure. Recent studies have focused on angiotensin-induced generation of ROS, including oxygen ions, free radicals, and peroxides, all of which are natural by-products of the normal metabolism of enzymes such as NADPH-oxidase. As ROS are generated, they are converted by intracellular superoxide dismutase (SOD) into hydrogen peroxide. Since hydrogen peroxide is itself a potent free radical species, it must be quickly degraded by enzymes such as catalase, glutathione peroxidase, and peroxiredoxins.

Recent studies indicate that ROS play a role in hypertension, and ROS have been demonstrated to contribute to neurogenic hypertension by inducing sympathoexcitation. ROS levels are elevated in SHR *(48)*, even prior to the onset of hypertension, and vascular, renal, and cardiac ROS production is also increased in this model *(49,50)*. Similarly, stroke-prone SHR (SHR-SP), DOCA, and endothelin-infusion models also display elevated ROS generation *(51)*. Centrally administered tempol (an SOD mimetic) decreases arterial pressure in these hypertensive models, and it reduces renal sympathetic nerve activity and heart rate *(52)*. These data support a role for central ROS generation in hypertension.

The mechanism by which excess ROS alter cardiovascular control is unclear. Some effects of ROS clearly occur in the periphery and alter endothelial and renal function. However, recent research has shown that ROS in central cardiovascular nuclei increase sympathetic activity, resulting in neurogenic hypertension. For example, ROS generation is elevated in the RVLM of SHR-SP *(53)*, SHR *(54)*, and one-clip hypertensive rats *(53)*,

and microinjection of tempol reduces sympathetic nervous system activity and arterial pressure. Increasing evidence suggests that ROS generation is involved in intracellular signaling pathways, including those utilized by AII. Central infusion of AII increases mean arterial pressure and sympathetic nerve activity, and coadministration of tempol abolishes these AII effects *(55)*. Similarly, AII-induced pressor and drinking responses are accompanied by increased superoxide production in the SFO, and SOD overexpression in the SFO eliminates these responses *(56,57)*. These results suggest that elevated AII can increase arterial pressure by increasing ROS generation within SFO neurons, thereby increasing activation of hypothalamic centers that control sympathetic nervous system activity.

20-HETE

The preceding sections describe a mechanism by which central angiotensin, nitric oxide, and reactive oxygen species may act independently or synergistically to elevate sympathetic nervous system activity and induce hypertension. In addition to neurogenic mechanisms, enhanced vascular responsiveness to circulating norepineprhine, angiotensin, dopamine, and endothelin may contribute to hypertension (Fig. 3). One potential intracellularly generated substance that is increasingly of interest in hypertension is the eicosanoid 20-hydroxyeicosatetraenoic acid (20-HETE), which is a by-product of arachidonic acid metabolism. Arachidonic acid is a membrane lipid that is metabolized into a number of physiologically active compounds through three enzymatic routes, including the cyclooxygenase, lipoygenase, and cytochrome P450 (CYP) pathways. The omega hydroxlyase isoform, CYP 450 *4A*, is the primary route for production of the hydroxyeicosatetraenoic acids (HETEs).

The primary effect of 20-HETE is to increase vascular resistance by blocking large-conductance calcium-activated potassium channels, depolarizing vascular smooth muscle and inducing contraction. 20-HETE also increases intracellular calcium through a direct effect on L-type Ca channels *(58)*, thereby increasing the degree of contraction. 20-HETE
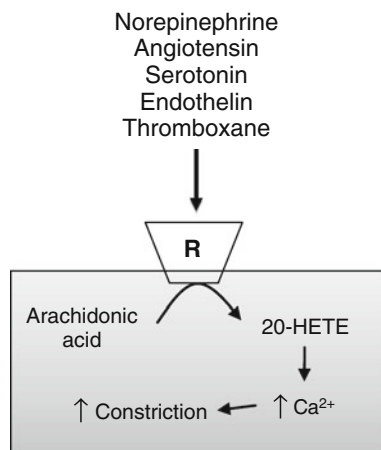
Fig. 3. Vascular smooth muscle responds to a number of circulating vasoconstrictor factors. Many of these substances bind to receptors and enhance the generation of 20-HETE from arachidonic acid metabolism as an intermediate in the vasoconstrictor signaling pathway.

acts via the intracellular pathway when activated by vasoconstrictor substances, e.g., norepineprhine, angiotensin II, endothelin, serotonin, and thromboxane A2 *(59,60)*. Thus elevated 20-HETE production in response to hormonal activation of vascular smooth muscle may increase vascular constriction and peripheral resistance.

There is a growing body of evidence demonstrating that CYP is overexpressed in hypertensive models and that this contributes to the development and maintenance of high blood pressure in these animals. Probably, the most studied model is the spontaneously hypertensive rat (SHR). In SHRs, hypertension develops between 5 and 10 weeks of age, and this time frame correlates with observed expression pattern of CYP *(60)*. Furthermore, the degree of hypertension can be attenuated by administration of $SnCl_2$, which reduces CYP function *(60)*. The role of CYP overexpression in hypertension is also observed in angiotensin-induced hypertension *(61–63)*, Lyon rats *(64)*, Dahl salt-sensitive rats *(65)*, androgen-induced hypertension *(66)*, and a reduced uterine perfusion model of preeclampsia *(67)*. Furthermore, nitric oxide appears to inhibit CYP activity and 20-HETE formation *(59)*, offering the possibility that in NO-depleted hypertension, 20-HETE production is elevated and contributes to elevated blood pressure. In addition to contributing to elevated blood pressure in genetic and experimental hypertensive models, CYP overexpression also appears to contribute to age-associated increases in blood pressure in normotensive rats. In aged (18-month-old) Sprague Dawley rats, blockade of CYP decreases vascular responsiveness to phenylephrine, while CYP inhibition has no effect on vasoconstrictor response in young (3-month-old) rats *(68)*. Similar results are observed in aged ovariectomized female rats, and estrogen replacement does not affect the enhanced vasoconstrictor responses *(69)*.

In addition to its role in hypertension, 20-HETE is widely studied as a factor in control of blood flow. One specific focus is on the cerebral vasculature, which has long been known to intrinsically autoregulate blood flow in response to changes in perfusion pressure (myogenic autoregulation). Myogenic tone is the reflex depolarization of vascular smooth muscle membrane in response to elevated pressure, leading to increased calcium entry and reflex constriction. Work by Harder suggests that 20-HETE plays a critical role in the myogenic reflex, in which an increase in perfusion pressure elevates intracellular diacylglycerol via phospholipase C activation, subsequently generating 20-HETE *(70)*. 20-HETE then blocks calcium-activated potassium channels on the cerebrovascular membrane, depolarizing the smooth muscle and initiating constriction. Similar results are observed in skeletal, renal, and cerebral arteries *(71–73)*, blockade of 20-HETE formation impairs autoregulation of both renal and cerebral blood flow in vivo *(58)*. These results suggest that 20-HETE plays a fundamental role in myogenic autoregulation.

A second form of autoregulation is related to regional concentrations of metabolic by-products. As by-product levels increase, vessels dilate to increase blood flow to the region. While this metabolic process is seemingly simple, the underlying mechanisms are extremely complex and remain to be fully resolved. An increasing number of studies indicate that astrocytes, glial cells which induce the blood–brain barrier, may respond to changes in extracellular metabolites as well as secreted neurotransmitters and release vasoactive components to modify vascular tone and blood flow *(74)*. Work from Newman's laboratory suggests that this proposed neurovascular coupling is achieved through astrocytic generation of 20-HETE, which is balanced by astrocytic generation of the vasodilatory epoxyeicosatetraenoic acids (EETs)—a second class of eicosanoids generated through arachidonic acid metabolism by alternative isoforms of CYP *(75)*.

Given the role of 20-HETE in autoregulation and its contribution to hypertension, there has been considerable interest in the contribution of 20-HETE of stroke pathogenesis. Cerebral ischemic events result in elevated arachidonic acid levels in cerebral spinal fluid *(76)*, which may then be metabolized into vasoactive 20-HETE. The resulting increase in vasoconstrictive effects may worsen ischemic-induced brain injury by preventing collateral flow to the ischemic region *(77)*. In normotensive rats exposed to transient occlusion of the middle cerebral artery (MCA), ischemia results in a large infarct that correlates with severe neurological impairment *(77,78)*. Furthermore, both CYP levels and 20-HETE are significantly increased (by nearly 150%) following MCA occlusion. When a CYP-specific antagonist is administered shortly after the ischemic event, the infarct size is greatly reduced, and neurological deficits also decreased. Similar results are observed in SHR and stroke-prone SHR (SHR-SP), which are more prone to stroke as well as to increased infarct size. 20-HETE production is increased in the cerebral vasculature of SHR and SHR-SP compared to normotensive controls, and following vascular occlusion, infarct size is greater, and regional blood flow is lower in SHR-SP versus normotensive rats *(79)*. Administration of a CYP-specific inhibitor reduces both infarct volume and arterial pressure in both hypertensive groups, although it is not effective in the normotensive rats. Furthermore, incubation of cerebral arteries from SHR and SHR-SP with a CYP inhibitor reduced the amount of reactive oxygen species generated to equal that of normotensive rats. Taken together, these results suggest that cerebral ischemic damage is potentiated by concomitant 20-HETE, and this damage may be potentiated by concomitant hypertension, which reduces restorative blood flow and generates reactive oxygen species formation, likely compounding the effects of ischemia.

SUMMARY

Based on research in animal models and humans, it is clear that the nervous system plays a significant role in the chronic elevation of arterial pressure. Research is beginning to identify mechanisms by which sympathetic nervous system activity is elevated in these models of hypertension. Increases in RVLM neuronal activity in response to an imbalance in excitatory and inhibitory input, diminished baroreceptor signaling, and enhanced excitatory input from the caudal pressor region of the medulla and PVN all play a role in hypertension. Studies also suggest that the RAAS contributes to sympathoexcitation, through both circulating angiotensin and endogenous neutrally derived angiotensin. Neuronal activity may also be altered by generation of reactive oxygen species within neurons and/or a reduction in neuronal nitric oxide formation in the brain or periphery. Finally, peripheral actions such as enhanced neuroendocrine signaling through elevated 20-HETE production appear to contribute significantly to hypertension. Future research will more fully elucidate the contribution of each of these factors to chronic hypertension and how they synergize with other factors to exacerbate stroke.

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5

Pathophysiology and Mechanisms Whereby Hypertension May Cause Stroke

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CONTENTS

Hypertension is the most important modifiable risk factor for stroke. The degree of elevation of blood pressure is tightly correlated with the risk of stroke. The risk curve is a continuum without any clear point separating the stroke-prone from the non-stroke-prone subjects *(1–3)*. Hypertension plays a key role in the pathogenesis of large artery atherosclerosis, which in turn causes ischemic stroke due to thrombotic arterial occlusion, artery-to-artery embolism, or a combination of these factors. The association between hypertension and lacunar infarct is well established. Cardioembolic stroke is also more prevalent in individuals with hypertension and cardiac disease. Additionally, hypertension is also a major risk factor for intracerebral hemorrhage and subarachnoid hemorrhage, two major subtypes of hemorrhagic stroke. This chapter reviews the effects of hypertension on cerebral blood vessels and addresses other mechanisms by which hypertension might cause stroke.

EFFECTS OF HYPERTENSION ON CEREBRAL BLOOD VESSELS

Atherosclerosis

Atherosclerosis may involve multiple arteries throughout the body, including the aorta, coronary arteries, the peripheral blood vessels, and the cerebral blood vessels. Fatty streaks, fibrous plaques, and complicated plaques are the pathologic hallmarks of atherosclerosis.

Atherosclerotic lesions begin with an inflammatory reaction followed by smooth muscle proliferation and thickening of the arterial wall. Hypertension, endothelial dysfunction, shear stress, elevated low-density lipoproteins, free radicals, and chronic inflammatory response are closely associated with the process of atherosclerosis *(4)*.

The earliest changes that precede the formation of atherosclerosis take place in the endothelium. These changes include increased endothelial permeability to lipoproteins, which is mediated by nitric oxide (NO); upregulation of endothelial adhesion molecules; and migration of leukocytes into the arterial wall, which is mediated by oxidized low-density lipoprotein *(4)*. It is now widely accepted that the hypertension-associated endothelial dysfunction promotes the development and progression of atherosclerosis. Nitric oxide is an important mediator of endothelium-dependent vasodilatation. Reduced endothelial NO leads to a proinflammatory, prothrombotic, and procoagulant effect on the endothelium and also promotes structural changes of vessel wall *(5)*. Increased oxidative stress may be an underlying mechanism leading to reduced vascular availability of endothelium-derived NO. Vascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, uncoupled NO synthase, and xanthine oxidase have been identified as major sources of reactive oxygen species in hypertension *(6,7)*. Increased vascular oxidative stress seems to be a pathway leading to endothelial dysfunction in hypertension. In particular, activation of NADPH oxidase has been suggested as a major mechanism leading to increased superoxide production and inactivation of nitric oxide. NADPH oxidase-dependent superoxide production may not only directly impair endothelial increased oxidation of the endothelial NOS cofactor tetrahydrobiopterin but also activate endothelial xanthine oxidase *(5)*. Impaired endothelium-dependent vasodilatation at the forearm was found to be associated with the development of cardiovascular events over time in a high-risk group of hypertensive patients *(8)*. Clinical studies have demonstrated an improvement in endothelium-dependent vasodilatation after treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in hypertensive patients. Considering that increased inflammatory status and atherosclerosis are factors related to development of clinical stroke, medication targeting endothelial dysfunction may prevent or slow the progression of atherosclerosis and thereby reduce the risk of stroke in the long term.

The common locations of atherosclerosis include the bifurcation of common carotid artery, the origin and intracavernous portion of the internal carotid artery (ICA), the first segment of the middle cerebral artery (MCA), the origin and the distal portion of the vertebral artery, and the mid-portion of the basilar artery. Vulnerable plaques in the coronary artery tend to have a thin fibrous cap and a large lipid core. Autopsy findings and histopathological examination of surgical endarterectomy specimens suggest that intraplaque hemorrhage, reparative neovascularization, and ulceration are the factors leading to plaque instability in the carotid artery *(9–11)*. Atherosclerosis of the MCA most commonly affects the M1 segment, which extends from the origin of the artery to the insula. The lenticulostriate arteries arise from this section, and the origins of these vessels can be affected by the development of atherosclerotic plaque, which may result in an isolated small subcortical infarct. Hemorrhage, ulceration, and calcification are less common in intracranial atherosclerotic plaques compared to extracranial plaques. An autopsy study from Hong Kong found that luminal stenosis caused by atherosclerotic plaque, percentage of lipid in
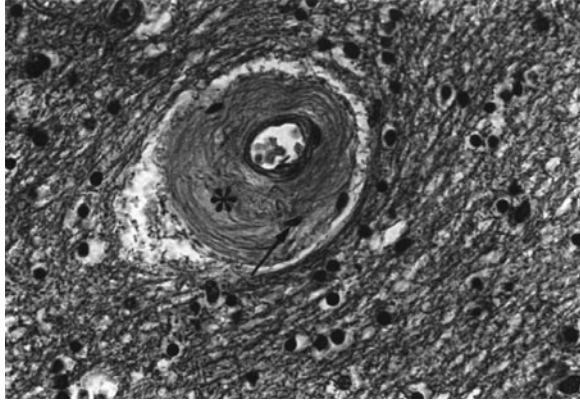
Fig. 1. Hyaline arteriosclerosis, roughly concentric vessel wall thickening by hyaline collagenous material (*asterisk*), with occasional surviving smooth muscle cell nuclei (*arrow*). (Source: Lammie *(86)*, Fig. 1.A.)

the lesions, and the presence of intraplaque neovasculature in the MCA are independent risk factors for MCA infarcts *(12)*.

Fibrinoid Necrosis and Lipohyalinosis

Fibrinoid necrosis is caused by the insudation of plasma proteins, i.e., fibrin, into the arteriolar wall. The affected area is deeply eosinophilic and structureless, or very finely granular (Fig. 1). In hypertensive individuals, the vessel wall may also be eosinophilic and structureless due to degeneration of muscle and collagen (hyalinization). On light microscopy, it may be difficult to distinguish between hyalinization and fibrinoid necrosis. Special stains such as the Putz stain may help in differentiating between fibrinoid and hyaline material *(13)*. Immunohistochemistry and electron microscopy have established that the fibrinoid areas do indeed contain fibrin, and electron microscopy clearly distinguishes fibrin with its characteristic periodicity from areas of hyalinization which contain only degenerated collagen and smooth muscle and unidentified amorphous material *(13, 14)*. Fibrinoid deposition may be very segmental so that the material appears only at widely separated points along the length of arterioles or only in a portion of its circumference.

Lipohyalinosis is a destructive vessel lesion characterized by a loss of normal arterial architecture, mural foam cells, and, in acute cases, evidence of fibrinoid vessel wall necrosis—a process which gradually occludes the already small lumen (Fig. 2) Fisher found that such vascular lesions involved small arteries of 40–200 μm diameter and caused correspondingly small, often asymptomatic, cerebral infarcts, particularly in the striatocapsule *(15, 16)*. He elected to substitute the term lipohyalinosis for the term fibrinoid because of what he perceived to be the general agreement that the affected arteriolar segments also contained lipid. Owing to his huge influence in this area, the term lipohyalinosis has come into widespread use, while fibrinoid necrosis has become the less-used term.

Fibrinoid necrosis and hyaline degeneration are different and independent consequences of hypertension involving different locations along the vessel, but fibrinoid necrosis can sometimes superimpose on previously established hyalinization. Lipohyalinosis is found
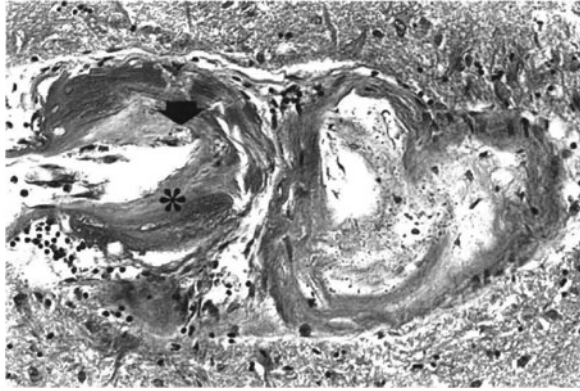
Fig. 2. Lipohyalinosis, an asymmetrically thickened, disorganized vessel wall with focal fibrosis (*asterisk*) and foam cell infiltration (*thick arrow*). (Source: Lammie *(86)*, Fig. 1.B.)

most commonly in a setting of chronic, nonmalignant hypertension, whereas fibrinoid necrosis is said to be found uncommonly especially with extreme blood pressure elevation such as those that occur in hypertensive encephalopathy and eclampsia *(17)*.

However, it should be noted that fibrinoid cannot convert into lipohyalinosis, and these two terms are not exactly the same. According to Fisher's observation, fibrinoid is not an acute stage of lipohyalinosis; rather fibrinoid is lipohyalinosis and is distinguished from mundane hyalinization by the deposit of fibrin in the vessel wall *(15)*. Indeed, lipohyalinosis has often been used by pathologists to confirm a clinical diagnosis of malignant hypertension, whereas fibrinoid necrosis is more often seen in patients whose clinical course and general autopsy findings reveal only benign hypertension *(13)*.

Cerebral Autoregulation

Cerebral autoregulation (CA) is the ability of the brain to maintain relatively constant cerebral blood flow (CBF) despite changes in perfusion pressure (Fig. 3) The lower and upper limits of autoregulation occur at mean arterial pressures of 50–60 and 150–160 mmHg, respectively, in normotensive humans. Cerebrovascular resistance decreases or increases with changes in mean perfusion pressure of brain and thus allows CBF to remain constant. Changes in resistance result from vasodilatation and vasoconstriction in the pial arteries and arterioles *(18)*. Many factors, such as chronic hypertension, sympathetic nerve activity, arterial CO_2 tension, and pharmacologic agents, may modify both upper and lower limits of autoregulation. In this chapter, we will mainly focus on the effect of chronic hypertension on CA.

In hypertensive individuals, both upper and lower limits of autoregulation are shifted to higher absolute values of mean arterial pressure. The resting values for CBF and oxygen consumption are normal in chronic hypertensive, although a marked increase in cerebrovascular resistance and a decreased tolerance to controlled hypotension have been observed *(19)*. Symptoms of cerebral ischemia occur at significantly higher values of mean arterial pressure in hypertensive patients. Furthermore, serious ischemic brain damage has followed an abrupt decrease in blood pressure to normotensive levels in some patients
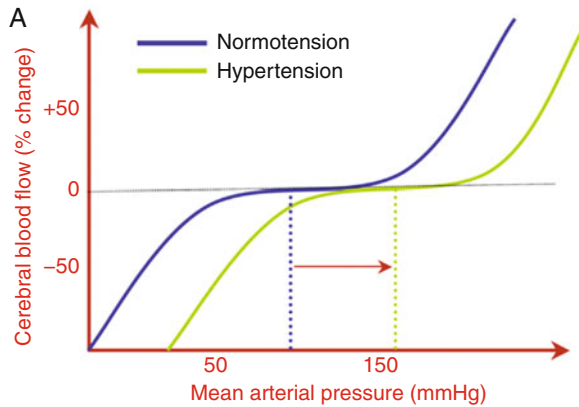
Fig. 3. Cerebral autoregulation and shift of autoregulatory *curve* to the *right* in the hypertensive individual. Cerebral blood flow is maintained constantly, despite changes in blood pressures within a certain range. Chronic hypertension moves the *curve* to the *right*. (Source: Ladecola and Davisson *(87)*, Fig. 4.A.)

(20). Observational studies have also noted that patients with accelerated hypertension can develop abnormal neurological signs after aggressive hypertensive treatment *(21)*.

The shift in autoregulation is related to the increase in myogenic tone induced by an increase in Ca^{2+} sensitivity of the myocyte *(22)*. Remodeling and hypertrophy also contribute to the shift by reducing the vascular lumen and increasing cerebrovascular resistance *(23)*.

The magnitude by which hypertension shifts the cerebral autoregulatory curve to the right is assumed to be symmetrical. However, studies suggest that at low levels of pressure, the shift to the right is relatively modest when compared to the shifts occurring at high levels of blood pressure *(24)*. It may be explained by a paradoxical increase in the passive compliance of hypertrophic cerebral arterioles *(25)*. An increase in passive compliance would be expected to affect vessels more during dilation than constriction and thus result in an increase in vascular diameter when the vessels are dilated in response to reduced levels of pressure *(26)*.

Neurovascular Coupling

Neurovascular coupling refers to the relationship between local neural activity and corresponding changes in CBF. The magnitude and spatial location of blood flow changes are tightly linked to changes in neural activity through a complex sequence of coordinated events involving neurons, glia, and vascular cells (Fig. 4). However, in several conditions such as hypertension, stroke, and Alzheimer's disease, the interaction between neural activity and cerebral blood vessels is disrupted, and the resulting homeostatic unbalance may contribute to brain dysfunction *(27)*.

The relationship between neural activity and CBF can be altered in hypertension. These alterations include changes in both the chemical mediators of neurovascular coupling and the dynamics of the vascular system itself. Functional imaging studies show that ionic channels in vascular smooth muscle can be altered in hypertension and diabetes leading to abnormal patterns of vasodilatation after neural activation *(28)*. Administration of
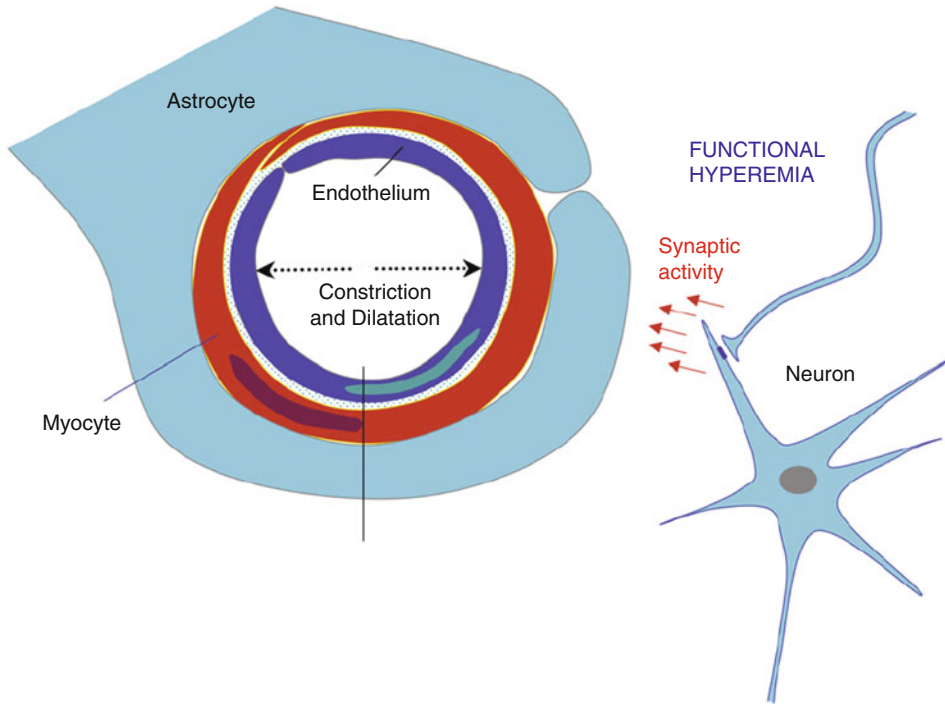
Fig. 4. Neurovascular coupling. A complex sequence of coordinated activities by neurons, glia, endothe-lial cells, and smooth muscle cells enables local harmonization of blood flow and neural activities. (Source: Ladecola and Davisson *(87)*, Fig. 2.)

angiotensin II (ANG II) to mice increases arterial pressure and attenuates the increase in somatosensory cortex CBF produced by whisker stimulation without reducing resting CBF. The effects of ANG II on neurovascular coupling are blocked by losartan, indicat-ing that they are mediated by AT1 receptors *(29)*. There is also evidence that hypertension alters functional hyperemia in human. The increase in CBF in the posterior parietal and thalamic areas produced by cognitive tasks is reduced in patients with chronic untreated hypertension when compared to normotensive individuals. More importantly, the attenuated CBF response is associated with a lower cognitive performance *(30)*. These findings sup-port the hypothesis that hypertension impairs neurovascular function and hence, vascular dysfunction may become a valuable therapeutic target in the future *(27)*.

MECHANISMS OF ISCHEMIC STROKE OR TIA IN TERMS OF HYPERTENSION

Large Artery Disease

THROMBOSIS

Age, hypertension, diabetes mellitus, smoking, and hyperlipidemia are well-known risk factors for atherosclerosis. Large artery atherosclerosis is the most common type of vascular pathology, in which fibrous and muscular tissues proliferate in the subintima, and fatty materials form plaques that can impinge on the vessel lumen. Platelets then adhere to plaque

and form clumps that serve as a nidus for the deposition of fibrin, thrombi, and clot *(31)*. Acute thrombosis begins with fissuring of the fibrous cap of the atherosclerotic plaque, and the release of tissue factors promotes the development of a clot adjacent to the plaque. Local occlusion can then lead to a significant decrease in blood flow and oxygen supply, which may cause ischemic brain damage.

In contrast to Caucasians, intracranial occlusive disease is common in Asian population *(32–35)*. Intracranial atherosclerosis accounts for 33–50% of stroke in Asian population *(32)*, up to 10% of stroke or TIA in the USA are caused by intracranial artery stenosis *(36)*. Severity of stenosis is widely accepted as the major prognostic risk factor in patients with symptomatic and asymptomatic ICA disease *(37,38)*, and has been reported to increase the risk of ischemic stroke in the territory of symptomatic intracranial arterial stenosis *(39)*. Furthermore, progression of MCA occlusion as assessed by an increase of flow velocity on TCD is associated with an increased risk of further cardiovascular events *(40)*.

In patients with intracranial artery stenosis, in situ thrombotic occlusion rarely leads to an infarction of the entire vascular territory as is often seen in patients with cardiogenic embolism. The initial lesions are usually located in the striatocapsular and border-zone areas. The ultimate size of the infarct may vary depending on the adequacy and the rate of development of the collateral circulation, the speed of arterial occlusion, and hemodynamic stability after the occurrence of stroke. In patients with sufficient collaterals, total thrombotic intracranial occlusion may remain entirely asymptomatic or result in a minor stroke or a TIA.

ARTERY-TO-ARTERY EMBOLISM

Artery-to-artery embolism is another important stroke mechanism in patients with extracranial large artery disease. Emboli are composed of clot, platelet clumps, or fragments of plaques that break off from the proximal vessels *(41)*. Proximal ICA and extracranial vertebral artery atherosclerosis is an important source of embolism. High-intensity transient signals (HITS) recorded over the MCA with TCD monitoring can be used to detect artery-to-artery embolism in patients with proximal artery disease *(39)*.

Artery-to-artery embolism is also an important but less well-recognized mechanism of stroke among patients with intracranial artery disease. Wong et al. *(42)* reported that among stroke patients with multiple acute infarcts and MCA stenosis, unilateral, deep, chainlike border-zone infarcts were the most common pattern. However, the number of microembolic signals predicted the number of acute infarcts on DW, which suggested an embolic mechanism for this pattern of stroke. A possible explanation is that emboli in the trunk of the MCA may simultaneously occlude several of the lenticulostriate perforating vessels.

BRANCH ATHEROMATOUS DISEASE

Atheromatous plaque, often referred to as microatheroma, can obstruct the orifices of penetrating arteries and occlude the lumen, causing an isolated small subcortical infarct. Pathological features of microatheroma include microdissection, plaque hemorrhage, and deposition of platelet-fibrin materials *(43)*. Branch atheromatous disease was first described in pontine infarction caused by basilar branch occlusion, but its concept can be applied to infarcts in the territory of lenticulostriate branches, thalamogeniculate branches, anterior choroidal artery, Huebner's artery, and thalamoperforating artery branches *(44)*. This pathogenic mechanism of stroke has been underappreciated in the past *(44–46)*. However,

recent studies have demonstrated that in patients with MCA stenosis, occlusion of a single penetrating artery to produce a small subcortical lacune-like infarct is relatively common *(42,47)*. These findings suggest that local branch occlusion and coexisting distal embolization may be a common stroke mechanism in patients with MCA disease.

Small Vessel Occlusive Disease

The classical example of small vessel disease is the occlusion of a single, nonbranching penetrating end artery (usually smaller than 500 µm in diameter), which causes small subcortical lacunar infarcts (1–20 mm in diameter) (Fig. 5) There are a number of potential causes of small vessel occlusive disease, e.g., embolism, vasospasm, etc.; however, lipohyalinosis and atherosclerosis remain the two major pathologies.

The most common locations for lacunes are the putamen and the pallidum, followed by the pons, thalamus, caudate nucleus, internal capsule, and corona radiate *(16)*. The incidence of cerebral lacunes has declined since the introduction of antihypertensive therapy, an indication that antihypertensive therapy is effective in the prevention of this type of stroke *(16)*. Initially, lipohyalinosis was thought to be the main cause of lacunar stroke. However, with recent advances in modern neuroimaging, microatheroma is now thought to be the most common mechanism of small vessel occlusion, especially in Asian populations with high prevalence of large intracranial artery stenosis *(48)*. The culprit atheromatous plaques are often seen in the proximal portion of the perforating artery (microatheroma), at its origin (junctional atheroma), or in the parent artery itself (mural atheroma). Infarcts are related to stenotic or occlusive plaques, some but not all of which may be complicated by overlying thrombus *(16)*. Subcortical infarcts caused by atheromatous disease are larger
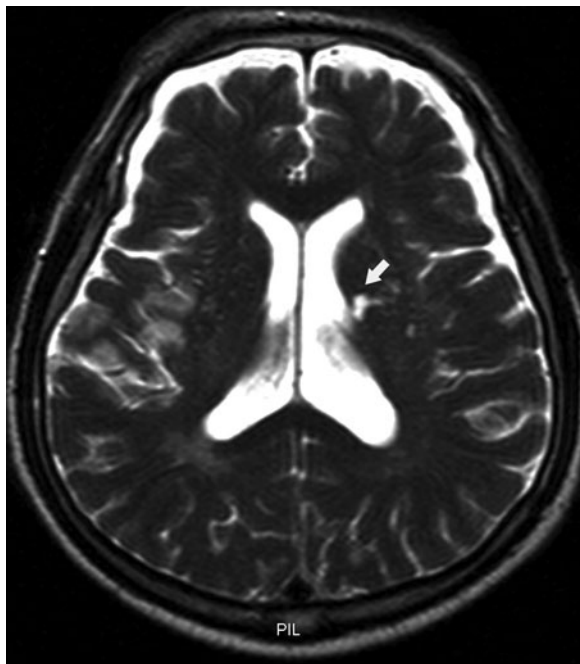
Fig. 5. Lacunar infarction. *White arrow* indicates a small lacunar infarction in *left* corona radiate.

in size, usually more than 5 mm in diameter, and associated with a more unstable clinical course than those caused by lipohyalinosis *(48)*.

Cardioembolism

In cardioembolic stroke, the embolus most commonly originates from the heart valves, endocardium, and atrial or ventricular cavities. Other clots may originate in systematic veins and then travel to the brain through cardiac defects, such as a patent foramen ovale, a process termed paradoxical embolism. A larger infarct is more common in cardioembolic stroke when compared to an artery-to-artery embolic stroke because the clots are larger and there is insufficient time to develop an effective collateral circulation. Atrial fibrillation is the most common cardiac source of brain embolism. Atrial fibrillation is more likely to develop in hypertensive patients with left ventricular hypertrophy and an increased left atrial size. A recent study also showed that regression of left ventricular hypertrophy with antihypertensive therapy reduced the risk of developing atrial fibrillation *(49)*. Hence, better blood pressure control in addition to anticoagulation may further reduce the risk of embolic stroke.

Hypoperfusion

Cardiac failure and systemic hypotension are the two major causes of systemic hypoperfusion. Systemic hypoperfusion is more generalized than cerebral arterial thrombosis or embolism and usually affects both cerebral hemispheres. Recent studies have demonstrated an association between blood pressure and heart failure. In a US study of over 48,000 patients admitted with acute heart failure, patients in the lowest quartile of systolic pressure (<120 mmHg) had the highest in-hospital and 3-month postdischarge mortality rate *(50)*. A prospective community-based study found that nondipping of nocturnal blood pressure conferred an additional risk of developing chronic heart failure beyond conventional blood pressure measurement *(51)*. Therefore, we speculate that good control of blood pressure may lower the risk of developing cardiac failure and thereby lower the risk of cerebral hypoperfusion.

Additionally, chronic hypertension leads to atherosclerosis and increased peripheral vascular resistance, which may further reduce the collateral reserve and result in severe ischemia distal to an arterial occlusion *(52)*. The border-zone areas between vascular territories are usually vulnerable to hypoperfusion, and when there is a profound decrease in systemic blood pressure, watershed infarcts occur in these areas.

Hypoperfusion caused by a process occurring at a distance from the brain (i.e., the heart or extracranial arteries) rarely produces major brain infarction. In contrast, decreased blood flow caused by a lesion directly at the site of brain tissue is not so benign. Occlusion of penetrating arteries often causes an infarct in the territory supplied by the obstructed artery. In addition, severe intracranial arterial disease also seems more likely to cause brain infarction than extracranial occlusive disease *(53)*.

Traditionally, hypoperfusion and embolism are considered independent mechanisms of stroke in patients with arterial occlusive disease. Caplan proposed that they often coexist in patients with severe occlusive disease *(54, 55)*. Arterial luminal narrowing and endothelial abnormalities promote clot formation and subsequent embolization, whereas reduced perfusion limits clearance of emboli, especially in the border zones. Impaired washout is

an important mechanism that combines hypoperfusion, embolization, and brain infarction *(54, 55)*.

MECHANISMS OF INTRACRANIAL HEMORRHAGES IN TERMS OF HYPERTENSION

Intracranial hemorrhages involve the brain parenchyma or subarachnoid space, or both. Approximately 15% of strokes are hemorrhagic. While this accounts for a small proportion of stroke, hemorrhagic stroke has a higher mortality rate compared to ischemic stroke. Hypertension and ruptured cerebral aneurysms are two major causes of intracranial hemorrhage, which are discussed subsequently.

Hypertensive Intracerebral Hemorrhage

Traditionally, hypertension has been considered the predominant cause of intracerebral hemorrhage (ICH) *(56)*. Hypertension-related ICH often leads to subcortical hemorrhage, such as in the putamen (Fig. 6) and adjacent internal capsule, thalamus, pons, and cerebellum. However, the importance of hypertension in the etiology of lobar hemorrhage should also be recognized. A study by Broderick et al. found that hypertension is nearly as common in primary lobar hemorrhage as in deep hemispheric, cerebellar, and pontine hemorrhages, and its association with lobar hemorrhage does not diminish with advancing age *(57)*. In this study, 67% of 66 patients with lobar ICH had hypertension, compared to 77 patients with deep hemispheric (73%), 11 with cerebellar (73%), and 9 with pontine (78%) hemorrhages.
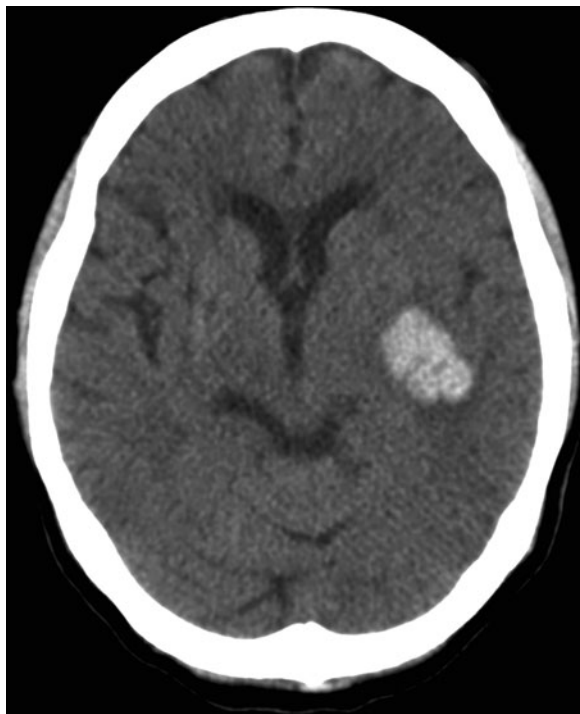
Fig. 6. Intracerebral hemorrhage. A small hypertensive intracerebral hemorrhage in *left* basal ganglia.

There are two important mechanisms that result in hypertensive ICH: (a) rupture of small penetrating arteries damaged by chronic hypertension and aging and (b) acute elevation of blood pressure leading to rupture of normal arterioles and capillaries.

CHRONIC HYPERTENSION

Chronic hypertension produces arteriolar changes consisting of fibrinoid necrosis, lipo-hyalinosis, medial degeneration, and microaneurysm formation, all of which make the vessel susceptible to rupture. The rupture usually occurs in the middle or distal portions of penetrating arteries at or very near to bifurcations. The role of microaneurysms in causing ICH was first proposed by Charcot and Bouchard in 1868, but has been debated over a century. There is accumulating evidence against the theory that the spontaneous ICH is due to a rupture of Charcot–Bouchard microaneurysms as it has never been clearly identified as the definite cause of spontaneous cerebral hematomas. Challa et al. *(58)* failed to demonstrate microaneurysms in hypertensive patients with spontaneous ICH. An electron microscopic study of ruptured arteries in hypertensive ICH showed severe degenerative changes in 46 of 48 ruptured arteries, but ruptured microaneurysms were found only in two cases *(59)*. These studies indicated that degenerative changes caused by age and hypertension can predispose to ICH, but it is not certain that a ruptured microaneurysm is the cause of the bleeding.

ACUTE HYPERTENSION

In clinical practice, many patients with ICH have no prior history of hypertension. In addition, pathologic evidence of chronic hypertension, such as left ventricular hypertrophy or other cardiac and renal changes, is often not found. Bahemuka et al. *(60)* found only 46% of fatal cases of spontaneous ICH had chronic hypertension or left ventricular hypertrophy. Similarly, in a case series of 154 patients with spontaneous ICH during 1 year, only 45% had a history of hypertension *(61)*. In these two studies, the location of hematoma, increased BP on admission, and absence of other etiologies suggest that the ICH is often caused by an acute elevation of blood pressure. Evidence also indicates that an acute increase in blood pressure and blood flow can precipitate rupture of normal arterioles and capillaries unprotected from these changes in the absence of prior hypertension. Usually, the more sudden and the more severe the change, the more likely the risk of rupture *(62)*.

The combination of a significant increase in cerebral blood flow and blood pressure may also lead to ICH following carotid endarterectomy or carotid artery stenting. A retrospective review of 4,494 patients who underwent carotid endarterectomy or carotid artery stenting found that strict control of postoperative blood pressure prevents ICH caused by cerebral hyperperfusion syndrome after CEA *(63)*. A more recent study also demonstrated that comprehensive management of hypertension can lower the incidence of ICH and hyperperfusion syndrome in high-risk patients following carotid artery stenting *(64)*.

ICH has been frequently associated with the use of illicit drugs, especially cocaine and amphetamine, which are known to have sympathomimetic effects. Cocaine-induced hypertension is a long-recognized risk factor of ICH. Some patients may also develop a hypertensive encephalopathy with multiple ICH and brain edema *(65)*. The exact mechanism by which these drugs cause ICH is not yet clear. One possible explanation is that the sudden elevation of blood pressure that occurs immediately after using drugs may cause an existing aneurysm or arteriovenous malformation in the brain to rupture. Interestingly, a

Fig. 7. Subarachnoid hemorrhage. Extensive blood clots occupy basal and perimesencephalic cisterns and both sylvian fissures.

higher frequency of an underlying vascular malformation has been noted in cocaine-related hemorrhage compared to amphetamine-related hemorrhage *(65,66)*.

Aneurysmal Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) (Fig. 7) occurs when a blood vessel near the brain surface leaks, leading to extravasation of blood into the subarachnoid space. SAH is most often caused by rupture of a saccular aneurysm. Saccular aneurysms are most commonly seen in the ICA–posterior communicating artery junction, anterior communicating artery–ACA junction, the apex of basilar artery, and the MCA bifurcation. Histopathologic features of aneurysms include degenerative changes, thinning of the media, inflammatory changes, atherosclerosis, and presence of medial and elastic defects of the aneurysmal wall *(67)*.

The mechanism of the origin, growth, and rupture of saccular intracranial aneurysm is largely unknown. Intracranial arteries are more susceptible to aneurysm formation than extracranial arteries because intracranial vessels are thinner, with less elastin; the external elastic lamina does not exist; and vessels lying in the subarachnoid space lack surrounding supporting tissue. A congenital deficit in the arterial media being a weak spot through which the inner layers of the arterial wall would bulge is a possible explanation and these focal deficits are often located at arterial bifurcations. Reduced production of type III collagen has also been reported to be associated with familial intracranial aneurysms *(68)*. In addition, acquired changes in the arterial wall are also likely to be important since hypertension, smoking, and alcohol abuse are known risk factors for SAH. These conditions lead to local thickening of the intimal layer of the arterial wall. This, in turn, may increase strain

on the more elastic portions of the vessel wall *(69)*. In animal models, saccular aneurysms can be produced by combining experimental renal hypertension and ligation of a carotid artery to alter hemodynamic stress in the circle of Willis. However, the administration of beta-aminopropionitrile alone, a potent irreversible inhibitor of lysyl oxidase which initiates cross-linkage formation in elastin and collagen, without the presence of hypertension does not induce aneurysm formation, which indicates that a vascular lesion and hemodynamic stress are both important in the pathogenesis of aneurysm formation *(52)*. In addition, abnormalities in structural proteins of the extracellular matrix have been identified in the arterial wall at a distance from the aneurysm itself *(70)*.

Stress on the vessel wall increases as the radius of the aneurysm enlarges. When the wall stress exceeds the wall strength, aneurysms rupture. Evidence indicates that aneurysms larger than 10 mm in diameter are more likely to rupture *(71)*. Aneurysms may rupture at any time, but are more prone to do so when blood pressure or blood flow increases during strenuous activity.

MECHANISMS OF SILENT BRAIN LESIONS IN TERMS OF HYPERTENSION

White Matter Lesions

White matter lesions (WMLs) (Fig. 8) are considered present if visible as hyperintense lesions on proton-density and T2-weighted images, without prominent hypointensity on T1-weighted scans *(72)*. WMLs are strongly associated with increasing age. However, in most studies, white matter changes are more common in hypertensive than in normotensive
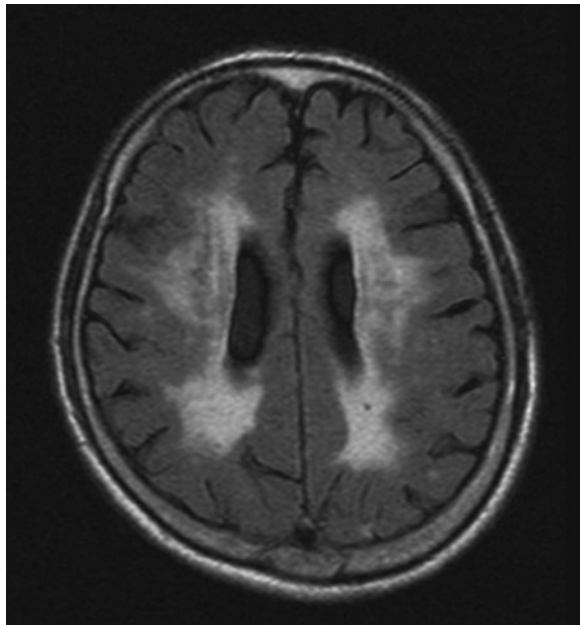
Fig. 8. White matter lesions. Extensive white matter changes (leukoaraiosis) are observed in both periventricular and subcortical white matter.

individuals, especially in the young. A population-based study showed that the duration of hypertension was associated with both periventricular and subcortical white matter lesions. Furthermore, subjects with successfully treated hypertension had only moderately increased subcortical and periventricular white matter lesions compared with normotensive subjects *(73)*. The importance of WML as a predictor of stroke risk *(72,74)* and vascular dementia *(73)* has been demonstrated in previous studies.

The pathology of WML is heterogeneous, including small infarction, gliosis, demyelination, vascular ectasia, and dilated perivascular spaces, all of which are also commonly seen in the experimental hypertension model *(75)*. The exact mechanism of WML is unclear, but hypertension-related arteriolosclerosis appears to be the most important causative factor, and the extent of WML is thought to reflect the extent of brain arteriolosclerosis *(76)*.

Silent Infarctions

Silent infarcts are defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger, with corresponding prominent hypointensities on T1-weighted images *(72)*. Silent brain infarcts and white matter lesions are thought to have the same vascular origin. However, the majority of silent infarcts are lacunar infarcts which may be caused by either large or small vessel disease, whereas WMLs reflect mainly small vessel disease. In terms of clinical outcome, studies indicate that both community-based normal elderly people *(72,77)* and stroke patients *(74,78)* with silent brain infarcts and white matter lesions are at a strongly increased risk of stroke, which cannot be explained by other stroke risk factors.

Cerebral Microbleeds

Microbleeds (MBs) (Fig. 9) are defined as punctate, homogeneous, rounded, lesions less than 0.5 cm in size, with signal loss or hypointensity on gradient echo MRI. The pathology of microbleeds is perivascular deposits of hemosiderin in the brain, which are regarded as evidence of previous rupture of small vessels *(79,80)*. MBs have been found in patients with both intracerebral hemorrhages and ischemic stroke. The presence of MBs predicts the recurrence of ICH in patients with primary lobar ICH and is associated with aspirin-associated ICH *(81)*. Hence, antiplatelet medications should be used with caution in patients with diffuse MBs. Various studies have shown that microbleeds are related with subsequent cerebral bleeding among patients with ischemic stroke including acute hemorrhagic transformation after thrombolysis *(82)*, although there is also some evidence against the importance of MBs as a predictor of hemorrhagic transformation *(83)*.

The mechanism of microbleeds is largely unknown. MBs have been found to be associated with increased age, hypertension, WMLs, lacunar infarcts, and intracerebral hemorrhage *(84,85)*. One recent study found that there were linear associations between MBs, WMLs, and lacunar infarcts. With increasing number of lacunar infarcts or severity of WMLs, the frequency and the number of MBs increased in parallel *(79)*. This finding indicates that microbleeds, white matter changes, and lacunar infarcts most probably share the same pathogenesis of advanced microangiopathy.
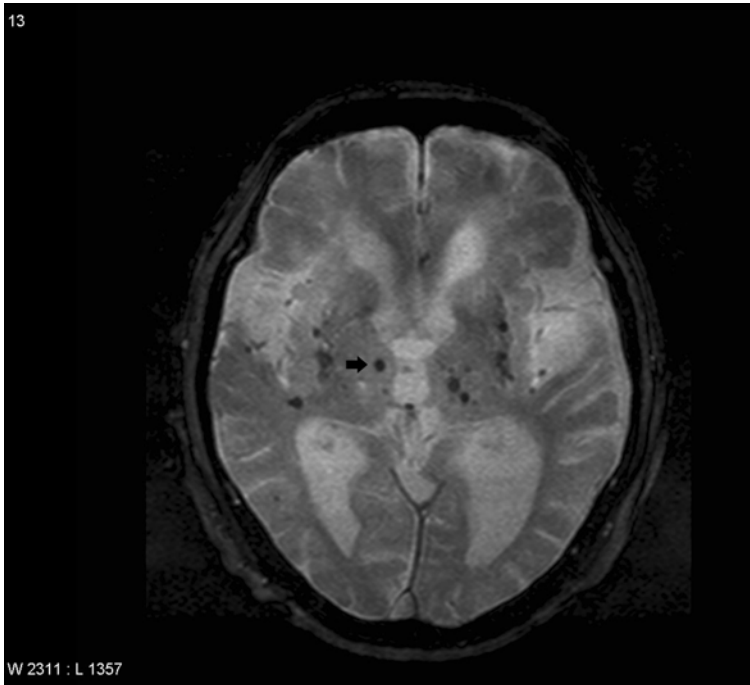
Fig. 9. Microbleeds. Several microbleeds are seen in both thalamus and basal ganglia. The *black arrow* indicates one of them. (Sources: Figs. 5, 6, 7, 8, and 9 taken from Dr Joon's collections.)

Conclusions

Hypertension has deleterious effects on the cerebral circulation. Hypertension alters the structure of blood vessels by producing vascular hypertrophy and remodeling and by promoting atherosclerosis in large cerebral arteries and lipohyalinosis in penetrating arterioles. In addition, hypertension also impairs endothelium-dependent relaxation and alters cerebrovascular autoregulation and neurovascular coupling. With these functional and structural alternations, hypertension facilitates vascular occlusions or degenerative change that is prone to rupture and bleeding, thereby causing both ischemic and hemorrhagic stroke. Better understanding of the underlying mechanisms may provide new insights into stroke management and prevention. Since hypertension is one of the few modifiable risk factors of cerebrovascular disease, optimal blood pressure control may significantly lower the risk of stroke.

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III Management of Blood Pressure for First Stroke Prevention, Immediately after Acute Stroke, and for Recurrent Stroke Prevention

6

Cardiovascular Risk Assessment and Summary of Guidelines for the Management of Hypertension

Tamar Polonsky, MD and George Bakris, MD

INTRODUCTION

Hypertension is one of the most prevalent health problems worldwide and the third largest cause of the global burden of disease *(1)*. More than a quarter of the world's adult population was estimated to have hypertension in the year 2000. The number is expected to rise to 29%—totaling 1.56 billion people—by the year 2025 *(2)*. While the prevalence in developed countries is expected to increase by 24%, it is projected that there will be an 80% increase in developing nations. Worldwide, 54% of ischemic heart disease and 47% of strokes are attributable to high blood pressure *(3)*. The rise in hypertension has been attributed to several factors, including the overall aging of the population, the dramatic increase in obesity, and a decrease in physical activity.

Untreated hypertension is associated with significant cardiovascular (CV) morbidity and mortality. Hypertension is an independent risk factor for the development of all of the clinical manifestations of cardiovascular disease, including coronary artery disease, peripheral artery disease, congestive heart failure, and stroke. In the USA, 69% of patients who experience their first myocardial infarction (MI), 77% with their first stroke, and 74% with congestive heart failure (CHF) have a blood pressure >140/90 mmHg *(4)*.

It is estimated that almost one in three adults has hypertension in the USA. There is significant variation in the prevalence of disease based on age, gender, and ethnicity. Data from the National Health and Nutrition Examination Survey (NHANES) 2005–2006 showed

that 29% of the total population have hypertension, with a stepwise increase with advancing age *(4)*. Among men and women ages 45–54 about 36% of the population carry the diagnosis, compared to 65–70% of people ages 65–74. From ages 45–64 the prevalence among men and women is similar; beyond age 65 significantly more women have hypertension than men (78 vs. 64%). Moreover, the Framingham estimate of US adults developing hypertension is 90%.

The prevalence of hypertension in African Americans is among the highest in the world and is increasing at a higher rate than other ethnic groups. Between 1988 and 2006 the prevalence of hypertension among non-Hispanic white men increased from 25.6 to 29.9%, compared to 37.5–41.8% among black men *(4)*. In contrast, the prevalence in Mexican American men decreased from 26.9 to 21%.

Despite the considerable health implications, the majority of people with hypertension are still not at recommended guideline goal. The data from NHANES 2005–2006 show that while 79% of people with hypertension were aware of their condition, only 69% were receiving treatment and only 45% had their blood pressure controlled to <140/90 mmHg, the level recommended as target for uncomplicated hypertension. This is an improvement from 37% in 2003–2004 *(4,5)*. Similar reports from other countries also reveal a poor record of BP control, regardless of the populations studied, the accessibility to or cost of medical care, or the treatment settings *(6,7)*.

For the majority of patients, the risk we attribute to hypertension is driven primarily by the systolic pressure. As age increases both systolic and diastolic pressures rise in parallel. However, after about age 50 the diastolic pressure tends to fall or plateau, while the systolic pressure continues to increase. As a result, systolic blood pressure is the major determinant of events, particularly in patients over the age of 50 *(8,9)*.

Controversy exists as to the importance of pulse pressure—the difference between systolic and diastolic pressures—in predicting future events. Initial studies suggested that pulse pressure was a powerful predictor. More recent analyses suggest that the significance of the pulse pressure is lessened after adjusting for the systolic pressure *(10–12)*.

HYPERTENSION AND CARDIOVASCULAR DISEASE

Hypertension serves as a predictor of cardiovascular events in a continuous and graded manner. A meta-analysis of 61 prospective studies, including one million adults, showed that for each 20/10 mmHg increase in BP starting from the level of 115/75 mmHg, the CV risk is doubled *(13)*. Data from the Framingham Heart Study also showed that compared with people who have normal blood pressure, the relative risk of a CV event increases as the blood pressure rises, within each age group *(3)*. By age 50, the overall lifetime risk of a cardiovascular event for a man with stage 1 or 2 hypertension is 62–65%, compared to 47% for men with normal blood pressure. The risk is 52 vs. 29% for women *(14)*. For hypertensive men and women at age 50, this translates into a life expectancy that is 5 years shorter than normotensive patients.

Studies with more than 3 years of follow-up demonstrate an independent effect of hypertension on the development of cardiovascular events in younger people as well. In a prospective study of more than 11,000 men ages 18–39 with a baseline systolic blood pressure (SBP) >160 mmHg, the risk of coronary heart disease increased two- to four-fold over 25 years *(15)*. Once people develop left ventricular hypertrophy, the risk of all cardiovascular events, but particularly the development of heart failure, increases even

further. This emphasizes the importance of treating hypertension early on in a patient's life.

Epidemiologic data suggest that even patients with mildly elevated blood pressure experience an increase in cardiovascular events. In the study of men ages 18–39 previously mentioned, the highest proportion of excess deaths (58%) was among men with prehypertension and stage 1 hypertension, defined as systolic blood pressures of 130–139 and 140–159 mmHg, respectively, leading to a decrease in life expectancy by 2.2 and 4.1 years *(15)*. Both men and women with prehypertension have been shown to have more than a 50% higher risk of cardiovascular events over 10 years than patients with normal blood pressure *(16)*.

In the majority of patients with hypertension, their diagnosis does not occur in isolation, but rather is found in association with other cardiovascular risk factors. Investigation of risk factor clustering showed that fewer than 20% of men and women have hypertension in the absence of additional risk factors. Specifically, more than half of patients have one or two additional risk factors *(17)*. Not surprisingly, the risk of cardiovascular events increases as the number of risk factors increases, even at the same level of blood pressure.

"Traditional" cardiovascular risk factors for coronary heart disease include diabetes, hypertension, family history (cardiovascular disease (CVD) before the age of 55 in men and 65 in women), tobacco use, and age (>55 for men and >65 for women). One of the most widely used techniques to evaluate the risk of hypertension in the context of additional risk factors is the Framingham Risk Score (FRS), which provides estimates of the 10-year risk of a coronary event based on a person's total cholesterol (C), HDL-C, hypertension, tobacco use, and age. One of the weaknesses of the FRS is that it does not include the presence of diabetes. However, data from the Framingham Heart Study have been used to incorporate diabetes to enhance risk estimates. For example, the 10-year estimated risk of a coronary event for a 45-year-old man is 4% if his only risk factor is stage 1 hypertension. The risk increases to 10% if he has an elevated total cholesterol and low HDL-C, to 21% if he has diabetes and uses tobacco, and reaches 40% if he has electrocardiogram evidence of left ventricular hypertrophy *(17)*. A form of the FRS may be used to calculate stroke risk.

Another important collection of CVD risk factors, of which hypertension is one, is the metabolic syndrome. This is really not a syndrome but rather a compilation of risk factors combined to denote substantial increase in risk of CVD. According to a US National Heart, Lung, and Blood Institute (NHLBI)/American Heart Association (AHA) work group, it is defined as the presence of three or more of the following: blood pressure elevation (≥130/85), impaired fasting glucose (>110 mg/dl), increased waist circumference (>102 cm for men and 88 cm for women), low HDL-C (<40 mg/dl), and hypertriglyceridemia (>150 mg/dl) *(18)*. Data from the Framingham Offspring Study showed that of the patients who did not have metabolic syndrome, 10% of the population had elevated blood pressure, compared to 32% of the people with metabolic syndrome *(19)*. Subjects were followed over 8 years for the development of cardiovascular events and the development of type II diabetes mellitus. The presence of metabolic syndrome conferred a relative risk of 4–6 and 24–30 for the development of CV events and diabetes, respectively.

Much of the increased risk associated with metabolic syndrome is thought to occur from obesity, particularly visceral adiposity. Obesity is one of the most common causes of hypertension, the prevalence of which is rising at an alarming rate *(20)*. It is now estimated that more than half of the US population is either overweight or obese, with the latter defined as a body mass index (BMI) >30 kg/m^2. Obesity leads to several physiologic changes,

including hyperinsulinemia and insulin resistance, endothelial dysfunction, increased activation of the sympathetic nervous system, sodium retention, and increased oxidative stress. In its seventh report, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has, therefore, highlighted obesity as one of ten cardiovascular risk factors (*see* Table 1) *(21)*.

Table 1
Cardiovascular Risk Factors

Hypertension
Diabetes Mellitus
Tobacco use
Age (>55 years for men, >65 years for women)
Family history of premature cardiovascular disease (<55 years for
    men, <65 years for women)
Microalbuminuria or estimated GFR <60 ml/min
Obesity
Dyslipidemia
Physical inactivity

Target organ damage
Heart
Left ventricular hypertrophy
Angina pectoris or myocardial infarction
Coronary revascularization
Heart failure
Brain
Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

Source: Adapted from JNC 7.

Population studies show that being obese promotes a clustering of risk factors and greatly influences their impact. Patients who are obese are more than twice as likely as lean patients to have more than three cardiovascular risk factors, a 40–60% increased risk of a cardiac event, and up to a 100% increase in cardiovascular death *(22–24)*. Given that more than half of the US population is either overweight or obese, the cardiovascular impact of obesity is substantial. Data from the CRUSADE registry of national outcomes in the setting of a non-ST elevation myocardial infarction (NSTEMI) showed that among obese patients, the mean age of a first NSTEMI was 3–12 years younger than lean patients, depending on the degree of obesity *(25)*.

Along with the rise in obesity, hypertension, and diabetes comes an increase in risk of the sequelae of these conditions, including chronic kidney disease (CKD) *(26)*. The JNC 7 recognizes CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min or the presence of >30 mg/l of microalbuminuria, as another cardiovascular risk factor. Hypertension and diabetes are the most common causes of CKD. Patients with CKD are more likely to die of CVD than to develop kidney failure *(27)*. A reduced eGFR poses an

increased cardiovascular risk, in part because it represents a higher prevalence of associated risk factors, such as uncontrolled hypertension and dyslipidemia. Several large studies have shown that patients with a reduced eGFR have higher blood pressure and total cholesterol and lower HDL-C, and are more likely to have ischemic heart disease, left ventricular hypertrophy, diabetes, and heart failure *(28–30)*. As a result, it has been postulated that reduced eGFR may be a marker for more severe vascular disease *(31)*.

Also, there is evidence that a reduced eGFR is an independent predictor of an adverse cardiovascular prognosis. For example, data from the Kaiser Permanente Renal Registry of more than one million adults showed a graded, independent association between eGFR and cardiovascular events. Patients with an eGFR of 40–59 ml/min experienced a 40% increase in events compared to those with normal renal function. Furthermore, there was a 100% increase for an eGFR of 30–44 ml/min and a 340% increase for an eGFR of less than 15 ml/min *(32)*. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT)— a study in which patients who had a myocardial infarction (MI) complicated by heart failure were randomized to valsartan, captopril, or both—each reduction in the eGFR by 10 ml/min, starting at 80 ml/min, was associated with a hazard ratio for death and nonfatal cardiovascular events of 1.10 *(33)*. Reduced kidney function is associated with several abnormalities, including increased levels of inflammatory markers, enhanced coagulability, increased arterial stiffness, and endothelial dysfunction, all of which may contribute to its role in cardiovascular morbidity and mortality.

More specifically, microalbuminuria is most often found in patients with diabetes and is one of the earliest signs of abnormal vascular responsiveness. As with a reduced eGFR, microalbuminuria is associated with generalized endothelial dysfunction, vascular permeability, increased inflammatory markers, and abnormalities in the coagulation system *(31)*
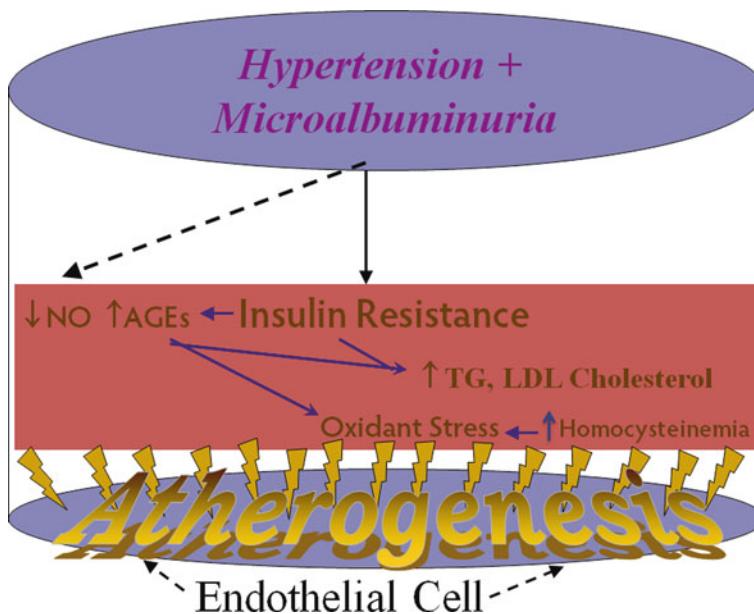
Fig. 1. Interaction of microalbuminuria with other factors that affect atherosclerosis development. NO, nitiric oxide; AGEs, advanced glycation endproducts; TG, triglycerides; LDL, low density lipoproteins.

(Fig. 1). As part of the National Kidney Foundation's Kidney Early Evaluation Program, a community-based screening program for CKD, patients with normal renal function were compared to those with a combination of microalbuminuria, reduced eGFR, and anemia. The latter group had the lowest survival—93% over 30 months vs. 98% in the patients without kidney disease *(27)*.

The relationship between hypertension and CVD has several important implications from both a diagnostic and therapeutic perspective. First, a diagnosis of hypertension should always prompt an investigation for other comorbidities noted in Table 1. Second, the presence of certain comorbidities may influence what is considered an appropriate treatment regimen, which will be discussed in the next section. Third, patients with several additional risk factors may have different treatment goals compared to a person with isolated hypertension, another issue which will be discussed in the next section.

GUIDELINES FOR THE MANAGEMENT OF HYPERTENSION

The association between hypertension and other CVD risk factors, such as diabetes, dyslipidemia, CKD, and obesity, forms the foundation of the recommendations by all national and international guidelines such as JNC 7, AHA, European Society of Hypertension– European Society of Cardiology (ESH–ESC), International Society of Hypertension–World Health Organization (ISH–WHO), and British National Institute of Clinical Excellence (NICE) guidelines.

The classification of hypertension was adjusted in JNC 7 from previous JNC reports, combining stages 2 and 3 (previously an SBP of 140–159 mmHg or DBP 90–99 mmHg, and SBP $\geq$160 mmHg or DBP $\geq$100 mmHg, respectively), and included a new diagnosis of prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg). Prehypertension was added to recognize the increased CV risk even with smaller elevations of systolic blood pressure above 115 mmHg *(13)*. The strategy for the classification and the management of hypertension in adults is shown in Table 2.

Pharmacological therapy of hypertension is initiated only after the initial evaluation of a patient is completed, and the diagnosis of hypertension is confirmed. Additionally, if hypertension is uncomplicated, the patient has had to fail a course of lifestyle modification in the presence of stage 1 blood pressure elevation (Table 2). Note that lifestyle changes *must* accompany all pharmacological treatments.

Several BP measurements performed according to accepted procedural guidelines are necessary for the diagnosis of hypertension. The initial assessment should include focused medical history, especially personal and family history of hypertension and antihypertensive drug use. In addition, the presence of risk factors for CVD or overt CVD/target organ damage is evaluated by both clinical history and physical examination as well as limited laboratory evaluation. Secondary forms of hypertension need to be excluded, with special attention to rule out commonly acquired causes of BP elevation such as sleep apnea and drug-induced hypertension.

GUIDELINE TREATMENT GOALS

All current guidelines emphasize that the patient's overall cardiovascular risk should be the basis upon which to decide whether to initiate pharmacological therapy and to what treatment goal. However, there are differences among panels in terms of which

Table 2
Goal Blood Pressure by Guideline Committees

	Year of publication	Hypertension without additional risk factors (mmHg)	Diabetes or chronic kidney disease (mmHg)	Established CV disease (mmHg)	CAD equivalent or high CAD risk[a] (mmHg)	LV systolic dysfunction (mmHg)	Proteinuria >1 g/day (mmHg)
JNC 7	2003	<140/90	<130/80	–	–	–	
ESH-ESC	2007	<140/90	<130/80	<120/80	–	–	<130/80, and lower if possible
AHA	2007	<140/90	<130/80	<130/80	<130/80	<120/80	–

[a]Defined as carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, or 10-year Framingham risk score of >10%.
CV cardiovascular, LV left ventricular, CAD coronary artery disease.

patient groups warrant more aggressive treatment goals. Moreover, the blood pressure goals themselves are somewhat arbitrary in some cases.

For the general population, JNC 7 recommends starting medication therapy if lifestyle intervention fails for stage 1 hypertension, with a goal blood pressure of <140/90 mmHg. If a patient has diabetes or chronic kidney disease, the treatment goal is ≤130/80 mmHg. This lower goal is designed to prevent both cardiovascular complications and progression of kidney disease. The AHA expands the number of patients who qualify for a lower blood pressure goal to those with established CAD with either stable or unstable angina, patients with CAD risk equivalents (diabetes, peripheral artery disease, carotid artery disease, abdominal aortic aneurysm), and high-risk patients, including those with CKD or a Framingham 10-year risk estimate of at least 10%. Additionally, the AHA states that those with left ventricular (LV) dysfunction should be treated to an even lower goal of 120/80 mmHg. The ESH guidelines recommend a blood pressure goal of ≤130/80 mmHg for those with metabolic syndrome or target organ damage.

Historically, there has been concern that a significant lowering of blood pressure, especially DBP, could be harmful—the so-called J-curve hypothesis. One potential reason why a lower DBP could cause harm is that coronary perfusion occurs primarily during diastole. A significantly reduced pressure may, therefore, result in myocardial ischemia. Recent data suggest that in the elderly and those with CHD, the reduction of DBP <60 mmHg is associated with increased CVD risk *(34,35)*.

The preponderance of prospective clinical trial data supports the general notion that <135/80 mmHg is better in terms of reducing cardiovascular events, especially strokes. However, is lower defined at the current guideline values or lower than a control group above a DBP of <80 mmHg? For example, the results of Hypertension Optimal Treatment (HOT) showed that diabetics in the lowest target group, a DBP <80 mmHg, had a 51% reduction in major cardiovascular events, compared to the group with a DBP goal of <90 mmHg *(36)*. However, in this trial there was very little separation between blood pressure groups and no group achieved a mean DBP below 80 mmHg. Similarly, in the Systolic Hypertension in the Elderly Program (SHEP) study, individuals in the active treatment group who achieved the average DBP of 68 mmHg had better overall outcomes and less coronary events compared to controls with an average DBP of 72 mmHg *(37)*. In this trial, by study definition no one had a DBP above 90 mmHg.

Most of these lower blood pressure goal recommendations or targets are not based on data from randomized prospective trials since few studies actually attained a mean BP of <130/80 mmHg (Fig. 2). Among ten major trials, the mean SBP ranged from 132 to 151 mmHg *(36–45)* (Fig. 2). As a result, much of the data to support the goal of <130/80 mmHg comes from epidemiologic studies and post hoc analyses of randomized clinical trials. For example, in the Prospective Studies Collaboration, which followed more than 900,000 patients, an increase in mortality from ischemic heart disease or stroke was already observed with BPs in the range of 135/85 mmHg, when compared to 115/75 mmHg *(13)*. In the Irbesartan Diabetic Nephropathy Trial, progressively lower achieved SBP to 120 mmHg predicted a decline in CV mortality and congestive heart failure, but not MI *(46)*. A SBP below this threshold was associated with an increase in CVD mortality and CHF events. In the International Verapamil SR–Trandolapril trial, the subgroup with a mean blood pressure of 125/75 mmHg experienced a 28% reduction in events, compared to the patients with a mean BP of 142/80 mmHg *(4)*.
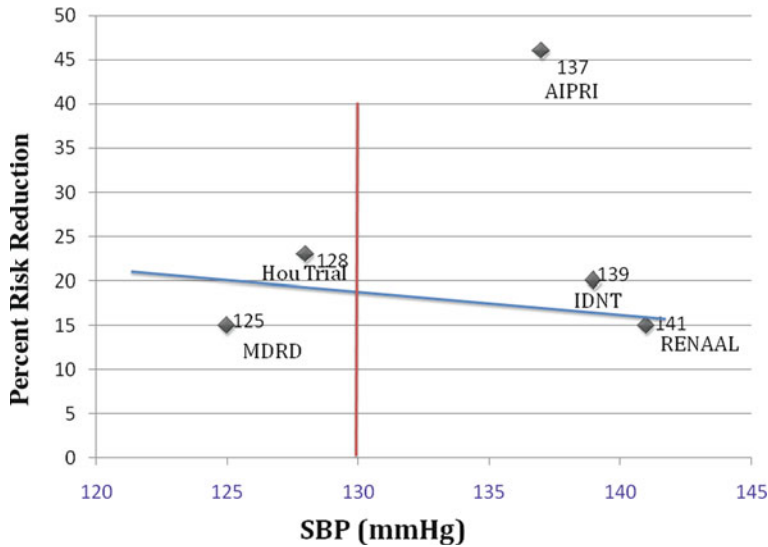
Fig. 2. Relationship between cardiovascular risk and blood pressure achieved.

For kidney disease outcomes all trials that randomized to different blood pressure levels failed to show an additional risk reduction of the lower blood pressure goal in relation to slowing the progression of kidney disease (Fig. 3). The exceptions are advanced proteinuric kidney disease, i.e., eGFR <40 ml/min with >1 g/day proteinuria *(47)*. Also, for diabetes this target is not supported by any prospective studies except for the ACCORD trial that will be completed in 2009. This trial is designed to answer the question regarding whether a lower level of blood pressure is needed to reduce cardiovascular risk *(48)*. Thus, all guideline recommendations for lower blood pressures come from hypothesis generating post hoc analyses of clinical trials or epidemiologic cross-sectional studies and as yet cannot be viewed as A-level evidence.

PHARMACOLOGICAL THERAPY

Multiple recent trials have compared the traditional diuretic- or β-blocker-based treatment strategies to those based on ACE inhibitors (ACEI), calcium channel blockers (CCB), or angiotensin receptor blockers (ARBs). In general, all major groups of antihypertensive agents have similar capacity to lower BP. A meta-analysis of 29 clinical trials that encompass 162,341 participants by the Blood Pressure Lowering Treatment Trialist's Collaboration group supports the concept that all agents that lower BP will reduce CVD risk *(49)*. However, some differences in the specific outcomes such as strokes (favoring diuretics and CCBs) and coronary events (favoring ACE inhibitors and beta-blockers) exist between certain groups (Fig. 4). One must keep in mind that most of the trials included in the meta-analysis were secondary prevention studies.

Regardless of the choice of medication, it is important to consider that most patients (>70%) will eventually require more than one medication to achieve adequate control, and for those who are greater than 20/10 mmHg above their treatment goal, or stage 2 hypertension, JNC 7, AHA, and ESH all recommend initiating two-drug therapy.
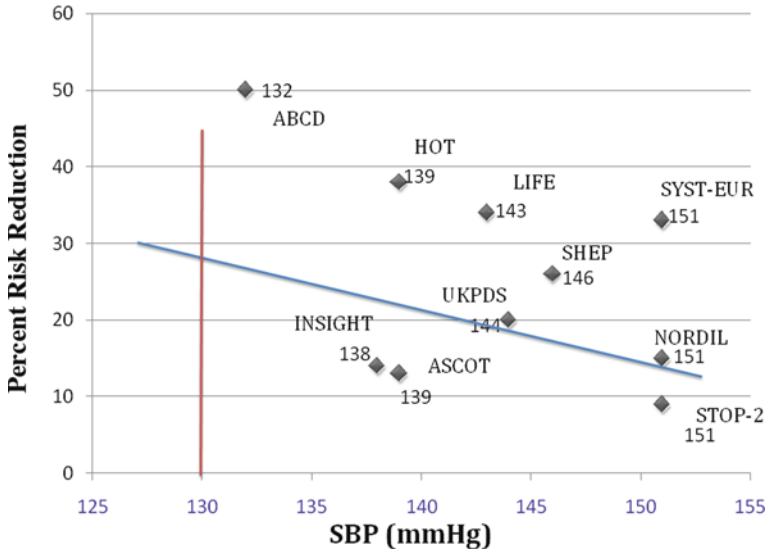
Fig. 3. Relationship between kidney disease outcomes and blood pressure achieved.

	No of events/patients		Difference in SBP/DBP (mm Hg)	Risk ratio (95% CI)	Risk ratio (95% CI)	*P* for homogeneity
	1st listed	2nd listed				
Angiotensin–converting enzyme inhibitor *v* diuretic or β–blocker						
Age <65	819/9,448	1,066/12,012	1.3/0.1		1.05 (0.96–1.14)	0.44
Age ≥65	1,795/10,783	2,525/14,429	2.0/0.5		1.01 (0.95–1.06)	
Calcium antagonist *V* diuretic or β–blocker						
Age <65	1,165/20,358	1,430/23,236	1.1/–0.2		1.06 (0.98–1.14)	0.38
Age ≥65	2,653/21,204	3,363/24,981	0.5/–0.4		1.02 (0.97–1.06)	
Angiotensin-converting enzyme inhibitor *V* calcium antagonist						
Age <65	548/5,130	568/4,919	0.9/0.6		0.91 (0.78–1.06)	0.37
Age ≥65	1,583/8,170	1,608/8,140	1.0/1.0		0.98 (0.92–1.05)	

0.5   1.0   2.0

Favors   Favors
1st listed   2nd listed

Fig. 4. Blood pressure-lowering regimens based on different drug classes for the outcome total major cardiovascular events and age groups <65 vs. ≥65. Negative blood pressure values indicate lower mean follow-up blood pressure in first-listed than in second-listed groups. From Turnbull et al. *(49)*.

Diuretic therapy, in the form of thiazide diuretics, remains a first-line agent for uncomplicated hypertension only by the JNC 7. All other guidelines suggest getting the blood pressure to <140/90 mmHg using either CCB, blockers of the renin–angiotensin system, diuretics, or beta-blockers. The various guidelines diverge on the role of beta-blockers. Beta-blockers are well-established therapy for patients who also have ischemic heart disease, heart failure, and arrhythmias; recent data suggest that beta-blockers may have a more limited role in other patients. For example, in the LIFE study the ARB losartan was more effective than the beta-blocker atenolol in CV protection (particularly stroke) in hypertensive patients with electrocardiographic left ventricular hypertrophy *(40)*. Furthermore, in the ASCOT study hypertensive subjects randomized to amlodipine (and if needed perindopril) had fewer CV events than those randomized to atenolol (and if needed bendrofluazide), although the difference in CV protection in the ASCOT study is largely attributed to the greater BP reduction in the amlodipine group *(41)*. A meta-analysis of outcome studies of beta-blocker-based therapy (almost exclusively atenolol) in hypertension showed limited stroke protection compared to that achieved by other drugs *(50)*.

Because of these data and the consistent evidence showing increased risk of new onset diabetes with beta-blockers, particularly when combined with diuretics *(4,40,41,51–54)*, the recent NICE, AHA, and ISH–WHO hypertension guidelines state that beta-blockers should not be first-line drugs. However, the ESH–ESC guidelines continue to recommend beta-blockers as first-line drugs, apart from hypertensives with metabolic syndrome or glucose intolerance *(55)*. Exceptions to this rule are the newer beta-blockers carvedilol, which also has alpha-adrenergic blocking properties, and nebivolol, which vasodilates by potentiating nitric oxide. Both agents have a neutral effect on glycemic control and enhance insulin sensitivity *(56,57)*.

The impact of various agents on glycemic control has gained increasing attention. Multiple trials have shown with beta-blockers (primarily atenolol), and thiazide diuretic leads to both a worsening of glycemic control among diabetic patients and an increase in the development of new-onset diabetes with impaired fasting glucose *(52,53,58–60)*. However, retrospective analysis of outcome trials does not support the assertion that increases in diabetes translate into a higher CV event rate *(60,61)*. This may relate to improvement in blood pressure, providing relatively greater CVD risk reduction trumping the risk associated with metabolic derangement. In addition, the risk of diabetes is not decreased when a thiazide is combined with an ACEI or ARB in obese patients with impaired fasting glucose *(54)*. Given that the primary determinant of CVD risk reduction is the lowering of blood pressure and not the class of medication *(49)*, one would ideally use medicines that do not worsen preexisting metabolic conditions.

GUIDELINE UPDATES AND JNC 8

With new data from outcome trials like the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH), there have been position papers put forth by some societies. These position papers primarily update the previous guidelines. One such example was the guideline put forth by the American Society of Hypertension that updated the approach to management of hypertension in the patient with diabetes *(62)*. The major new finding is the earlier use of calcium antagonists in concert with RAAS blockers (Fig. *5*).

If Blood Pressure > 130/80 mmHg in Diabetes (*eGFR* ≥ 50 *ml/min*)

(*if systolic BP* < 20 *mmHg above goal*) **Start ARB or ACE Inhibitor titrate upward**	**(*if systolic BP* ≥ 20 *mmHg above goal*)** **START with ACEI or ARB + thiazide diuretic* or CCB**

Recheck within 2–3 weeks

If BP Still Not at Goal (130/80 mmHg)

Add Long-Acting Thiazide Diuretic* or CCB	**Add CCB or (diuretic) or beta-blocker****

Recheck within 2–3 weeks

If BP Still Not at Goal (130/80 mmHg)

Consider and Aldosterone Receptor Blocker
If CCB used, Add other subgroup of CCB
(i.e., amlodipine-like agent if verapamil or diltiazem already being used and the converse)
OR could add alpha–blocker is not using vasodilating beta-blocker with alpha effects

Recheck within 4 weeks

If BP Still Not at Goal (130/80 mmHg)

Refer to a <u>Clinical Hypertension Specialist</u>#

Fig. 5. Updated paradigm to approach blood pressure control in patient with diabetes. *chlorthalidone preferred over hydrochlorothiazide; **vasodilator beta blockers such as carvedilol, nebivolol preferred because of neutral metabolic effects; #http://www.ash-us.org/specialist_program/directory.htm.

Several important trials have been published since JNC 7 that may influence future recommendations in JNC 8. These trials provide new insight into issues related to combination therapy in various groups and treatment in the elderly. In the ACCOMPLISH trial, patients who were at high risk for CVD events were randomized to benazepril plus amlodipine or hydrochlorothiazide (HCTZ) *(63)*. Despite comparable blood pressures (131.6/73.3 with amlodipine vs. 132.5/74.4 with HCTZ), the patients randomized to amlodipine experienced a 19.6% reduction in CV events. Moreover, these similar levels of blood pressure were borne out in a substudy using ambulatory blood pressure monitoring in over 800 of the 11,506 participants. This substudy showed a slightly lower blood pressure in the diuretic combination group with a CVD benefit still observed in the calcium channel blocker-based therapy group. ACCOMPLISH highlights the benefit of fixed combination medicines for effective blood pressure management and risk reduction, and suggests that amlodipine should be considered as a first-line agent.

A second study examining fixed combination medications at a much earlier state of diabetes is the ADVANCE trial, which added perindopril/indapamide vs. placebo to patients with diabetes and a usual regimen, regardless of baseline blood pressure *(64)*. Those patients randomized to perindopril/indapamide experienced an 18% reduction in death from cardiovascular cause, regardless of initial blood pressure.

The ONTARGET study addressed combinations of renin–angiotensin system blockers *(65)*. In the trial, patients at high risk for CVD events were randomized to either telmisartan, ramipril, or both. Telmisartan was found to be noninferior to ramipril in the prevention of CVD events. Despite a superior decrease in blood pressure, the combination of both

an ACEI and an ARB increased the risk of renal complications and hypotension, without any benefit in CVD outcome. While there is data to suggest that the combination of an ACEI/ARB may be more effective in reducing death or hospitalization in patients with heart failure *(66)*, ONTARGET suggests that there is no indication for this combination in patients with preserved ventricular function.

Lastly, the Hypertension in the Very Elderly Trial (HYVET) addressed blood pressure management in the elderly *(67)*. Older patients have the highest prevalence of hypertension and experience a large proportion of CV events secondary to hypertension. However, patients older than 80 years are underrepresented in clinical trials, and so the benefits of treatment are unclear. In HYVET, patients over 80 years were randomized to indapamide, plus perindopril if needed, or placebo, for a SBP goal of 150 mmHg. Active treatment was associated with a 30% reduction in stroke, 21% reduction in death from any cause, and a 23% reduction in death from cardiovascular cause. HYVET suggests that older patients can gain significant benefit from treatment of their hypertension, albeit with slightly less aggressive treatment goals (target BP 150/80 mmHg).

How might these trials be incorporated into JNC 8, and what other changes could we expect to see? First, JNC 7 emphasizes the benefit of a diuretic-based therapy for the initial treatment of hypertension, with the addition of an ACEI/ARB for patients who are at higher risk or with stage 2 disease. ACCOMPLISH suggests that, at the very least, amlodipine–ACEI is a reasonable initial therapy in those with a blood pressure >20/10 mmHg above the goal. While JNC 7 discusses the importance of dual-drug therapy for patients who are above 20/10 mmHg of their target BP, there could be greater emphasis on the benefit of fixed-dose combination pills, in terms of patient adherence and achievement of blood pressure lowering.

Another change could be that the ACCORD trial fails to demonstrate a benefit of CV risk reduction with a lower blood pressure goal at which point these lower goals will have to be amended to <140/90 mmHg. The randomized arm of the trial for more aggressive glucose control was stopped early due to excessive mortality *(68)*, so one awaits the final outcomes. As a final note, guidelines are not meant to be the "holy grail" of management but merely an intellectual attempt at critical review of data from trials to provide recommendations that can serve the clinician in understanding how to apply the results to their patients.

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7

Acute Blood Pressure Management After Ischemic Stroke

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INTRODUCTION

High blood pressure (BP) is a major modifiable risk factor for stroke. Subjects with a BP <120/80 mmHg have half the lifetime stroke risk of those with higher blood pressures *(1)*.

A large body of evidence (discussed in detail in Chapter 2, 3, 10, and 11) has conclusively demonstrated that effective long-term treatment of chronic hypertension significantly decreases the incidence of first-time and recurrent strokes and lowers cardiovascular mortality. Antihypertensive treatment leading to a 5–6 mmHg reduction in diastolic blood pressure (DBP) reduces stroke incidence by 42% *(2)*. Among patients who have already suffered a stroke, an average reduction in BP by 9/4 mmHg leads to a reduction of total stroke by 28% and a reduction of major cardiovascular events by 26% over a 4-year period *(3)*.

Though the role of BP lowering in the long-term care of subjects with an ischemic stroke is well established, the management of hypertension immediately after an acute stroke is controversial, largely due to a concern about the possibility of worsening acute cerebral ischemia by acutely lowering BP *(4)*. This chapter reviews the physiological basis required for understanding this controversy, discusses the pros and cons of lowering BP after an acute stroke, summarizes the studies on cerebral blood flow (CBF) and clinical outcome after BP lowering in acute stroke, and finally lists the guidelines of various US and international organizations for BP management after acute stroke.

HYPERTENSION IN ACUTE ISCHEMIC STROKE

Incidence and Natural History

An elevated BP is commonly seen among patients with an acute ischemic stroke. In a study of 563,704 adult patients in the National Hospital Ambulatory Medical Care Survey, a systolic blood pressure (SBP) >140 mmHg was noted in 63% of the patients *(5)*. In the International Stroke Trial, among 17,398 patients with an acute stroke, the mean SBP was 160 mmHg at the time of admission and 82% of the enrollees had SBP >140 mmHg *(6)*.

It has also been observed that there is a spontaneous reduction of BP in most acute stroke patients even without any specific antihypertensive treatment. Wallace and Levy reported that patients with acute stroke had a significant spontaneous decrease in BP by the tenth hospital day *(7)*. Blood pressure starts to decline within minutes to a few hours after stroke onset *(8)*. The maximum decline occurs over the first 24 h followed by a more gradual fall to reach a steady state over the next 7–10 days; however, ∼40% of patients remain hypertensive *(9)*.

Mechanisms of Early Hypertension in Acute Ischemic Stroke

In many patients with an acute ischemic stroke, high BP is merely a reflection of poorly controlled preexisting hypertension. However, hypertension is noted in previously normotensive patients as well *(10)*. Several explanations for this hypertensive response have been proposed. These include the "white-coat effect" and the stress of hospitalization, the "Cushing reflex" (hypertension and bradycardia seen in the setting of raised intracranial pressure), ischemic damage to the brain stem or hypothalamus, and activation of various neuroendocrine systems *(11)*.

Effect of Hypertension on Outcome

MORTALITY

There is conflict in relation to the evidence linking high BP at the onset of stroke with mortality, long-term outcome, and stroke progression. Several observational studies have shown an association between high BP after stroke and poor outcome *(9)*. Other studies, however, have either found no relationship between increased BP and outcome, or demonstrated better outcomes with higher BP *(12,13)*. Finally, a "U"-shaped relationship between BP and clinical outcome has also been noted. In the International Stroke Trial, SBP of 150 mmHg was found to be a key point from which a decrease in every 10 mmHg of systolic pressure was associated with 17.9% increase in mortality and an increase of every 10 mmHg of SBP increased the mortality by 3.8% *(6)*. A systematic review by Willmot et al. concluded that high systolic, mean, and diastolic BPs in acute ischemic stroke were significantly associated with death and dependency *(9)*. A more recent analysis of 1,772 patients from the Virtual International Stroke Trials Archive (VISTA) who were enrolled in hyperacute stroke (<8 h duration) trials showed that high SBP at onset, large variability in SBP, and smaller (versus larger) falls in SBP over the first 24 h were all associated with worse functional outcome *(14)*.

STROKE PROGRESSION

The relationship between high BP and stroke progression is not well established. Various studies have reported a positive, negative, or no association between high BP and worsening of neurological deficits in acute ischemic stroke *(12,13,15)*.

HEMORRHAGIC TRANSFORMATION

An increased risk of hemorrhagic transformation of the infarction with higher blood pressures has been reported. However, the risk of hemorrhagic transformation was independent of the BP in the International Stroke Trial *(6)*. Elevated BP has also been found to be a risk factor for cerebral hemorrhage after thrombolytic treatment. An analysis of data from the Tinzaparin in Acute Ischemic Stroke Trial (TAIST) also found that hemorrhagic transformation, cerebral edema, or mass effect on day 10 was not associated with baseline BP *(16)*.

COEXISTING CONDITIONS

Due to shared vascular risk factors, patients with stroke are frequently found to have coronary artery disease. In the placebo arm of the RANdomized Trial of Tirilazad mesylate in Acute Stroke (RANTTAS), 11% of acute stroke patients had heart failure; 6% had cardiac ischemia, angina, or myocardial infarction; and 3% had pulmonary edema *(17)*. The presence of these associated medical conditions might warrant treatment of hypertension.

CEREBROVASCULAR PATHOPHYSIOLOGY

In order to be able to appraise the controversy over BP management in acute ischemic stroke, it is necessary to understand normal cerebrovascular physiology and the alterations caused by chronic hypertension and cerebral ischemia.

Normal Cerebrovascular Physiology

The brain has limited fuel reserves and is therefore dependent on blood flow for a constant supply of oxygen and energy substrates. Cerebral blood flow (CBF) has to be maintained at an adequate level (∼50 ml/100 g/min) to meet the metabolic needs of brain tissue, despite variations in systemic BP. Under normal conditions, CBF is regulated by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR): CBF = CPP/CVR. CPP represents the difference between mean arterial pressure (MAP) and venous pressure. Under normal conditions, venous pressure is quite low and CPP is almost equivalent to the MAP.

Cerebral autoregulation is the phenomenon by which CBF is maintained at a constant level, despite variations in systemic BP within a certain range (MAP of ∼60–150 mmHg). Within this range, when CPP rises, CVR also rises due to arteriolar vasoconstriction. The inverse is observed when the CPP falls. Above the upper limit of autoregulation, there may be "breakthrough" vasodilation leading to vasogenic cerebral edema. A CPP below the lower limit of autoregulation can result in decrease in CBF, and potentially cerebral ischemia.

Effect of Chronic Hypertension on Cerebral Blood Flow and Autoregulation

Chronic hypertension induces several changes in the wall of blood vessels. Hypertension leads to smooth muscle hypertrophy and vascular remodeling and collagen deposition that, in turn, lead to a decrease in luminal diameter and vascular stiffening. These changes lead to elevated lower and upper limits of cerebral autoregulation in chronic hypertensives (i.e., a shift of the cerebral autoregulatory curve to the right). Focal and diffuse decreases in resting CBF have also been reported. Hypertension also alters endothelium-dependent relaxation of cerebral blood vessels. Lastly, the normal increase in CBF induced by neuronal activation is also attenuated in patients with chronic hypertension *(18)*.

These adaptive responses are aimed at protecting blood vessels from higher pressures, but they also lead to an inability of blood vessels to appropriately dilate in the face of lower BP or increased metabolic demand, and thus increase the susceptibility of brain to cerebral ischemia. Strandgaard and Tominaga reported symptoms of cerebral hypoxia at a MAP of 68 mmHg in chronic hypertensives compared to 40 mmHg in normotensives *(19)*. The clinical consequences of lowering blood pressure below the lower autoregulatory threshold in hypertensives may be worsening of the neurological deficit or development of new neurological deficits.

Cerebral Blood Flow and Autoregulation in Acute Cerebral Ischemia

It has been suggested that focal cerebral ischemia leads to a central "core" or "islands" of severely ischemic tissue with failure of electrical activity and ionic pump function. Surrounding this core is a zone of ischemic tissue with flow between the thresholds of electrical and ion pump failure. This region of structurally viable but functionally impaired tissue has been termed the "penumbra." The ability of the "penumbra" to survive depends not only on the degree of flow reduction, but also on the duration of reduction. This tissue is potentially salvageable with restoration of flow, but further decrease in CBF to this area (e.g., as result of reduction in BP) might lead to irreversible neuronal death.

Autoregulation has been shown to be lost in the area of cerebral infarction and significantly impaired in the peri-infarct area. Symon and coworkers studied vascular reactivity in baboons immediately after occlusion of the middle cerebral artery (MCA). They found loss of autoregulation to decreased CPP that was dependent on the intensity of ischemia. Autoregulation was absent where flow was <20% of basal flow and partly preserved where flow was >40% of basal flow *(20)*. Autoregulation has also been studied in humans and found to be lost in 80% of cases with occlusion of the MCA and 60% of cases without occlusion. Meyer et al. studied 32 patients with ischemic cerebrovascular disease and found that impaired autoregulation was most pronounced immediately after the ischemic episode, and in patients with brainstem, large hemispheric, or subcortical lesions *(21)*. Lastly, studies have demonstrated impairment of dynamic autoregulation after an acute ischemic stroke not only in the affected hemisphere but also in the unaffected hemisphere *(22)*.

ACUTE TREATMENT OF HYPERTENSION AFTER ISCHEMIC STROKE

The Controversy

As discussed earlier, the long-term control of BP in patients with acute ischemic stroke is clearly beneficial. However, the immediate lowering of BP after an ischemic stroke leads to concerns about worsening cerebral ischemia. Other pros and cons of lowering BP in the acute setting are listed in Table 1. Evidence-based decisions should be ideally predicated on

Table 1
Reasons for and Against Blood Pressure Reduction Immediately After an Acute Ischemic Stroke

For	Against
High BP associated with mortality	Chronic hypertensives may develop cerebral ischemia due to shift of the autoregulatory curve
Lowering BP might decrease hemorrhagic transformation (especially after thrombolytic use)	Cerebral ischemia might be exacerbated by lowering BP due to impaired autoregulation in ischemic areas
Lowering BP might decrease cerebral edema	Risk of converting ischemic areas to irreversible infarction
Lowering BP might be indicated for other medical reasons (e.g., myocardial infarction)	BP decreases spontaneously in the first week, even without treatment
Patients might be more compliant with the use of antihypertensives if stared in the hospital	Decreased perfusion distal to a large-vessel stenosis might be worsened
Pilot trial data from recent trials suggest that lowering BP acutely is safe	Lowering blood pressure might exacerbate or propagate intravascular thrombus
	Case reports of neurological worsening after BP reduction
	No convincing trial data to support acute BP reduction

the results of well-designed, large randomized clinical trials of BP lowering in this setting. Unfortunately, no adequately powered trials have been conducted that can currently answer this question though efforts are underway to design and conduct such studies.

Effect on Cerebral Blood Flow

There are a few small case series of patients with an ischemic stroke where CBF was studied after pharmacological reduction of BP. In a recent systematic review, Sare et al. identified 11 studies that tested the effects of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), nitrates, and diuretics on CBF in patients with acute ischemic stroke. These studies are summarized in Table 2. Analysis of randomized clinical trials revealed no alteration in CBF with any antihypertensive class. Nonrandomized trials showed an increase in CBF for CCB (standardized mean difference 0.43, 95% CI 0.01–0.85). Notably, all studies were small, were varied considerably in study design, and had various methodological flaws *(23)*.

Recently, Powers et al. used IV nicardipine to lower MAP by 16 ± 7 mmHg in nine subjects with systolic BP >145 mmHg, 1–11 days after an acute ischemic stroke. Positron emission tomography was used to measure CBF before and after BP reduction. Compared to the contralateral hemisphere, there were no significant differences in the percent change in CBF in the infarct ($p = .43$), peri-infarct region ($p = 1.00$), or remainder of the ipsilateral hemisphere ($p = .50$). Two subjects showed CBF reductions of greater than 19% in both hemispheres. The authors concluded that some individuals might have a drop in global CBF with BP reduction, possibly associated with an upward shift of the autoregulatory limits

Table 2
Effect of Antihypertensive Agents on Cerebral Blood Flow and Flow Velocity in Acute Ischemic Stroke

Authors	Patients	Intervention	Design	Time to randomization	Time to Measure	Methods	Effect
Waldemart et al.	12	Oral captopril	BAS	5 days	1 h	SPECT	CBF – no change
Nazir et al.	25	Oral perindopril	RCT	4–8 days	6–8 h	SPECT, TCD	CBF/CBFv – no change
Dyker et al.	24	Oral perindopril	RCT	7 days	8 h	TCD	CBFv – increased
Nazir et al.	24	Oral losartan	RCT	2–7 days	6–8 h	SEPCT, TCD	CBF – no change, CBFv – reduced
Gelmers et al.	10	IV nimodipine	BAS	"Acute Stroke"	Following infusion	Xenon-CT	CBF – no change
Hakim et al.	10	IV nimodipine	RCT, BAS	48 h	7 days	PET	CBF – no change
Fieschi et al.	5	IV nimodipine	BAS	4 h	Following infusion	Xenon-CT	CBF – increased
Lisk et al.	11	Oral nicardipine	RCT, BAS	72 h	3 days	SPECT	CBF – no change
Infield et al.	41	Oral nimodipine	RCT, BAS	12 h	24 h	SPECT	CBF – increased
Eames et al.	37	Oral bendrofluazide	RCT	<96 h	7 days	TCD	CBFv – no change
Rashid et al.	90	Transdermal nitroglycerine	RCT	<72 h	2 h	TCD	CBFv – no change
Wilmot et al.	18	Transdermal nitroglycerine	RCT, BAS	<5 days	1 h	Xenon-CT, TCD	CBF/CBFv – no change

BAS Before–after study, *RCT* randomized controlled trial, *SPECT* single photon emission computed tomography, *TCD* transcranial Doppler, *PET* positron emission tomography, *CBF* cerebral blood flow, *CBFv* cerebral blood flow velocity

Source: Modified from Table 1, Sare et al. which should be referred to for individual citations for the listed studies (23).

due to chronic hypertension. However, selective regional impairment of autoregulation in the affected hemisphere was not observed *(24)*.

Effect on Neurological or Functional Outcome

Case Studies

There are many case reports and small case series of ischemic stroke patients who had worsening of the neurological deficit after abrupt lowering of BP. In most cases, the drop in BP was substantial and the minimum drop in BP that produced symptoms appears to be about 24 mmHg *(25)*.

Randomized Clinical Trials

Several small studies have addressed BP reduction after acute strokes; however, there are no adequately powered, well-designed randomized clinical trials. The best available evidence is summarized below.

- The low-dose β-blockade in acute stroke trial ("BEST" trial) found that low-dose atenelol or propranolol used in patients within 48 h of a stroke, despite leading to a significant drop in BP, did not lead to a significant difference in mortality, neurological deterioration, functional outcome, and length of stay in the hospital *(26)*.
- A post hoc analysis of NINDS tPA trial showed that BP reduction in the first 24 h after an acute stroke appeared to be safe. At 3 months, there was no difference in outcome between patients in the placebo arm who received antihypertensive therapy compared to those who did not *(27)*.
- The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) trial randomized patients with acute stroke and a BP of more than 200/110 mmHg to receive Candesartan cilexetil or placebo. The trial was stopped prematurely when a 47.5% reduction in mortality and cardiovascular events was noted in the group treated with candesartan *(28)*. However, there was no significant difference in BP between the two groups, and hence the benefit cannot be attributed to BP reduction.
- The Intravenous Nimodipine West European Stroke Trial (INWEST) randomized patients with acute strokes presenting within 24 h of symptoms into three treatment arms—placebo, low-dose (1 mg/h), and high-dose (2 mg/h) nimodipine. This trial noted worsening of clinical outcomes with lower DBPs *(29)*.
- In the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) pilot trial, 179 patients with an acute stroke (25 patients had ICH) were randomized to treatment with placebo or antihypertensives (β-blockers or ACE inhibitors). There were no significant adverse effects of antihypertensive treatment, and there was a borderline significant reduction in mortality at 90 days in the actively treated group *(30)*.
- Finally, in a recent Cochrane review of 1,153 patients enrolled in 12 randomized controlled trials of BP manipulation (11 trials lowering BP, 1 increasing BP) within 1 week of an ischemic or hemorrhagic stroke, the authors found insufficient evidence to evaluate the effects of altering BP on outcome during the acute phase of stroke *(31)*.

Thus, the available evidence is insufficient to provide accurate guidance on the management of BP immediately after a stroke and therefore, treatment of this condition is largely empiric. Hopefully, the results of planned large-scale studies will provide evidence to guide the management of this common problem. Important ongoing studies in this area are summarized in Table 3.

Table 3
Ongoing Studies of Blood Pressure Reduction After an Acute Ischemic Stroke

Trial name	Inclusion criteria	Intervention	Outcome measures
Acute Candesartan Cilexetil Outcomes Stroke Trial (ACCOST)	• Presenting with acute ischemic stroke within 72 h • Mean BP >120/70 mmHg	Phase I: Candesartan Cilexetil (AT1 receptor antagonist) or placebo for 4 weeks Phase II: Candesartan or ACE inhibitor with BP target of <140/85 mmHg	• Primary outcome: All cause mortality, vascular mortality • Secondary outcome: Neurological recovery, functional recovery
Blood Pressure Lowering in Acute Stroke Trial (BLAST)	• Acute ischemic stroke within 48 h of symptom onset • Previous hypertension	Valsartan or placebo for 7 days or till discharge	Primary outcome: • 30-Day Glasgow outcome scale • Modified Rankin scale
Scandinavian Candesartan Acute Stroke Trial (SCAST)	• Presenting with acute ischemic stroke within 30 h • Systolic BP $\geq$140 mmHg	Candesartan or placebo for 7 days	Primary outcome: • Death or disability at 6 months • Combination of vascular death, myocardial infarction, or stroke at 6 months
Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS)	• Patients within 24 h of acute ischemic or hemorrhagic stroke • Within 24 h of last dose of antihypertensive therapy	Antihypertensive treatment for 2 weeks	• Primary outcome: Mortality and rate of dependency at 2 weeks • Secondary outcome: Neurological and functional status, discharge destination, and BP at 2 weeks and 6 months

Table 3
(Continued)

Trial name	Inclusion criteria	Intervention	Outcome measures
Efficacy of Nitric Oxide in Stroke (ENOS) Trial	• Patients with hemorrhagic or ischemic stroke • Motor weakness for at least 1 h • Can be treated within 48 h • Prestroke Rankin score >3	Patients will be randomized to receive treatment with a glyceryl trinitrate patch or to receive no patch for 7 days. Patients taking antihypertensives randomized to continue or discontinue their medication for 7 days	Primary Outcome: Mortality rate and Rankin score at 90 days. • Secondary Outcome: Recurrent stroke, symptomatic deep vein thrombosis, symptomatic pulmonary embolism, or symptomatic intracranial hemorrhage at 7 days, major extracranial hemorrhage at 10 days, blood pressure recorded during 7-day treatment, length of hospital stay, discharge disposition, Barthel Index, quality of life as measured by EuroQol, and abbreviated mental test score at 90 days
Telmisartan Acute Stroke Trial (TAST)	Patients must have suffered ischemic or hemorrhagic stroke; onset date of stroke is less than 5 days; systolic BP >140 mmHg	Telmisartan 80 mg once a day or placebo	Primary Outcome: Quantitative cerebral blood flow (xenon CT) before and 1.5 h after first treatment. • Secondary Outcome: Middle cerebral artery blood flow velocity and pulsatility index (transcranial doppler), central blood pressure, augmentation index, peripheral blood pressure, and heart rate

Source: Modified from Aiyagari and Badruddin (*35*).

Guidelines for BP Management in Acute Ischemic Stroke

Current evidence-based guidelines from American Heart association and American Stroke Association recommend a cautious approach to lowering of BP. In patients treated with thrombolytic therapy, they recommend lowering of BP to an SBP not more than 185 mmHg and a DBP not greater than 110 mmHg prior to treatment and keeping the SBP below 180 mmHg and the DBP below 105 mmHg for 24 h. For other patients, they recommend withholding antihypertensives during the acute period unless SBP exceeds 220 mmHg or DBP exceeds 120 mmHg. If BP is to be lowered, the guidelines recommend cautious lowering of blood pressure by ~15% in the first 24 h. It is also suggested that antihypertensive treatment may be restarted at 24 h in previously hypertensive patients who are neurologically stable if there are no other contraindications *(32)*.

The European Stroke Organization guidelines have similar recommendations for patients treated with thrombolytics. They do not recommend routine BP lowering in the setting of an acute ischemic stroke unless BP is extremely high (>220/120 mmHg) on repeated measurements, or there is severe cardiac failure, aortic dissection, or hypertensive encephalopathy *(33)*.

CHOICE OF ANTIHYPERTENSIVE AGENTS

Large comparative studies between various antihypertensive classes and BP reduction after acute ischemic stroke have not been made. Ideally, the agent chosen for administration should have a rapid and short duration of action without significant adverse neurological effects such as sedation or increase in intracranial pressure. Intravenously administered agents are preferred. In the USA, they include labetalol, hydralazine, esmolol, nicardipine, nitroglycerine, nitroprusside, and enalapril. Urapidil and fenoldopam are also used in Europe. The doses and advantages and disadvantages of these medications are summarized in Table 4.

Table 4
Preferred Antihypertensive Agents in the Treatment of Stroke-Associated Hypertension

Drug	Mechanism of Action	Intravenous Dose	Advantages	Disadvantages
Labetalol	α_1-, β_1-, and β_2-receptor antagonist	Test dose 5 mg, then 20-to-80-mg bolus every 10 mins up to 300 mg; IV infusion 0.5–2 mg/min	Does not lower CBF 20-to-80 mg Does not increase ICP	May exacerbate bradycardia
Esmolol	β_1-receptor antagonist	500-µg/kg bolus, then 50–300 mg/kg/min	Does not lower CBF Does not increase ICP	May exacerbate bradycardia
Sodium nitroprusside	Vasodilator	0.25–10 µg/kg/min	Potent antihypertensive	May increase ICP Can cause cerebral steal Potential for cyanide toxicity
Nitroglycerin	Vasodilator	5–100 µg/kg/min	Can be helpful for concomitant cardiac ischemia	May increase ICP Can cause cerebral steal
Hydralazine	Vasodilator	2.5-to-10-mg bolus	Can be given as IV bolus when labetalol is contraindicated due to bradycardia	May increase ICP Can cause cerebral steal
Nicardipine	L-type calcium channel blocker	5–15 mg/h	Does not decrease CBF	May increase ICP Long duration of action
Enalaprilat	ACE inhibitor	0.625–1.25 mg every 6 hrs	Does not decrease CBF	Variable response Long duration of action

CBF Cerebral blood flow *ICP* intracranial pressure.
Source: Modified from Aiyagari et al.

CONCLUSION

Elevated BP in the setting of an acute stroke is a common problem, the optimal management of which is not well established. There appears to be some consensus that patients who have received thrombolytic treatment should have their BP controlled in accordance with published guidelines. For other patients, it is hoped that large-scale, ongoing, and planned studies will provide evidence that can be used to guide treatment. However, one should also keep in mind that ischemic stroke is a heterogeneous disease with different pathogenic mechanisms and underlying etiologies. Even for a given stroke type, there is likely to be a significant variation in the collateral circulation of different patients. These factors will also need to be considered in the treatment of an individual patient.

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8

Hypertensive Encephalopathy and Acute Blood Pressure Management After Hemorrhagic Stroke

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CONTENTS

INTRODUCTION

In the USA, hypertension affects approximately 76% of men and 64% of women by 75 years of age. Among the 73 million individuals in the USA with hypertension, almost 80% are aware of their high blood pressure and 69 % receive antihypertensive treatment. However, less than 50% have controlled blood pressure, placing these individuals at risk for developing neurological emergencies such as hypertensive crisis and intracerebral hemorrhage *(1)*.

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment, the majority of hypertensive patients will eventually require two or more antihypertensive medications to reach their goal blood pressure *(2)*. Over time, individuals with chronic uncontrolled blood pressure experience end-organ damage, and undertreated individuals are the most susceptible to abrupt rises in blood pressure which can result in acute end-organ dysfunction *(3)*. Hypertensive encephalopathy and intracerebral hemorrhage are two of the most serious acute complications of hypertension affecting the brain.

HYPERTENSIVE ENCEPHALOPATHY

Historical Overview

The term malignant hypertension was first used by Volhard and Farh in 1914 after noting that many patients with severe hypertension had fundoscopic changes such as retinopathy

and papilledema in addition to renal insufficiency. They defined malignant hypertension as an elevated blood pressure with signs of acute end-organ damage *(4)*. Keith and Wagener subsequently broadened the definition of malignant hypertension by noting that renal dysfunction was not an obligatory requirement for acute hypertensive damage. They also used the term "accelerated hypertension," defined as severe blood pressure elevation with retinal hemorrhages and exudates in the absence of papilledema *(5)*. Oppenheimer and Fishberg coined the term "hypertensive encephalopathy" in 1928 when they described a 19-year-old student with malignant hypertension and associated headache, convulsions, and neurologic deficits *(6)*.

Malignant hypertension and accelerated hypertension have largely been replaced in today's vernacular by the collective term hypertensive crisis, which includes both hypertensive emergencies and urgencies. A hypertensive emergency is characterized by a severe elevation in BP (>180/120 mmHg) complicated by evidence of impending or progressive target organ dysfunction. Hypertensive urgency is an acute severe rise in blood pressure without progressive target organ dysfunction. Diastolic pressures are typically >120 mmHg in both clinical settings *(2,7)*.

Epidemiology

Nearly 1% of hypertensive patients in the USA will experience a hypertensive crisis *(3)*. The majority of these patients have essential hypertension; however, individuals with secondary hypertension frequently experience labile blood pressure placing them at risk for hypertensive crisis. Another group of individuals at risk for hypertensive crisis are those that abruptly discontinue antihypertensive medications, especially centrally acting drugs like clonidine *(8)*. Patients with hypertensive crisis are frequently young, male, Black, or Hispanic and of lower socioeconomic status *(9)*.

A retrospective study of 200 patients with malignant hypertension identified during the 1960s–1980s reported a 2-year survival rate of 50–80% *(10)*. More recent studies have reported 5-year survival rates of 74% and 10-year survival rates approaching 70% *(11,12)*.

In an observational study from Italy, hypertensive crisis represented 25% of 1,634 medical emergencies/urgencies that presented to the emergency department. Nearly one-fourth had end-organ dysfunction of which neurologic deficits accounted for 21%, and hypertensive encephalopathy was reported in 16% *(13)*. A retrospective study of 452 patients with hypertensive crisis presenting to emergency departments in Brazil reported similar results *(14)*.

Clinical

Hypertensive encephalopathy is a hypertensive emergency that is due to failure of the upper limit of cerebrovascular autoregulation. It presents as a sudden onset of neurological signs and symptoms in the setting of acutely elevated blood pressure *(15)*. The most common neurological manifestations are headache and visual disturbances. Others include altered mental status, nausea, vomiting, seizures, and focal deficits *(15,16)*. It is the rate of blood pressure rise rather than the absolute blood pressure value that is thought to induce the encephalopathy *(15)*. Even though the majority of patients with hypertensive emergency present with only one type of end-organ damage, evidence of other organ dysfunction is sometimes seen *(13)*. The fundoscopic examination of individuals with hypertensive

encephalopathy frequently, but not always, reveals retinal exudates, hemorrhages, and papilledema *(17,18)*.

Improperly treated, hypertensive encephalopathy may result in cerebral hemorrhage, coma, and death. However, with appropriate treatment, hypertensive encephalopathy is usually completely reversible *(13)*.

Pathophysiology

Although the exact pathophysiology of hypertensive encephalopathy is not completely understood, the effect of elevated blood pressure on cerebrovascular autoregulation has been well studied. Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and intracerebral pressure (ICP) or central venous pressure if the latter is higher *(19)*. Autoregulation is the intrinsic ability of the cerebral vasculature to maintain relatively constant cerebral blood flow within a wide range of cerebral perfusion pressures by altering the resistance in the precapillary arterioles *(19,20)*. The cerebral resistance adapts to varying cerebral perfusion pressures, in part by activating the sympathetic nervous system and supressing the renin–angiotensin–aldosterone system (RAAS) *(21)*. Local mediators such as nitric oxide (NO), a vasodilator released in response to shear stress, and endothelin-1, a vasoconstrictor which activates the RAAS, are released by the endothelium and also contribute to the maintenance of cerebral blood flow *(22)*.

During a hypertensive emergency, the endothelium responds to the abrupt increase in blood pressure by releasing NO *(22)*. When hypertension is sustained or severe, this endothelial vasodilator response is overwhelmed, eventually leading to a state of increased resistance. Ongoing endothelial damage from persistent hypertension causes the production of inflammatory cytokines and increases endothelin-1. These events increase endothelial permeability, inhibit fibrinolysis, and activate coagulation *(23)*. An aggrandizement of the RAAS also plays a prominent role in vascular injury and tissue ischemia *(24)*. These changes result in a breakdown of the blood–brain barrier, cerebral edema, and microhemorrhages.

In normotensive individuals, the upper limit of the MAP whereby flow increases proportionally is approximately 150 mmHg. This limit is higher in chronic hypertensives. In a baboon model of chronic hypertension, the upper limit at which cerebral blood flow exceeded the plateau was between 155 and 169 mmHg *(25)*. Normotensive individuals can develop end-organ damage with acute increases of diastolic blood pressure as low as 100 mmHg, whereas chronically hypertensive individuals usually do not develop end-organ damage until diastolic blood pressures reach 130 mmHg *(3)*. Individuals with chronically elevated blood pressure may have a structural and functional adaptive response with luminal narrowing and arterial hypertrophy from sustained smooth muscle contraction, which increases cerebrovascular resistance. This structural and functional adaptive response protects the capillary bed from an acute rise in blood pressure *(21,25)*. However, the brain is left vulnerable to ischemia at low blood pressures *(26)*.

The pathophysiology of hypertensive encephalopathy has been debated over the last century, but technological advances continue to provide insightful clues into its complicated pathogenesis. Acutely, there is failure of cerebral autoregulation at very high pressures *(27)*. One theory proposes that overregulation or spasm of cerebral vessels in response to acutely rising blood pressure leads to decreased cerebral blood flow, ischemia, development of intra-arterial thrombosis, and cytotoxic edema *(28)*. Another theory proposes a

breakthrough phenomenon whereby forced vessel dilation leads to hydrostatic edema *(29)*. The preponderance of recent evidence supports the latter theory *(30)*.

Understanding the pathophysiology of hypertensive encephalopathy is imperative when considering acute treatment. If hypertensive encephalopathy was due to overregulation of the cerebral vasculature leading to ischemia and cytotoxic edema, acute goal-directed treatment would allow for increases in systemic blood pressure to maintain cerebral perfusion pressure and prevent further ischemia *(31,32)*. In contrast, treatment of perfusion breakthrough directs acute therapy toward a relative reduction of blood pressure rather than permissive hypertension *(31)*.

Workup

While evaluating patients with hypertensive encephalopathy, in addition to performing a thorough neurological examination, evidence for increased jugular venous pressure, abdominal bruits, abnormal peripheral pulses, and pulmonary edema should be sought. Laboratory studies should include a complete blood count, metabolic profile, urinalysis, cardiac enzymes, and toxicology studies. In addition, an electrocardiogram and chest radiograph may be useful for detecting cardiac ischemia, left ventricular hypertrophy, pulmonary edema, and aortic dissection. Neuroimaging should be performed early to evaluate for evidence consistent with hypertensive encephalopathy or alternative causes of neurological dysfunction.

MAGNETIC RESONANCE IMAGING

In cases of hypertensive encephalopathy, brain magnetic resonance imaging (MRI) typically reveals increased signal intensity on fluid-attenuated inversion recovery imaging (FLAIR) sequence. Lesions may be iso- or hypointense on T1-weighted images *(18)*. Evidence for restricted diffusion is typically absent supporting the perfusion breakthrough hypothesis *(31,33,34)*. Lesions predominantly involve the subcortical white matter and have a propensity for the posterior circulation regions such as the occipital lobe, cerebellum, and brain stem (Fig. 1) *(18,33)*. The lesions may be symmetric or asymmetric and may be completely reversible with proper blood pressure lowering *(30,31,33)*. The predominant involvement of the occipital lobes is thought to be due to the paucity of sympathetic innervation of the posterior circulation, thus rendering the vasculature more susceptible to vasodilatory responses *(35,36)*.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

The typical neurological and imaging findings of hypertensive encephalopathy are similar to the syndome "posterior reversible encephalopathy syndrome (PRES)" that has also been reported with eclampsia and certain immunosuppressant agents such as cyclosporine *(37–40)*. A retrospective study of patients with PRES from the Mayo clinic attributed the underlying etiology to hypertension in 68%, eclampsia in 11%, and immunosuppressive medication in 11%. Imaging findings improved during follow-up in all cases *(37)*. An Austrian study of 30 patients with a clinical neuroradiologic diagnosis of PRES reported an indistinguishable MRI appearance across predisposing risk factors *(41)*. The pathophysiology of PRES is thought to be similar to hypertensive encephalopathy, although a clear correlation with elevated blood pressure has not been established *(30,37)*.
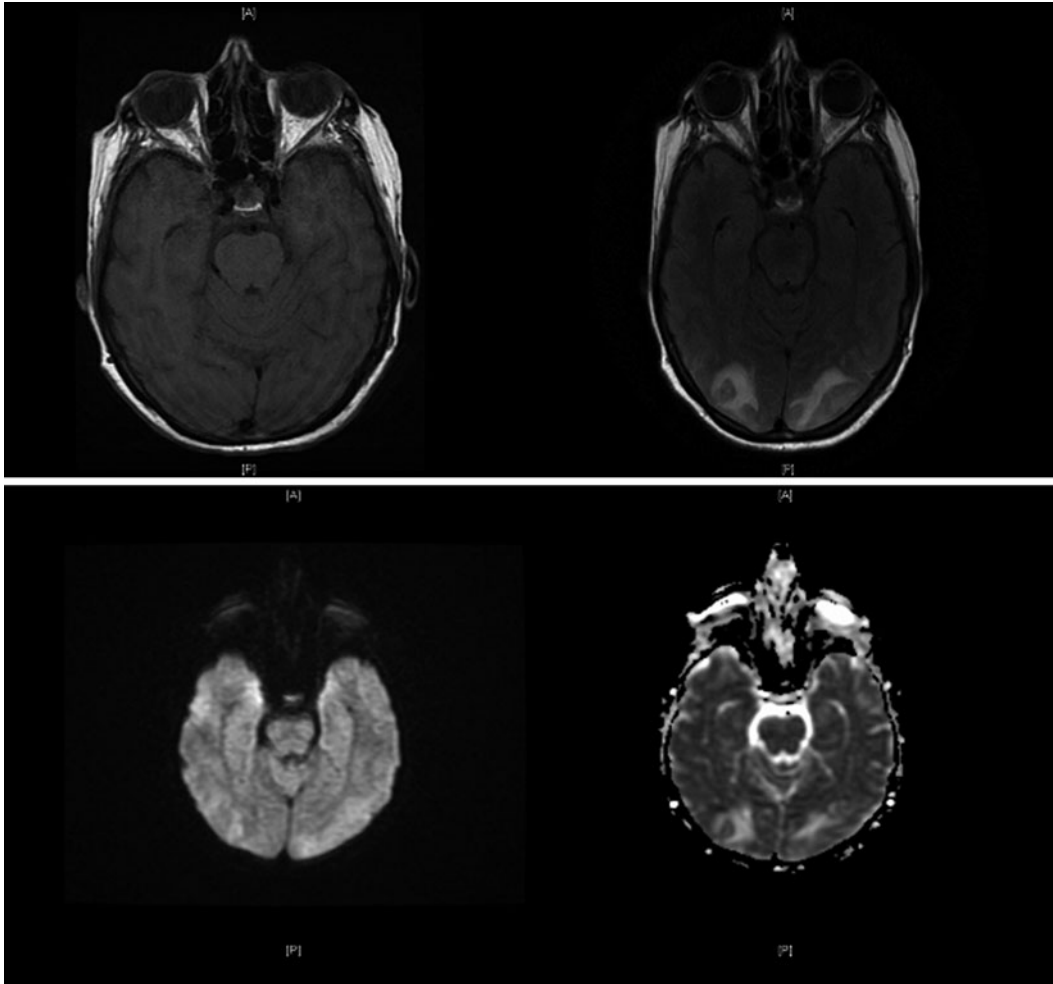
Fig. 1. MRI of the brain in a 62-year-old woman presenting with hypertensive encephalopathy reveals predominance of vasogenic edema in the subcortical posterior white matter. Unenhanced T1-weighted image (*upper left*) showing isointense lesion; T2-weighted FLAIR image (*upper right*) showing increased signal in posterior *white* matter; Diffusion-weighted image and ADC map (*lower left and right*) showing no evidence of restricted diffusion.

Treatment

In patients with a hypertensive urgency, blood pressure can gradually be lowered over 24–48 h with oral medications in a nonintensive care unit setting. However, all patients with hypertensive emergency should be treated with intravenous medications in an intensive care unit, commonly with invasive blood pressure monitoring *(17)*. In order to prevent hypoperfusion and cerebral ischemia in patients with a right-shifted autoregulation curve, rapid blood pressure correction should be avoided *(42)*. Short-acting and easily titratable antihypertensive infusions are preferred (Table 1), and intramuscular and sublingual routes should be avoided *(42–44)*. It may be reasonable to lower the diastolic blood pressure by

Table 1
Antihypertensive Agents Used in Neurological Emergencies

Agent	Dosing	Onset/duration of action	Advantages	Disadvantages
Esmolol	500 μg/kg IV bolus or 25–300 μg/kg/min IV infusion	120 s/ 18–30 min	Short acting and metabolized via red blood cells	Bradyarrhythmia, heart failure
Fenoldopam	0.1–0.3 mg/kg/min IV infusion	4–5 min/10–15 min	No CNS effects or toxic metabolites	Headache, tachycardia
Hydralazine	10–20 mg IV bolus	10 min/ >1 h	Safe in pregnancy	Unpredictable drop in BP, tachycardia
Labetalol	5–20 mg IV bolus every 15 min, up to 2 mg/min IV infusion	2–5 min/4–6 h	Maintains cardiac output and cerebral blood flow	Bronchospasm, bradycardia
Nicardipine	5–15 mg/h IV infusion	5–15 min/4–6 h	Cerebral vasodilation, reduces cerebral ischemia	Reflex tachycardia
Sodium Nitroprusside	0.25–10 μg/kg/min IV infusion	Immediate/2–3 min	Immediate onset	Possible increase in ICH, cyanide toxicity

IV Intravenous, *CNS* central nervous system, *BP* blood pressure, *ICH* Intracerebral hemorrhage

10–15% over 30–60 min or reduce the MAP by 25% over 8 h if the MAP at presentation exceeds 150 mmHg *(19,43)*. If neurological deterioration occurs during blood pressure control, treatment should be suspended *(19)*. Volume resuscitation with saline should be considered, as many patients presenting with hypertensive emergencies are dehydrated *(43)*.

Certain blood pressure-lowering agents should be avoided during treatment of hypertensive encephalopathy. Sublingual nifedipine can cause a sudden uncontrolled blood pressure drop within 5–10 min after administration that may precipitate cerebral ischemia *(43,45)*. Elderly individuals are particularly susceptible to this rapid reduction in pressure *(46)*. Nitroglycerine is a potent venodilator and may cause hypotension with reflex tachycardia. Nitroglycerine also reduces preload and cardiac output which may compromise cerebral perfusion *(43)*. Hydralazine is a vasodilator that when given parenterally may cause an unpredictable fall in blood pressure lasting up to 12 h *(47)*. Sodium nitroprusside is an arterial and venous dilator that may theoretically decrease cerebral blood flow while increasing intracranial pressure although the clinical significance is contested *(48)*. Additionally, nitroprusside contains 44% cyanide by weight which is metabolized to thiocyanate, requiring intact liver and renal functions for adequate removal *(49)*. Cyanide toxicity may cause cardiac arrest, coma, encephalopathy, seizures, and irreversible focal neurological deficits *(50)*.

Labetalol, nicardipine, and esmolol are the preferred initial agents for blood pressure treatment in hypertensive encephalopathy *(19)*. Labetalol is a combined selective alpha 1-adrenergic and nonselective beta-adrenergic blocker *(51)*. Onset of action of IV labetalol is within 2–5 min and peaks at 5–15 min with duration of 2–6 h *(52)*. Cardiac output and cerebral blood flow are maintained while systemic vascular resistance is reduced *(51,52)*. Nicardipine is an IV dihydropyride-derived calcium channel blocker *(53)*. Onset of action begins within 5–15 min and duration is 4–6 h *(54)*. Nicardipine exhibits vascular selectivity and has strong cerebral vasodilatory activity that has been shown to reduce cerebral ischemia *(53)*. Esmolol is a cardioselective beta-adrenergic blocker that is extremely short acting. Onset of action is within 120 s with duration of 18–30 min *(55)*. The metabolism of esmolol is via esterases in the cytosol of red blood cells and is not affected by renal or hepatic dysfunction *(55)*. It may be used as both a bolus and an infusion, but is contraindicated in patients with bradyarrhythmias and heart failure *(55)*. Lastly, IV fenoldopam, a selective dopamine-1 receptor agonist which vasodilates the systemic arteries and causes diuresis, may be considered *(56)*. The onset of action is within 4–5 min with duration of 1,015 min *(56)*. Fenoldopam has no central nervous system effects or toxic metabolites, and side effects are typically mild vasodilatory symptoms such as headache *(56)*.

Once blood pressure is adequately controlled with initial treatment and neurological symptoms resolve, oral antihypertensive agents can be started while IV agents are slowly weaned *(42)*. The long-term treatment goal is blood pressure <140/90 mmHg and <130/80 in patients with diabetes or renal disease *(2)*. The majority of patients will require two or more antihypertensive agents from different drug classes to reach their goal blood pressure *(2)*. Adoption of lifestyle modifications should include weight loss, healthy diet, physical activity, limited alcohol intake, and smoking cessation *(2)*. Management strategies should focus on individual patient goals and foster patient adherence.

Summary

Hypertension is a widely prevalent disease, and nearly 1% of hypertensive individuals will experience a hypertensive crisis in their lifetime. Hypertensive encephalopathy is a clinical manifestation of hypertensive crisis characterized by headache, visual disturbance, altered mental status, seizures, and focal neurological deficit in the setting of an abrupt blood pressure increase. Cerebral autoregulation may fail with an acute severe increase of blood pressures, leading to endothelial permeability, fibrin deposition, and vasogenic edema with a characteristic imaging distribution in the occipital lobes. MRI abnormalities and clinical symptoms are typically reversible with appropriate prompt treatment.

ACUTE BLOOD PRESSURE MANAGEMENT AFTER HEMORRHAGIC STROKE

Epidemiology

Intracerebral hemorrhage (ICH) accounts for approximately 10% of all strokes in the USA. The 30-day mortality has been reported to be 35–52% with more than half occurring in the first 2 days *(57–59)*. ICH can be classified as either primary or secondary. Primary or spontaneous ICH accounts for about 80% of cases and is usually associated with chronic hypertension *(60,61)*. Nearly 61,000 individuals per year in the USA and about 90,000 individuals per year in the European Union are affected *(1,62)*. The Oxford Community Stroke Project and the Oxford Vascular Study reported that the number of ICH in individuals older than 75 years of age has not significantly changed from 1981 to 2006 *(63)*. However, as the prevalence of cerebral amyloid angiopathy increases as the population ages, the volume of ICH cases will likely increase, and increasing age has been associated with higher mortality *(64)*.

Clinical

ICH is an emergency that necessitates expeditious recognition due to the high frequency of progressive deterioration within the first few hours *(57)*. Impaired consciousness, vomiting, and severe headache at initial presentation increase the likelihood of ICH rather than ischemia *(65)*. However, clinical presentation is inadequate to definitively differentiate ICH from other stroke subtypes, making neuroimaging mandatory *(66)*. Independent predictors of 30-day mortality include age, ICH volume, initial Glasgow Coma Scale score, hydrocephalus, and elevated blood pressure at presentation *(66–68)*. In one prospective study, over 38% of patients with ICH had a hematoma volume increase >33%, and the majority of those with an increase demonstrated at least some hematoma growth on CT scan within the first hour after presentation *(69)*. In addition, approximately 50% of patients with hematoma growth experienced neurological deterioration within 20 h of admission *(69)*, and elevated blood pressure at presentation has been correlated with hematoma growth *(68)*. At 3 months, hematoma growth has been associated with a 5.2-fold increase in mortality *(70)*.

Although optimal therapy has not been established, current treatment options for ICH include surgical therapies such as clot evacuation, hemicraniectomy, and ventriculostomy

for hydrocephalus, and medical therapies such as airway management, blood pressure lowering, ICP and CPP management, seizure prevention and treatment, temperature control, nutritional support, and deep venous thrombosis prophylaxis *(57)*. Despite a 2007 update by the American Heart Association (AHA) to its ICH guidelines, there remains no Class I Level A-specific treatment recommendation for ICH *(64)*. This is largely due to a paucity of large randomized controlled trials. Therefore, treatment strategies for ICH are quite variable throughout the world *(64,71)*. More recently, renewed enthusiasm has given way to a surge in clinical research of potential ICH treatment, and one such area of interest is acute blood pressure management *(57)*.

Arterial hypertension is the most prevalent comorbidity in ICH patients, but a history of hypertension alone has not been associated with poor outcome *(64,68)*. Elevated blood pressure is common after ICH regardless of hypertension history *(61)*. The National Hospital Ambulatory Medical Survey from 663 participating hospitals reported that 75% of 45,330 patients presenting with ICH had initial systolic blood pressure measurements >140 mm Hg *(72)*. The relationship between elevated presenting blood pressure and acute ICH is not completely understood *(61,72)*. One theory is that elevated blood pressure following stroke represents inadequately treated chronic hypertension *(73)*. This has been challenged since blood pressure usually spontaneously decreases within 10 days after acute stroke without antihypertensive medication *(74)*. Another theory is that the elevated blood pressure is a consequence of the ICH. The acute stress response to stroke involves increased sympathetic tone as well as upregulated levels of circulating catecholamines, which may increase blood pressure *(75)*. Brain natriuretic peptide, a vasoactive hormone, increases in the acute phase of stroke and appears to correlate with higher blood pressure levels *(76)*.

Controversy: To Treat or not to Treat

Acute blood pressure management after ICH is controversial. The main argument for lowering blood pressure is to prevent hematoma expansion *(57)*. Retrospective studies have correlated systolic blood pressure >170 mmHg at presentation with hematoma growth *(77)*. A retrospective comparison of 51 ICH patients with hematoma expansion to 100 ICH patients without hematoma expansion revealed a significant statistical difference in the blood pressures recorded within 48 h *(78)*. A 10 mmHg diastolic blood pressure increased the risk of hematoma expansion 10.6 times within the initial 24 h *(78)*. However, two prospective studies reported no correlation between hematoma growth and elevated blood pressure at presentation *(69,79)*. In addition, the effect of sustained blood pressure elevation on hematoma growth could not be ascertained due to the rapid treatment of blood pressure in greater than three-fourths of patients *(69,79)*.

The case against aggressive blood pressure lowering after acute ICH is the theoretical risk of inducing perihematoma ischemia by decreasing CPP *(57,61)*. Animal models have suggested that cerebral blood flow transiently decreases following ICH and is lowest in the perihematoma region *(80)*. An MRI study of hyperacute ICH patients showed restricted diffusion in the perihematomal rim that was associated with poor outcomes *(81)*. However, cerebral blood flow (CBF) measured by positron mission tomography in patients with acute small- to medium-sized supratentorial ICH 6–22 h after onset demonstrated no

significant changes in global or perihematomal blood flow after a 15% MAP reduction using IV nicardipine or labetalol *(82)*.

Clinical Trials

A growing body of data continues to support the safety of acute blood pressure lowering after ICH to MAP <110 mmHg. A retrospective study of 244 Japanese patients who presented with blood pressure more than 180/105 mmHg and received IV antihypertensive drugs reported early functional improvement in those whose systolic blood pressure was less than 138 mmHg within the initial 24 h *(83)*. Another retrospective study of 122 patients suggested that aggressive blood pressure lowering within the first 24 h may decrease the risk of neurological deterioration *(84)*.

A small prospective single-center study of 22 consecutive patients with spontaneous ICH reported that lowering MAP to 100–110 mmHg within 120 min of emergency department arrival was safely tolerated in 77%, while the other 23% required vasopressor rescue *(85)*. Koch et al. randomized 42 patients to standard blood pressure treatment of MAP 110–130 mmHg or aggressive blood pressure lowering MAP to <110 mmHg within 8 h of ICH onset *(86)*. Intensive blood pressure lowering was not associated with increased risk of neurological deterioration compared to standard treatment *(86)*.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial was a phase I multicenter, open-label, nonrandomized safety trial of early blood pressure lowering after supratentorial ICH. ATACH recruited 60 subjects with evidence of chronic hypertension and elevated systolic blood pressure >170 mmHg presenting within 12 h of symptom onset *(87)*. Subjects were consecutively enrolled into one of three tiers of increasing blood pressure-lowering intensity (170–200, 140–170, and 110–140 mmHg) with IV nicardipine within the first 24 h, provided no safety concerns were raised in the more conservative tiers *(87)*. Aggressive systolic blood pressure lowering (110–140 mmHg) was well tolerated with minimal risk of early neurological decline, in-hospital mortality, or hematoma growth. ATACH-2 is an ongoing phase III international multicenter, randomized controlled trial that aims to determine the efficacy of intensive blood pressure treatment in patients with chronic hypertension and spontaneous ICH.

The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) was a randomized blinded outcome trial that enrolled 404 patients from 44 hospital sites in Australia, China, and South Korea *(88)*. Eligible patients were at least 18 years old with spontaneous ICH within 6 h of onset, systolic blood pressure of 150–220 mmHg at randomization, and no contraindications to blood pressure lowering. Subjects were randomized to early systolic blood pressure <140 mmHg or standard treatment per guideline recommendations (target systolic blood pressure <180 mmHg). Mean hematoma growth at 24 h was 13.7% in the intensive treatment group and 36.3% in the standard treatment group ($p = 0.04$). The absolute risk of hematoma growth ≥33% was reduced by 8% ($p = 0.05$). INTERACT2 began in 2008 and aims to determine the effects of intensive blood pressure treatment on clinical outcomes in 2,800 patients with acute ICH. Anticipated completion is 2011.

These recent studies suggest that early aggressive lowering of blood pressure in ICH is safe, and the results of the larger planned trials will hopefully provide conclusive evidence of the effects of intensive blood pressure lowering on clinical outcome.

Guideline Recommendations

The AHA guidelines for ICH treatment recommend that target blood pressure should be based on individual factors including history of hypertension, elevated ICP, age, etiology of hemorrhage, and duration from onset *(57)*. After spontaneous ICH, the AHA recommends maintaining systolic blood pressure <180 mmHg or MAP <130 mmHg *(57)*. Systolic blood pressure > 200 mmHg or MAP >150 mmHg should be treated with a continuous infusion of antihypertensive medication. When systolic blood pressure is >180 mmHg or MAP >130 mmHg in the setting of suspected ICP elevation, ICP monitoring should be considered and cerebral perfusion pressure 60–80 mmHg maintained during blood pressure lowering. If systolic blood pressure is >180 mmHg and elevated ICP is not suspected, then blood pressure should be reduced sensibly, target 160/90 mmHg or MAP 110 mmHg, with 15-min interval neurological checks *(57)*.

In 2006, the European Stroke Initiative (EUSI) published recommendations for spontaneous ICH management *(71)*. Regardless of hypertension history, EUSI recommends lowering MAP no greater than 20% that of presentation *(71)*. In patients with a history of hypertension, antihypertensive medication is initiated when systolic blood pressure is >180 mmHg or diastolic blood pressure is >105 mmHg, with target blood pressure of 160–170/100 mmHg or MAP of 120–125 mmHg. In patients without a history of hypertension, antihypertensive medication is initiated when systolic blood pressure is >160 mmHg or diastolic blood pressure is >95 mmHg, with target blood pressure of <150/90 mmHg or MAP of <110 mmHg *(62)*. The EUSI also recommends maintaining CPP of at least 60–70 mmHg when ICP is elevated *(62)*.

The AHA recommends that labetalol, nicardipine, esmolol, enalapril, hydralazine, sodium nitroprusside, and nitroglycerine be considered for blood pressure reduction in patients with ICH *(57)*. However, there is limited data regarding the optimal antihypertensive agent to use after acute stroke; therefore, antihypertensive agents should be selected on an individual basis *(89)*. In neurological crisis, the ideal intravenous antihypertensive drug is one that rapidly and predictably reduces blood pressure, has a short half-life to avoid prolonged overtreatment, and has limited adverse side effects *(56)*. Labetalol and nicardipine have frequently been the agents of choice in clinical trials of blood pressure management after ICH *(61,77,82,86,87,90)*. Less desirable agents include sodium nitroprusside, hydralazine, enalapril, and nitroglycerine as these agents may have unpredictable effects on blood pressure or potentially cause adverse effects on cerebral blood flow and intracranial pressure *(91)*.

Labetalol doses between 5 and 25 mg have been reported to reduce systolic blood pressure by 6–19% and diastolic blood pressure by 3–26% in hemorrhagic stroke patients without adverse hemodynamic effects or neurologic deterioration *(92)*. In a retrospective analysis of 90 patients who received either intravenous bolus labetalol ($n = 64$) or nicardipine infusion ($n = 26$) within 24 h of hospital admission for an acute stroke (54% ICH), the nicardipine group received fewer additional antihypertensive agents ($p = 0.013$) and fewer dose adjustments ($p < 0.001$), and had less blood pressure variability ($p = 0.003$) during the 24-h observational period *(91)*. In ICH patients, 33% of the nicardipine group achieved goal blood pressure within 60 min of administration, while only 6% of the labetalol group achieved goal blood pressure within 60 min *(91)*. There was no significant difference in the frequency of hypotension or bradycardia between the two groups *(91)*. In patients with ICH, blood pressure can be safely maintained below 160/100 mmHg after 24 h, and

oral antihypertensive agents may be initiated *(61)*. Long-term blood pressure control is imperative as the majority of patients with ICH have chronic hypertension *(61)*.

Summary

Although ICH represents only a small proportion of all strokes, mortality is high. The majority of patients with ICH present with elevated blood pressure. However, optimal acute blood pressure management after ICH is controversial. Current guidelines should be consulted for blood pressure-lowering recommendations after ICH, although limited Class I evidence exists. More recently, preliminary randomized controlled trial data suggest that more intensive blood pressure-lowering strategies are feasible and safe, and larger trials are currently underway to determine whether clinical outcomes are improved. Long-term hypertension control is essential in patients after ICH to prevent recurrence and other end-organ damage.

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9

Recurrent Stroke Prevention I: Diuretic and Angiotensin-Converting Enzyme Inhibitors (ACEIs) – The PROGRESS Trial

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CONTENTS

BACKGROUND TO THE PROGRESS STUDY
DESIGN OF THE PROGRESS TRIAL
IMPLEMENTATION OF THE TRIAL
RESULTS
CONTEXT AND INTERPRETATION
REFERENCES

BACKGROUND TO THE PROGRESS STUDY

The rationale and design of the Perindopril Protection Against Secondary Stroke Study (PROGRESS) was published in 1996 *(1)*, while recruitment had already commenced in 1995. The study design involved a randomized, double-blind, placebo-controlled trial approach in which the blood pressure-lowering component was the angiotensin-converting enzyme inhibiting agent perindopril with and without the addition of the thiazide diuretic indapamide. The primary outcome measure was recurrent stroke of all types (fatal, nonfatal, ischaemic and hemorrhagic). The total sample size was over 7,000 patients from almost 200 centres in ten countries worldwide with a follow up of a mean 4 years. The major findings were published in 2001. PROGRESS was the first study to show definitively that ACEI-based blood pressure-lowering regimens reduced the risk of recurrent stroke. This was particularly for haemorrhagic stroke and, importantly, was independent of baseline blood pressure. In other words, the benefits were not only for hypertensive patients, but for all participants.

Before PROGRESS, there was quite strong evidence that treatment of hypertension was a powerful means of primary stroke prevention (*see* Chapters 2 and 3). A number of meta-analyses of the existing evidence established that blood pressure reduction was associated with fewer incident stroke events *(2)* and there was a view, however questioned, that the

introduction of blood pressure-lowering agents since the 1950s was a major contributor to the gradual reduction of mortality from stroke from about that time *(3)*. It was apparent that there was a linearly increasing risk between elevation of blood pressure and risk for stroke based on both epidemiological and clinical trial evidence *(4)*. Some suggested that there may be a J-shaped relationship between blood pressure and stroke risk *(5)*. However, the evidence regarding risk for recurrent stroke and its association with blood pressure was less clear. Perhaps some of the more persuasive information came from a further analysis of the United Kingdom Transient Ischemic Attack Study *(6)*, which was published at about the time of the commencement of PROGRESS. The authors were able to demonstrate that in people with established cerebrovascular disease, blood pressure level is an important risk factor not only in the hypertensive range, but also in what in many countries still today is considered normotensive (Fig. 1).
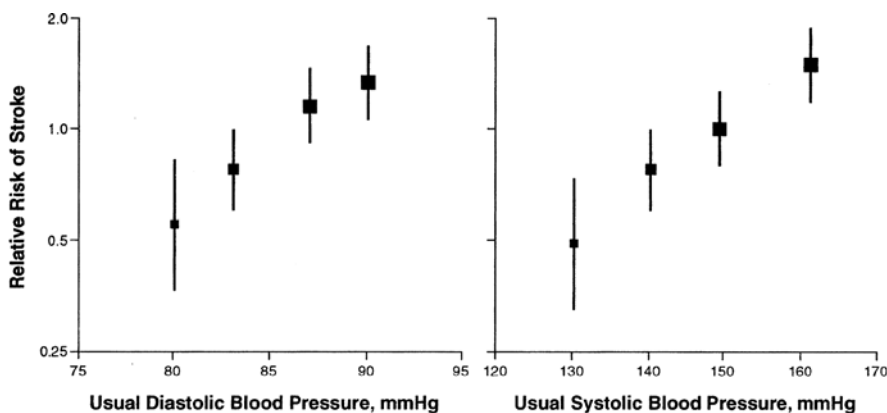
Fig. 1. The UKTIA study showed the association between rising blood pressure and increased risk for stroke, both for diastolic and systolic blood pressure and also in normotensive individuals *(6)*.

An important inference from the study was that a consistent 5 mmHg lowering of blood pressure would yield a secondary stroke risk reduction by a third. Interestingly, there was no "safe" blood-pressure level, thus establishing the continuous relationship between blood pressure and stroke risk and questioning the concept of the J-shaped curve.

The UKTIA study was, however, not a blood pressure-lowering treatment trial. As mentioned earlier, the effect of hypertension treatment on first-stroke incidence had been studied in a meta-analysis approach comprising almost 50,000 individuals and 5 years of follow-up from the Hypertension Detection and Follow-up Program (HDFP), the Medical Research Council Hypertension Trial (MRC), the Systolic Hypertension in the Elderly Trial (SHEP) and 13 smaller trials *(7)*. The mean effect of the average decline in blood pressure of 6 mmHg was a relative reduction of 38%, equally for fatal and non-fatal, strokes (Fig. 2).

The initial attempts to establish the effect of blood pressure lowering as a secondary stroke prevention strategy produced two studies with conflicting results (*see* Chapters 2 and 3). Both were conducted during the 1970s and were diuretic-based. One showed a significant secondary stroke risk reduction *(8)*, but the other did not *(9)*. The pooled data of these two studies estimated, however, a reduced secondary stroke risk from antihypertensive treatment by 38%, but with a large confidence interval. The uncertainty was increased by the more recently published Dutch TIA trial *(10)* and the Swedish TEST trial *(11)*. Both of these
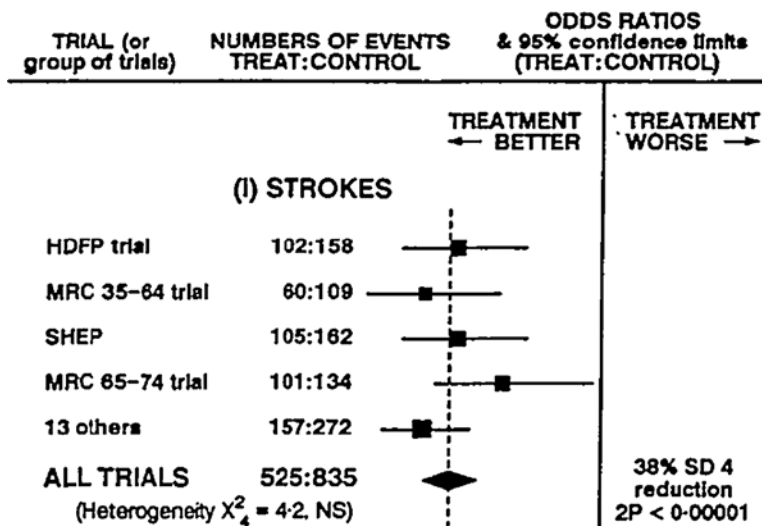
Fig. 2. Stroke odds ratio reduction in pooled unconfounded antihypertensive drug trials comprising almost 50,000 patients and 5 years of follow-up. *Solid squares* represent the treatment:control odds ratios. The *squares' sizes* correspond to the relative weight of the trial in the pooled measure. The *horizontal lines* denote 95% confidence intervals for the individual or combined studies, as does the *diamond shape* for the pooled data *(7)*.

were atenolol-based studies, produced relatively small decreases in blood pressure and were negative. The efficacy of atenolol in cardiovascular disease prevention has been questioned, and its use as a first-line agent more recently has been banned by the National Institute of Clinical Excellence in the United Kingdom. The combined results from these four trials predicted only a 19% decrease in secondary stroke risk by hypertension treatment – a figure thus much lower than that which could be inferred both from primary prevention trials and epidemiological studies. Some support for these modest possible secondary prevention effects came from some experimental studies. For example, the suggestion that chronic treatment of spontaneously hypertensive rats with ACEIs caused regression of vascular changes associated with the development of hypertension *(12)*.

These uncertainties provided the major rationale for the PROGRESS study. At the time, antihypertensives were not considered standard treatment for stroke patients and their value was debated. The high recurrence of stroke after the initial event was already known but became even more evident after the publication of the UK TIA trial (5% stroke recurrence in the first year and 3% for each of the following 4 years). The introduction of ACEI's as potent antihypertensive agents into clinical practise also constituted a strong rationale for conducting the trial.

Perindopril and Indapamide

Perindopril is an inhibitor of the angiotensin-converting enzyme (ACE), a kinase that converts angiotensin I (AT1) to angiotensin II (AT2) by stripping its two terminal amino acids. This translates into lower blood pressure by decreased concentrations of the strong vasoconstrictor AT2. Perindopril exerts its action by reducing peripheral vascular resistance with resulting decreased blood pressure, increased peripheral blood flow (in particular in

end-organs as the brain and the kidney) with no change in heart rate. ACE also inactivates bradykinin which constitutes a proposed adjuvant blood pressure-lowering mechanism. Increasing the activity in the kallicrein–bradykinin system is believed to be the mechanism behind the cough that may occur with ACE inhibitors *(13)*. Perindopril is converted in the liver into its active metabolite perindoprilat, which is its only metabolite with ACE-inhibiting properties. Perindopril is eliminated via the urine with an effective half-life of just over 24 h, which allows steady state after 4 days and once-daily dosage. The decrease in blood pressure stabilises rapidly, normally within a month. Perindopril has been shown effective in mild, moderate as well as severe hypertension *(14)* (Fig. 3).
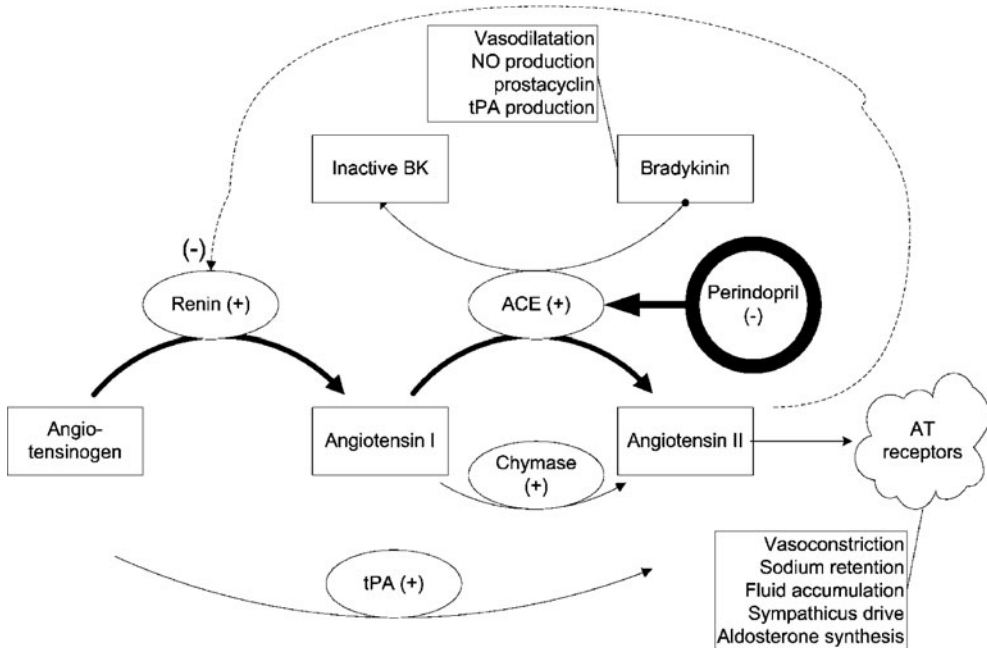
Fig. 3. By the action of renin, angiotensinogen (AG) is converted to angiotensin I (AT1) and then by the action of angiotensin-converting enzyme (ACE) to angiotensin II. There are however alternative metabolic routes to AT2 from AT1, and also directly from AG. AT2 exerts a blood pressure increasing effect by increasing vasoconstriction, but has also other effects. AT2 also negatively feeds back on renin, modulating its action. ACE also inactivates the cytokine bradykinin, which may be responsible for some of the ACE inhibitor specific side effects.

Indapamide is a diuretic chemically related to the thiazide-class diuretics. It increases the secretion of salt and water by inhibiting the resorption of sodium and chloride in the kidneys' distal tubuli. This leads in turn to increased excretion of potassium and magnesium. Its immediate blood pressure-lowering effect is a result of the decreased plasma volume, while the long-term blood pressure lowering is to a larger extent accountable to a decrease of the total peripheral vascular resistance *(15)*. Indapamide is rapidly absorbed from the gastro-intestinal tract and immediately active. It is mainly eliminated through metabolisation and urinary excretion. It can be given once daily, and steady-state plasma concentration is reached within a week. Indapamide has been proven effective in clinical studies of mild and moderate hypertension, but is to be combined with another class of drugs in severe

hypertension. Thiazides and related diuretics show a plateau effect in its antihypertensive action, while side effects are dose-related.

The treatment of hypertension with perindopril and indapamide shows an additive synergistic effect from both drugs. Further, the ACEI lessens the risk for hypokalemia, which is a common clinical problem in the treatment of hypertension with thiazide diuretics.

DESIGN OF THE PROGRESS TRIAL

Organization

PROGRESS was an academic initiative and conducted as an industry-independent, multi-centre study. The trial was coordinated by the University of Auckland, New Zealand, but directed from seven regional centres in Australia, China, France, Italy, Japan, Sweden and the United Kingdom. An independent monitoring committee was established to oversee unblinded safety data throughout the course of the study. The aim was to determine balance of benefits and risks conferred by an ACE inhibitor-based blood pressure-lowering regimen among patients with a history of stroke or TIA and a wide range of blood pressure at entry. The trial design was that of a secondary stroke prevention study and thus included patients with already manifest cerebrovascular disease, defined as TIA (also amaurosis fugax) or stroke (ischaemic or haemorrhagic with the exception of subarachnoid haemorrhage) within the past 5 years. Given that this was a pharmacological treatment trial, the inclusion and exclusion criteria stipulated that participants could not have a contraindication for any of the interventional compounds or have a medical condition that could preclude full participation in the study. Importantly, patients did not need to be hypertensive (defined as blood pressure above 160 mmHg systolic or 90 mmHg diastolic) to be included. In other words, patients were treated with blood pressure-lowering agents or placebo even if they were normotensive at entry. Patients who were already on ACEI were not excluded, but it was recommended that those treated with other antihypertensives were preferred.

The sample size was calculated from the conservative (*see* the UKTIA study *(6)* above) assumption of a 1.5–2% annual rate of recurrent stroke and a blood pressure difference between those on active substance and placebo of 4 mmHg. Sampling for a 90% power of detecting a 30% secondary stroke risk reduction over 4–5 years would require a minimum of 200 strokes in the control group and thus 3,000 patients in each treatment arm.

The main outcome of the study was recurrent stroke, ischaemic or haemorrhagic, by the WHO definition *(16)*. Secondary outcomes in the main study included stroke death or disability at 6–12 months, and total serious cardiovascular events including death, cognitive impairment, disability and dependency by the Barthel *(17)* and Lindley *(18)* classifications. A number of substudies were incorporated such as the investigation of genetic variations *(19)*, impacts of age *(20)*, sex and region *(21)*, diabetes *(22)*, silent brain infarcts *(23)*, platelet volume *(24)*, natriuretic peptide *(25)* and C-reactive protein *(26)*, cerebral white-matter changes *(27)*, blood lipids *(28)*, inflammation and haemostasis *(29, 30)*, atrial fibrillation *(31)* as well as health services-related research *(32, 33)*.

IMPLEMENTATION OF THE TRIAL

Patients were selected by clinicians at participating centres in Australia, Belgium, China, France, Japan, Italy, New Zealand, Sweden and the United Kingdom. After informed consent, all participants entered an open-label run-in phase during which all were given

perindopril increased up to 4 mg/day over 4 weeks. The study group chose this rather unconventional design to test in all eligible patients whether they tolerated the study drug before randomisation, thus minimising the number of drop-outs due to non-tolerance and increasing study power. At randomisation, patients were allocated to active substance or placebo. If there was a contraindication to diuretics, this determined as to whether it was added to the randomised perindopril or placebo (clinician discretion). Otherwise, randomisation to active substance inferred giving both perindopril and indapamide or placebo. The daily dose was 4 mg of perindopril and 2.5 mg of indapamide, except for in Japan where 2.0 mg was the standard dose, due to local regulations. The randomisation procedure involved stratification for age group, sex, region and baseline blood pressure as well as stroke subtype and mono/combination therapy. The patients were then seen after 2 weeks, 1, 3, 6, 9 and 12 months and then half-yearly for the duration of the study.

RESULTS

From the 7,121 patients entering the run-in phase, 1,016 withdrew during the subsequent 4 weeks. The main reasons were blood pressure-lowering related causes, including dizziness (3.4%), the ACEI specific cough (2.7%) and proposed intolerance (2.3%). This left 6,105 patients for randomisation by the abovementioned procedure – 3,051 to active treatment and 3,054 to placebo. Fifty-eight percent of patients in both groups were assigned to combination therapy (Fig. 4). When the inclusion phase was over, baseline characteristics were presented *(35)* showing a balanced distribution between patients on active treatment and placebo, respectively. About half of all randomised patients were classified as hypertensive from their blood pressure at the first visit. The mean initial blood pressure for all participants was 147/86 and 159/94 mmHg among those classified as hypertensive. The mean blood pressure of non-hypertensive patients was 136/79 mmHg. The assignment to single or combination therapy was, however, not randomised and was based on individual clinician preference. The patients allocated to combination treatment were younger, to a larger extent men, had higher blood-pressure and more often had coronary heart disease.

The mean follow-up time for those surviving for the length of the study was 4.1 years, and a mean 3.9 years for all those patients entered, or a total of 23,782 patient-years. Twenty-two percent of the patients had discontinued their medication at the end of the study (or their death before that), equally distributed among patients on active treatment or placebo and hypertensive or normotensive. In patients receiving active treatment, 11.9% discontinued it because of a positive decision to do so, or side effects such as 2.2% due to cough. An additional 2.2% were diagnosed with heart failure and were actively treated with an ACEI. In the placebo group 9.5% discontinued medication because of an active decision to do so, or because of side effects. An additional 2.3% discontinued because of heart failure. During the course of the trial, only three cases of angio-edema were recorded, none of them fatal.

For the whole study base, patients assigned to active treatment had a systolic blood pressure reduction of 9.0 mmHg compared to patients assigned to placebo, and a diastolic blood pressure reduction of 4 mmHg. These differences appeared shortly after the initiation of treatment and then were maintained without much change during the remainder of the study (Fig. 5).
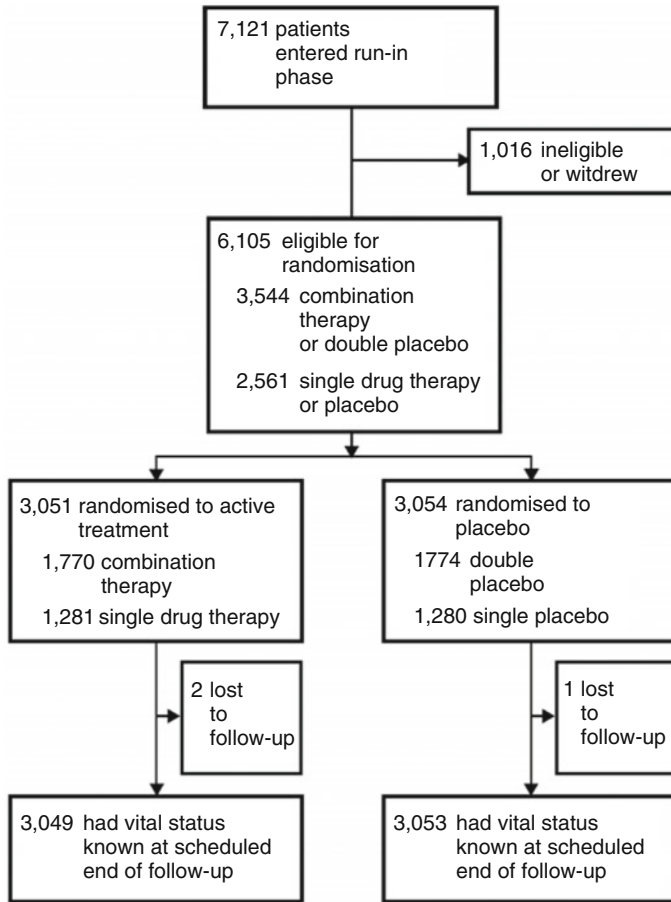
Fig. 4. The design and logistics of the PROGRESS trial. An eligible 7,121 patients went through the run-in phase to yield the 6,000+ patients tolerating the trial drug and ready to be included in the study *(34)*.
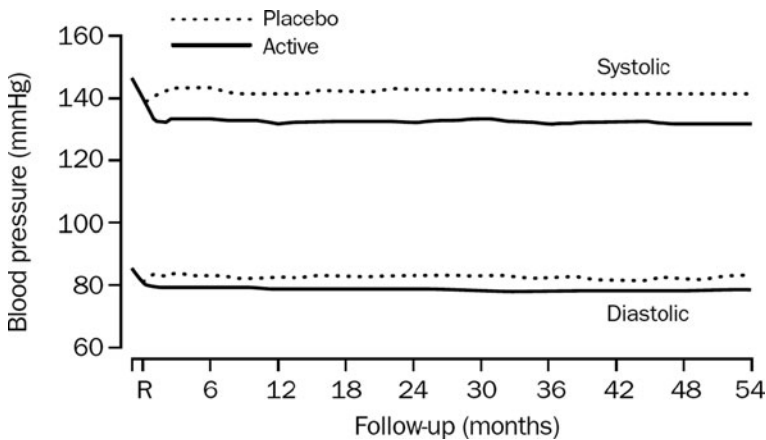
Fig. 5. Blood pressure change in study groups. A 9/4 mmHg drop in blood pressure in the active treatment group was observed soon after institution of treatment that remained more or less unchanged during the course of the study *(34)*.

The reduction of blood pressure was much greater, 12/5.0 mmHg, among the patients on combination therapy compared to 4.9/2.8 mmHg for those on ACEI monotherapy. The blood pressure reduction did not differ much between patients classified as normotensive or hypertensive at study entry.

During the course of the trial, 727 stroke events were recorded in the participants. This affected 10% ($n = 307$) of the active-treatment group and 14% ($n = 420$) of the patients that were given placebo, yielding a relative risk that was 28% (95%CI: 17–38%) lower in the perindopril/indapamide group. The distribution of ischaemic to haemorrhagic stroke was about 5:1 and similar in both groups. There were, however, more strokes in the placebo group with a fatal or disabling outcome (Fig. 6).
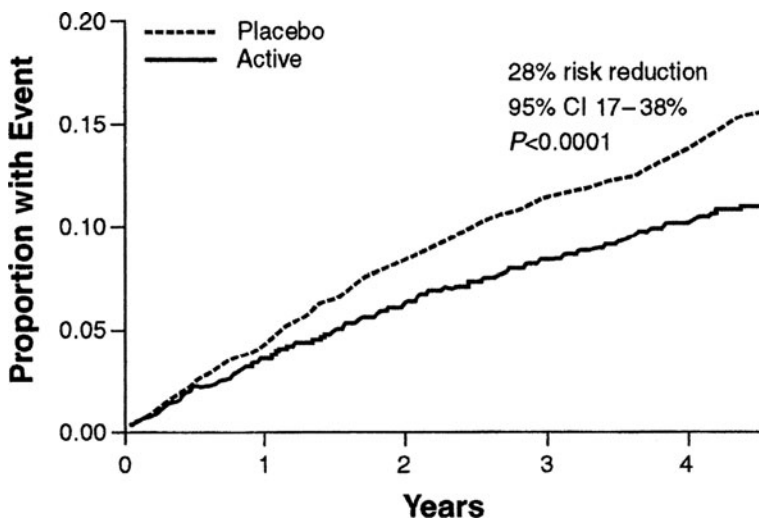
Fig. 6. Cumulative incidence of stroke in the two treatment arms of the PROGRESS trial. After a similar incidence for the first 6 months, there is markedly lower incidence in the active-treatment arm for the remainder of the study *(34)*.

The cumulative incidence curves diverged after about 6 months and continued to separate throughout the remainder of the study. The active-treatment arm had a yearly incidence of 2.7% compared to 3.8% in the placebo group. This was not modified by subgrouping ischaemic/haemorrhagic stroke, time from stroke to enrollment or ethnic background. The two treatment arms showed the same picture for incidence of major vascular events with an annual incidence in the treatment group of 4.1% compared to 5.5% in the placebo group (Fig. 7).

When patients treated with the combination of perindopril and indapamide were considered separately, they were found to have had a blood pressure lowering of 12/5 mmHg (as mentioned earlier) and had a 43% lower risk of recurrent stroke. This was significantly different from the effect of monotherapy, where there was an observed 5/3 mmHg lowering of blood pressure and a recurrent stroke risk indistinguishable from that of the placebo group. This absence of effect remained after subgroup stratification. The effect of the combination therapy was observed in all subgroups as well, with a risk reduction of 46% for fatal or disabling stroke, 36% for ischaemic stroke and 76% for haemorrhagic stroke, but with a large (95%CI: 55–87%) confidence interval. The same picture was observed for secondary
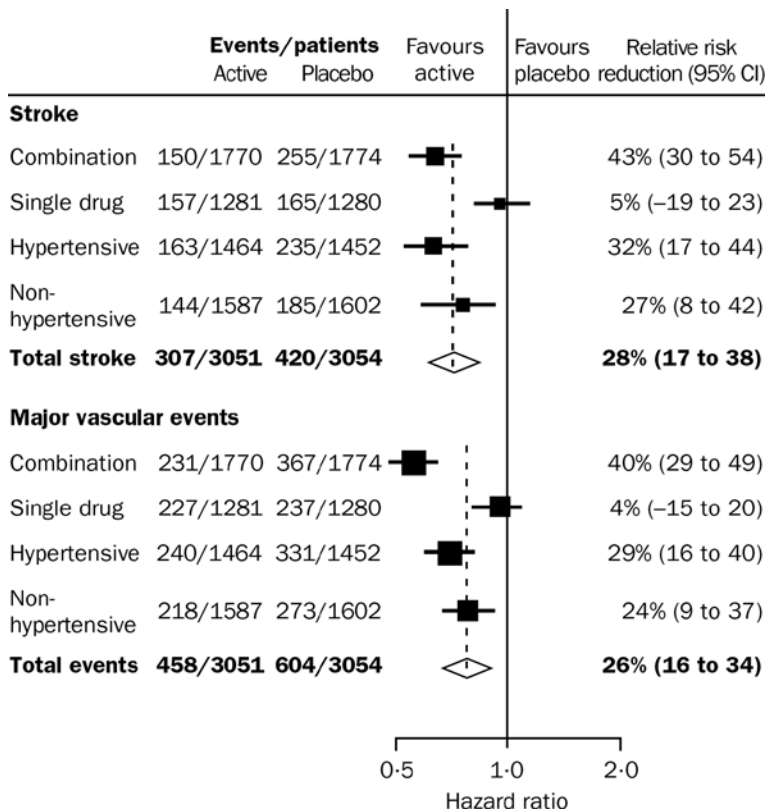
Fig. 7. Effects of active treatment vs. placebo on stroke and major vascular events in subgroups of patients *(34)*. The position of *black squares* represent the effect size and their area the underlying number of patients in subgroups with *horizontal lines* denoting 95% confidence interval of the effect size. The *diamonds denote* the overall effect size and its confidence interval.

outcome events. Combination therapy reduced the risk of major vascular events by 40% compared to placebo, while treatment with perindopril only did not. Combination therapy was also associated with a 42% reduction in non-fatal myocardial infarction.

During the course of the study, 1,026 patients had a major vascular event of which 379 were fatal. Patients in the active-treatment group had fewer non-fatal strokes, deaths from coronary heart disease and non-fatal myocardial infarction. The rate of overall vascular death was, however, not discernable between groups. During the follow-up period 625 patients died, of whom 379 from vascular causes, but this was similar between treatment groups. The number of hospital admissions during the study was 9% lower in the active-treatment group, and their median hospital stay was 2.5 days shorter (Fig. 8).

The PROGRESS investigators also published data on the effect of Perindopril-based therapy on cognitive decline *(36)*. Patients meeting DSM-IV dementia criteria were recorded in 6.3% ($n = 193$) of the actively treated participants compared to 7.1% ($n = 217$) in the placebo group, resulting in a non-significant 12% risk reduction. However, the risk for overall cognitive decline, measured as a 3-or-more-point decline in the Mini-Mental-State-Examination *(37)* was 19% (9.1% vs. 11%; 95% CI: 4–32%) less in the group
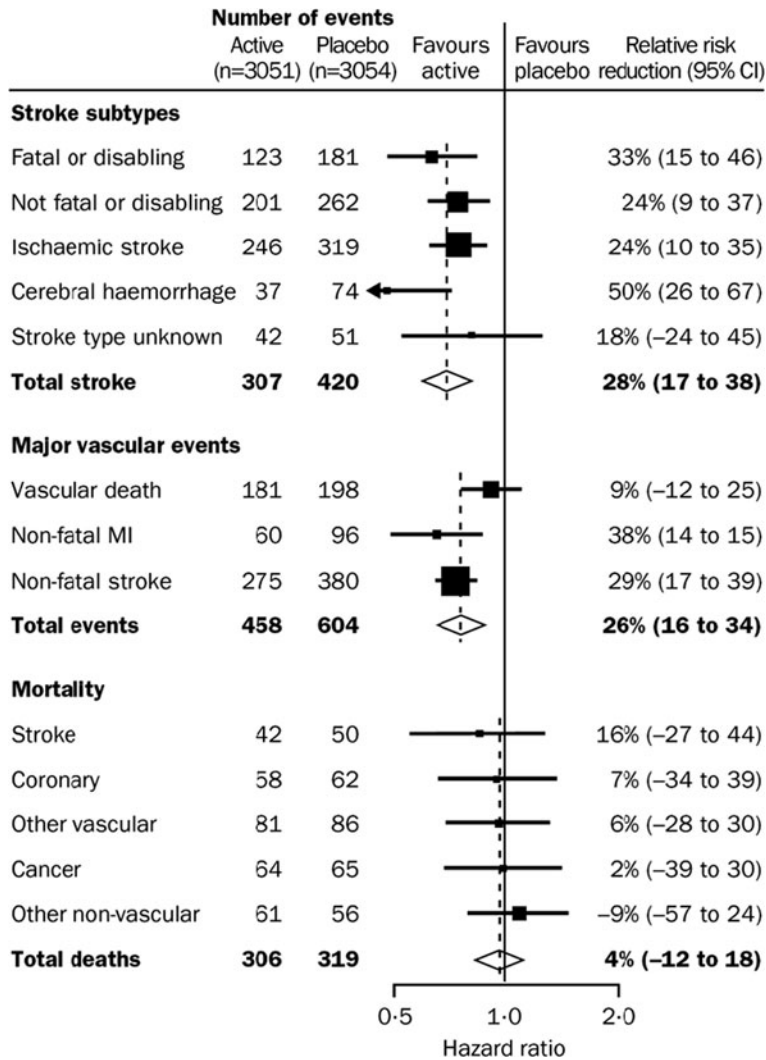
Fig. 8. Effects in study arms on subtypes of stroke, major vascular events and mortality *(34)*. MI = myocardial infarction. Conventions as in Fig. 6.

receiving active treatment. In the subgroup analysis there was a significant 34% reduction of risk for the composite measure "dementia with recurrent stroke" (Fig. 9).

To summarise the overall PROGRESS results, blood pressure lowering with a perindopril-based regime showed a significant 28% risk reduction on the primary outcome measure of recurrent fatal or non-fatal stroke of any type. This was the first study to definitively show that blood pressure lowering could be an effective secondary stroke prevention strategy. Importantly, the benefits were independent of the baseline blood pressure; in other words, the participants did not need to be hypertensive to benefit from active treatment and normotensive participants had similar reductions in recurrent stroke risk. While taken in the context of subgroup analyses, combination therapy was particularly efficacious, as was the effect on the likelihood of developing intracerebral haemorrhage as an outcome event.

	No. of Events/Total Participants		Favors Active	Favours Placebo	Risk Reduction (95% CI), %
	Active	Placebo			
Effects in All Participants					
"Dementia With Recurrent Stroke"	43/3051	65/3054			34 (3 to 55)
"Other Dementia"	150/3051	152/3054			1 (−24 to 22)
All Dementia	**193**/3051	**217**/3054			12 (−8 to 28)
Effects in Subgroups					
Combination Therapy	106/1770	136/1774			23 (0 to 41)
Single Drug Therapy	87/1281	81/1280			−8 (−48 to 21)
Hypertensive	100/1464	114/1452			13 (−16 to 34)
Not Hypertensive	93/1587	103/1602			12 (−18 to 34)
No Baseline Cognitive Impairment	72/2574	104/2591			31 (6 to 50)
Baseline Cognitive Impairment	121/477	113/463			−5 (−42 to 22)

0.5   1.0   2.0
Odds Ratio

	No. of Events/Total Participants		Favors Active	Favors Placebo	Risk Reduction (95% CI), %
	Active	Placebo			
Effects in All Participants					
"Cognitive Decline With Recurrent Stroke"	48/3051	86/3054			45 (21 to 61)
"Cognitive Decline"	228/3051	248/3054			9 (−10 to 24)
All Cognitive Decline	**276**/3051	**334**/3054			19 (4 to 32)
Effects in Subgroups					
Combination Therapy	144/1770	181/1774			22 (2 to 38)
Single Drug Therapy	132/1281	153/1280			15 (−8 to 34)
Hypertensive	133/1464	164/1452			21 (0 to 38)
Not Hypertensive	143/1587	170/1602			17 (−6 to 35)
No Baseline Cognitive Impairment	205/2574	244/2591			18 (0 to 32)
Baseline Cognitive Impairment	71/477	90/463			27 (−2 to 48)

0.5   1.0   2.0
Odds Ratio

Fig. 9. Cognitive impairment and dementia in different treatment groups in the PROGRESS trial *(36)*. Active treatment was favoured for dementia with recurrent stroke and all cognitive decline.

CONTEXT AND INTERPRETATION

The same lack of evidence or conflicting study data that constituted the rationale for the PROGRESS study also inspired other researchers to investigate related research questions at around the same time. For example, data from the Heart Outcomes Prevention Evaluation (HOPE) study *(38)*, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study *(39)* and the Study on Cognition and Prognosis in the Elderly (SCOPE) study *(40)* were published and provide support for as well as contrast to the PROGRESS findings. As mentioned earlier, the clear message from the PROGRESS study was that blood pressure lowering significantly lowers the risk of recurrent stroke and that this is not restricted to certain stroke subtypes, age groups, gender type, hypertensive or normotensive status. Further, the treatment regime was also proven feasible and safe, with only a few percent of withdrawals during the 4 years of the study and only a slight excess of minor side effects in the active-treatment group over placebo. It also showed that the J-shaped risk curve concept

suggested by previous studies was most likely the result of confounding, since the effect of active treatment was the same regardless of baseline blood pressure.

The HOPE trial provides one of the most important comparisons to the PROGRESS study. Here, the investigators studied the ACEI ramipril, which in monotherapy in stroke patients yielded a 3/1 mmHg blood pressure reduction, a 32% secondary stroke risk reduction and a 20% myocardial infarction risk reduction compared to placebo. This was a stronger risk reduction than predicted from epidemiological data alone, consistent with the PROGRESS findings and led to the hypothesis of a secondary stroke risk lowering effect by ACEIs additive to the effects of lowering blood pressure alone. However, this must be balanced by the knowledge that when a subset of HOPE patients were studied with 24 h blood pressure monitoring, the blood pressure reduction was found to be greater. Also, the patients with the lowest baseline blood pressure did not show benefit of ramipril in the HOPE study.

Although the LIFE study design was quite different in that asymptomatic hypertensive patients with left ventricular hypertrophy were recruited, the results were of importance in the context of PROGRESS. The effects of losartan, an angiotensin II type 1 receptor blocker (ARB), belonging to another class of agents modulating the renin–angiotensin–aldosterone system (RAAS) were investigated. When compared to a beta-blocker, atenolol, there was a stroke risk reduction despite no difference in blood pressure between the two groups, thus strengthening the additive-effect hypothesis for agents interfering with the RAAS system. The LIFE investigators also found a 25% diabetes incidence reduction in the treatment group, adding another proposed benefit to these classes of drugs. The SCOPE trial investigators studied candesartan, another ARB class drug, compared to placebo in elderly mildly hypertensives, finding a 28% reduced stroke risk, seemingly independent of blood pressure lowering. In addition, other studies have shown ACEIs and ARBs may reverse functional cardiac failure *(41)* and promote vascular remodelling *(42)*. Two other studies later added to the knowledge base on RAAS modulators: The ONTARGET *(43)* study investigated the ARB telmisartan, the ACEI ramipril, or the combination of both for reducing vascular outcomes including stroke in people over 55 years old with vascular disease. The TRANSCEND *(44)* study investigated telmisartan against placebo in patients that were candidates for treatment with but showed adverse effects to ACEI. Since up to one in five patients are intolerant to ACEI; there was hope that ARB treatments would be more feasible and still give the same vascular protection. The HOPE study had already showed benefit of ramipril in a similar cohort and the intention of ONTARGET was to show, besides greater protection by the ACEI+ARB combination, that ARB was better tolerated and not inferior in effect to ramipril. It failed, however to show any effect of the combination beyond that of either drug alone, while there were more adverse effects, and this despite 2.4/1.4 mmHg greater blood pressure lowering. The TRANSCEND study could not show any benefit of telmisartan over placebo in reducing neither primary nor secondary outcomes, maybe due to underpowering caused by a lower than expected event rate in the study or the fact that many of the subjects had received RAAS modulators already before randomisation into the study. The PROFESS *(45)* study failed to show benefit of telmisartan over placebo for protection against recurrent stroke in 20,000 stroke patients despite a 3.8/2.0 mmHg lower blood pressure in the ARB group, thus weakening the support for effects of this drug class on recurrent stroke. However, less than half of the patients were followed for at least 2 years.

There are pragmatic implications of the results of the PROGRESS trial. For example, if there is a linear relationship between blood pressure and stroke risk it seems reasonable that stroke sufferers be prescribed antihypertensive treatment even though they fall short of being diagnosed as hypertensive. The finding that perindopril alone did not result in as much protection against secondary stroke unless a thiazide (indapamide) is added has been widely debated. The difference should first be considered in the context of the subanalysis and then in the degree of blood pressure achieved. The 5/3 mmHg blood pressure lowering would be associated to an anticipated 30% reduction in secondary stroke risk *(46)*. Future studies may explain whether the effects of the combination is unique, a class effect between any ACEI (or even ARB) and diuretic or attributable to the blood pressure lowering per se. The latter seems more likely and is supported by later meta-analyses *(47)*. The fact that individual study physicians decided on monotherapy or combination therapy may also have contributed to a confounding of the results, selecting patients that most would have benefited from perindopril. The study was not powered to answer the question of secondary stroke risk reduction by indapamide treatment alone. The Chinese PATS *(48)* trial however evaluated indapamide against placebo for stroke risk reduction in 5,665 patients and reported a hazard ratio of 0.71 (95% CI 0.58–0.88). A report from the Blood Pressure Lowering Treatment Trialists' Collaboration found all major classes of antihypertensives effective in preventing first strokes. So, is secondary stroke prevention different and which should be the drug of choice? We still lack evidence on whether there are strong class effects of ACEI's *(49)* or whether individual drug characteristics within the class outweigh the common features. Further, genetic profiling and drug substitution studies *(50)* suggest that antihypertensive treatment may yet need individual tailoring of pharmacotherapy for optimising results, for instance, depending on whether individuals are high-renin, low-renin or aldosterone-sensitive.

Regardless, PROGRESS results have provided the most specific evidence for secondary stroke prevention thus far. The effect is quite powerful with the possibility to avoid one serious vascular event in every 11 patients treated with perindopril and indapamide over 5 years, in addition to other preventive measures such as lifestyle adjustment and the use of antiplatelet agents or statins. The PROGRESS results have changed the way we approach blood pressure lowering in stroke patients. Its legacy is that it is has now entered the realms of standard poststroke management.

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10 Recurrent Stroke Prevention II: Angiotensin Receptor Blockers—The LIFE, MOSES, PRoFESS, and Other Trials

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CONTENTS

Glossary of Terms

ACCESS	Acute Candesartan Cilextil Therapy in Stroke Survivors
CHARM	Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity
DETAIL	Diabetics Exposed to Telmisartan and Enalapril
HOPE	Heart Outcomes Prevention Evaluation
IDNT	Irbesartan in Diabetic Nephropathy Trial
IRMA II	Irbesartan Reduction of Microalbuminuria
LIFE	Losartan Intervention for Endpoint Reduction in Hypertension Study
MARVAL	Microalbuminuria Reduction with valsartan
MOSES	Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Stroke Prevention
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes

RENAAL	Reduction of End-Points in Non-Insulin Dependant Diabetes Mellitus with the Angiotensin II Antagonist Losaratan
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease
VAL-HeFT	valsartan Heart Failure Trial
VALIANT	valsartan in Acute Myocardial Infarction Trial
VALUE	valsartan Antihypertensive Long-Term Use Evaluation

INTRODUCTION

Elevated blood pressure is an important modifiable risk factor for stroke. Numerous large randomized clinical trials have demonstrated that lowering blood pressure prevents first and recurrent stroke, and that to a large extent, the degree of blood pressure reduction is a major determinant of the degree of risk reduction. An issue that is often debated is whether certain antihypertensive classes such as angiotensin receptor blockers (ARBs) have unique "stroke or cardiovascular preventive" properties independent of blood pressure reduction. In this chapter we will review the pharmacology and clinical effects of ARBs on primary and secondary stroke prevention as well as a variety of other clinical conditions including hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, atrial fibrillation, and vascular cognitive impairment.

THE RENIN–ANGIOTENSIN SYSTEM AND PHARMACOLOGY OF ANGIOTENSIN RECEPTOR BLOCKERS

The renin–angiotensin system (RAS) has an important regulatory role in the control of blood pressure. Angiotensinogen is an α2 globulin secreted by the liver. It is converted to angiotensin I by renin, an enzyme produced by the juxtaglomerular apparatus in the kidney in response to decreased intra-renal blood pressure or decreased delivery of Na^+ or Cl^- ions to the renal tubules. Angiotensin I, an inactive precursor, is converted to the biologically active angiotensin II (AII) by the angiotensin-converting enzyme (ACE). In addition to ACE, several other enzymes including trypsin, cathepsin, cage, and chymase can also convert angiotensin I to AII.

The effects of AII are largely mediated by two major receptor subtypes: AT1 and AT2. Activation of the AT1 receptor leads to a myriad of effects including vasoconstriction, sympathetic activation, aldosterone secretion, retention of sodium and water, endothelial dysfunction, inflammation, oxidative stress, thrombogenesis, cell proliferation, and connective tissue deposition. AT2 receptor expression is increased under stress and its activation has opposite effects such as vasodilatation and natriuresis. The regulation of the balance between AT1 and AT2 receptors is not yet well understood *(1,2)*. Activation of non-AT1 receptors may have protective effects against cerebral ischemia.

The ARBs selectively target the AT1 receptors. Compared to the ACE inhibitors, they have certain pharmacokinetic advantages. ARBs do not affect vasodilatory peptides such as bradykinin and substance P that are also degraded by ACE and thus have a lower incidence of cough and angioedema compared to ACE inhibitors. ACE inhibitors allow the continued production of AII via the ACE-independent pathways described earlier, while ARBs block the effect of AII from all sources and thus might provide a higher degree of inhibition

of the effects of AII *(1)*. Lastly, by blocking AT1 receptors, ARBs increase AII synthesis by a feedback mechanism. Under stress, this leads to AT2 receptor activation which has vasoprotective properties *(2)*.

The currently available ARBs in the United States include Candesartan (Atacand^{TM}), Eprosartan (Teveten^{TM}), Irbesartan (Avapro^{TM}), Losartan (Cozaar^{TM}), Olmesartan (Benicar^{TM}), Telmisartan (Micardis^{TM}), and valsartan (Diovan^{TM}).

THE CLINICAL EFFECTS OF ARBs

Effect on Hypertension

ARBs exert their antihypertensive effect by selective blockade of AT1 receptors. The antihypertensive efficacy of ARBs is comparable to other major classes of blood pressure lowering drugs *(3)*. Overall, dose–response effects of ARBs are less pronounced, and differences in blood pressure lowering efficacy between the usual initiation doses and maximum doses are only about 4–8 mmHg. Generally, there is a lack of dose-dependent side effects which may foster use of higher doses of ARBs as needed *(3)*.

Variability of response with ARBs may be influenced by population group, dietary salt intake, or selection of dose *(3)*. ARBs have similar blood pressure lowering effects in the young and old and in men and women. ARBs may have less single-agent efficacy in black compared to white patients which may be a dose-dependent effect. Racial differences in blood pressure response, however, are not observed when ARBs are combined with thiazide diuretics *(3)*. Combinations of ARBs with diuretics or ARBs with calcium channel blockers may be very efficacious agents for blood pressure control.

First and Recurrent Stroke Prevention Trials

We now review key clinical trials that feature ARBs for first and recurrent stroke prevention. In relation to these studies we discuss background, methods, main efficacy and safety findings, and practical implications of the results. The LIFE trial was primarily a first stroke prevention study (~8% had a history of cerebrovascular disease) as were ONTARGET and TRANSCEND (~21 and ~22% had a history of stroke or transient ischemic attack, respectively). MOSES and PRoFESS were recurrent stroke prevention studies. ACCESS was an acute stroke treatment trial.

LIFE

Background: The LIFE study focused on left ventricular hypertrophy (LVH), an important manifestation of preclinical cardiovascular disease and an independent risk for all cardiovascular complications in hypertension *(4)*. Angiotensin II has been associated with establishment of LVH. By blocking angiotensin II, it might be possible to reverse LVH. Furthermore, in the treatment of hypertension at the time of the LIFE trial, no drug had prevented cardiovascular morbidity and mortality beyond reductions in blood pressure achieved with beta-blockers and diuretics. The chief aim of LIFE was to determine if selective blocking of angiotensin II would improve LVH beyond blood pressure lowering and, in addition, reduce cardiovascular morbidity and mortality.

Methods: LIFE was a double-blind, randomized, parallel-group trial *(4)*. 9,193 persons aged 55–80 years with essential hypertension (blood pressure in the sitting position: 160–200/95–115 mmHg) and LVH according to electrocardiographic measure were assigned to losartan-based or atenolol-based blood pressure lowering therapy for at least 4 years. The primary efficacy outcome was the composite of the following cardiovascular events: stroke, myocardial infarction, and death. Cox regression analysis was used to compare treatment groups.

Main Efficacy and Safety Findings: Blood pressure dropped by 30.2/16.6 and 29.1/16.8 mmHg in the losartan and atenolol treatment groups, respectively *(4)*. The primary efficacy outcome endpoint occurred in 508 losartan and 588 atenolol participants (relative risk 0.87, 95% confidence interval (CI) 0.77, 0.98; $p = 0.021$). Of the individual components of the primary efficacy composite outcome, only fatal and nonfatal stroke was statistically significantly different favoring the losartan treatment group (relative risk 0.75, 95% CI 0.63, 0.89; $p = 0.001$). In addition, new-onset diabetes mellitus occurred less frequently in the losartan treatment group (relative risk 0.75, 95% CI 0.63, 0.88; $p = 0.001$). Finally, there was greater reduction in LVH in the losartan treatment group after more than 4 years of study.

Overall, losartan was better tolerated than atenolol in relation to pre-specified adverse events, and discontinuation of therapy due to adverse events, drug-related adverse events, and serious drug-related adverse events occurred significantly less frequently with losartan *(4)*.

Practical Implications: Losartan-based therapy provided better cardiovascular prevention, especially in relation to stroke, than atenolol-based therapy at a similar reduction of blood pressure, and had a better safety profile than atenolol-based therapy *(4)*. Losartan had other cardiovascular benefits, and overall might confer cardiovascular prevention beyond blood pressure lowering effects.

ONTARGET

Background: Angiotensin-converting enzyme inhibitors (ACE-Is) have been shown to reduce mortality and morbidity from cardiovascular diseases in persons with a history of vascular disease or high-risk diabetes (end-organ damage) without heart failure *(5)*. The role of ARBs under these circumstances has been less-well defined. In ONTARGET, the ACE-I ramipril was compared to the ARB, telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes mellitus without heart failure for efficacy and safety.

Methods: A single-blind run-in phase was carried out over 3 weeks and was followed by a double-blind, randomized assignment of 8,576 patients to 10 mg of ramipril per day, 8,542 assigned to 80 mg of telmisartan per day, and 8,502 assigned to both drugs (combination therapy group) *(5)*. The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure. A noninferiority analysis was developed to compare treatment groups.

Main Efficacy and Safety Findings: During the course of the trial as compared to the ramipril treatment group, the telmisartan treatment group had lower blood pressure by 0.9/0.6 mmHg as did the combination therapy group by 2.4/1.4 mmHg *(5)*. There was

equivalence (i.e., noninferiority criteria met) between the occurrence of the primary outcome in the ramipril (16.5%) and telmisartan (16.7%) treatment groups. Stroke occurred in 4.3% receiving telmisartan, 4.7% receiving ramipril, and 4.4% receiving combination therapy. The telmisartan group, however, had lower rates of cough (1.1 vs. 4.2%) and angioedema (0.1 vs. 0.3%) but a higher rate of hypotensive symptoms (2.6 vs. 1.7%) than the ramipril treatment group. The rate of syncope did not differ between the two groups (0.2%). The combination therapy group experienced the composite primary outcome endpoint in 16.3% of participants, but when compared to the ramipril treatment group the combination therapy group had increased risk of hypotensive symptoms (4.8 vs. 1.7%), syncope (0.3 vs. 0.2%), and renal dysfunction (13.5 vs. 10.2%).

Practical Implications: Telmisartan was shown to be equivalent (noninferior by statistical testing) to ramipril in high-risk patients and was associated with less risk of angioedema. Combination therapy, however, was associated with more adverse events without an increase in clinical benefit. Combination therapy must be used with caution, as although it reduces proteinuria to a greater extent than single therapy, it may worsen major renal outcomes *(6)*.

TRANSCEND

Background: It is estimated that ACE-Is are not tolerated in up to 20% of persons *(7)*. TRANSCEND was designed to determine whether the ARB, telmisartan, would be effective and safe in those intolerant to ACE-Is with cardiovascular disease or diabetes mellitus with end-organ damage but no heart failure.

Methods: Intolerance to ACE-Is was defined as prior discontinuation of the agent by a physician for reason of intolerance with a specific cause *(7)*. Patients were randomized to telmisartan 80 mg per day ($n = 2,954$) or placebo ($n = 2,972$) after a 3-week run-in phase. The primary outcome endpoint was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure.

Main Efficacy and Safety Findings: Patients were followed for a median of 56 months. Mean blood pressure was lower in the telmisartan treatment group during the study by 4.0/2.2 mmHg. 15.7% of the telmisartan group were observed to have the primary outcome vs. 17.0% in the placebo group ($p = 0.216$). A secondary outcome which included the composite of stroke, myocardial infarction, and cardiovascular death occurred less frequently with telmisartan (13.0 vs. 14.8%) but was not statistically significant in an adjusted analysis ($p = 0.068$). Stroke alone was not a main focus of the reported analysis *(7)*. Fewer telmisartan patients were hospitalized for cardiovascular reasons (30.3 vs. 33.0%; $p = 0.025$), and fewer patients permanently discontinued study medication in the telmisartan group (21.6 vs. 23.8%; $p = 0.055$). Hypotensive symptoms were more common in the telmisartan treatment group (0.98 vs. 0.54%).

Practical Implications: Telmisartan was well tolerated in patients who where ACE-I intolerant *(7)*. There were no statistically significant differences between telmisartan and placebo in relation to main outcome events though there were efficacy trends favoring the telmisartan treatment group. The eligibility criteria were similar for ONTARGET, TRANSCEND, and HOPE; however, in TRANSCEND there were more women, ethnically diverse patients, a higher frequency of statin use (TRANSCEND vs. HOPE), and a

higher frequency of use of beta-blockers and antiplatelet agents *(8)*. Thus, there were differences in the study populations. Overall, TRANSCEND was a statistically underpowered study, and a pooled analysis of data from TRANSCEND and PRoFESS is discussed below.

MOSES TRIAL

Background: This study was designed to determine if eprosartan, an ARB, would be more effective than nitrendipine, a long-acting calcium channel blocker, in reducing stroke and cardiovascular morbidity and mortality among hypertensive patients with stroke for the same level of blood pressure lowering control *(9)*.

Methods: 1,405 high-risk hypertensives with a history of either ischemic or hemorrhagic stroke or transient ischemic attack in the past 24 months were randomized to receive either eprosartan or nitrendipine *(9)*. Mean study follow-up was 2.5 years. The primary outcome was the composite of total mortality and all cardiovascular and cerebrovascular events, including recurrent ones.

Main Efficacy and Safety Findings: During the course of study, blood pressure reduction was similar for the eprosartan (137.5/80.8 mmHg) and nitrendipine (136.0/80.2 mmHg) treatment groups *(9)*. After 3 months, 75.5% of the eprosartan-treated and 77.7% of the nitrendipine-treated patients had reached a blood pressure target of <140/90 mmHg. Of 461 primary outcome events, 206 occurred in the eprosartan treatment group and 255 in the nitrendipine treatment group. The incidence density ratio (IDR) for the primary outcome favored eprosartan treatment and was 0.79% (95% CI 0.66, 0.96; $p = 0.014$). Also, the IDRs favored eprosartan for cardiovascular events (0.75; 95% CI 0.55, 1.02; $p = 0.06$) and cerebrovascular events (0.75; 95% CI 0.58, 0.97; $p = 0.03$).

Practical Implications: The MOSES study was potentially limited by a relatively small number of study subjects and fewer than anticipated outcome events for comparison between the two treatment arms *(10)*. The study results, however, add to the evidence base that ARBs may prevent recurrent stroke events and may do so by non-blood pressure lowering effects.

PRoFESS

Background: This study further tested the hypothesis that blockade of the renin–angiotensin–aldosterone system (RAAS) with an ARB could safely lower the risk of recurrent stroke *(11)*.

Methods: 20,332 patients who had an ischemic stroke were assigned to either telmisartan 80 mg per day ($n = 10,146$) or placebo ($n = 10,186$) *(11)*. The main outcome was recurrent stroke, and secondary outcomes were major cardiovascular events (e.g., death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure) and new-onset diabetes mellitus.

Main Efficacy and Safety Findings: Study subjects were randomized in a median interval of 15 days *(11)*. For a median follow-up of 2.5 years, the mean blood pressure was lower in the telmisartan treatment group by 3.8/2.0 mmHg than in the placebo group; 8.7% of telmisartan-treated patients and 9.2% of placebo-treated patients had a subsequent stroke (hazard ratio 0.95, 95% CI 0.86, 1.04; $p = 0.23$). Major cardiovascular events occurred in 13.5% of telmisartan- and 14.4% of placebo-treated patients ($p = 0.11$). There was no difference in the incidence of new-onset diabetes mellitus.

Practical Implications: This study did not show a significant reduction of recurrent stroke or cardiovascular events after 2.5 years of follow-up and did not show a significant reduction in new-onset diabetes mellitus. Post hoc exploratory analysis of the PRoFESS database suggested, however, that there might be a time-dependent effect of telmisartan therapy *(12)*. Specifically, there was no significant difference in the event rates in the first 6 months after randomization for the primary outcome, though there was a modest increase in events in the telmisartan treatment group. A difference emerged later, however, favoring reduction of recurrent stroke in the telmisartan treatment group. A key limitation of the study is that it was statistically underpowered to show a difference in the primary outcome endpoint. Had the study been carried out for a longer period of time, it is speculated that there may have been a significant reduction in recurrent stroke.

POOLED ANALYSIS OF PRoFESS AND TRANSCEND

The ONTARGET, TRANSCEND, and PRoFESS investigators provided the results of a pre-specified analysis combining the results of TRANSCEND and PRoFESS *(7)*. As previously mentioned in this text, the latter two studies were statistically underpowered to show a definitive difference with active treatment. Since several studies including HOPE had showed a benefit of RAAS blockade in the prevention of cardiovascular events in high-risk patients and the eligibility criteria for HOPE, ONTARGET, and TRANSCEND were similar (with the exception of ACE-I intolerance in TRANSCEND), a pooled analysis of data was carried out.

Of interest, the combined TRANSCEND and PRoFESS data showed the following key findings: (1) For the composite outcome of *cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure*, overall the study results favored telmisartan therapy over placebo (odds ratio 0.93; 95% CI 0.86, 0.99; $p = 0.026$). In stratified analysis, however, the combined data were only statistically significant in favor of telmisartan therapy at >6 months study duration time (odds ratio 0.86, 95% CI 0.80, 0.94; $p = <0.001$), and though not statistically significant, the data trended against telmisartan in the 0–6 month time period *(7)*; and (2) For the composite outcome endpoint of *cardiovascular death, myocardial infarction, and stroke*, the combined analysis showed a statistically significant outcome in favor of telmisartan ($p = 0.013$), and similar findings in relation to a nonstatistically significant trend against telmisartan in the 0–6 month time period ($p = 0.074$) and statistically significant findings in favor of telmisartan-associated reduction of cardiovascular events in the >6 month time period ($p < 0.001$) *(7)*.

The findings from the pooled analysis suggest that telmisartan, a generally safe blood pressure lowering agent, confers a modest added benefit to other proven cardiovascular prevention therapies in persons who are ACE-I intolerant and have vascular disease or high-risk diabetes mellitus *(7)*. Recently, the US FDA approved telmisartan for such an indication.

ACCESS

Background: This study evaluated the effect of modest acute blood pressure reduction using candesartan in hypertensive patients with an ischemic stroke *(13)*.

Methods: The study planned to recruit 500 patients with an acute ischemic stroke with a motor deficit and hypertension (mean of at least two blood pressure measurements ≥200 mmHg systolic and/or ≥110 mmHg diastolic 6–24 h after admission or ≥180 mmHg

systolic and/or ≥105 mmHg diastolic 24–36 h after admission). Patients were started on candesratan (4 mg) or placebo on day 1. On day 2, the dose was increased to 8 or 16 mg candesartan cilexetil or placebo if blood pressure exceeded 160 mmHg systolic or 100 mmHg diastolic. Treatment was targeted to a 10–15% blood pressure reduction within 24 h. In all patients a 24-h blood pressure profile was obtained on day 7. In patients in the candesartan cilexetil group who were hypertensive (mean daytime blood pressure >135/85 mmHg), candesartan cilexetil was increased or an additional antihypertensive drug (hydrochlorothiazide, felodipine, metoprolol) was added. In hypertensive placebo-treated patients, candesartan cilexetil was started and was adjusted to lower blood pressure to <140/90 mmHg (office blood pressure) or <135/85 mmHg (mean daytime blood pressure, automatic blood pressure monitoring). The primary endpoint was case fatality and disability, measured as functional status (Barthel Index) 3 months after the end of a placebo-controlled 7-day phase. The combined secondary endpoint included overall mortality and cerebrovascular and cardiovascular events occurring within the study period *(13)*.

Main Efficacy and Safety Findings: The study was prematurely stopped due to an imbalance of endpoints after 342 patients had been randomized *(13)*. There were no differences in blood pressure in the two groups in the first 7 days of the study or during the entire duration of the study. The Barthel Index revealed no significant differences on day 0 or at 3 months, but cumulative vascular events (candesartan vs. placebo: 9.8 vs. 18.7%, $p = 0.026$) and 12-month mortality (candesartan vs. placebo: 2.9 vs. 7.2%, $p = 0.07$) were significantly in favor of the candesartan arm or trended in favor of the agent. There was no difference in drug tolerability or side effects between the two groups *(13)*.

Practical Implications: ACCESS was a small underpowered study, and in essence compared only 7 days of treatment with candesartan to placebo; since after 7 days, all but two patients in the placebo arm were also started on candesartan. The duration of follow-up for the primary outcome was limited (3 months). Thus, the results of ACCESS are probably more helpful in planning a larger definitive trial (*see* Table 3, Chapter 7), rather than arriving at a conclusion about the benefits of candesartan treatment in patients with acute hypertension after an ischemic stroke.

EFFECT ON CARDIOVASCULAR DISEASE AND NEPHROPATHY

Since AII has widespread effects throughout the entire vascular tree, it might be expected that ARBs would have beneficial effects on cardiovascular and renal disease as well. This has been borne out in several clinical trials.

Cardiovascular Disease

(a) *Patients without heart failure*: The effect of ARBs on cardiovascular outcomes in high risk subjects without heart failure has been studied in several large randomized trials. Of these, LIFE, MOSES, ONTARGET, and TRANSCEND have been discussed in detail above. In the VALUE trial, 15,425 hypertensive subjects at high risk for cardiac events were treated with hydrochlorothiazide and either a valsartan- or amlodipine-based regimen for a mean of 4.2 years. There was no difference in the primary endpoint of cardiac mortality and morbidity. However, the amlodipine arm had a greater early reduction in blood pressure which has been offered as an explanation for the lack of difference in outcomes *(14)*.

Clinical Implications: Based on the available trial data, the evidence indicates that ARBs appear to be superior to beta-blockers and perhaps as effective as ACE inhibitors or calcium channel blockers for cardiovascular protection in patients with hypertension without heart failure or lowered cardiac ejection fraction.

(b) *Patients with heart failure*: Four large randomized clinical trials have evaluated the role of ARBs in patients with heart failure. VAL-HeFT included 5,010 subjects with heart failure who were treated with valsartan (160 mg twice daily) or placebo in addition to their current treatment regimen for an average of 23 months *(15)*. Two primary endpoints were studied: mortality and a combined endpoint of mortality and vascular morbidity. The results revealed no difference in mortality between the two groups; however, treatment with valsartan significantly reduced the endpoint of combined mortality and morbidity by 13.2% compared to placebo (hazard ratio $= 0.87$, $p = 0.0009$) *(15)*.

Similarly, in the CHARM study, a program that included 7,601 subjects, there was no significant difference in all-cause mortality between patients with heart failure treated with candesartan or placebo *(16)*. The results of both CHARM and VAL-HeFT were, however, confounded by the use of concomitant therapies such as beta-blockers or ACE inhibitors.

In the CHARM-Alternative trial which included 2,028 heart failure patients intolerant to ACE inhibitors, treatment with candesartan resulted in a 23% reduction ($p = 0.0004$) in the primary outcome measure: risk of cardiovascular death or hospitalization for heart failure compared to placebo at end of nearly 3 years of treatment *(17)*.

The CHARM-Added trial included 2,548 subjects with heart failure on ACE inhibitors. The addition of candesartan to the therapeutic regimen in these patients led to a significant reduction of the primary endpoint (38 vs. 42%) (composite of cardiovascular death or hospitalization for heart failure) compared to placebo-treated patients *(18)*. However, there was a higher incidence of renal dysfunction and hypokalemia in patients treated with a combination of ARBs and ACE inhibitors in this trial *(18)*.

The VALIANT trial included 14,703 patients who had a recent myocardial infarction and had signs of heart failure. Patients were treated with valsartan, captopril, or both agents. There was no difference in all-cause mortality at 2 years between the valsartan and captopril arms. The combination of the two agents resulted in no additional benefit, however the incidence of adverse events was increased *(16)*.

Clinical Implications: In patients with heart failure, the results of the trials suggest that ARBs may have cardioprotective effects similar to ACE inhibitors; however, the combination of ARB and ACE inhibitor therapy does not appear to confer an additive benefit.

Renal Disease: Clinical trial data supports the notion that ARBs are effective in improving renal outcomes in hypertensive patients, particularly in those with diabetes. In IDNT ($n = 1,715$), the incidence of the primary endpoint (composite of doubling of baseline serum creatinine, development of end-stage renal disease, or all-cause mortality) was significantly lower with irbesartan compared to placebo ($p = 0.02$) or amlodipine ($p = 0.006$) *(19)*. The RENAAL trial ($n = 1,513$) included hypertensive subjects with diabetic nephropathy and showed a similar primary outcome as the IDNT study. Treatment with losartan significantly decreased the risk of the primary outcome measure compared to treatment with placebo ($p = 0.02$) *(20)*. In two other trials, IRMA-II and MARVAL, the use of ARBs has been shown to reduce the development of nephropathy compared to placebo

(in the IRMA-II trial) or amlodipine (in the MARVAL trial) *(21,22)*. The DETAIL trial (*n* = 250) randomized hypertensive subjects with early diabetic nephropathy to treatment with telmisartan or enalapril. At the end of the 5-year study, there was no difference in the reduction of the glomerular filtration rate between the two groups *(23)*.

Clinical Implications: In patients with diabetic nephropathy with or without hypertension, ARBs seem to have a renoprotective effect that is equivalent to ACE inhibitors and superior to calcium channel blockers.

SHOULD ARBs BE FIRST-LINE AGENTS FOR STROKE PREVENTION

Blood pressure reduction is the most important treatment for both first and recurrent prevention of stroke. For first stroke prevention, although individual clinical trials have suggested a possible additional class benefit of certain antihypertensive agents over and above blood pressure reduction, composite analysis of the major antihypertensive trials does not appear to support a specific drug class effect on vascular outcome *(24)*. For recurrent stroke prevention, the results of the recently published PRoFESS trial, did not show a clear class benefit of ARBs *(11)*. However, it has been suggested that the study was underpowered and if the subjects were followed for a longer time period, the results might have demonstrated a significant benefit in patients treated with telmisartan. On the other hand, the combination of ACE-inhibitors and diuretics has been shown to be effective in recurrent stroke prevention *(25)*. Thus, based on the currently available information, there does not appear to be a compelling reason to choose ARBs over ACE inhibitors or calcium channel blockers for stroke prevention. In patients intolerant of ACE inhibitors, ARBs may be a reasonable alternative *(26)*.

OTHER POTENTIAL USES OF ARBs

Atrial Fibrillation

ARBs and ACE-Is might prevent atrial electrical and structural remodeling associated with AF and, therefore, could prevent occurrence of atrial fibrillation *(27)*. In the LIFE trial, a clinical signal of reduced new-onset atrial fibrillation events by about one-third was observed *(3)*. Thus far, however, the data have not been consistent for reduction in the incidence of AF with these classes of drugs *(27)*.

Vascular Cognitive Impairment

Use of blood pressure control agents has been hypothesized to lead to preservation of cognitive function *(28–32)*. Specifically, drugs that activate AT2 receptors, such as ARBs, diuretics, and calcium channel blockers may be cerebroprotective *(33)*. For example, ARBs block angiotensin II access to the AT1 receptor site which may lead to stimulation of the AT2 receptor site and beneficial effects on the brain. Furthermore, it has been hypothesized that ACE-Is that are centrally active (i.e., those that cross the blood–brain barrier) may protect against dementia beyond high blood pressure control *(34)*. Whereas the majority of longitudinal epidemiological studies have supported an association between elevated blood pressure and cognitive decline, randomized studies have shown heterogeneous and possibly conflicting results in relation to blood pressure lowering and its effect on preservation of cognitive function *(35)*.

Feigin and colleagues have summarized the reasons for lack of definitive results from clinical trials of blood pressure lowering agents *(36)*: (1) insufficient power to detect modest treatment effects; (2) measurement error in relation to the diagnosis of dementia and cognitive impairment; (3) variation in treatment effects for different types of blood pressure lowering agents; and (4) bias due to missing data, variation in baseline factors such as blood pressure level, and the inclusion of subjects with cognitive impairment at study entry. Overall, assessment of cognition in cardiovascular trials has been carried out in the form of nonprimary analyses. More recently, concentrated focus on cognition has been a key aspect of cardiovascular trial development with blood pressure lowering agents.

In relation to ARBs and cognition, the Study on Cognition and Prognosis in the Elderly (SCOPE) included 4,937 patients aged 70–89 years with mild-to-moderate hypertension and Mini-Mental State Examination (MMSE) score ≥24 *(37)*. Double-blind treatment with candesartan or placebo was initiated with open-label therapy as needed to control blood pressure. Mean follow-up was for 3.7 years. In low cognitive function cases (i.e., MMSE 24–28), the MMSE declined less in the candesartan treatment group than in the placebo treatment group (mean difference 0.49, 95% CI 0.02, 0.97; $p = 0.04$). In the PRoFESS trial, cognitive decline in patients with ischemic stroke was not affected by the use of telmisartan and was not different between the two antiplatelet regimens, aspirin plus extended-release dipyridimole or clopidogrel *(38)*. Some small studies of ARBs have been conducted in relation to cognition *(39)*; however, well-thought out, large-scale, and adequately statistically powered trials with cognitive endpoints as the primary focus of study are needed to definitively test hypotheses regarding blood pressure lowering and cognitive preservation.

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11 A Practical Guide to Recurrent Stroke Prevention

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INTRODUCTION

The risk of recurrent stroke following a first event is high. Within the first year, up to 14% of patients presenting with ischemic stroke will go on to have another stroke *(1)*, and up to 40% in the following 5 years *(2)*. Risk is highest in the first month after stroke *(1)*. Recurrent stroke is associated with poorer outcome, with higher mortality and functional disability, than first stroke. Recurrent stroke risk is modulated by subtype and associated risk factors, which can guide both targeted and general recurrent prevention strategies. This chapter provides an overview of stroke subtypes and risk factors, and outlines an approach to secondary prevention based on best medical evidence and current published guidelines.

OVERVIEW OF STROKE SUBTYPES AND RISK FACTORS

Classification by Stroke Subtype and Epidemiology

Ischemic stroke may be classified into subtypes according to distribution and presumed mechanism. Several classification schemes are in current use. For example, the TOAST criteria classify ischemic stroke by presumed etiological mechanism on the basis of clinical presentation and supportive evidence (Table 1). Cardioembolic strokes are associated with the highest short- and long-term mortality rates, followed by large-artery atherothrombotic strokes and lacunar strokes *(3,4)*. Short-term (30-day) and long-term (1 and 5 year) recurrence rates are highest for large-artery atherothrombotic strokes, followed by cardioembolic and cryptogenic etiologies. Lacunar strokes have the lowest recurrence rate *(1,4)*. Identification of stroke subtype can thus aid in determination of prognosis, in addition to guiding etiology-specific interventions.

Table 1
TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)[a]
– *Clinical characteristics:* symptoms of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.), brainstem, or cerebellar dysfunction; carotid bruit; recurrent TIA in the same vascular territory supportive
– *Imaging:* imaging showing cortical, cerebellar, brainstem, or subcortical infact >1.5 cm; documentation of >50% stenosis of extracranial internal carotid artery. Diagnosis cannot be made if imaging studies are normal or show only minimal changes

Cardioembolism (high-risk/medium-risk)[a]
– *Clinical characteristics:* symptoms of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.), brainstem, or cerebellar dysfunction
– *Imaging:* at least one cardiac source for embolus; imaging showing cortical, cerebellar, brainstem, or subcortical infarct >1.5 cm; evidence of previous TIA or stroke in more than one vascular territory is supportive

Small-vessel occlusion (lacune)[a]
– *Clinical characteristics:* presentation with traditional clinical lacunar syndrome without evidence of cortical dysfunction. History of DM or HTN is supportive
– *Imaging:* CT/MRI normal or revealing relevant brainstem or cortical lesion <1.5 cm; absence of potential cardioembolic sources; absence of >50% stenosis of ipsilateral carotid artery

Stroke of other determined etiology[a]
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

[a]Possible or probable depending on results of ancillary studies.
After Adams et al. *(116)*.

Risk Factors

Nonmodifiable risk factors for first and recurrent ischemic stroke include age, sex, and ethnicity, with increased risk for all types of stroke among African-Americans and Hispanics and increased risk for intracranial hemorrhage among African-American, Hispanic, and Asian populations. Nonmodifiable risk factors are worth documenting, as they may help in identifying populations at increased risk and in whom increased vigilance for cardiovascular risk factors and reduction of modifiable risk factors may be most beneficial. Modifiable and nonmodifiable risk factors for ischemic stroke are listed in Table 2.

Intracerebral Hemorrhage

Intracerebral hemorrhages may be classified as primary (spontaneous) or secondary (due to trauma or an underlying vascular, ischemic, or mass lesion) (Table 3). Primary ICH may occur in deep (e.g., basal ganglia, thalamus, and/or internal capsule) or lobar brain structures. Table 4 lists risk factors for ICH. Apart from trauma and underlying structural lesions, which are beyond the scope of this chapter, the most important modifiable risk factor for spontaneous ICH is hypertension, which is responsible for the majority of deep

Table 2
Modifiable and Nonmodifiable Risk Factors for First and
Recurrent Ischemic Stroke

Nonmodifiable risk factors
    Age
    Race (blacks and Hispanics)
    Sex (male)
    Family history of stroke or TIA

Well-documented modifiable risk factors
    Hypertension
    Smoking
    Diabetes mellitus
    Asymptomatic carotid disease
    Sickle cell disease
    Hyperlipidemia
    Atrial fibrillation

Less well-documented or potentially modifiable risk factors
    Obesity
    Physical inactivity
    Alcohol consumption ≥5 drinks/day
    Hyperhomocysteinemia
    Drug abuse
    Hypercoagulable diathesis
    Oral contraceptive use

hemispheric ICH *(5)*, as well as a substantial proportion of lobar bleeds *(6)*. Lobar ICH is associated with amyloid angiopathy *(7)*, and the presence of apolipoprotein E e4 and e2 alleles confers a higher risk of lobar ICH *(5)*.

Transient Ischemic Attack

The distinction between "stroke" and "TIA" is increasingly irrelevant, as it becomes clearer that the entities represent different points on the same spectrum of pathophysiology. Classically, TIA has been used to refer to a neurological deficit of presumed vascular (usually ischemic) etiology with full recovery of symptoms within 24 h. However, sensitive neuroimaging techniques such as magnetic resonance (MR) diffusion-weighted imaging (DWI) sequences may reveal ischemic changes even in patients presenting with short-lived symptoms. A proposed new tissue-based definition of TIA specifies transient neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with no evidence of infarction *(8,9)*. Ischemic TIA shares etiological mechanisms and risk factors with stroke, and is associated with a high risk of recurrent ischemic and other vascular events.

Most TIAs are presumed to be of cardioembolic, large-artery atherosclerotic, or artery-to-artery etiology, but small-vessel lacunar disease can also present with transient reversible symptoms *(10)*. TIAs associated with large-vessel atherothrombosis are associated with higher risk of subsequent stroke, particularly in the first week *(10)*. Overall, up to 10.5%

Table 3
Hemorrhagic Stroke Subtypes

Primary (spontaneous)
    Hypertensive
    Amyloid angiopathy
    Coagulopathy
        Endogeneous (prothrombotic diathesis, thrombocytopenia)
        Acquired (antithrombotic or thrombolytic therapy)

Secondary
    Trauma
    Underlying vascular malformation
        Arteriovenous malformation
        Cavernous angioma
        Venous angioma
        Aneurysm
    Hemorrhagic transformation of ischemic stroke
    Venous thrombosis
    Underlying mass lesion
        Primary neoplasm
        Metastatic neoplasm
        Abscess
    Other (inflammatory, toxic, sickle cell disease)

Table 4
Risk Factors for Primary (Spontaneous) Intracerebral Hemorrhage
(ICH)

Nonmodifiable
    Age
    Race, ethnicity (African-American, Asian)
    Cerebral amyloid angiopathy
    Apolipoprotein E e2 or e4
    Positive family history

Modifiable
    Hypertension
    Coagulopathy
        Endogenous (hemophilia)
        Acquired (antithrombotic, antiplatelet, or thrombolytic therapy)
    Heavy alcohol use
    Other substance abuse, including cocaine
    Tobacco use
    Ischemic stroke

of TIA patients go on to develop an ischemic stroke in the first 90 days postevent, with the greatest risk in the first week. Hemispheric symptoms are associated with a higher early and long-term risk of stroke than are monocular events (i.e., amaurosis fugax). The ABCD *(2)* score (Table 5) stratifies risk of early stroke after TIA according to risk factors including age, blood pressure, clinical presentation, diabetes, and duration of symptoms *(11)*. Patients with high scores (over 5 on the 7-point scale) were found to be at substantially higher risk for stroke (8.1% within 48 h of the index event) *(11)*.

Based on the foregoing, it is clear that all hemorrhagic and ischemic events should be treated as emergencies and evaluated promptly and thoroughly. A basic approach to evaluation of a first stroke or TIA is outlined in Table 6.

Table 5
Stratification of Risk Following TIA: ABCD *(2)* Score

Risk factor		Points
Age (years)	≥60	1
BP	Systolic >140 mmHg	
	Or diastolic ≥90 mmHg	1
Clinical features	Unilateral weakness	2
	Speech disturbance without weakness	1
	Other	0
Duration of symptoms (min)	≥60	2
	10–59	1
Diabetes		1

Maximum 7 points; scores over 5 were associated with 8.1% 2-day rate of stroke.
After Johnston et al. *(11)*.

Table 6
Basic Evaluation for First Ischemic Stroke or Transient Ischemic Attack

– Neuroimaging (MRI with diffusion weighted imaging (DWI) is preferable to CT in patients able to undergo it, allowing assessment of small-vessel ischemic changes, clinically silent strokes, and microhemorrhages suggestive of amyloid angiopathy)
– 12-lead EKG
– 24–48 h telemetric or ambulatory cardiac monitoring for arrhythmia
– Oxygen saturation
– Noninvasive imaging of the extracranial vessels
  o Carotid duplex studies (inexpensive, noninvasive; estimates degree of stenosis based on velocity parameters; allows characterization of extent and morphology of plaque) *or*
  o MR angiography (adequate screening study; routine MR angiography does not allow visualization of plaque morphology; may overestimate degree of stenosis in areas of slow or turbulent flow) *or*
  o CT angiography (rapid; high-resolution; iodinated dye load may be a contraindication in patients with compromised renal function)
– Intracranial vascular imaging
  o MR angiography *or*
  o CT angiography *or*
  o Transcranial Doppler (TCD) studies

– Echocardiography
  o Transthoracic echocardiography (estimates cardiac function; allows visualization of anterior wall for segmental motion abnormalities or thrombus; saline contrast study can assess shunt due to PFO)
  o TEE (invasive study; optimal for evaluating atrium and atrial appendage, PFO, interatrial septal aneurysm; allows visualization of the aortic arch)
– Laboratory studies
  o CBC with differential and platelet count
  o Basic chemistry profile
  o Fasting blood glucose
  o Prothrombin time/international normalized ratio (PT/INR); partial thromboplastin time (PTT)
  o Thyroid studies
  o Cardiac enzymes
  o Fasting lipid profile

Indicated in select cases
– Hematological evaluation for prothrombotic state or coagulopathy
  o Protein C, Protein S, Antithrombin III activities
  o Activated Protein C resistance/Factor V Leiden
  o Fibrinogen
  o D-dimer
  o Anticardiolipin antibody
  o Lupus anticoagulant
  o Homocysteine
  o Prothrombin Gene 20,210A mutation
  o Factor VIII
  o VonWillebrand factor
  o Plasminogen activator inhibitor-1
  o Endogenous tissue plasminogen activator activity
– Sedimentation rate
– Lumbar puncture
– Digital subtraction angiography (gold standard for estimating carotid stenosis; vascular malformation; dissection; suspected arteritis. Invasive study, 1% risk of stroke, hemorrhage)
– Toxicology screen, blood alcohol level
– Transcranial Doppler studies with embolus monitoring

After Easton et al. *(9)* and Sacco et al. *(23)*.

ETIOLOGY-SPECIFIC INTERVENTIONS IN SPECIFIC STROKE SUBTYPES

Cardioembolic Stroke

Cardiogenic embolism is associated with a range of cardiac pathologies, including artificial heart valves and valvular abnormalities, atrial fibrillation, left ventricular thrombus (often in the setting of acute myocardial infarction), and low ejection fraction due to

cardiomyopathy. The status of patent foramen ovale (PFO) and interatrial septal aneurysm as risks for cryptogenic stroke is controversial. Cardiac disease is associated with a high risk of first and recurrent ischemic stroke, and should be aggressively treated.

Nonvalvular atrial fibrillation is the most common cause of cardioembolic stroke *(12,13)*, with increased risk especially in the elderly *(14)*. Anticoagulation with warfarin is associated with a 60–70% or higher relative reduction in stroke risk, in contrast to antithrombotic therapy with aspirin, which confers an estimated 20% risk reduction, mostly due to a reduction in the rate of small noncardioembolic strokes *(15,16)*. It is possible to identify a group of patients at relatively lower risk (1–1.5% annually) for first ischemic stroke in whom initial therapy with aspirin and heart rate control may be a reasonable alternative *(17–19)*. A first ischemic stroke or TIA is associated with a high risk of recurrence, however, and patients presenting with an ischemic event should be anticoagulated with a goal INR of 2.5 (range 2.0–3.0) unless there are contraindications *(18)*. Efficacy declines with INR < 2.0 *(20,21)*, and low-dose warfarin therapy in atrial fibrillation is associated with only modest reduction in stroke risk, with no significant benefit in decreased risk of major hemorrhage compared to adjusted-dose warfarin *(22)*. For patients who cannot tolerate warfarin, aspirin has been recommended *(18,23)*. One component of an ongoing clinical trial investigating the safety and efficacy of combination therapy with aspirin and clopidogrel vs warfarin *(24)* was prematurely terminated following findings of superiority of adjusted-dose warfarin. A second component comparing the safety and efficacy of the combination of aspirin and clopidogrel to aspirin monotherapy in patients ineligible for randomization to warfarin has shown that combination therapy is more efficacious than monotherapy for the reduction of vascular events, especially stroke, though there was an increased risk of major hemorrhage *(25)*.

Valvular heart disease is associated with a high risk of stroke. The American College of Chest Physicians has published guidelines for management of antithrombotic therapy in patients with valvular heart disease *(26)*. Full anticoagulation with warfarin is recommended for most patients with rheumatic valvular disease and mechanical prosthetic valves, with a target INR of 2.5 (range 2.0–3.0) for rheumatic heart disease, even in the absence of atrial fibrillation. A target INR of 3.0 (range 2.5–3.5) is recommended in patients with certain mechanical prosthetic valves. Addition of low-dose aspirin (50–100 mg daily) may be considered in patients with additional risk factors including atrial fibrillation, hypercoagulable state, low ejection fraction, or prior systemic embolus (including stroke) despite therapeutic INR, unless there is a high risk of bleeding complications *(26)*.

Patients with acute MI may develop transient arrhythmias or intraventricular thrombus, predisposing to embolic events. Up to 20% of patients with large anterior wall myocardial infarcts suffer stroke or systemic embolism. The risk may be highest in the first 3 months post-MI. Adjusted-dose warfarin with a goal INR of 2.0–3.0 for 3 months to 1 year should be considered in patients with documented left ventricular thrombus and stroke or TIA *(23)*. Aspirin should be used concurrently for coronary indications in patients with ST segment elevation *(27)*.

Cardiomyopathy of ischemic or other etiology is associated with increased risk of stroke, with the risk of ischemic stroke inversely proportional to documented ejection fraction *(28)*. An ongoing clinical trial *(29)* is investigating the safety and efficacy of aspirin vs dose-adjusted warfarin in patients with ejection fraction <30%. At present, either antiplatelet therapy or adjusted-dose warfarin with a goal INR of 2.0–3.0 is recommended for secondary prevention in these patients *(23)*.

The status of patent foramen ovale (PFO), persistence of an intracardiac fetal communication between the venous and arterial circulations predisposing to paradoxical embolus, as a risk factor for stroke is unclear *(30,31)*. While common (27–29%) in unselected populations *(32)*, PFO may be prevalent in young patients with cryptogenic stroke *(33)*, and is associated with annual recurrence rates between 1.5 and 12%. Large left-to-right shunt *(34)*, associated interatrial septal aneurysm *(35)*, concurrent hypercoagulable state, and presence of venous thrombosis *(36)* may be implicated in increased stroke risk associated with PFO. Antiplatelet therapy is a reasonable preventive therapy in patients with cryptogenic stroke and isolated PFO *(18)*. Those with documented hypercoagulable state or venous thrombosis may benefit from anticoagulation with adjusted-dose warfarin. Surgical or percutaneous PFO closure may be considered in those with recurrent stroke despite medical therapy, though there are at present insufficient data to evaluate the safety and efficacy of closure vs medical management *(37)*. Clinical trials in patients with PFO and ischemic stroke are ongoing to answer important questions in relation to percutaneous PFO closure and antithrombotic therapies in these patients.

Large-Vessel Extracranial Atherothrombotic Disease

Atherothrombotic disease caused by atherosclerotic plaque of the extracranial arteries can cause ischemia via two mechanisms: low flow from high-grade stenosis and artery-to-artery embolism from propagation of atherosclerotic debris and thrombus. While early schemes for assessing stroke risk focused on the degree of carotid artery stenosis, plaque morphology is increasingly appreciated as a risk factor *(38)*. Irregular, ulcerated, and echolucent plaque is associated with an up to fourfold increase in stroke risk, independent of degree of stenosis and other risk factors *(39–41)*. Degree of stenosis and plaque morphology may be evaluated with carotid duplex imaging, CT angiography (CTA), or digital subtraction angiography. Magnetic resonance angiography (MRA) may be a useful screening test. MRA avoids radiation exposure and may be obtained without injection of contrast dye. However, the technology tends to overestimate the degree of stenosis in turbulent or low-flow areas, and may have inadequate resolution to characterize plaque morphology.

Three major clinical trials have established the efficacy of carotid endarterectomy in the treatment of symptomatic carotid stenosis in centers with combined perioperative morbidity and mortality rates of <6% *(42–44)*. Unequivocal benefit, with 11–17% risk reduction in the first 1–3 years, was demonstrated for patients with stroke or TIA and 70–99% ipsilateral carotid artery stenosis. The greatest benefit was seen in patients operated on within 2 weeks of the ischemic event *(10,45)*. There was significant though lesser benefit for patients with moderate degrees of stenosis (50–69%) *(46)*. Patients who achieved the greatest benefit were men, >75 years old, presenting with stroke rather than TIA, and presenting with hemispheric symptoms rather than transient monocular blindness *(46,47)*. Documented intracranial stenosis was associated with enhanced benefit from CEA *(48)*. Patients with symptomatic high-grade stenosis may thus be considered for endarterectomy, if surgical risk is deemed acceptable. Others may be managed medically, with risk factor reduction and antiplatelet therapy.

Percutaneous angioplasty and stenting of the carotid arteries with distal protection have been investigated in patients considered high risk for endarterectomy, and has been shown to be noninferior to endarterectomy in two randomized clinical trials to date *(49,50)*. CREST, another major trial, is ongoing *(51)*. EVA 3-S and SPACE, trials carried out in

Europe, provide a different perspective, however, on the potential value of extracranial carotid artery angioplasty and stenting, with less encouraging results for key vascular outcomes with angioplasty with stenting *(52)*.

Angioplasty with stenting may be a reasonable approach in patients who, because of poor surgical risk due to major medical comorbidities or lesion anatomy, are poor candidates for endarterectomy. Poorer outcomes may be observed in patients 80 years of age and older, and the procedure should be undertaken with caution in this age group *(53)*.

Complete occlusion of the carotid artery may be associated with a "stump syndrome," with symptomatic distal embolization or propagation of clot. Short-term (3–6 months) anticoagulation with warfarin may be considered in these cases, in addition to risk factor management. Extra- to intracranial bypass surgery has not been shown to be effective in the past *(54)*, though currently a clinical trial is re-evaluating the procedure in selected patients with documented evidence of poor hemodynamic reserve *(55,56)*.

Intracranial Atherothrombotic Disease

While intracranial atherosclerosis accounts for about 8% of ischemic strokes in the United States *(2)*, it is the most common stroke subtype worldwide, with rates up to 50% or greater in race-ethnic populations including African-Americans, Hispanics, and Asians *(57)*. Intracranial disease is associated with a relatively high rate of recurrent stroke, with up to 12% annual and 19.7% 2-year recurrence rate *(58)*, even with appropriate medical therapy *(59,60)*. Recurrence rates may be higher in patients who fail to respond to aspirin therapy initially *(59)*. Retrospective *(61)* and prospective preliminary studies *(59)* had suggested a benefit of warfarin over aspirin in recurrent stroke prevention in these patients. However, a randomized prospective clinical trial *(58)* comparing high-dose (1,300 mg daily) aspirin to warfarin (target INR 2–3) documented higher rates of adverse events in the warfarin arm, with no significant efficacy benefit over aspirin. Intracranial angioplasty and stenting for high-grade intracranial stenosis are feasible *(62)*, but may be associated with a high rate of complications and restenosis.

Optimum treatment for this stroke mechanism is yet to be established, but risk factor reduction and antiplatelet therapy are appropriate first-line therapies. Warfarin therapy is of unclear benefit, and may be associated with increased risk of bleeding complications. Intracranial angioplasty and stenting are at present considered investigational *(23)*, and an NIH-sponsored clinical trial, Stenting vs Aggressive Medical Management for the Prevention of Recurrent Stroke (SAMMPRIS), is ongoing *(63)*.

Arterial Dissection

While vertebral or carotid arterial dissection accounts for a low frequency (1–2%) of ischemic stroke overall, younger patients are disproportionately affected, with up to 25% of strokes in this population attributed to dissection *(64)*. Subintimal dissection can result in cerebral ischemia due to vessel stenosis or occlusion or to propagation and distal embolization of thrombus. Patients with heritable connective tissue disorders (Ehlers–Danlos Type IV, Marfan's syndrome, polycystic kidney disease, osteogenesis imperfecta), fibromuscular dysplasia, arteritides, and generalized arteriopathy are at increased risk, as are patients with a family history of spontaneous dissection *(64)*. Dissection may develop after trauma, including seemingly minor trauma (e.g., abrupt neck flexion, whiplash injury, Valsalva). In a substantial proportion (up to 50%) of cases, no clear precipitant is identified *(65,66)*. Risk

of recurrence is low (0.3–3.4%) but is highest in the first month following the event *(67,68)*. Early recurrence in the territory of the affected artery is more common when the lesion is not fully recovered *(68)*, presumably due to propagation and embolization of subintimal and intraluminal thrombus. In the absence of associated subarachnoid hemorrhage, arterial dissection may not be a contraindication to thrombolytic therapy. While the natural history of spontaneous extracranial arterial dissection is of healing and recanalization in the majority of cases *(68)*, anticoagulation with heparin and warfarin in the first 3–6 months after the event is reasonable to prevent embolization, followed by antiplatelet therapy once repeat imaging demonstrates resolution or stabilization of the lesion. Small case series and meta-analyses have not demonstrated early anticoagulation to be superior to antiplatelet therapy, and antiplatelet therapy is a reasonable alternative in patients unable to tolerate anticoagulation or as initial therapy. In patients with persistent dissection and high-grade target artery stenosis or pseudoaneurysm formation, or those with recurrent events despite anticoagulation or antiplatelet therapy, endovascular therapy (stenting) may stabilize the vessel wall and reduce stenosis. Avoidance of activities that entail Valsalva maneuver-like movements or potential neck injury may be prudent.

Intracerebral Hemorrhage

Spontaneous intracerebral hemorrhage (ICH) is associated with high mortality and morbidity. Risk of recurrent ICH ranges from 1.4 to 24% *(69–71)*. Most studies report recurrence rates around 5–6%. Factors associated with increased risk include hypocholesterolemia *(72)*, poorly controlled hypertension *(72)*, alcohol and sympathomimetic substance abuse *(73)*, amyloid angiopathy *(7,74)*, stroke distribution (i.e., higher recurrence of lobar bleeds) *(70)*, and the presence of microbleeds on gradient-echo magnetic resonance imaging *(75)*. Apart from cases with underlying vascular or mass lesions, which are beyond the scope of this chapter, there are no etiology-specific interventions for spontaneous ICH. Risk factor reduction, including blood pressure lowering, should be undertaken *(76)*. Anticoagulation and antithrombotic therapy should be undertaken with caution in patients with a history of spontaneous ICH, particularly in the setting of amyloid angiopathy or presence of high-risk ApoE profile with lobar ICH. A decision analysis based on epidemiological data recommended withholding anticoagulation in patients with lobar ICH and atrial fibrillation. Risks were lower for patients with deep hemispheric ICH *(77)*. In patients with compelling indications for anticoagulation (e.g., mechanical valve), bridge therapy with heparin, which is easily titrated and quickly reversed, is recommended in the acute phase, with cautious reinstitution of adjusted-dose warfarin with close monitoring and INRs in low range of therapeutic target, 3–4 weeks after the event *(23)*. The risk of recurrent bleed is low in patients with small or asymptomatic bleeds with a compelling indication for anticoagulation *(78,79)*.

NON-ETIOLOGY-SPECIFIC INTERVENTIONS AND RISK FACTOR MODIFICATION

As noted above, nonmodifiable risk factors should be identified and documented, modifiable risk factors aggressively targeted, and general or non-etiology-specific preventive measures instituted in all stroke and TIA patients.

Hypertension

Elevated blood pressure, with its high relative risk and high prevalence in the population, is perhaps the most important modifiable risk factor for ischemic stroke and ICH. All forms of hypertension (systolic, diastolic, and combined systolic and diastolic) are associated with increased risk, and a monotonic relationship between blood pressure and stroke has been demonstrated beginning with blood pressures as low as 115/75 mmHg *(80)*. Meta-analyses of randomized controlled clinical trials document 30–40% risk reduction with BP lowering, regardless of BP level at entry *(81)*. Current emphasis has shifted from defining categories of hypertension to a focus on absolute BP level. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines recommend a goal BP of <140/90 in most individuals, and <130/80 in those with diabetes mellitus or chronic kidney disease. The JNC-7 classification scheme for hypertension is shown in Table 7.

Table 7
JNC-7 Classification of Hypertension

SBP/DBP	*JNC-7 Category*
<120/80	Normal
120–130/80–89	Prehypertension
≥140/90	Hypertension
140–159/90–99	Stage 1
≥160/100	Stage 2

After Chobanian et al. *(82)*.

Specific classes of BP-lowering agents may provide differential protection for stroke; the topic is covered in the Chapters 7, 10, and 11. Most studies show that the absolute amount of BP lowering is key, and JNC-7 guidelines recommend a combination of lifestyle modifications and pharmacotherapy for BP lowering *(82)*. Lifestyle changes including weight reduction, regular aerobic exercise, and heart-healthy diet, along with moderate alcohol consumption for those who drink, and smoking cessation, are effective, with systolic BP reductions of up to 10 mmHg *(82)*. Most patients with systolic BP >20 mmHg above target or diastolic BP >10 mmHg above target will require more than one pharmacological agent in order to reach target BP, and initiation of BP-lowering therapy with combination therapy is reasonable. A diuretic or combination of diuretic and angiotensin-converting enzyme inhibitor (ACE-I) is recommended as initial therapy in most patients.

Antithrombotic Therapy

Antithrombotic therapy has been shown to be effective in recurrent stroke prevention. Three classes of antiplatelet agents are currently available and widely used: acetylsalicylic acid (aspirin), thienopyridines (ticlopidine, clopidogrel), and aspirin in combination with extended-release dipyridamole. Aspirin, which inhibits platelet aggregation by irreversible inhibition of cyclooxygenase-1 resulting in inhibition of thromboxane A2 formation, is inexpensive, well-tolerated, and available without prescription. For recurrent stroke prevention, aspirin doses of 50–325 mg daily have been shown to be effective

(83). Higher doses are associated with increased risk of bleeding, and may, because of dose-dependent inhibition of endothelial-derived prostacyclin (PGI_2), be associated with decreased antithrombotic effect.

Thienopyridines interfere with ADP-mediated activation of the platelet GIIb/IIIa receptor complex by selective and irreversible inhibition of the $P2Y_{12}$ ADP receptor. Maximum effect takes 5–7 days. Ticlopidine is rarely used at present because of an association with thrombotic thrombocytopenic purpura and other side effects *(84)*. Clopidogrel, however, is appropriate for clinical use.

Dipyridamole may have antiplatelet effects through several mechanisms, including increased intracellular levels of cyclic-AMP, increased prostacyclin, and enhanced nitric oxide effects. Extended-release dipyridamole is currently available in a combination preparation with aspirin. The limiting side effects tend to be headache and gastrointestinal disturbance.

Anticoagulation with warfarin has not been shown to be superior to antiplatelet therapy in recurrent prevention of noncardioembolic stroke *(58,85,86)*, and in the absence of other indications, antiplatelet therapy is recommended over anticoagulation. Aspirin 50–325 mg daily, clopidogrel 75 mg daily, and aspirin–extended-release dipyridamole 25/200 mg twice daily are all acceptable agents. Combination of aspirin and extended-release dipyridamole, if tolerated, has been shown to be more effective than aspirin alone *(87)*. Combination therapy with aspirin and clopidogrel has not been shown to be effective over monotherapy with aspirin *(88)* or clopidogrel *(89)*, and is associated with a higher risk of bleeding complications than monotherapy with clopidogrel *(89)*. It is therefore not recommended in routine prevention of recurrent stroke *(90)*, although it may be considered if there are other indications such as acute coronary syndrome or recent stent placement.

Dyslipidemia

Dyslipidemia, including elevated total cholesterol, low HDL cholesterol, high LDL cholesterol, elevated triglycerides, and lipoprotein(a), are established risk factors for coronary heart disease and carotid atherosclerosis. Patients with elevated cholesterol, coronary heart disease, or stroke of atherosclerotic origin should be managed following The National Cholesterol Education Program (NCEP III) guidelines *(91)*, which classify patients according to coronary heart disease (CHD risk and risk equivalents including diabetes and symptomatic carotid disease. These guidelines emphasize lifestyle changes (weight reduction, increased physical activity, heart-healthy diet high in fiber and poly- and monounsaturated fats and low in saturated fats and cholesterol) and drug therapy (Table 8).

In terms of drug therapy, HMGCoA reductase inhibitors (statins) have been shown to reduce stroke risk, possibly through pleiotropic mechanisms including anti-inflammatory activity, in addition to cholesterol lowering *(92,93)*. The recent Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial *(94)* demonstrated reduced risk of recurrent fatal or nonfatal stroke, major cardiovascular events, and stroke or TIA in patients with primarily prior stroke or TIA and without known coronary disease. Patients were treated with atorvastatin or placebo. There was a higher incidence of hemorrhagic

Table 8
NCEP III Guidelines for Cholesterol Goals/Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy

Risk category	LDL goal	LDL level at which to initiate lifestyle changes	LDL level at which to consider drug therapy
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130
2+ risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10–20%: ≥130 10-year risk <10%: ≥160
0–1 risk factor	<160	≥160	≥190 (160–189: LDL lowering drug optional)

CHD = coronary heart disease.
After Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) *(91)*.

stroke in the active treatment arm, but total adverse events were not significantly different between the treatment groups. A recent prospective cohort study revealed no increase in ICH recurrence with statin use *(95)*.

Based on results of the SPARCL trial, AHA guidelines have been modified to recommend institution of statin therapy with substantial lipid-lowering properties in patients with atherosclerotic ischemic stroke or TIA, even in the absence of known coronary artery disease. Niacin or gemfibrozil may be considered for treatment of low HDL cholesterol *(96)*.

Diabetes Mellitus

Diabetes is a potent risk factor for first stroke. It is associated with micro- and macrovascular pathology. Patients with diabetes have poorer outcomes following first stroke, with greater functional disability *(97)* and higher mortality *(98)*. Diabetes is associated with higher incidence of small-vessel lacunar and large-vessel atherothrombotic stroke *(97,99)*, but may be associated with lower incidence of ICH *(99)*. Two community-based studies have shown diabetes to be a significant independent predictor of recurrent stroke *(100,101)*. However, while tight glycemic control in patients with diabetes has been shown to reduce the risk of microvascular complications such as nephropathy, retinopathy, and peripheral neuropathy, its role in preventing macrovascular complications including stroke has not been conclusively proven.

Current guidelines recommend aggressive control of associated risk factors including dyslipidemia and hypertension, with goal systolic BP <130 and ACE-I and angiotensin receptor blocking (ARB) agents considered for first-line therapy. Glycemic control is recommended to reduce microvascular complications in patients with diabetes *(102)*. An ongoing clinical trial is investigating the effects of glitazone therapy for secondary stroke prevention in patients with insulin resistance (IRIS).

Hormone Replacement Therapy

The epidemiological observation that premenopausal women have a lower risk of stroke than age- and other risk factor-matched men was attributed at least in part to potentially protective effects of estrogen. Furthermore, observational studies suggested that hormone replacement therapy (HRT) may be protective against stroke and cardiovascular disease in postmenopausal women *(103)*. However, three randomized clinical trials have failed to show benefit in cardiovascular risk reduction *(104–106)*, and two showed increased risk of stroke and cardiovascular events in the HRT arm *(104*,*106)*. Institution of HRT for cardiovascular protection is therefore not recommended, and postmenopausal women with a prior history of stroke or TIA should not be placed on HRT *(23)*.

Tobacco Use

Cigarette smoking increases stroke risk through a variety of mechanisms, including increased viscosity and fibrinogen levels, vascular endothelial damage, increased platelet aggregation, and vasoconstriction. Smoking is associated with a 1.5- to 2-fold increase in stroke risk *(107)*. The risk rises in a dose-dependent fashion, and passive exposure to cigarette smoke may be associated with increased cardiovascular risk. Smoking cessation is effective. Stroke risk declines with cessation and excess risk disappears within 5 years of cessation *(108*,*109)*, though those with a history of heavy smoking may not return fully to baseline risk *(109)*. Individuals who smoke should be urged to quit, and a combination of counseling, social support, and pharmacotherapy (in the form of short-term nicotine replacement and smoking cessation aids such as bupropion) may be beneficial *(110)*. Smokers should not be encouraged to take up other forms of tobacco (snuff, pipes, chewing tobacco), as these carry health risks as well.

Alcohol Use

Excessive alcohol consumption is associated with increased risk of all stroke types *(111)*. However, for ischemic stroke, moderate alcohol consumption (1–2 alcoholic drinks per day for men; 1 drink daily for nonpregnant women) may be associated with reduced risk, and a J-shaped risk curve for alcohol consumption and ischemic stroke risk has been proposed *(111*, *112)*. Because of high potential for abuse and associated morbidities, patients who do not drink should not be encouraged to drink alcohol; however, light to moderate alcohol consumption may be maintained. Heavy drinkers (>5 alcoholic drinks daily) should be counseled to cease or reduce consumption.

Physical Activity

A physically active lifestyle is associated with decreased cardiovascular risk. With regular physical activity there may be lower blood pressure and serum glucose and improved lipid profile, as well as a reduction in inflammatory markers *(113*,*114)*. Patients who are physically able should be counseled to engage in moderate physical activity (walking, swimming, bicycling, gardening) most days of the week. Those with physical disability may benefit from a supervised exercise regimen (Table 9) *(115)*.

Table 9
Recommendations for Exercise Programs for Stroke Survivors

Mode of exercise	Goals	Intensity, frequency, and duration
Aerobic		
– Large-muscle activities (walking, treadmill, stationary cycle)	– Increased independence in ADLs – Increased walking speed and efficiency – Increased tolerance for physical activity – Reduced cardiovascular risk	– 50–80% maximal heart rate – 20–60 min sessions – 3–7 days/week
Strength		
– Circuit training – Weight machine – Free weights – Isometric exercise	– Increased independence in ADLs	– 1–3 sets of 10–15 repetitions of 8–10 exercises involving the major muscle groups – 2–3 days/week
Flexibility		
– Stretching	– Increased ROM in involved extremities – Decreased contractures	– 2–3 days/week – Hold each stretch 10–30 s
Neuromuscular – Coordination and balance activities	– Improved safety in ADLs	– 2–3 days/week

From Gordon et al. *(115)*.

Conclusion

Recurrent stroke is preventable. Best practice guidelines should be followed in managing risk factors and in recommending antithrombotic therapies and other interventions. Lifestyle changes are effective in reducing stroke risk, and should be aggressively pursued.

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IV   MECHANISMS AND SEQUELAE OF ELEVATED BLOOD PRESSURE ON BRAIN FUNCTION AND COGNITION

12 Vascular Cognitive Impairment and Alzheimer Disease: Are These Disorders Linked to Hypertension and Other Cardiovascular Risk Factors?

Fernando D. Testai, MD, PhD *and Philip B. Gorelick,* MD, MPH

CONTENTS

INTRODUCTION

Alzheimer disease (AD) and vascular forms of cognitive impairment (VCI) traditionally have been considered separate or divergent disorders *(1)*. AD, for example, has been defined as a "degenerative" disease characterized by neuritic plaque and neurofibrillary tangle pathology, neuronal loss, and deposition of amyloid in the brain parenchyma and brain blood vessels. On the other hand, VCI has been characterized as disorders caused by cerebrovascular disease which may vary from mild to severe cognitive dysfunction *(2)*. Practically, mixed neuropathology including both AD and VCI is common in the elderly, and vascular risk factors and atherosclerosis may be important in the genesis of both VCI and AD *(3–6)*. Furthermore, AD and stroke pathogenic mechanisms may be synergistic *(7)*.

The pathogenic mechanisms and clinical manifestations of these disorders may be subtle as even the occurrence of stroke symptoms *without* a history of clinical stroke or TIA reported to a physician (referred to as "whispering strokes") may be associated with cognitive impairment, and the risk of this may increase with the presence of each additional cardiovascular factor. *(8,9)*. Overall, subclinical or "silent" strokes are the most common type of strokes with an estimated 9 million silent infarcts and 2 million silent

hemorrhages compared to about 780,000 clinical strokes in the USA *(10)*. "Silent" strokes are significant, therefore, as they may be associated with cognitive impairment and may be preventable.

The combination of AD neuropathology and hemispheral infarction may be sufficient to cause dementia *(11)*. This is important as the introduction of a vascular component to the process that causes cognitive impairment leads to the possibility of prevention. For example, the progression of cerebral white matter lesions and lacunar infarcts, the most common form of stroke lesions underlying VCI, may be associated with a variety of vascular risk factors such as cigarette smoking, elevated blood pressure, and baseline lesion load *(12)*. Lifestyle management and medical therapies have been shown to be effective ways to reduce or delay stroke and cardiovascular disease risk and possibly consequent cognitive complications *(13)*.

In this chapter we review pathophysiologic mechanisms and epidemiological evidence that link hypertension and other vascular risk factors to VCI and AD. We will show that these two disorders may have shared vascular risk factors and may be prevented by prevention or treatment of vascular factors.

PATHOPHYSIOLOGIC MECHANISMS AND EPIDEMIOLOGICAL EVIDENCE

Hypertension, VCI, and AD

Hypertension is a highly prevalent vascular risk factor, and the association of this condition with dementia or cognitive decline has been shown in many epidemiological studies. Examples of this association are discussed below.

The Honolulu Asia Aging Study clarified the association of midlife hypertension and risk of dementia in a cohort of 3,703 Japanese-American men. Among individuals with untreated hypertension, the relative risk of dementia was about four times higher in subjects with SBP >160 mmHg compared with those with SBP 110–139 mmHg (OR 4.8; 95% CI 2.0–11.0), and 3.8 times higher among individuals with DBP 90–94 mmHg compared with DBP of 80–89 mmHg (OR 3.8; 95% CI 1.6–8.7). These results were consistent for patients with AD and VCI dementia subtypes *(14)*. Treated hypertension was not a risk factor for the occurrence of later-life dementia, however, suggesting a direct cause-effect phenomenon and highlighting the importance of the potential for early blood pressure management to delay or even prevent cognitive decline.

In the Atherosclerosis Risk in Communities (ARIC) study, cognitive assessments were administered to 10,963 subjects aged 45–64 years separated by 6 years. In this study, hypertension was defined by SBP ≥140 mmHg, DBP ≥90 mmHg, or use of antihypertensive medications. Hypertension or diabetes before the age of 60 years was independently associated with cognitive decline over 6 years measured by the digit symbol subtest of the Wechsler Adult Intelligence Scale-Revised *(15)*. Other vascular risk factors at baseline such as smoking, carotid intima–media wall thickness, and hyperlipidemia, however, were not associated with cognitive changes.

These and other population-based studies, such as the Rotterdam, Göteborg, Uppsala, Finland, and Framingham studies, provide evidence that supports hypertension as a vascular

risk factor associated with late cognitive impairment or decline *(16–20)*. The interaction between both variables is complex and J- and U-shaped relationships have been described *(21–23)*.

Different pathophysiological mechanisms have been proposed to explain the association of hypertension with cognitive impairment or decline. Hypertension may cause cerebrovascular damage in strategic areas of the brain involved in cognition. For example, the Rotterdam Scan Study has shown an association between the presence of silent brain infarcts and the risk of dementia and cognitive decline in individuals aged 60–90 years who were free of dementia and stroke at baseline. The presence of silent brain infarcts at baseline almost doubled the risk of dementia (HR 2.26; 95% CI 1.09–4.70). Furthermore, the occurrence of subsequent infarcts was associated with a steeper decline in global cognitive function *(24)*. In a multivariate regression analysis, cerebrovascular risk factors such as higher age, female sex, cigarette smoking, and elevated blood pressure, as well as baseline lesion load, predicted small vessel disease progression at 3 years which paralleled cognitive deterioration *(12)*.

The location of the infarct may predict the cognitive domain affected and ultimately the type of dementia. In the Rotterdam Scan Study, thalamic infarcts were associated with decline in memory and nonthalamic infarcts with psychomotor slowing *(24)*. In another study done in African Americans, the CT and MRI findings of patients with AD ($n = 78$), vascular dementia ($n = 66$), and stroke without dementia ($n = 41$) were compared. On CT, white matter lesions, nonlacunar infarcts, and left subcortical infarcts were predictors of vascular dementia. Atrophy of the temporal sulci, dilated temporal horns and third ventricle, and right hemisphere infarcts on brain MRI distinguished AD from vascular dementia *(25)*.

Pathological studies have shown an association between hypertension and AD. In autopsy studies, the densities of neurofibrillary tangles and senile plaques, both hallmarks of AD, were elevated in hypertensive patients without dementia. In the Honolulu Heart Program/Honolulu-Asia Aging Study, SBP ≥160 mmHg in midlife was associated with brain atrophy and greater number of senile plaques in the neocortex and hippocampus *(26,27)*.

A similar association between hypertension and AD has been shown in neuroimaging studies. A study of 511 nondemented subjects aged 60–90 years showed that higher DBP 5 years before MRI predicted hippocampal atrophy, and that higher number of white matter lesions in MRI was associated with more severe atrophy of the hippocampus and amygdala as characteristically seen in individuals with AD *(28)*. Proton MR spectroscopy studies have shown a higher myoinositol/creatine ratio in cognitively intact hypertensive older patients compared to healthy age-matched controls. Interestingly, the myoinositol/creatine ratio in the hypertensive group was similar to that observed in early AD patients, providing further evidence of common pathophysiologic changes in both conditions *(29)*.

Based on the epidemiological association between hypertension and cognitive decline, it has been proposed that blood pressure-lowering treatments could possibly ameliorate and prevent cognitive decline in patients with hypertension without a history of stroke. However, the results of several studies addressing this hypothesis have shown conflicting results. In a cross-sectional study of 2,212 African Americans aged over 65 years, antihypertensive treatment, excluding centrally acting sympatholytic drugs, was associated with

a lower risk of diagnosis of cognitive impairment defined by the Community Screening Instrument for Dementia score (OR = 0.56; $p < 0.01$) *(30)*.

Similar results were observed in the phase 2 of the Systolic Hypertension in Europe (Syst-Eur2) randomized trial. This study was a double-blind, placebo-controlled trial which included nondemented hypertensive patients aged above 60 years. Antihypertensive study intervention was started after randomization in the active treatment group and after termination in the control group. The median follow-up was 3.9 years, and the blood pressure in the placebo arm was 7.0/3.2 mmHg higher than in the active treatment arm. In this study, long-term antihypertensive therapy reduced the risk of dementia by 55% ($p <0.0001$) *(31)*.

However, in the Systolic Hypertension in Elderly Prevention (SHEP) trial, antihypertensive treatment did not reduce the incidence of dementia in patients aged above 60 years with isolated systolic hypertension *(32)*. A subsequent analysis showed that cognitive and functional evaluations in this trial were biased toward the null effect due to differential dropout *(33)*. Similarly, the placebo-controlled Study on Cognition and Prognosis in the Elderly (SCOPE) failed to show a benefit in terms of cognitive decline associated with blood pressure lowering in elderly hypertensive patients *(34)*. The design of this trial allowed the use of open-label active antihypertensive therapy as needed. As a consequence, 84% of the patients in the placebo group received antihypertensive treatment, significantly decreasing the blood pressure difference between the active treatment and the control groups. A recent systematic review comparing SHEP, Syst-Eur2, and SCOPE concluded that there is no convincing evidence from these trials that blood pressure lowering prevents the development of dementia *(35)*.

More recently, the Hypertension in the Very Elderly (HYVET) trial investigated the risks and benefits of hypertension treatment among subjects aged 80 years or older with SBP 160–200 mmHg and DBP < 110 mmHg. In this double-blinded placebo-controlled trial, patients were randomly assigned to receive placebo or 1.5 mg of indapamide with the option of taking 2–4 mg of perindopril. The SBP treatment goal was 150 mmHg, and the DBP goal was 80 mmHg. Individuals enrolled in this study had no prior history of dementia, and cognitive function was assessed at baseline and annually with the Mini-Mental State Examination (MMSE). Patients with MMSE <24 points or a drop of 3 points in 1 year underwent expert evaluation and were classified as having cognitive decline or dementia.

This study was stopped prematurely after an interim analysis showed a reduction in stroke and mortality in the active treatment group. 3,336 subjects had at least one annual follow-up examination. During the mean follow-up period of 2.2 years, the rates of dementia in the active treatment and placebo groups were not significantly different (HR 0.86; 95% CI 0.67–1.09) *(36)*. Early termination, short follow-up, and inclusion of individuals with low MMSE at baseline have been suggested as confounders that might explain the lack of a beneficial effect of lowering blood pressure on the occurrence of dementia *(37)*.

A meta-analysis including results obtained in HYVET and other placebo-controlled trials of blood pressure-lowering treatment showed decreased risk of dementia in the active treatment group (relative risk 0.87; $p = 0.045$; 95% CI 0.76–1.00) *(36)*. Overall, clinical equipoise exists in relation to the potential beneficial effects of blood pressure lowering on maintenance of cognitive vitality.

Other Cardiovascular Risk Factors, VCI, and AD

Diabetes Mellitus and Insulin

The possible influence of diabetes mellitus and glucose and insulin levels on dementia and cognitive decline has been a recent focus of interest *(3)*. In epidemiologic studies there has been controversy about the role of diabetes mellitus as a risk factor for AD, and clinically, there has been concern that tight control of glucose might lead to hypoglycemia and brain damage. Some of the latter concern has been allayed. In an average 18-year follow-up of 1,144 patients with type 1 diabetes and mean age 27 years enrolled in the Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, there were no substantial long-term declines in cognitive function despite relatively high rates of recurrent and severe hypoglycemia *(38)*. Forty percent of the subjects had at least one hypoglycemic coma or seizure event. Higher glycosylated hemoglobin levels, however, were associated with moderate and statistically significant declines in motor speed ($p = 0.001$) and psychomotor efficiency ($p < 0.001$). These DCCT/EDIC findings, however, cannot be generalized to older patients. In another study, exaggerated postprandial plasma glucose excursions in older type 2 diabetic persons were associated with impaired global, executive, and attention function, suggesting that tighter control of postprandial glucose might prevent cognitive decline in older diabetic patients *(39)*.

A number of epidemiological studies have linked diabetes to dementia, impaired cognitive performance or risk of developing cognitive impairment, and vascular dementia, especially in the elderly and in subjects with severe systolic hypertension or heart disease *(40–44)*. In relation to AD, there has been controversy. The Framingham Study, for example, did not show that diabetes increased the risk of incident AD overall; however, it could be a risk factor for AD in those without other risk factors such as elevated plasma homocysteine levels and the apolipoprotein E epsilon 4 genotype *(45)*. In the Religious Orders Study, there was a relation between diabetes and cerebral infarction but not AD pathology *(46)*.

In addition, there has been interest in the possible role of insulin signaling in cognitive impairment and decline. Insulin receptors are located in the limbic system in high concentration and may affect cognitive performance *(47)*. In a small study, insulin infusion was shown to improve cognitive function and mobilize beta amyloid from neurons or reduce its breakdown to an unfavorable form *(48)*. Furthermore, in the Honolulu-Asia Aging Study both low and high fasting insulin levels were associated with increased risk of developing dementia *(49)*; in the Columbia Aging Study hyperinsulinemia was associated with a higher risk of AD and memory decline *(50)*; and in the Uppsala Longitudinal Study of Adult Men, impaired acute insulin response in midlife was associated with increased risk of AD up to 35 years later *(51)*. Additionally, the Nurses' Health Study showed higher fasting insulin levels in subjects with cognitive decline, possibly independent of diabetes *(52)*. Finally, the insulin-degrading enzyme which has been implicated in the degradation of amyloid beta-protein and the intracellular amyloid precursor protein may act synergistically with APOE e4 in increasing the risk of late-onset sporadic AD in Han Chinese *(53)*.

In relation to brain structure and function, increased peripheral insulin has been associated with reduced AD-related brain atrophy, cognitive impairment, and dementia severity *(54)*. In addition, the combination of insulin and other diabetes medication has been associated with lower brain neuritic plaque density *(55)*.

B Vitamins and Homocysteine

Homocysteine (Hcy) is a sulfur amino acid that may be elevated secondary to deficiencies of vitamin B_{12} and folate *(56)*. Hcy is associated with endothelial dysfunction, vascular disease, neuropsychiatric disorders, clinical stroke, silent stroke, and brain white matter disease. Homoscyteine has also been linked to hippocampal neuronal loss, amyloid and glutamate neurotoxicity, and cognitive impairment and AD *(56)*. Administration of folic acid and vitamins B_6 and B_{12} can lower Hcy levels.

The literature is replete with epidemiological studies that link Hcy to cognitive decline or other important markers of cognition. We now explore a few examples. In the Framingham Study, increased plasma Hcy was an independent risk factor for developing dementia and AD *(57)*. In the Hordaland Homocysteine Study, increased plasma Hcy was an independent risk factor for memory dysfunction, and a "favorable" change in folate or Hcy concentrations over time led to better memory performance *(58)*. In the Northern Manhattan Study, cross-sectional data provided evidence that Hcy was a risk for white matter disease *(59)*. In the Baltimore Memory Study, higher Hcy levels were associated with worse cognitive function across a broad range of domains *(60)*. In the Northern Manhattan Study, in persons older than 65 years, elevated Hcy was independently associated with decreased cognition *(61)*. Other studies such as the Columbia Aging Project and one early report from the Rotterdam Study showed no link between high Hcy and AD or total Hcy and cognitive impairment, respectively *(62,63)*.

Several more recently published epidemiological studies have suggested the following relationships between Hcy and cognition. In the population-based prospective Three-City Study, the association of high Hcy and low cognition in elderly persons was observed only in those with low folate levels *(64)*. In the Framingham Offspring Study, higher Hcy levels were associated with smaller brain volumes and silent brain infarcts on magnetic resonance imaging (MRI), even in healthy, middle-aged adults *(65)*. In the Oxford Project to Investigate Memory and Aging, decrease in brain volume was greater among those with lower vitamin B_{12} and holotranscobalamin levels and higher plasma Hcy and methylmalonic acid levels at baseline *(66)*.

Clinical trials of vitamin supplementation to lower Hcy and improve cognition, thus far, have been disappointing. In one such study, supplementation with daily folate (1,000 µg) and vitamins B_{12} (500 µg) and B_6 (10 mg) failed to improve cognition in healthy persons 65 years of age or older with plasma Hcy concentrations of at least 13 umol/liter *(67)*. Similarly, a high-dose regimen of B vitamin supplements did not slow cognitive decline in persons with mild to moderate AD *(56)*.

Metabolic Syndrome, Body Mass Index, and Related Factors

A number of epidemiologic studies provide a link between metabolic syndrome, BMI or related factors, and cognitive impairment. Key findings from these studies are summarized in Table 1 *(68–78)*. In addition, more recently published studies have provided further verification of some of the findings in Table 1. Specifically, midlife central obesity was shown to independently increase the risk of dementia in later life *(79)*, and increased BMI in midlife was associated with MR spectroscopic findings consistent with neuronal or myelin abnormalities primarily in the frontal lobes *(80)*. Finally, impaired insulin secretion as early as

Table 1
Key Relationships of Select Cardiovascular Risk Factors and Cognition

Metabolic Syndrome (MetS), Body Mass Index (BMI), and Related Factors
1. MetS is associated with every grade of leukoaraiosis *(68)*, AD *(69,70)*, and may not be associated with cognitive decline in the oldest old *(71)*
2. BMI is associated with AD pathology in persons with and without dementia *(72)* and word-list learning and Digit-symbol Substitution Test and word-list learning in healthy, nondemented, middle-aged men and women *(73)*, and declining BMI is associated with increased risk of AD *(74)*
3. Central obesity and older age are negatively associated with hippocampal volumes and positively associated with white matter hyperintensities *(75)* and vascular risk factors *(76)* including obesity *(77)* cluster and increase the risk of AD or dementia
4. Diabetes type 2 duration and hyperglycemia may contribute to brain atrophy *(78)*

Dietary Factors: Risks and Benefits on Cognition and Cognitive Decline
1. Dietary factors which may increase risk of cognitive impairment: high intake of calories and fats may be associated with a higher risk of AD in persons carrying the APOE e4 allele *(95)*; saturated fats may increase risk of cognitive impairment *(96)*; and saturated or *trans*-unsaturated fats may increase risk of AD *(97)*
2. Dietary factors which may decrease risk of cognitive impairment: fatty fish and marine omega-3 polyunsaturated fatty acids (PUFAs) reduce risk of cognitive impairment *(96)*; high intake of unsaturated, unhydrogenated fats may protect from AD *(97)*; n-3 fatty acids and weekly consumption of fish may reduce risk of AD *(98)*; fatty fish may reduce risk of AD and dementia for those without APOE e4 allele *(99)*; Mediterranean diet reduces risk of AD and mortality *(100)*; plasma phosphatidylcholine reduces risk of all-cause dementia *(101)*; and higher folate intake may decrease the risk of AD *(102)*
3. Dietary factors which may influence cognitive decline: a diet high in saturated or *trans*-saturated fat or low in nonhydrogenated unsaturated fats may be associated with cognitive decline *(103)*; vitamin E from foods or supplements may be associated with less cognitive decline *(104)* as may fish consumption *(105)*, vegetables *(106,107)*, and high intake of folate *(108)*; and high dietary intake of copper in conjunction with a diet high in saturated and *trans*-fats may be associated with accelerated cognitive decline *(109)*
4. Dietary factors which may not be associated with increased or decreased risk on cognition or decline: high intake of total, saturated, and *trans*-fat and cholesterol and low intake of monounsaturated fatty acids (MUFAs), PUFAs, n-6 PUFA, and n-3 PUFA on risk of dementia or its subtypes *(110)*; dietary, supplemental or total intake of carotenes and vitamins C and E on risk of AD *(111)*, antioxidants vitamins C, E and beta carotene and zinc or copper on cognition *(112)*; vitamin E had a weak or no protective effect on cognitive impairment *(113)*; and omega-3 fatty acids in patients with mild to moderate AD did not delay the rate of cognitive decline *(114)*

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midlife was shown to increase the risk of AD up to 35 years later *(51)*. Metabolic syndrome, obesity, BMI, and related factors serve as targets for intervention to reduce the risk of cognitive impairment and decline.

CHOLESTEROL

Cholesterol and other lipid substances play an important role in normal brain function *(81)*. Abnormal central nervous system cholesterol homeostasis likely plays a role in the

pathogenesis of AD via complex interactions of membrane cholesterol, ox sterols, APOE, amyloid precursor protein (APP) processing, and A beta-peptide aggregation and toxicity *(81)*. Membrane cholesterol, for example, may be an important regulator of APP processing and may promote amyloidogenic processing through beta- and gamma-secretase instead of nonamyloidogenic processing via alpha-secretase.

Despite all of the interest in cholesterol as a risk for cognitive impairment and decline and the possible role of statin agents to reduce these risks *(82)*, epidemiological studies have provided mixed results about cholesterol as a risk factor for dementia or cognitive decline and the role of statin agents *(83–88)*. These studies also highlight the possible importance of APOE when dealing with cholesterol relationships and cognition and emphasize that elevated cholesterol in midlife may be a risk for later cognitive impairment, but this relationship may not hold in late life as cholesterol may decrease due to aging or as a result of cognitive decline *(89–91)*. Finally, clinical trials of statin agents have not conclusively shown a benefit in prevention of cognitive impairment or decline *(92,93)*.

DIET AND RELATED FACTORS

Diet may be a factor which increases or decreases risk of cognitive impairment and decline. Oxidative stress is one of the mechanisms whereby this may happen *(94)*. There are many publications which address this topic. In Table 1 we highlight the results of select studies which show risks or benefits of diet on cognition and cognitive decline *(95–114)*. In addition, a recently published clinical trial of cognitively healthy persons 65 years of age and older showed no overall effect of 26 weeks of eicosapentaenoic and docosahexaenoic acid supplementation (fish oil) on cognitive performance *(115)*.

HORMONAL FACTORS

Estrogens may exert beneficial effects on the aging brain by inhibiting beta-amyloid formation, stimulating cholinergic activity, reducing oxidative stress, and protecting against vascular risks *(116)*. Although some observational epidemiological studies have suggested a benefit of hormonal replacement therapy on a number of important outcomes such as cognition and cardiovascular disease *(116,117)*, an important clinical trial, the Women's Health Initiative Memory Study, has shown that estrogen therapy did *not* reduce the incidence of dementia or mild cognitive impairment, and when pooling the results of estrogen alone and estrogen plus progestin, there were increased risks of both endpoints *(118)*. In addition, there was an adverse effect on global cognition in those treated with estrogen *(119)*. In another randomized controlled clinical trial, estrogen therapy administered for 1 year to women with mild to moderate AD did not slow disease progression nor improve global cognition or functional outcomes *(120)*.

The North American Menopause Society issued a position statement in 2008 recommending that health care professionals weigh the risks and benefits of estrogen and progestogen administration for use around the time of menopause for certain disorders (e.g., osteoporosis or fractures) *(121)*. It is believed that timing and duration of use of postmenopausal hormone replacement may hold the key to effective and safe administration of these medications.

Compared to hormone replacement therapy for women, there is a paucity of information about the efficacy and safety of testosterone and androgens to improve cognition or prevent cognitive impairment in men *(122,123)*.

EXERCISE AND OTHER LIFESTYLE FACTORS

A healthy lifestyle is believed to prevent cognitive impairment *(2–5,13,124)*. One of the components of healthy lifestyle is exercise. Exercise may have beneficial effects which could prevent cognitive decline such as lowering of blood pressure, improving the lipid profile, protective effects on the vascular endothelium, and other benefits. Overall, physical activity may oppose functional and structural changes of the brain that occur with aging *(125)*, and epidemiologic observational studies suggest a benefit of exercise for prevention of cognitive impairment and decline *(126–130)*. For example, increased cardiorespiratory fitness might reduce brain atrophy in AD *(125)*.

A recently published clinical trial of subjects with a mean age of 68.6 years with subjective memory impairment showed that a 6-month program of exercise provided a modest improvement in cognitive function over an 18-month follow-up period *(130)*. For those who can partake in exercise and other healthy lifestyle choices, provision of habitual exercise, social interaction, adequate nutrition, and educational activities are reasonable prescriptions to improve well being in later life, for stroke and cardiovascular disease prevention, and possibly for prevention of cognitive impairment or decline *(3,13,131)*. Similarly, modest alcohol consumption might prevent cognitive impairment or at least do no harm *(3)*, whereas, heavier alcohol consumption may be associated with smaller brain volume *(132)*.

Whereas case-control trials have been inconsistent in relation to smoking, pooled analysis from cohort studies shows a substantial association with dementia (RR of 1.99; 95% CI 1.33–2.98) *(133,134)*. The effect of smoking on the risk of dementia may be age-dependent and more deleterious at younger ages *(134)*. This observation may be explained, at least in part, by selection bias due to censoring by death in the elderly *(134)*.

In a meta-analysis of 19 prospective studies and 17,023 participants, current smokers had a greater yearly decline in MMSE than those who never smoked, and current smokers had increased cognitive decline compared to former smokers *(135)*. In another epidemiological study of 10,211 men aged 40–59 years at baseline and followed by 40 years, the hazard ratio (HR) of death from dementia among heavy smokers was 1.58 (95% CI 1.03–2.43) compared to nonsmokers *(136)*.

INFLAMMATION AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Cytokine-mediated mechanisms may be involved in the pathogenesis of AD and other forms of cognitive impairment in the elderly *(137)*. Observational epidemiological studies have suggested a possible protective relationship of NSAIDs on cognition *(138,139)*. Despite the encouraging but not confirmatory observational study evidence pointing to the possible benefits of NSAIDs on cognitive function, clinical trials have not verified the observational study findings. In a study of mild to moderate AD patients who were about 74 years of age, neither rofecoxib (25 mg/day) nor low-dose naproxen (220 mg twice daily), compared to placebo, slowed cognitive decline *(140)*. In another clinical trial study, men and women aged 70 years and older with a family history of AD received either celecoxib (200 mg twice a day), naproxen (220 mg twice a day), or placebo *(133)*. Neither celecoxib nor naproxen improved cognitive function, and there was some evidence to suggest a detrimental effect of naproxen.

POSSIBLE NOVEL OR EMERGING FACTORS

Several possible novel or emerging cardiovascular risk factors for cognitive function include cystatin C, serum uric acid (UA), and cerebral microbleeds. Cystatin C, a measure of kidney function, co-localizes with brain beta-amyloid, and high levels of cystatin C may be associated with cognitive impairment *(141)*. Serum UA may be associated with cognitive impairment; however, this relationship may be mediated by severity of cerebral ischemia such as brain white matter hyperintensities *(142)*. Cerebral microbleeds may portend risk of cognitive impairment and brain macrobleeds *(143)*.

Finally, it has been suggested that the presence of atherosclerosis or atrial fibrillation may be linked to AD *(3,144)*. Linkage of these factors to AD could provide new avenues for prevention.

CONCLUSION

Our approach to dementia and cognitive impairment has shifted *(145)*. Now, cognitive impairment is conceptualized along a continuum of milder to more severe forms whereby we have moved our focus from effects to causes of cognitive impairment. The latter approach is well suited for prevention of dementia and cognitive impairment and for the maintenance of cognitive vitality as a mechanistic-based approach to the prevention of these disorders when they manifest at early stages is likely to be prudent *(3)*. Whereas observational epidemiological studies provide evidence of benefit for control of traditional cardiovascular disease risk factors for the maintenance of cognitive vitality, such hypotheses need to be tested in large-scale clinical trials to provide more definitive proof of efficacy and safety *(2,3)*. Key targets for these trials include hypertension and diabetes *(146)*.

The distinction between AD and VCI has been challenged and has become somewhat blurred given the possible shared risk factors and pathophysiologic mechanisms for these disorders *(147,148)*. By better understanding underlying mechanisms we may be able to better prevent and treat these important disorders of elderly individuals.

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13 Cerebral Small Vessel Disease, Hypertension, and Cognitive Function

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CONTENTS

INTRODUCTION

Vascular cognitive impairment (VCI) is a heterogeneous condition arising from a variety of neurovascular pathology, including large vessel ischemic infarction, hemorrhage, and the combination of cerebrovascular and Alzheimer's pathology *(1)*. However, VCI is primarily associated with subcortical gray and white matter pathology arising from small vessel disease. Hypertension is a major factor in the development of small vessel disease. In this chapter, we will focus on linkages between hypertension, small vessel disease, cognitive decline, and dementia.

PATHOPHYSIOLOGY OF SMALL VESSEL DISEASE

Small vessel disease is not a unitary entity. It is associated with both focal lacunar infarction in subcortical regions of gray and white matter as well as more diffuse, less well-defined deterioration. The "small vessels" consist of intracerebral end-arteries and arterioles, most often located in border zone areas that are vulnerable to ischemic changes associated with aging *(2,3)* and exacerbated by chronic hypertension *(4)*. These changes include microvascular fibrosis and basement membrane thickening, which in turn lead to a narrowing of the arteriole lumen *(5)*.

Lacunar infarctions are most often found in basal ganglia structures, in periventricular white matter, and in other subcortical gray matter structures, such as the thalamus *(6)*. The advent of modern neuroimaging techniques such as MRI has resulted in a proliferation of studies examining the presence, severity and effects of white matter hyperintensities (WMH), and its underlying pathologic substrate. The underlying white matter lesions (WML) that show as WMH on MRI are thought to consist of the combination of demyelination, lacunar infarction, and axonal loss *(7)*. The histopathology of WML reveals diffuse pallor of the white matter and rarefication of the myelin sheaths. This demyelination tends to spare subcortical U-fibers *(8)*. Reactive gliosis consistent with ischemic injury and cell death are also seen *(9)*. The volume of WMH is inversely related to brain volume measures, such as brain parenchymal fraction (BPF), which supports the hypothesis that axonal loss and cell death are associated with WMH. Vascular abnormalities such as microangiopathy of penetrating vessels, tortuosity of hyalinized vessels, and more focal fibrinous necrosis accompany white matter lesions *(8)*.

HYPERTENSION AND SMALL VESSEL DISEASE

The relationship between hypertension and small vessel disease is complex involving an interaction between extensive cardiovascular/cerebrovascular autonomic systems. While this relationship is covered more extensively in other chapters in this text, in the simplest forms, hypertension induces vascular hypertrophy, which in turn leads to increased vascular resistance *(4)*. After the acute rise in pressure, stretch receptors in arterial walls feedback to "reset" the system, thereby attempting to lower blood pressure. Small vessel disease is thought to occur because of episodic hypoperfusion secondary to hypertension *(10)* leading to cerebral arteriosclerosis of the penetrating vessels *(11)*. Similar to a fluid-filled balloon which is squeezed on one end causing a displacement of fluid toward the distal zone, when pressure is released, the same distal area of previously high volume experiences a dramatic drop in volume. In older adults whose arteries may be less elastic and "brittle," such dramatic shifts require more time for recovery leaving areas transiently underperfused. Likewise, in the cerebrovascular system, given their size and location, smaller diameter vascular distributions or border zone areas appear most vulnerable to ischemic changes associated with hypertension. Periventricular white matter regions are also particularly vulnerable to hypoxic injury following sudden changes in blood pressure as these areas are perfused by long- and small-diameter medullary arteries.

WHITE MATTER HYPERINTENSITIES AND COGNITION

WMH are commonly found in T2-weighted MRI images of the elderly; 92% of the community sample enrolled in the Rotterdam Scan Study *(12)* and 95% of the Cardiovascular Health Study sample *(13)* showed at least a mild degree of WMH. However, WMH may not be associated with cognitive decline in everyone, and many consider these changes relatively benign. Questions arise to how or to what degree white matter pathology affects cognition. In cross-sectional studies, WMH have been associated with cognitive impairments and dementia *(14,15)*. While severity of the disease burden inversely relates to cognitive performance, the relationship of reduced cognitive performance can be observed even when burden is relatively small *(16)*. The Cardiovascular Health Study reported on

3,301 community elderly with no history of stroke or transient ischemic attack who underwent MRI and two measures of cognitive function. Using templates, radiologists graded WMH on a scale from 0 (none) to 9. Higher grades were associated with greater age, silent stroke on MRI, and higher systolic blood pressure (SBP). The grade of WMH was also found to correlate with cognitive impairment; the higher the grade, the greater likelihood of cognitive dysfunction *(13)*. The authors concluded that asymptomatic white matter findings might not be clinically insignificant or benign. In a separate study, Gouw et al. *(17)* examined the relationship between cognition and WMH in 639 nondemented elderly subjects 65–84 years of age. The volume of WMH correlated with decreased performance on the Mini-mental State Examination (MMSE), a widely used cognitive screening test that has been criticized for its failure to assess executive functioning (i.e., initiation, planning, higher-order problem-solving behaviors) or processing speed domains. That the relationship was found despite the relative insensitivity of the outcome measure supports a robust relationship between volume of WMH and cognition.

Pattern of Cognitive Dysfunction in Patients with White Matter Hyperintensities

Compared to Alzheimer's disease which presents with prominent impairments in episodic memory, the heterogeneous nature of VCI makes it more difficult to characterize a prototypical cognitive presentation. Often, executive function is labeled as a core VCI deficit. Executive function is the term used to describe an array of cognitive functions believed dependent on frontal lobe and related subcortical function. Behaviors such as nonverbal reasoning, planning, initiation, problem-solving, working memory, and higher-order aspects of attention fall under the "executive" rubric. These behaviors are assumed to be supported by many distributed and parallel neural networks and various "executive functions" can be disrupted dependent on the extent and nature of the network disruption. Several studies have suggested a pattern of deficits in VCI marked by executive dysfunction, slowed information processing, inconsistent new learning and memory, bradykinesia, and disturbances in affect or emotional regulation *(18–19)*. This pattern has been linked with the presence and severity of WMH in patients with and without other subtypes of VCI-related pathology, such as large artery infarction *(18)*. Of note, however, is a recent study by Reed et al. *(20)*, which found that the presence of executive function in vivo was not strongly predictive of the presence of underlying cerebrovascular pathology assessed at autopsy. This raises questions of the specificity of executive dysfunction to VCI, especially in patients with mixed cerebrovascular and Alzheimer's pathology.

Location of White Matter Hyperintensities and Cognition

Location of the white matter changes appears to have a differential effect on cognitive functioning. WML in periventricular regions may disrupt bundles of cholinergic fibers resulting in cholinergic denervation *(21)* which could contribute to the development of cognitive decline and executive dysfunction. In a study examining the role of WMH and executive function, Oosterman et al. *(22)* examined the performance of 151 subjects with WMH on several tasks of executive functioning. The authors found significant correlations with WMH and performance on tasks of inhibition, planning, and working memory.

Of interest, periventricular WMH correlated with inhibition and working memory, while diffuse WMH correlated with planning ability.

The Rotterdam Scan Study is a prospective population-based cohort study examining age-related changes to the brains of cognitively intact elderly people at several follow-up periods from 1995 to 2002. Using 1,077 participants from this study cohort, Prins et al. *(23)* determined that over the course of the study, higher severity of periventricular white matter lesions, but not subcortical white matter lesions, increased the risk of dementia. The association between periventricular WML and dementia was independent of the presence of cerebral infarcts, incident stroke, or generalized brain atrophy. De Groot et al. *(15)* reported similar findings.

Debette et al. *(24)* examined the relationship between subcortical and periventricular WMH on performance on the MMSE and Dementia Rating Scale over two assessments (mean duration 3 years) in 170 patients with mild cognitive impairment. Relative to patients whose cognitive scores did not change or improved over the assessments, individuals who demonstrated a decline had a higher number of periventricular and subcortical white matter hyperintensities at baseline. The rate of global cognitive decline was also associated with higher number and an increase in the amount of white matter abnormalities. This was especially apparent when comparing periventricular hyperintensities and decline in the executive function domain. Another study by Bombois et al. *(25)* reported that presence of subcortical hyperintensities was also associated with executive dysfunction, regardless of mild cognitive impairment (MCI) subtype.

Prins et al. *(26)* examined 1,440 nondemented subjects from the original Rotterdam Scan Study on imaging and neuropsychological variables at three time intervals. The authors evaluated the relationship between cerebral small vessel disease and rate of decline in select domains of cognitive function. They found that periventricular lesions, infarcts, and generalized atrophy correlated with the rate of decline in global cognitive function. Increasing severity of periventricular and subcortical white matter lesions was associated with steeper declines on tasks of information processing speed while subcortical lesions alone were significantly associated with declines on a task of executive function (i.e., verbal fluency). It could be that damage to the long association efferent fibers in the periventricular regions would have relative importance in impacting connectivity and thus cognitive function. The presence of periventricular lesions may signal the loss of functional integrity in frontal–subcortical systems. Indeed, the periventricular region has a high number of long association fibers which connect subcortical to cortical regions. However, some have questioned whether the periventricular and deep subcortical WMH arise from similar processes *(27)*, raising questions of why differences in severity or cognitive pattern should be expected.

Volume of White Matter Hyperintensities and Cognition

Recent interest has focused on determining if a critical volume of WMH must be reached before one experiences a disruption in cognitive function. Visual rating scales have historically been employed to estimate the amount of WMH volume *(13)*. Using these methods, higher graded severity of WMH negatively correlated with cognitive performance. Studies which have utilized computerized quantification show similar inverse relationships between WMH volume and cognitive performance, particularly in the domains of visual scanning

and motor speed *(28)*, visuospatial memory *(28)*, verbal recognition memory *(29)*, working memory *(29)*, and new learning *(28)*. Recently, Wright et al. *(30)* examined 656 subjects from the Northern Manhattan Study (NOMAS). They calculated WMH volume using semi-automated MRI methods. Examining WMH volume as both as a continuous variable and by quartiles, the authors found that WMH volume was inversely related to cognitive performance on tasks of sensorimotor ability, cognitive flexibility, and mental sequencing. Further, they determined that having WMH volume of 0.75% of cranial volume or greater was associated with poorer cognitive performance which the authors concluded provides evidence of a threshold effect.

Lacunar Infarction and Cognition

Subcortical structures, based on extensive functional neuroanatomic connectivity, also interact with frontal regions in a distributed neural network. The smaller penetrating arteries such as the anterior and posterior choroidal, lenticulostriate, Heubner's artery, and tuberothalamic that perfuse subcortical gray matter and white matter are especially vulnerable to occlusive change and subsequent brain ischemia following increases in blood pressure. Given that these structures receive their blood supply through deep penetrating arteries, subcortical structures such as the thalamus and basal ganglia are vulnerable to vascular injury secondary to hypertension. Indeed, studies have shown abnormal blood flow in basal ganglia and related frontal regions (e.g., anterior cingulate) in patients with high blood pressure who did not otherwise demonstrate cognitive impairment or other signs of cerebrovascular disease *(31)*.

Five frontal–subcortical loops have been identified *(32)*, three of which have direct relevance to cognitive function. The disconnection hypothesis offers that lesions at various points within these parallel networks can result in three somewhat distinct neurobehavioral syndromes. Damage to the dorsolateral prefrontal circuit results in a dysexecutive syndrome; a compromised orbitofrontal circuit results in social disinhibition; and disruption in the anterior cingulate medial frontal circuit manifests in marked apathy. Figure 1 highlights these three frontal–subcortical circuits. Subcortical structures are believed to serve as critical "nodes" within these distributed networks. Given the role of subcortical nuclei in integrating information and modulating output, a strategic lacunar infarct may result in a more pronounced frontal–subcortical behavioral syndrome, but general compromise of white matter pathways could also serve to disrupt the functioning of one or all three of these pathways.

Basal Ganglia and the Thalamus and Cognition

Stroke confined to the basal ganglia has been demonstrated to impact cognitive function in almost all domains assessed *(33)*. The basal ganglia nuclei have been extensively studied in their role in movement. Lesions of basal ganglia nuclei result in alterations in muscle tone, abnormal movements, ideomotor apraxia, reduced spontaneous movement, and slowing of movements. Recently, interest has focused on the role of the basal ganglia in larger neural networks including those involving cognition, emotion, and behavior. These studies have implicated the basal ganglia in mood regulation, goal-directed behavior, and higher order cognitive function *(34–36)*. The basal ganglia also have a relationship with core limbic structures including the hippocampus and amygdala that are critical to drive-related
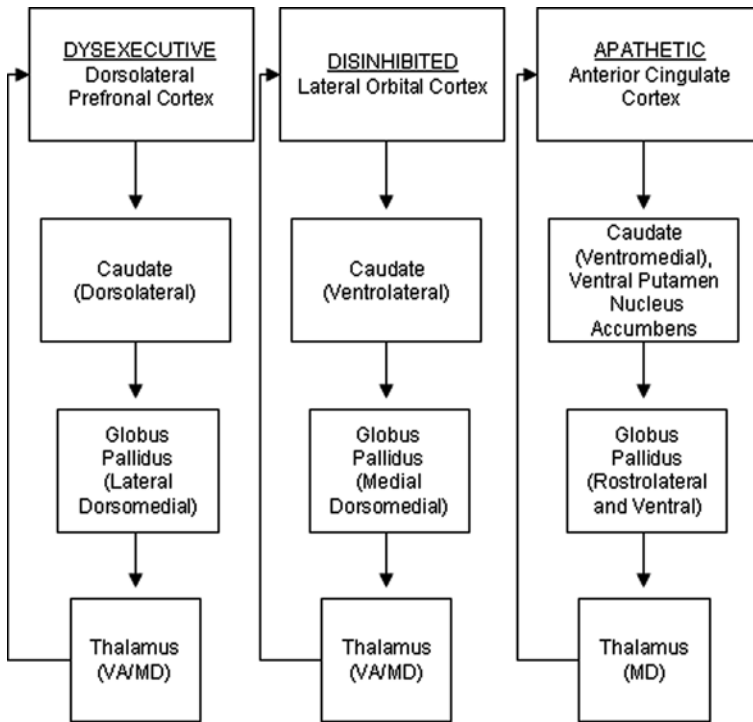
Fig. 1. Frontal–subcortical circuits.

behaviors associated with reward and reinforcement. The extent of direct and reciprocal connections suggests that the basal ganglia facilitate the integration of complex affective, social, and cognitive processes, and thereby influence the affective or motivational salience of the input reaching the prefrontal systems *(32,37–40)*.

Consistent evidence supports the role of the basal ganglia in many cognitive functions including implicit or procedural memory, motor learning, sequencing, stimulus-response based learning, and attention *(34,41)*. Other studies have focused on the basal ganglia's contribution to higher-order cognitive function including working memory *(42–44)*, response inhibition, response generation, and cognitive flexibility *(41,45)*.

The thalamus is comprised of many functionally distinct nuclei involved in many parallel and reciprocal cortical–subcortical neural loops. The thalamus exists as an important relay station with rich connections to the basal ganglia and frontal lobes. Individual thalamic nuclei have been demonstrated to be involved in many cognitive functions including language, memory, response inhibition, working memory, and attention *(46–48)*.

The thalamus receives its blood supply from several vessels. Specific nuclei and various neurobehavioral syndromes often are observed following strategic infarcts confined to these vessels. The paramedian thalamic artery arises from the basiliar artery and often supplies bilateral anteromedial regions involved in memory systems, specifically the mediodorsal nucleus of the thalamus. Bilateral infarction of the distribution of the paramedian thalamic artery is not surprisingly associated with a dementia syndrome *(49)* and may also present with personality changes including apathy, disinhibition, and psychosis *(50)*. As the principle target of output for basal ganglia and thalamus is the frontal lobes, localized lesions

in these regions result in widespread disruption of frontal–striatal circuits. Carrera et al. *(51)* examined 71 patients with MRI documented stroke confined to four "classic" thalamic territories and compared each on tests of cognition. The authors detailed that patients with strokes confined to three of the classic territories, the anterior, paramedian, and inferolateral, all demonstrate some degree of cognitive impairment, most consistently in areas related to executive functions. Deficits in verbal fluency, initiation, and anterograde memory with better recognition performance were observed in patients with anteromedian territory involvement. As such, the cognitive changes usually observed in patients with subcortical white matter hyperintensities and/or lacunar infarctions resemble a frontal–subcortical disconnection syndrome.

SMALL VESSEL DISEASE AND MOOD

While poststroke depression is a commonly reported finding after large vessel stroke and subcortical lacunes *(52)*, the data on the relationship between SVD and vascular depression are mixed *(53,54)*. The research which does support a relationship reports very modest effects. O'Brien et al. *(55)* found that in a group of nondisabled elderly subjects, while basal ganglia lacunes showed weak correlation with objective measure of depression, WMH have a greater influence on depressive symptoms than infarcts. Critical to note here is that depressive *symptoms* versus a depressive *syndrome* are associated with WMH. Turning again to the basal ganglia lesion literature, in individuals with basal ganglia dysfunction, one often observes apathy, loss of motivation and diminished spontaneity, reduced verbal output, paucity of facial expression, diminished motor behavior, and increased response latency *(37,39)*. These symptoms are observed in depression, but are not always indicative of a depressive episode *(56)*. Given the psychiatric changes associated with frontal–subcortical disruption, especially the medial frontal system, it is likely that individuals who present with depression actually demonstrate abulia, anhedonia, or other forms of mood dysregulation versus a frank depression.

HYPERTENSION AND COGNITIVE DYSFUNCTION

NHANES (2003–2006) *(57)* reports that hypertension prevalence is 70.6% in individuals aged 65 and older. Hypertension and small vessel disease are long-established risk factors for stroke and vascular dementia (VaD) *(58)*. It is also well documented that lowering blood pressure in hypertensive patients decreases the risk of stroke and cerebral white matter disease *(12)*. It is less clear if lowering blood pressure will have similar protective effects on cognition and the prevention of dementia. Research suggests that the relationship between hypertension and cognition is not linear. Beyond hypertension-specific variables (i.e., how well hypertension is controlled, duration, systolic blood pressure (SBP)/diastolic blood pressure (DBP) level), other determinants such as age and ApoE4 allele status play a role in the development and extent of subcortical white matter lesions *(12)* and possibly cognitive decline.

Qiu et al. *(59)* and Birns and Kalra *(16)* provide a meticulous review of cross-sectional observational studies, longitudinal studies, and randomized clinical trials examining the relationship between hypertension, cognitive decline, and dementia. We refer the reader to these reviews for detailed overview of the studies. As mentioned earlier, some of this

research is limited by an overreliance on the MMSE as a primary outcome measure which is prone to lack sensitivity to white matter compromise (i.e., executive dysfunction, decreased psychomotor processing speed). As such, we will only briefly discuss those studies which include domain-specific cognitive outcome measures.

Cross-Sectional Studies

Significant research has been dedicated to exploring the relationship between hypertension and cognitive change. However, the findings are often mixed. Differences in the reported impact of hypertension on specific domains of cognitive functioning are complicated by differences in methodology such as the definition of hypertension, marker of hypertension (e.g., SBP versus DBP), cognitive domains assessed, sample variables (i.e., age, gender, race), treatment with antihypertensives (e.g., yes or no, specific type of medication), and presence of comorbid conditions or other risk factors for cognitive decline. Cross-sectional studies using outcome measures more sensitive to white matter changes (and presumably changes associated with elevated blood pressure) have inconsistently demonstrated a relationship between elevated blood pressure and cognitive decline and dementia *(60–63)*.

Approximately 20 cross-sectional studies examining the effects of hypertension on domain-specific cognitive measures have been conducted. Hypertension at an earlier age, of more chronic duration, and if poorly controlled tends to adopt a linear, inverted "U"-shaped *(64,65)* or "J"-shaped *(66)* relationship with cognition. Hypertension has been demonstrated to adversely impact simple attention *(67,68)*, executive function *(66,68)*, and psychomotor speed *(66,68–71)*. Thus, the cognitive domains impacted (i.e., executive functions, processing speed) are similar to those affected in patients with cerebral white matter disease and VCI. There are other cross-sectional studies with detailed neuropsychological batteries which report no relationship with hypertension and cognition *(72–74)*. Some argue that age effects contribute to these conflicting findings. Qiu et al. *(59)*, in their review of this literature, offer a plausible hypothesis in that a certain level of blood pressure is necessary to support cognitive functions. Additionally, low blood pressure in the elderly could in itself serve as a marker for cognitive impairment. Longitudinal studies appear to offer more insight into the impact of hypertension on cognition.

Longitudinal Observational Studies

Despite methodological differences, in longitudinal studies with detailed neuropsychological batteries, the research demonstrates that mid-life hypertension increases the risk for cognitive dysfunction later in life. Birns and Kalra *(16)* review 22 longitudinal studies, 15 of which include domain-specific cognitive measures. Indeed, all 22 studies report a relationship with cognitive dysfunction and chronic hypertension. Across 15 studies, the specific cognitive domains vulnerable to the effects of chronic hypertension are executive functions *(68,75)*, attention *(76)*, psychomotor speed *(77)*, and verbal memory *(75)*. However, interpretation of many longitudinal studies is complicated by the various forms of antihypertensive treatments, many of which appear to have differential impact on remediating or preventing further cognitive decline.

Using data from the Honolulu Asia Aging Study, Peila et al. *(78)* examined the cognitive performance of hypertensive middle-aged cognitively intact men at three time periods over

a total of 12 years. The authors found that for normotensive patients and for patients being treated with antihypertensives, there was less cognitive decline compared to patients who were never treated for hypertension as assessed using the Cognitive Abilities Screening Instrument (CASI). Moreover, for each year of treatment with antihypertensives, there was a reduction in the risk of incident dementia. Murray et al. *(79)* conducted a longitudinal analysis of the effects of antihypertensive medications on cognition in 1,617 cognitively intact African-American participants over three time periods; baseline, 2 years and 5 years. They found that antihypertensive medication reduced the odds of demonstrating cognitive impairment by 38% compared to individuals who did not use medication. In participants with uncontrolled hypertension who did not use medication, incident cognitive impairment was 6% higher compared to participants with controlled blood pressure who were continuously taking medication.

Randomized Placebo-Controlled Clinical Trials

Hypertension, diabetes, and advancing age are strong risk factors for dementia. Lowering blood pressure has been demonstrated to reduce stroke risk, but it is less clear if lowering blood pressure can reduce white matter disease burden and affect any changes in cognition. While the relationship of hypertension and cognitive decline is likely multifactorial, given the social and economic burden associated with cognitive impairment and dementia, recent investigations have focused on treatment of hypertension to prevent further or later cognitive decline. Birns and Kalra *(16)* detail eight studies focusing on the effects of antihypertensives on cognition. Again the findings across trials are mixed. It would appear that lowering blood pressure with various therapeutic agents does not appear to impair cognition, but there is also less overwhelming evidence that reducing blood pressure improves cognition or prevents dementia. Figure 2 summarizes these findings. Those studies which do support a positive association with antihypertensive treatment and cognition suggest that the effect may depend on the type of antihypertensive drug used (e.g., calcium channel blocker, diuretic, angiotensin receptor antagonist) and the benefits appear in areas of global functioning as measured by the MMSE versus exerting significant effects in individual cognitive domains. In studies with more rigorous outcome measures, it appears that ACE inhibitors and calcium channel blockers are associated with less deleterious effects on cognitive function than other medications such as thiazide, which may have sedating effects.

In a study of 2,902 nondemented patients, patients were randomized to antihypertensive treatment with nitrendipine with possible additional enalapril malteate and hydrochlorothiazide versus no medication. Forette et al. *(80)* in the extended follow-up of the Systolic Hypertension in Europe (Syst-Eur) trial found that the incidence of dementia was reduced by 55% in the treatment group. While the authors originally hypothesized that antihypertensives would reduce the risk of vascular dementia (VaD), the follow-up study found that the incidence of dementia was reduced for all dementia subtypes (predominantly Alzheimer's disease), which the authors offered may reflect the protective benefits of calcium channel blockers on the shared pathology of AD, VaD, and mixed presentations.

A secondary analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) study endeavored to determine if lowering blood pressure would reduce the risk of dementia and cognitive decline among individuals with cerebrovascular

Type of Agent	Impact on Cognitive Outcome Variable			Domain Specific
	Positive Impact	Negative Impact	No Significant Impact on Cognitive Function	
ACE inhibitor	(82)		(86)	
alpha−agonist hypotensive		(85)		Increased processing speed/reaction time on vigilance task (i.e., sedating)
alpha−blocker			(87)	
angiotensin receptor blocker			(83)	
beta−blocker			(80, 81, 86, 87)	
calcium channel blocker	(84, 85)			Increased vigilance/attention (i.e., alerting) [85]
thiazide diuretic	(84)	(86, 87)	(80, 81)	

Fig. 2. Studies examining effects of antihypertensives on cognitive outcome.

disease *(81)*. The study included 6,105 participants with a history of TIA or ischemic stroke in a randomized double-blind, placebo-controlled study. Cognitive decline was assessed at baseline, 6-month, 12-month, and annually using the Mini Mental State Examination (MMSE), with decline being a reduction of three or more points between two visits. Active treatment reduced the risk of "cognitive decline with recurrent stroke" by 19% and risk of developing dementia by 31% in participants with no cognitive impairment at the baseline assessment. However, active treatment did not appear to impact participants classified as cognitively impaired at the outset of the study. The authors concluded that the benefits of treatment are primarily the consequence of stroke prevention than a direct effect on dementia or cognitive decline. A follow-up substudy comprised of 192 individuals who had a baseline and follow-up (mean duration 36 months) MRI supported this conclusion as the risk of developing new WMH was reduced by 43% in the active treatment group *(82)*.

Skoog et al. *(14)* in the Study on Cognition and Prognosis in the Elderly (SCOPE) examined the effects of antihypertensives on cognition as measured by MMSE in a randomized placebo-controlled study of 4,937 patients aged 70–89 years with mild to moderate hypertension followed over the course of 3–5 years. This study compared subjects with slightly lower baseline MMSE scores to those with higher scores. Despite a reduction in blood pressure, individuals with lower cognitive functioning scores at baseline were at a higher risk of significant cognitive decline and dementia.

In the Systolic Hypertension in the Elderly Program (SHEP) trial (1985–1990), the original findings did not support that treatment with antihypertensives had any benefit on cognition. The original study compared the incidence of cognitive decline between participants receiving low-dose diuretic and/or β (beta)-blocker and those who received a placebo. Di Bari et al. *(83)* reexamined the findings after considering the rates of differential

dropout in the groups. In the original SHEP trial, 4,736 participants with isolated systolic hypertension were randomized to active treatment or placebo and followed over 5 years. All participants were administered the short Comprehensive Assessment and Referral Evaluation and dementia score was determined based on performance on the cognitive component score and their reported basic activities of daily living. When the authors examined the dropout rates, they determined that individuals with a high number of nonfatal cardiovascular events were more likely to drop out. The authors concluded that only the healthiest subjects in both groups returned for follow-up cognitive assessment, which may have attenuated the recognition of a benefit of antihypertensives on cognition.

Conclusions

The relationship between cerebral small vessel disease, hypertension, and cognitive functioning is complex. What is clear is that WMH on MRI are not "benign" insignificant incidental findings. Just as these serve as markers for cerebrovascular disease and increased risk for stroke, the cumulative impact of WMH and poorly controlled hypertension raises the risk for cognitive deterioration, dementia, and mood and behavior disturbance due to frontal–subcortical disconnection. It is less clear, however, what treatment can be used to preserve cognitive functioning or to prevent cognitive decline or behavioral change. Given this clinical equipoise, results of additional well-designed clinical trials of blood pressure lowering in those at risk of cognitive decline or dementia are needed to guide clinicians in the treatment of these patients.

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14 Cerebral Microbleeds, Small-Vessel Disease of the Brain, Hypertension, and Cognition

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CONTENTS

INTRODUCTION

Cerebral microbleeds (CMB) have been increasingly recognized on neuroimaging since the widespread application of magnetic resonance imaging (MRI) techniques tailored to detect foci of magnetic susceptibility. CMB are most often clinically asymptomatic and are a result of rupture of small blood vessels in basal ganglia or subcortical white matter *(1–4)*.

CMB were first described after the clinical use of gradient-echo (GRE) or T2*-weighted MRI *(1,5,6)*. GRE MRI is a technique highly sensitive in the detection of old and recent cerebral hemorrhage *(1,6)*. The reduction of the signal on GRE sequences is caused by hemosiderin, a blood breakdown product which causes magnetic susceptibility-induced dephasing leading to T2* signal loss. CMB appear larger on GRE sequences as compared to the actual tissue lesions because of the so-called "blooming effect" of the MR signal

at the border of these lesions *(7,8)*. GRE MRI can detect millimeter-sized paramagnetic blood products (including hemosiderin) in brain parenchyma *(9)*. As hemosiderin remains in macrophages for many years after hemorrhage *(10,11)*, GRE sequences allow for reliable assessment of an individual's hemorrhagic burden over time. Furthermore, more recent technical advances in MRI software and hardware have yielded significant improvements in sensitivity, which has led to increased detection of CMB in different populations *(12–15)*. Novel techniques such as susceptibility-weighted imaging (SWI) have considerably increased CMB detection rates *(13)*.

CMB are defined as small rounded foci which appear hypointense and distinct from vascular flow voids, leptomeningeal hemasiderosis, or nonhemorrhagic subcortical mineralization *(1,16)* (Fig. 1). Choice of precisely sized parameters does not appear to have a major effect on CMB detection *(2)*.

Radiopathologic studies have demonstrated that these areas of GRE hypointensity correlate well with brain parenchymal areas of hemosiderin-laden macrophages *(1,8,17)*. These pathologic data suggest that CMB result from specific underlying small-vessel pathologies such as hypertensive vasculopathy *(18)*, cerebral amyloid angiopathy (CAA) *(19–21)*, or cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) *(22–25)*. Their presence and number may also reflect the severity of these small-vessel pathologies and thus predict clinical outcome (including risk of dementia and cognitive decline) in these diseases.

In this chapter, we discuss the pathophysiology, prevalence, and risk factors for CMB in different populations. We also discuss the potential clinical implications of CMB in relation to cognition and disability in individuals harboring these lesions.
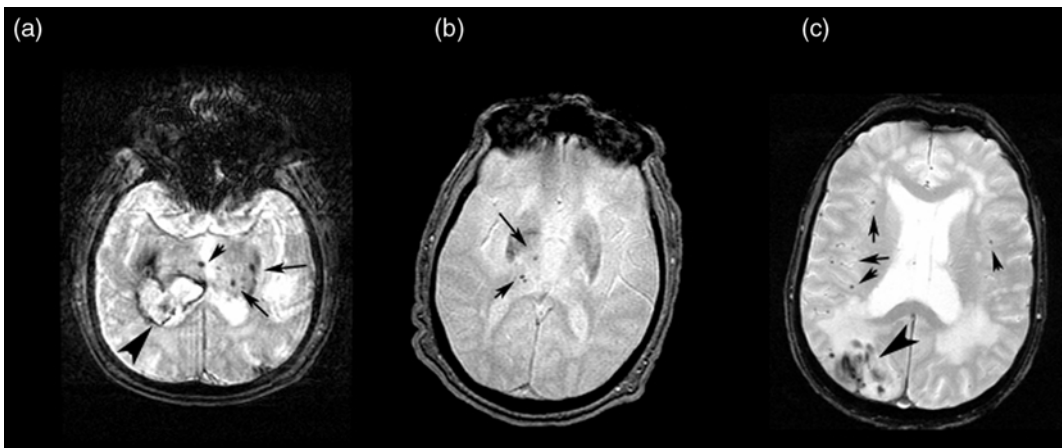
Fig. 1. Examples of CMB in different populations. Gradient-echo MRI sequences **a** in a patient with long-standing history of hypertension with deep intracerebral hemorrhage (*large arrowhead*). This patient also has CMB in contralateral deep structures including the thalamus (*arrows*). **b** In a patient with CADASIL. Multiple CMB are seen in the thalamus a common location for CMB in CADASIL. **c** In a patient with probable CAA demonstrating a parietal lobar intracerebral hemorrhage (*large arrowhead*) and numerous CMB in the frontal lobe (*arrows*).

CEREBRAL MICROBLEEDS IN SPECIFIC CEREBRAL SMALL-VESSEL DISEASES

Cerebral Microbleeds in Hypertension-Related Vasculopathy and Cerebrovascular Disease

Evidence suggests that cerebral microbleeds are common in patients with hypertension-related cerebral vasculopathy, although few studies have restricted analyses exclusively to this group *(26)*. Recently, in a small study, Copenhaver et al. evaluated microbleeds in black patients with ICH (a high proportion having hypertension). Compared to white subjects, black subjects had greater number of microbleeds in multiple territories and 93% had hypertension compared to 62% of white subjects *(26)*.

Elevated blood pressure is common in patients with cerebrovascular disease and incidence of stroke rises with increasing blood pressure levels *(27,28)*. The reported prevalence of CMB in these populations is highly variable (range 18–68%) *(29–35)*. This is likely due to limitations surrounding many of these studies, including nonselective clinical criteria, inclusion of multiple stroke subtypes, and variable size-based definition of microbleeds.

Chronic blood pressure elevation may increase an individual's risk for CMB. In order to investigate this, Lee et al. evaluated the relationship between CMB and cardiac damage induced by chronic hypertension. Left ventricular hypertrophy was evaluated in 102 consecutive survivors of acute stroke (72 with ischemic stroke, 30 with ICH) *(35)*. Left ventricular mass index was measured by transthoracic echocardiography. Cerebral microbleeds were detected in 64% of patients. In multivariable analysis, history of previous stroke and the number of CMB were associated with left ventricular hypertrophy, suggesting that poorly controlled blood pressure may increase the number of CMB.

Cerebral microbleeds have been well described in patients with ICH *(6,10,16,17,36,37)*. The presence of CMB has been shown to be nearly tenfold more common in this population than in healthy elderly *(36)*. Several studies examining patients presenting with primary ICH (deep and lobar) have reported prevalence of CMB to range between 54 and 70%, with the majority of subjects having multiple CMB *(36,38)*. Individuals with CMB were more likely to be hypertensive, have a previous history of stroke, have more lacunar infarcts, and more extensive white matter lesions. Roob et al. found there to be a correlation between cerebral microbleed distribution and the location of primary ICH. Individuals with deep ICH tended to have CMB in the basal ganglia and thalamus as compared to individuals with lobar ICH.

Cerebral Microbleeds in CAA

Cerebral microbleeds have been extensively studied in CAA *(10,14,16,39,40)*, the disease which accounts for the majority of primary lobar ICH in the elderly *(41)*. The Boston criteria are a set of validated criteria and have been established to identify those lobar ICHs caused by CAA *(41)*. The presence of multiple, strictly lobar hemorrhages (including microbleeds) detected by gradient-echo MRI sequences has been shown to be highly specific for severe CAA in elderly patients with no other definite cause of ICH (termed *probable* CAA-related ICH) *(41)*. These criteria have been compared against the established gold standard of CAA, examination of histologic specimens from autopsy, hematoma evacuation, or cortical biopsy *(41)*. Thirty-nine primary lobar ICH patients aged ≥55 years

with available pathologic tissue were diagnosed on clinical and radiologic grounds with possible or probable CAA. Thirteen patients were diagnosed with probable CAA, and all demonstrated pathological evidence of CAA in cerebral blood vessels. Eleven of these patients underwent GRE imaging, and 73% showed evidence of multiple hemorrhagic lesions, including microbleeds. Sixteen of 26 patients (63%) with the diagnosis of possible CAA (single lobar macro or microhemorrhage) demonstrated pathologic evidence of CAA. Interestingly, in patients with probable or possible CAA there was no association between number of microbleeds and age, sex, APOE genotype, or other vascular risk factors including hypertension, coronary artery disease, diabetes, or previous stroke *(16)*.

The distribution of microbleeds in CAA shows a posterior cortical predominance *(42)*, as has been reported previously in lobar macrohemorrhages *(43,44)*. In 59 patients with probable CAA, microbleeds occurred more frequently in the temporal and occipital lobes when taking into account the relative size of each lobe *(42)*. The lesions also tended to cluster in the same lobe in subjects with multiple lesions. The distribution of new microhemorrhages at follow-up correlated with the distribution of baseline microbleeds *(42)*. Finally, in those patients who experience recurrent lobar ICH, the location of the hematoma is positively associated with the distribution of baseline microbleeds *(16)*. This is supported by pathologic data which show that CAA pathology favors the posterior cortical regions, particularly the occipital lobe *(45,46)*.

Cerebral Microbleeds in CADASIL

In patients with CADASIL the reported frequency of microbleeds has ranged from 25 to 69%, with one large prospective cohort study finding that CMB occur in approximately 35% of patients with the disease *(22–25)*. The main clinical manifestations of CADASIL include attacks of migraine with aura, mood disturbances, recurrent ischemic strokes, and progressive cognitive decline *(47)*. In various studies, CMB were most commonly found in the thalamus, subcortical white matter, basal ganglia, and brainstem *(22–24)*. There is minimal overlap between regions of CMB and regions of lacunar infarction or prominent WMH in CADASIL *(22,23)*.

Dichgans et al. performed a pathological examination of CMB in CADASIL. The investigators examined seven autopsy cases of CADASIL and found evidence of hemosiderin-laden macrophages in six out of seven cases *(23)*. In all cases, macrophages were found in the vicinity of 100–300 μm blood vessels which showed characteristic degenerative changes of CADASIL. There was no evidence of amyloid deposition or vascular malformations supporting the involvement of CADASIL-related ultrastructural modifications of the vessel wall in these lesions.

An ongoing two-center prospective cohort study has investigated risk factors for CMB and the impact of CMB on clinical outcome in CADASIL *(22)*. The study showed that CMB are independently associated with blood pressure levels and HbA1c. The number of CMB was also associated with lacunar infarct volume and extent of WMH. CMB were found to be an independent predictor of neurologic disability.

Until recently, blood pressure had not been thought to play a significant role in the pathophysiology of genetic small-vessel diseases *(23,24,48)*. In the above-described CADASIL study, CMB were independently associated with blood pressure levels. However, the average blood pressure values in subjects with CMB and in those without were found to be in the

normal range (<140/90). When hypertensive patients (those individuals with blood pressure >140/90) were removed from the analysis, the association between CMB and blood pressure remained highly significant *(22)*. This suggests that small increases in blood pressure may contribute to CMB in CADASIL through an additive effect on the ultrastructural vessel wall modifications caused by Notch3 mutations *(23,49)*. Further studies are needed to determine which factors (pulsatility, cerebrovascular resistance, or vessel wall stiffness) most strongly influence the rupture of the cerebral microvessel wall in the setting of CADASIL and moderate elevations of blood pressure. Acceptable blood pressure values in the setting of an existent cerebral microangiopathy may well differ from established normal ranges recommended for the general population.

SPECIALIZED METHODS FOR IMPROVED DETECTION OF CEREBRAL MICROBLEEDS

A variety of MRI factors (including sequence parameters, spatial resolution, magnetic field strength, and postprocessing techniques) can lead to improved CMB detection *(39)*. For example, application of 3D T2*-weighted MRI at submillimeter spatial resolution has recently been shown to detect more CMB when compared to conventional 2D GRE at lower resolution *(50)*. Another study found that individual CMB identified in CAA subjects had approximately double the contrast index (a measure of conspicuity) when imaged with 1.5 mm slices compared to 5 mm slices *(14)*.

MICROBLEEDS IN POPULATION-BASED STUDIES: THE ROLE OF LOCATION

Cerebral microbleeds have been noted in numerous healthy populations *(15,51–55)*. Most *(15,51–54)* but not all *(55,56)* of these studies show hypertension to be a risk factor for CMB. Results from a recent pooled analyses of these studies demonstrated an increased risk of CMB in subjects with hypertension (OR 3.9, 95% CI 2.4–6.4) *(4)*. Overall, these investigators also found an increased risk of CMB with diabetes in these populations (OR 2.2, 95% CI 1.2–4.2) *(4)*. These studies were not able to distinguish the risk associated with specific location of CMB (lobar versus deep CMB).

However, more recent population-based studies from the Rotterdam *(15)* and the AGES-Reykjavik studies *(56)* provide further evidence to support a potential etiologic distinction between lobar and deep CMB. In the Rotterdam study, Vernooij et al. demonstrated that APOE ε4 carriers more often had strictly lobar CMB than noncarriers. In contrast, cardio-vascular risk factors (including elevated systolic blood pressure) and presence of lacunes and white matter lesions were associated with CMB in deep, but not lobar, locations. The study included 1,062 subjects with a mean age of 69.6 years. In this study, rates of CMB were increased compared to prior studies (ranging from 17.8 to 38.3%). The higher prevalence of CMB compared to previous studies is likely due to both the higher mean age of the cohort (69.6 years) and the study's use of specialized high-resolution GRE sequences. In the AGES-Reykjavik study (1,962 subjects with a mean age of 76 years), 61% had CMB located in the cerebral lobes and greater than a third were located in posterior regions (parietal or occipital lobes), a pattern suggestive of CAA *(42)*. Furthermore, APOE ε4ε4 genotype was associated with increased likelihood of having a cerebral microbleed.

To summarize, there are several lines of evidence supporting the hypothesis that CMB in strictly lobar locations are due primarily to CAA and those involving deep hemispheric or brainstem structures are due primarily to hypertension-related vasculopathy. Therefore, CMB in strictly lobar locations may be a result of underlying subclinical CAA pathology and not related to traditional cardiovascular risk factors such as hypertension. These findings are consistent with previous studies in CAA which demonstrate that hypertension and other vascular risk factors are not associated with the number of CMB. In addition, vascular risk factors do not seem to independently influence outcome *(16)*. Finally, the association between strictly lobar CMB and the APOE ε4 allele in the above population-based studies is consistent with previous studies which demonstrate this association in subjects with probable or possible CAA *(57)*. By contrast, CMB located in deep regions (such as the basal ganglia or thalamus) are associated with high systolic blood pressure and wider pulse pressures. CMB in deep locations were not associated with APOE genotype *(15)*.

This hypothesis is further supported by histopathologic studies which examine CMB and associated vascular pathologies *(1,17,41)*. In these studies, CMB associated with hypertensive vasculopathy more commonly occurred in basal ganglia, thalamus, brainstem, and cerebellum *(1)*, whereas CAA-associated CMB had a lobar (or less commonly, cerebellar) distribution *(41)*.

CEREBRAL MICROBLEEDS AND CLINICAL IMPAIRMENT

In addition to the potential role of CMB as markers of specific small-vessel disease, they may also have direct effects on cognition and disability. Neuropathological studies demonstrate tissue damage associated with CMB *(17,41,58)*, thus providing a potential mechanism for clinical impairment.

Microbleeds in CAA have been shown to be related to disease progression, recurrent ICH, and CAA-related clinical impairment *(16,59)*. Microbleeds are more common than macrohemorrhages and tend to accumulate over time. Greenberg and colleagues evaluated 94 elderly patients (≥ 55 years) presenting with lobar ICH for a number of baseline hemorrhages *(16)*. Among those patients who underwent MRI 16-months later, 50% experienced new, frequently multiple microbleeds. Predictors of new microbleeds included larger number of hemorrhages at baseline and the presence of the APOE ε2 or ε4 allele. Both the number of hemorrhages at baseline and the number of new microbleeds at follow-up were associated with increased risk of recurrent hemorrhage (3-year cumulative risk 14%, 17%, 38%, and 51% in subjects with 1, 2, 3–5, or ≥ 6 baseline hemorrhages, respectively). In individuals with cognitive impairment there was a trend toward increased number of baseline hemorrhages. Finally, the incidence of cognitive impairment, functional dependence or death at follow-up was increased by the number of hemorrhages at baseline (mean 27.9 months, HR 1.9, 95% CI 1.2–2.8 for each increase in category of baseline hemorrhages).

CMB have also been associated with clinical disability in CADASIL *(22,60)*. In a two-center cohort study of 147 patients with CADASIL, the number of CMB was independently associated with functional dependence (defined as modified Rankin score ≥3), with an odds ratio per additional microbleed of 1.16 (95% CI 1.01–1.34, $p = 0.034$) after adjustment for other confounding variables *(22)*. However, multivariable analysis did not demonstrate that the overall burden of CMB was associated with cognitive function.

For patients with cerebrovascular disease, a small case-control study of patients with ischemic stroke or TIA found that individuals with CMB performed significantly worse than those without them on standard tests of executive function *(61)*.

Finally, CMB may have an impact on mortality in patients with cognitive impairment or dementia. A large longitudinal study has recently demonstrated that CMB were the strongest predictor of mortality in a memory clinic population (HR $= 1.5$, 95% CI 1.1–2.0) *(62)*. This may suggest that CMB vascular pathology acts in synergy with neurodegenerative mechanisms associated with Alzheimer's disease to increase mortality in these patients.

If CMB have direct effects on brain function rather than simply marking the presence of other cerebrovascular pathologies, one would expect the location of CMB to play a role. In analyses of the two-center CADASIL cohort, CMB in the caudate were independently associated with lower global cognitive scores (based on the Mattis dementia rating scale; $p = 0.027$), and CMB in the frontal lobes showed a trend toward lower global cognitive scores ($p = 0.056$) *(60)*. Similarly, a small study of stroke or TIA patients suggested CMB in the frontal lobes and basal ganglia were associated with executive dysfunction *(61)*. These findings need further confirmation in large well-controlled studies of different populations including in individuals without prior stroke.

MICROBLEEDS, HYPERTENSION, AND COGNITION

Hypertension has been established as a risk factor for cognitive impairment and dementia in numerous studies. An association between high blood pressure and the risk of Alzheimer's disease was also reported in cohort studies with a 15–21-year long follow-up *(63,64)*. Furthermore, the presence of hypertension has been shown to be associated with a
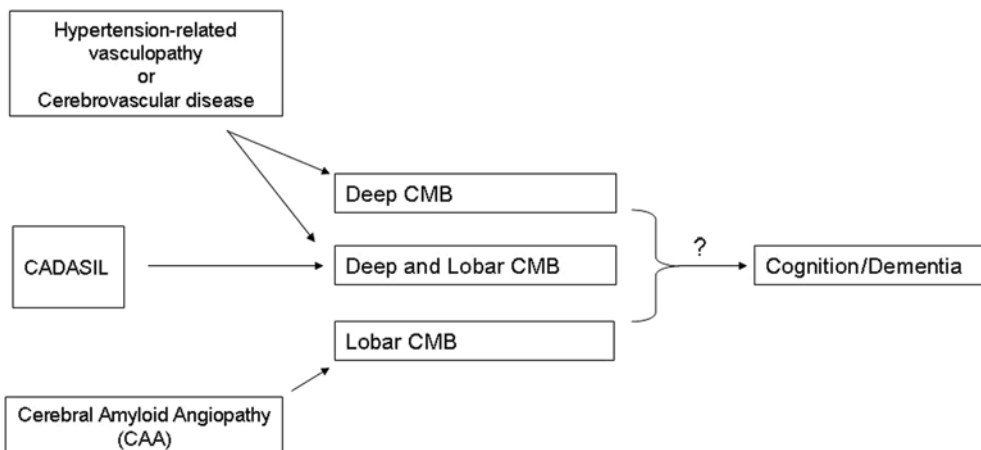
Fig. 2. The influence of cerebrovascular pathology on CMB location and its relationship to cognition. As depicted in the diagram, small-vessel diseases such as hypertension-related vasculopathy, cerebral amyloid angiopathy, and CADASIL can predispose an individual to developing CMB. Hypertension-related vasculopathy most commonly leads to development of CMB in deep areas, while cerebral amyloid angiopathy predisposes individuals to lobar CMB. In CADASIL, CMB develop in both deep and lobar locations (see text for details). CMB: cerebral microbleeds.

greater rate of cognitive decline in patients with Alzheimer's disease *(65)*. Finally, higher blood pressures have been associated with greater cognitive decline in patients after stroke in the PROGRESS trial *(66)*. There is some suggestion that the blood pressure effect may be related to attenuation of progression of white matter hyperintensities or brain atrophy *(67–69)*. Whether the influence of hypertension on cognition is mediated, at least in part, through CMB has not been investigated (Fig. *2*).

Future therapeutic trials should examine the specific effects of blood pressure reduction on cerebral microbleed burden to more precisely define the relationship between hypertension, CMB, and cognition. Studies such as these should help define the clinical impact of CMB and consequently influence future treatment decisions in individuals harboring these lesions.

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15 Imaging Effects of Hypertension on the Brain: A Focus on New Imaging Modalities and Options

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CONTENTS

INTRODUCTION

Recent developments in neuroimaging have allowed better qualification and quantification of the effects of hypertension (HTN) on the brain in vivo. Although magnetic resonance imaging (MRI) is generally recognized to be the most sensitive imaging modality to the effects of HTN, computerized tomography (CT), positron emission tomography (PET), and single photon emission tomography (SPECT) still provide useful information in many circumstances. CT is the most prevalent imaging modality used throughout the world due to both its availability and relatively low cost. The recent introduction of multislice rapid CT scanners has increased its sensitivity to many of the effects of HTN on the brain, and it has reinvigorated interest in the use of CT not only for clinical assessment but also in basic and applied clinical research. Similarly, there has been an increase in the use of PET to characterize the metabolic effects of HTN with the relatively recent advances and use of 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) PET (FDG-PET). The purpose of the current chapter is to describe the advances in CT, MRI, and PET for characterizing these effects on the brain.

Effects of Hypertension on the Brain

The effects of HTN on brain structure and function can be grouped into three primary categories including (1) primary and secondary effects of HTN on cerebral vasculature, (2) primary and secondary effects of HTN on cerebral tissue integrity, and (3) secondary effects of HTN on brain metabolism and function. Although detailed discussions of the effects of HTN on each of these domains can be found in Chapters 4, 5, and 14, we briefly review each of these effects to provide the framework for the description of advances in neuroimaging.

Effects of Hypertension on Cerebral Vasculature

HTN has direct and substantial effects on cerebral vasculature. These effects include increased thickness of the arterial wall in the small arteries and atherosclerosis in large vessels. However, gross cerebral blood flow in hypertensive patients is relatively unchanged due to autoregulation of cerebral blood flow (except in cases of long term uncontrolled HTN). Although at a macro level the total cerebral blood flow does not change, more specific and quantitative analyses of regional cerebral blood flow (as compared to whole-brain flow) demonstrate significant effects of HTN including increases in velocity within major arteries as well as hypoperfusion in frontal *(1)*, temporal *(1)*, subcortical, and limbic regions *(2)*. Relatively recent developments in imaging capabilities that allow assessment of the integrity of vessels and arteries include computerized tomography angiography (CTA) and CT perfusion (CTP) using rapid multislice CT systems, as well as magnetic resonance angiography (MRA) and MR perfusion. The technological developments and increased accessibility of high-field MRI systems (3-T and above) have dramatically increased the effectiveness and sensitivity of both MRA and MR Perfusion to the effects of HTN on local vasculature.

Effects of Hypertension on Cerebral Tissue Integrity

HTN is associated with large- and small-territory infarcts, rarefaction of white matter, severe white matter disease, and cerebral atrophy *(3,4)*. The most familiar and dramatic effects of HTN are infarcts which can be quantified and imaged with standard CT and MRI. The sensitivity of CT to characterize the lesions is limited when the infarct is small or when there are diffuse or small lesions. In these cases, MRI is the modality of choice with the ability to differentiate and quantify the involved vascular territory, assess the presence of compromised tissue perfusion, and distinguish between the infarct and surrounding tissue.

In addition, hypertension can be associated with dramatic changes in tissue integrity beyond the clearly defined infarct. These changes include white matter disease, global and local effects on gray and white matter volume, and integrity of white matter in the absence or in addition to lesions. In terms of atrophy of cerebral tissue, HTN interacts significantly with age. The greatest reductions in brain volume are generally observed in the 5th to 9th decades of life *(5)*. Uncontrolled HTN may also preferentially affect thalamus volume with trends for reduced volume in parietal and temporal lobes as demonstrated in Table 1). The characterization of total and regional cerebral volume is most easily assessed using volumetric MR imaging. Volumetric imaging has been used for the last two decades and has since changed very little. The primary advances involve measurement using semiautomated algorithms and increased spatial resolution for differentiation of small structures.

Table 1
MRI Volumes Normalized to Total Cranial Volume of Hypertensive
Patients and Healthy Control Subjects

Regions	Control (n = 20)	Hypertensive (n = 27)
Thalamus	0.45 ± 0.11	0.385 ± 0.065
Parietal brain	8.82 ± 1.07	8.3 ± 0.825
Temporal brain	4.905 ± 0.445	4.845 ± 0.59

Values are mean $\pm$ SD in cm^3 expressed as a percentage of total cranial volume: $100 \times$ (structure volume/total cranial volume). Although the MR imaging technique used in this study demonstrated sensitivity for clearly defined brain regions, the spatial resolution and scanner signal strength at 0.5 T were low.

Adapted from Beason-Held et al. *(1)*.

HTN is also associated with reduced whole-brain fractional anisotropy (explained in detail in the section on diffusion tensor imaging), or integrity of white matter *(6,7)*, and an increase in hyperintense white matter lesions *(8,9)*. Reduced white matter integrity is especially seen in white matter lesions of the deep structures *(10,11)*, including both the thalamus and the caudate *(12)*. Whereas white matter lesions can be visualized and quantified using MRI sequences sensitive to changes in local water content, the integrity of white matter including the integrity of axonal bodies and myelin relies on the use of diffusion tensor imaging (DTI), which is most effective in higher field MR systems.

Effects of Hypertension on Cerebral Function and Metabolism

HTN is a major risk factor not only for stroke but also for development of dementia and cognitive impairment *(13–21)*. Uncontrolled HTN increases these risks *(18,19,22)*. Behaviorally, HTN is associated with cognitive slowing, memory impairments, deficits in executive function, and delayed memory *(23)*. Advances in functional neuroimaging (PET, SPECT, and functional MRI) allow the examination of the factors that underlie these behavioral changes.

COMPUTED TOMOGRAPHY

General Principles

Computed tomography (CT) imaging involves the use of rotating X-ray equipment. Multiple X-rays are beamed into the body and the strength of these beams is measured as they leave the body. In dense tissue or bone, the residual X-ray beam is weaker, whereas in less dense tissue the residual X-ray is stronger. Information on the strengths of the transmitted beams is used to construct images of tissue density. CT imaging has the unique ability to offer clear images of different types of tissue, such as soft tissue, bone, muscle, and blood vessels. At present, the major neurologic clinical application of CT is in acute stroke diagnosis, as CT is exceptionally sensitive to blood and blood products. In addition to standard CT, CT perfusion allows quantification and assessment of cerebral perfusion. Unlike standard CT, CT perfusion relies upon the repeated collection of a series of images to characterize the time–attenuation curves (TOC). In other words, CT perfusion is a change in

CT intensity (or Hounsfield Unit, HU) over time following a bolus of iodine-based contrast agent.

Uses in Assessment of the Effects of Hypertension

Beyond the use of CT for acute stroke assessment, hemorrhage, and presence of aneurysms, both CT perfusion (CTP) and CT angiography (CTA) have some, although limited, potential use in imaging the effects of HTN on tissue and vasculature.

CT Perfusion

CT perfusion is, and has been, an evolving technology. Standard CT is historically not sensitive to HTN or even ischemic change within 4–6 h of the ischemic event *(24)*. CTP, however, is sensitive to ischemic change almost immediately *(24)*. CTP, unlike standard structural CT imaging, provides quantitative measurements of the uptake time required for an intravenous contrast agent to infuse tissue and as such is sensitive to the effects of HTN. Quantitative measures of cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), and T_{max} (the time for maximum contrast perfusion) can be extracted. Generally, total cerebral blood volume (CBV) is insensitive to ischemic changes because autoregulation (except in extreme cases) measures of regional CBF are shown to be reduced in HTN *(25)*. Although very little has been investigated with regard to HTN in the absence of stroke, both TTP and T_{max} are accepted as sensitive measures of local tissue perfusion with predictive validity in stroke (relating to cognitive outcomes). T_{max} is likely the most sensitive as it examines tissue perfusion in a smaller spatial region than rCBF and is sensitive to both total perfusion and changes in the shape of the hemodynamic response.

CT Angiography

CTA is well established for evaluation of atherosclerotic disease of the extracranial carotid *(26)*, carotid wall thickness *(27)*, and in carotid stenosis *(28)*. However, its usefulness is limited for evaluation and quantification of intracranial plaque. This is potentially because it has yet to be evaluated with the newer, multidetector CT systems. The primary historic measures in evaluation of CTAs are visual rating scales. However, because of the increased sensitivity in new technology, more quantitative methods are becoming the standard in research studies and will likely become clinically popular as normative data are established. These quantitative measures generally focus on artery wall thickness *(27)*, amount of stenosis *(29)*, and surface shape irregularity *(29)*.

General Advantages

There are three primary advantages of CT over MRI. These include availability, speed, and cost. Virtually every hospital has at least one CT with many emergency departments at major medical centers also containing a CT machine. CT perfusion also has the advantage of short acquisition time. A standard CTP sequence adds only ∼5 min to any imaging protocol and requires a small volume of contrast media (∼50 mL). Similarly, CT angiography can also be added into a clinical protocol with very little increase in scan time (∼5 min) and, if performed following CTP, does not require any additional injection of contrast media.

General Disadvantages

Overall, for the structural and functional correlates of HTN, CT is less useful than MRI. This is especially the case in evaluation of hyperintense lesions common in patients with cerebrovascular risk factors but that require significant gray-white differentiation and tissue contrast to be visualized. Second, although CT is safer in patients who are either not MRI safe or unable to provide accurate information about MR safety, there is significant radiation exposure. Third, single-slice CTs used in CT perfusion provide limited coverage of brain tissue although the recent accessibility and availability of rapid multislice systems improve upon this. Finally, CTP values have significant variability over time. This variability is in part dependent upon the size as well as tissue heterogeneity of the imaged vascular territory *(30)*. As such, the change in tissue perfusion must be greater than the observed variability in CTP sensitivity. This latter concern limits the usefulness of CTP in the assessment of HTN without significant TIA or stroke. Also, a significant issue in the quantification of this method is the lack of normative volume data for CTP at present *(31)*.

MAGNETIC RESONANCE IMAGING

MR Imaging involves the interaction between a static magnetic field, local magnetic fields, and radio waves. While MRI is not the most used neuroimaging tool, it is the most sensitive to the effects of HTN on the brain. It is exceptionally sensitive to hydrogen (in water) and to blood, but can be used to measure any atom which has an odd number of protons and is abundant in the human body. Such atoms include hydrogen, carbon-13, sodium, fluorine, and phosphorus. Conventional MR Imaging relies predominantly on hydrogen because of its abundance in the human body. However, sodium imaging has tremendous potential for evaluation of the effects of HTN on brain structure.

General Principles

Generally, six main factors contribute to MRI. These include the properties of nuclear spin, the properties of the radio frequency (RF) excitation, the properties of tissue relaxation, the strength of the static magnet field, the timing of RF pulses, and the sensitivity of signal detection. The total MR signal is a combination of the sums of proton density reduced by T1, T2, and T2* relaxation. As such, each relaxation component offers distinct information about tissue character. T1-weighted images are generally more spatially sensitive, making them useful in assessments of structure and volume. T2-weighted images are more sensitive to pathology, especially when that pathology affects local water content.

Uses in Assessment of the Effects of Hypertension

HTN is associated with not only large- and small-territory infarcts and rarefaction of white matter and more severe white matter lesions, but also cerebral tissue loss assessed by reduced cerebral volume *(3,4)*. Two primary dependent measures are commonly used to examine the effects of HTN on the brain. These include characterization of white matter lesions and cerebral volume. The incidence of white matter hyperintensities approaches nearly 100% by age 85 and they are commonly observed in periventricular locations as well as subcortically *(32–35)*. These hyperintense lesions reflect local increases in water content and are believed to also reflect demyelination *(36–40)*. Both the number and extent
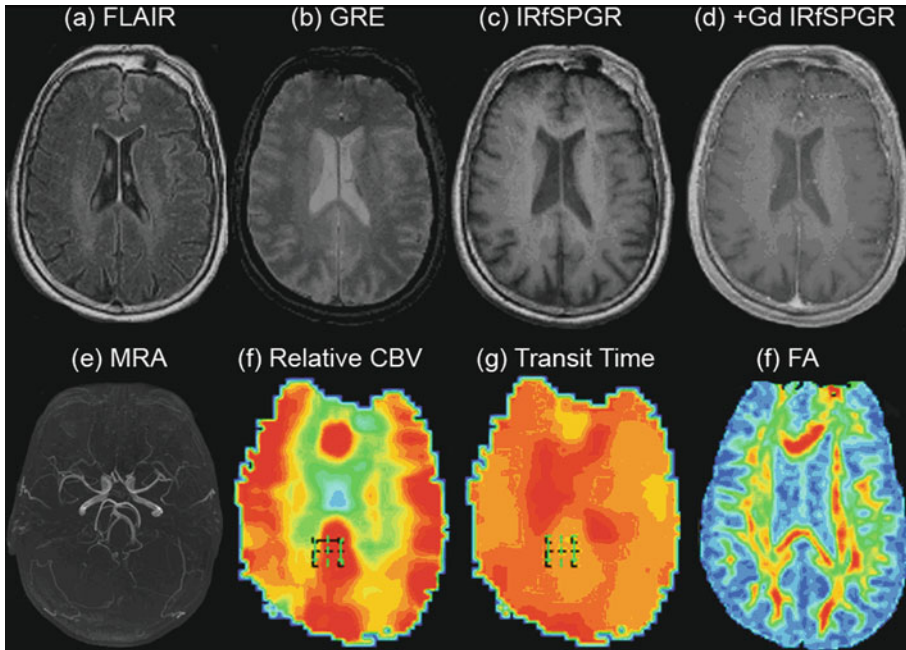
Fig. 1. High-field MRI HTN Protocol (**a**) FLAIR, (**b**) gradient recalled echo, (**c**) inversion recovery fast spoiled gradient recalled echo in steady state, (**d**) postintravenous gadolinium as in (**c**), (**e**) 3D time-of-flight MR angiogram, (**f**) perfusion map of relative cerebral blood volume, (**g**) perfusion map of tissue transit time, and (**h**) fractional anisotropy (FA) map derived from the diffusion tensor imaging.

of these lesions correlate with increased age *(41,42)*, with some evidence for an increased incidence in women *(41)*. These hyperintense white matter lesions are believed to reflect some type of covert vascular brain injury and commonly relate to HTN *(4,43)*. These lesions are commonly observed on fluid attenuated imaging (FLAIR; *see* Fig. 1a) or T2-weighted fast-spin echo imaging (FSE).

Similar to the presence and volume of white matter lesions, total and regional cerebral volume loss is also related to lifetime history of HTN *(4,43,44)*, with the greatest burden observed in cerebral white matter *(45)*. The pattern of regional cerebral white matter loss is not uniform. Frontal white matter volume loss may be a more sensitive measure to the effects of HTN when compared to total brain volume *(46)*. There is also some evidence to suggest that HTN is also related to greater atrophy in the thalamus and temporal lobes *(8)*. Generally, cerebral volume is assessed with standard volumetric T1-weighted imaging (*see* Fig. 1c, d) with and without contrast agents.

Magnetic Resonance Angiography

MR angiography is commonly used for diagnosis and assessment of the integrity of arteries and vessels in the human body. The level of detail provided is related both to the overall signal and quality of the imaging but also the field strength of the MRI system used. When compared to CT angiography, MRA provides more spatial resolution allowing better detail, particularly in smaller vessels (*see* Fig. 1e for a representative MRA performed

at 3 T). Standard clinical MRA are presently used for assessment of occlusion, aneurysm, and vascular malformations.

Recent advances in MRA technology including the application of phase-contrast techniques (phase-contrast angiography or PCA) have transitioned MRA from a purely diagnostic tool into a valuable technique for assessment of cerebrovascular risk as well as information into the effects of cerebrovascular risk factors on the human brain. In addition to structural information, PCA allows the characterization of velocity of flow within any given vessel (although the accuracy in small targets has yet to be determined). In addition to measures of velocity and diameter, PCA also allows the relatively simple calculation of total cerebral blood flow (CBF). In MRA, total CBF is usually estimated as the sum of total flow in the three main arteries. PCA has been shown to be sensitive to the effects of age on CBF *(47)* as well as in patients with significant cerebrovascular disease *(48)*. It has not, however, been interrogated with reference to HTN in otherwise healthy adults although it has significant potential in this population.

MR Perfusion-Weighted Imaging

MR-based perfusion-weighted imaging provides measures of relative cerebral blood volume (*see* Fig. 1f) as well as characterization of regionally specific tissue transit times (*see* Fig. 1g). Simply, MRP requires a series of lower spatial resolution images to be acquired covering the entire cerebral volume. These are acquired in concert with the injection of a bolus of intravenous contrast agent. This agent affects the local T2* signal. Over time, this increased signal can be followed to calculate the total time between injection and uptake in tissue. The total amount taken up into cerebral tissue is reflected in the calculation of relative cerebral blood volumes. Although the effects of HTN in otherwise healthy adults have not yet been studied on cerebral tissue perfusion directly, there is significant evidence to suggest that HTN does have an effect on cerebral tissue perfusion. In patients with an acute stroke who were treated with pharmacologically induced blood pressure elevation there was a significant effect on total relative cerebral blood flow such that there was increased tissue perfusion with increased (abnormal) blood pressure. Most important, total tissue perfusion correlated significantly with cognitive function *(49)*.

General Advantages

In assessing the effects of HTN on brain structure and function, the advantages of MRI, especially at high-fields (3 T and above), are numerous. Structural assessments are almost always more detailed and clinically useful than CT. This applies for volumes of small structures where the potential tissue volume loss is small in otherwise healthy adults as well as for characterization of effects on cerebral white matter. Developments of quantitative phase-contrast techniques have huge potential in this application, although yet to be fully examined. In addition, MR perfusion can be accomplished in about 40 s and can then be followed with a postcontrast image acquisition without adding significant time to imaging protocols. Advanced applications with MRI including diffusion tensor imaging (DTI), arterial spin labeling (ASL), and functional MRI (FMRI) also add to this significant list of advantages. Each of these will be discussed in detail in the following sections.

General Disadvantages

There are significant disadvantages with MRI relative to CT as well. First, MRI is significantly more expensive. Second, because of the large number of images acquired during a given study, interpretation of the data takes additional time. Third, MRIs are not nearly as accessible both in location or acquisition time relative to CTs. MRI studies generally take significantly longer than CTs ($\sim$ 35–50 min). Finally, there are significant patient-related challenges in the use of MRI including the extensive list of contraindications. Although many devices (i.e., implants, clips, coils) have been tested and approved for MRI, these devices still affect image quality. Patients must be able to provide an accurate history for metal work and medical procedures. Most MRIs have stricter weight limits for patients than do CTs with the average allowable patient weight for 1.5–3.0 T systems being under 300 lb. Finally, patient compliance in terms of motion and ability to lay still are a common concern in many studies and affect not only the ability to conduct the study but also to interpret the images acquired.

FUNCTIONAL MRI

Functional magnetic resonance imaging (FMRI), a derivative of MR imaging, allows for the visualization of task-related brain activation *(50)*. During FMRI studies, a series of images (or volumes) are acquired as a participant performs a given task. The time-course of changes in local MR signal is then associated with the timing of the task being performed. To accomplish the temporal resolution required to investigate the time-course, spatial resolution is compromised. To overcome this significant limitation, the lower-resolution FMRI studies are generally statistically mapped onto a higher resolution anatomical scan. Essentially, FMRI functions by utilizing the properties of blood flow and oxygen concentration changes that occur following neuronal firing. Most FMRI studies utilize the blood oxygen level dependent (BOLD) response. Different FMRI techniques have been attempted to more directly measure neuronal activity by utilizing higher temporal resolutions, however none have been able to achieve the high spatial resolution of BOLD FMRI.

General Principles of BOLD FMRI

The link between neural activation and CBF is the general basis of BOLD FMRI. When an area of the brain is activated by the demand to perform a task, the local neurons begin to fire and increase local metabolic activity. This increase in local metabolic activity leads to an increase in CBF to the activated area *(51)*. This is known as the hemodynamic response. This increase in CBF exceeds the demands of the activated neurons. The result is an increase in the concentration of local oxyhemoglobin associated with a relative decrease in deoxyhemoglobin. The paramagnetic properties of deoxyhemoglobin lead to a signal loss on T2* weighted sequences, which can be visualized as a transient increase in local signal in the capillary bed of activated neurons *(47–49)*. Figure 2 demonstrates the fluctuation of the MR signal as it correlates with functional changes in the area of brain associated with task performance and rest. In the example depicted in Fig. 2, a 40-year-old patient was asked
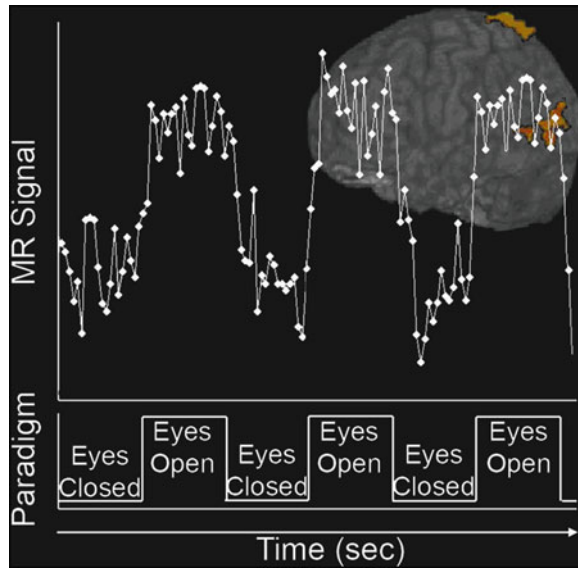
Fig. 2. Functional MRI time course (*top graph*) representing the activation in the tertiary visual areas while a patient was instructed to close and then open their eyes in blocks of 20 s.

to fixate on a small fixation cross while concentric circles expanded from this central fixation point at a rate of 8 Hz for a period of 20 s. This 20-s period was followed by a rest condition where the patient was presented the same stimulus while the patients' eyes were closed. This cycle repeated three times.

Uses

Although FMRI has not yet assumed a definitive role in the diagnostic evaluation of HTN, recent animal and poststroke studies suggest its possible application in this use. FMRI is now routinely used in poststroke assessment of brain function and recovery. Generally, the primary measures used are the total volume of activation relative to controls in tissue both ipsilaterally and contralaterally to the infarct. These studies generally investigate the relative response either as a function of stroke or as a function of re-mapping of cortical controls following stroke. These studies not only offer information on cortical control of cognitive and motor functions but also on the local tissue perfusion during cognition *(52)*. Here, the application of FMRI allows for the visualization of microvascular abnormalities, or hemodynamic impairment that may be associated with stroke risk. Animal models of transient HTN have shown that increase in BOLD FMRI signal and regional CBF are associated with induced transient HTN *(53,54)*. For example, the mean maximum BOLD signal intensity for voxels correlating to BP in the male rat sensory motor cortex was $5.6 \pm 6\%$ when BP increase was between 31 and 45 mmHg, and $9.6 \pm 6\%$ when the BP increase was >60 mmHg *(51)*. These studies suggest that FMRI may be a useful tool in the detection of HTN related microvascular pathology; however, a more definitive link on the effect of HTN on the BOLD signal needs to be further evaluated in studies of otherwise healthy hypertensives.

General Advantages

One of the major advantages of using FMRI is that it is a noninvasive technique requiring no use of intravenous contrast. Rather, FMRI relies upon the relative concentrations of oxy-hemoglobin to deoxyhemoglobin in the blood as an endogenous contrast agent. This allows the clinician or researcher the availability to administer a number of scans on a single subject without sacrificing health or safety or having to control for change in contrast concentrations over time or over brain regions. The relevance of using FMRI to study HTN lies in its ability to visualize CBF as a function of neuronal activity. Also, even though the spatial resolution is lower than in structural MRI, the dense vasculature in cortical tissue still allows for a relatively high spatial resolution (∼1–3 mm3) *(55)*. Unlike PET, studies using FMRI do not need to rely on an averaging across subjects because FMRI can accurately detect activation changes on the individual level. This is a crucial advantage as the effects of hypertension are highly variable and likely interact with a number of other factors (age, other cerebrovascular risk factors, significant medical history). As MRI has become a mainstay clinical and research tool, availability of this technique has increased although the usefulness at lower fields is still debated.

General Disadvantages

Despite FMRI's ability to provide spatially clear visualization of regional brain activation, it does have limitations imposed by the reliance on the cerebral microvascular system and the time-course of changes in blood flow. In a healthy adult, the time to peak for a hemodynamic response from the initiation of cognitive or motor activity is 5–7 s. As such, the temporal resolution of FMRI is not as temporally accurate as other methods including electrophysiology and even optical coherence tomography (when applied to the cortex) *(55)*. Also, since stressors, including claustrophobia, can transiently raise blood pressure and thus increase CBF, nonneural changes may have an influence on the BOLD signal which, if they change over the course of the study, are difficult to account for in statistical models *(53)*. FMRI requires a high degree of patient compliance and is particularly sensitive to head movement and respiratory artifacts. It also requires significant postprocessing.

DIFFUSION TENSOR MR IMAGING

Diffusion tensor magnetic resonance imaging (DTI) is a relatively new technique that allows quantitative assessment of highly organized tissue, such as in white matter and nerve fibers. A unique application of DTI is to visualize the orientation and the connectivity of the white matter fiber tracts in the brain based on the principal diffusion directions *(56–58)*. This capability provides us with a new avenue to correlate the functional activation maps with structural changes in the fiber tracts (e.g., tract thickening, thinning, sprouting) throughout the course of neurological disorders.

General Principles

DTI is a special form of diffusion-weighted imaging that allows the assessment and visualization of white matter and nerve fibers on a millimeter-level scale *(59)*. Although white and gray matter can be visualized and differentiated with standard MRI pulse sequences,

standard MRI does not allow for the examination of the integrity or directionality of white matter tracts. DTI takes advantage of the diffusivity of water and the restrictions imposed on the diffusion of water by the myelin and axonal bodies associated with white matter fiber tracts. When fiber tracts are dense, for example, the restriction imposed by their density leads to directionally dependent or anisotropic diffusion. By analogy, if an ink drop is placed in a narrow or oval tube the diffusion of that ink drop will adjust to the shape of the tube. In contrast, if a drop of ink is placed in a large bowl of water the drop of ink will be more spherical or the diffusion will be fairly isotropic. It is this shape of the restriction of diffusion that is assessed with DTI. In well organized and intact white matter fiber tracts the shape of water diffusion will occur preferentially along those tracts (i.e., more anisotropic). When there is less organization or a lack of aligned and organized fiber structures (i.e., gray matter, cerebrospinal fluid, axonal loss, or demyelination) the shape of water diffusion will be more isotropic. Commonly, the degree of alignment and anisotropy is calculated as the fractional anisotropy (FA). FA values range from 0 to 1, where 0 represents isotropic diffusion and 1 represents anisotropic diffusion. Higher FA values are believed to represent such factors as degree of myelination and axonal density. The FA values are dependent not only upon the shape of diffusion (eigenvalues) but also the primary direction of diffusion (eigenvectors). These values can be combined in various methods to provide estimates of the axial and radial diffusivity in addition to more standard measures of water diffusion. Axonal diffusivity reflects the integrity of axonal bodies while radial diffusivity is a measure of the degree of myelination *(60)*. Examples of various diffusion tensor images for a 30-year-old healthy adult are presented in Fig. 3.
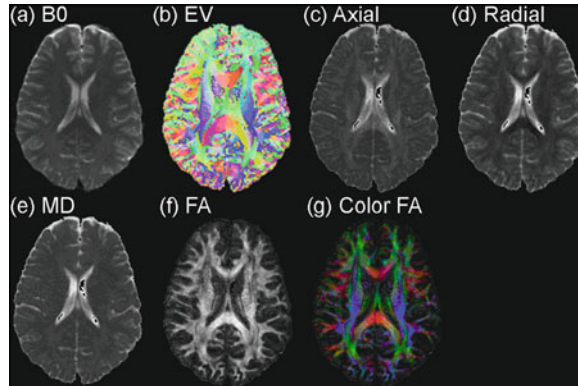
Fig. 3. Components and measures of diffusion tensor imaging which include the B0 image (**a**), a primary eigenvector image (**b**), maps of axial (**c**) and radial diffusivity (**d**), mean diffusivity (**e**), fractional anisotropy (**f**), and maps including the directionally dependent FA maps (**g**).

Uses and Measures

The power of diffusion tensor imaging (DTI) goes far beyond producing ADC, FA, RA, and other scalar-based maps. Although the specifics are still not well understood, FA is believed to reflect many factors including the degree of myelination and axonal density and/or integrity *(61–64)*. More discrete analysis of the axial ($\lambda_\parallel$) and radial diffusivity ($\lambda_\perp$) also provide potential measures of the mechanisms that underlie changes in white matter *(65,66)*. $\lambda_\parallel$ reflects diffusivity parallel to axonal fibers. Increases in $\lambda_\parallel$ are thought to

reflect pathology of the axon itself. $\lambda_\perp$ reflects diffusivity perpendicular to axonal fibers and appears to be more strongly correlated with myelin abnormalities, either dysmyelination or demyelination. At least one study has clearly demonstrated that FA is very sensitive to the effects of hypertension on cerebral structure *(67)*. In a relatively small sample study 30 hypertensive inpatients (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or both) and 30 healthy elderly subjects underwent DTI on a 1.5 T scanner, with DTI performed along 13 directions. The preliminary evidence revealed a significant decrease in FA value in the optic radiation in hypertensive patients (0.44 ± 0.06) compared to controls (0.47 ± 0.05) ($p < 0.05$). However, the study has limitations such that the imaging methods used may not be sensitive to more discrete WM changes associated with HTN. Further, no information is provided in regard to the health of the 30 hypertensive inpatients, giving the results of the study low generalizability *(67)*. A larger study with increased MR field strength and improved signal-to-noise ratio demonstrated at the whole-brain level a significant decrease in FA and corresponding increase in mean diffusivity (MD) in hypertensive patients (blood pressure > 140/90 or taking antihypertensive medication). The mean FA/MD (mm^2/s $\times 10^{-3}$) values (standard error) for normotensive controls was 0.317 (0.039)/0.792 (0.057) compared to the hypertensive controls 0.298 (0.035)/0.822 (0.064). This study also demonstrated an increase in mean percent lesion load of hypertensive controls 4.57(6.91) compared to normotensive controls 3.29(5.8) *(68)*. Other studies are currently underway to demonstrate the relationship between HTN, cerebral white matter microstructure, and cognition in midlife adults.

General Advantages and Disadvantages

Diffusion tensor imaging shares many of the advantages and disadvantages of standard MR imaging. However, in addition to those listed, DTI provides the advantage of providing an in-vivo assessment of axonal integrity as well as the contributions of HTN on axonal and myelin structural integrity. DTI is relatively fast at higher field strengths (∼5 min) and does not require the same degree of patient compliance as FMRI. There are multiple applications for postprocessing and most major MRI manufactures provide on-scanner packages to quickly produce these common images. The disadvantages of DTI have to do with the lack of knowledge about how certain factors such as edema affect the local signal. Additionally, it is unknown how white matter lesions, which are common in HTN, affect local DTI signal measurements.

ARTERIAL SPIN LABELING

Arterial spin labeling (ASL), an alternative to the BOLD method of neuroimaging, combines FMRI's ability to measure cerebral blood flow with the benefits of exogenous contrast agents, while remaining a noninvasive technique. ASL allows for the characterization of blood flow within brain tissue, but allows for direct visualization, rather than the indirect measure provided by the BOLD method. Perfusion is quantified by measuring the magnetic state of inflowing blood in relation to the magnetic state of static tissue. ASL is, in particular, relevant to the study of the effects of HTN in the brain because it is potentially not affected by differential vasodilatation effects.

General Principles and Technique

ASL allows for rapid quantitative measurements of perfusion in the brain *(69)*. Much like PET, arterial spin labeling takes advantage of the principles of exogenous tracers. Instead of invasive radiotracer injection, however, in ASL arterial blood water is first magnetized, then imaged via MRI. Arterial blood water is magnetized, or "labeled," immediately below the region of interest via a 180° radio frequency inversion pulse. The application of this pulse to the region below the slice of interest results in inversion of the net magnetization of the blood water; that is, the water molecules in the blood are now magnetically labeled and can be detected via MR imaging. After a period of time known as the "transit time," the magnetically labeled (i.e. paramagnetic) blood water travels to the region of interest and exchanges with the un-magnetized water present in the tissue altering total tissue magnetization. During this inflow of the inverted spin water molecules, total tissue magnetization is reduced, thereby reducing the MR signal and image intensity. At this point, an image (known as the "tag image") is taken. The experiment is then repeated without labeling the arterial blood to create another image (known as the "control image"). To produce an image showing blood perfusion, the tag image is subtracted from the control image. The resulting image reflects the total amount of arterial blood delivered to each voxel in the region of interest within the transit time *(70)*.

Several methods of ASL perfusion imaging exist. In continuous ASL (CASL), a continuous radio frequency pulse is applied to the targeted region below the slice of interest, resulting in continuous inversion of the magnetization of arterial blood water. Because of this continuous inversion, a steady-state develops in which regional magnetization in the brain is directly related to cerebral blood flow *(71)*. In pulsed ASL (PASL), a short (approximately 10 ms) radio frequency pulse is used to label blood water spins over a very specific area *(70)*, which allows for minimization of the distance between the labeling region and the imaging slice *(71)*. Both have advantages and disadvantages.

Uses and Measures

ASL has been used to measure the effects of cerebrovascular risk factors, such as HTN, on regional cerebral blood flow, in an attempt to correlate regional cerebral blood flow with specific risk factors. For example, HTN was found to be significantly associated with higher regional cerebral blood flow (adjusted $\beta = 6.5$ mL/min/100 g; 95% confidence interval: 1.4 mL/min/100 g, 11.7 mL/min/100 g) compared to other cerebrovascular risk factors such as body mass index (BMI), carotid artery stenosis, and diabetes mellitus *(69)*. Through further study via CASL, HTN is believed to exert its effects on human cognition by creating a state of vulnerability for neurodegenerative diseases. Other studies have used ASL to characterize perfusion abnormalities, and found that cerebral blood flow asymmetries as visualized by CASL correlate with severity and outcome in acute ischemic stroke *(72)*; here, ASL has the potential to predict stroke risk based on perfusion characteristics.

General Advantages

Probably the most noteworthy advantage of the ASL technique is that the use of a contrast agent or radioactive tracer is not necessary; instead, the contrast provided by the inverted magnetization of arterial blood water allows for effective characterization of perfusion difference when a specific brain region is activated. This technique is highly relevant

in the study of HTN because it allows for the direct visualization of regional cerebral blood flow. Images of perfusion difference do not require any modeling, filtering, or regressing; visualizations of perfusion difference are simply a subtraction of resting perfusion maps from active perfusion maps *(70)*. Unlike the BOLD technique, in which signal drift results in decreased ability to detect slow variations in neural activity, ASL allows for the characterization of slow variations because drift effects are minimized in the successive paired subtraction of images acquired with and without labeling *(73)*. Changes in ASL signal as a result of regional brain activation are more defined than those changes observed via the BOLD technique; this allows for more concrete definition of regions of activation and characterization of cerebral blood flow.

General Disadvantages

Despite the higher accuracy (than BOLD imaging) in regional cerebral blood flow changes visible via ASL, this technique does have a number of intrinsic limitations. For example, the time taken for the inverted-spin water molecules to travel from the region of inversion to the region of interest is nonzero; therefore, T1 relaxation occurs during this period, minimizing the contrast viewable via ASL imaging *(71)*. In addition, in the control minus labeled images obtained from ASL, intravascular signal may contaminate the results of the perfusion difference subtraction *(71)*. Head motion artifacts are more significant because the subtraction is necessary and requires high concordance between subsequent images. In addition to the intrinsic limitations of ASL, arterial spin labeling methods are somewhat difficult to carry out on clinical MR scanners and do not have the availability of BOLD FMRI.

POSITRON EMISSION TOMOGRAPHY AND SINGLE PHOTON EMISSION COMPUTERIZED TOMOGRAPHY

General Principles and Technique

PET imaging applications include functional neuroimaging, metabolic imaging, and evaluation of specific pathology that can bind to a given tracer. Each of these are reviewed. PET functional neuroimaging is based on an assumption that areas of high blood flow (because of neuronal activity) are also areas of high radioactivity. SPECT neuroimaging is similar to PET in that they both detect a radioactive tracer with gamma rays. The difference arises in that the tracer used in SPECT releases gamma rays that are directly detected. PET, on the other hand, uses a tracer that releases positrons that annihilate with electrons and subsequently form a pair of gamma photons *(74)*. This allows for better localization of the source of the radiation. 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG-PET) uses a glucose analog to monitor metabolic activity by highly metabolic organs and lesions *(75)*. The glucose analog is taken up by glucose utilizing cells, where it is phosphorylated and therefore "trapped" until it decays.

Uses and Measures

PET scanning is on the forefront of evaluating the functional effects of HTN on the brain as it relates to regional cerebral brain perfusion (rCBF) *(25)*. HTN has been associated with a decrease in resting rCBF compared to healthy controls of similar age *(1)*. Longitudinal

studies support these effects, with HTN being associated with a greater decrease in rCBF than age alone *(1)*. Importantly, these effects are not global, but regionally specific with differential effects in regions associated with memory and attention *(1)*. These studies highlight the usefulness of rCBF even in resting perfusion studies. Additionally, functional imaging studies with PET are also sensitive to the effects of HTN. In cognitively challenging working memory tasks, there is a decrease in baseline rCBF (no performance of the challenging task) and reduced rCBF in frontal and parietal cortices during performance of the working memory task demonstrating an alteration in cerebral reserve and an alteration in task-dependent uptake *(76)*. Similar alterations during functional PET have been reported for tasks which involve spatial memory and parietal lobe involvement *(25)*. One common theme is the role of the thalamus in HTN. Many studies implicate underperfusion of thalamic and striatal structures in patients with HTN compared to age-matched adults *(77)*. In addition to characterizing differences between hypertensive and nonhypertensive controls, rCBF as measured with PET also shows sensitivity to duration *(77)* and severity of HTN *(1)*. Additionally, and clinically important, both PET and SPECT and resulting measures of rCBF are sensitive to HTN treatment *(76,78)*. For example, single photon emission ^{99}mTc-hexamethylpropylene amine oxime (^{99}mTc-HMPAO) SPECT in arterial hypertensive patients revealed an rCBF decrease (21–22%) in the upper frontal, posterior parietal and occipital brain regions, and a lesser rCBF decrease (15–16%) in the temporal, anterior parietal, and inferior frontal cortex. After 6 months of hypotensive therapy rCBF significantly increased by an average of 10–11% in the anterior parietal, 8–10% in the occipital, 7% in the posterior parietal, 5–7% in the superior frontal, 4–7% in the inferior frontal, and 4–6% in the temporal cortex *(76)*.

FDG-PET, as well as ^{15}O PET, may prove to have far-reaching uses in the realm of cerebral ischemia and atherosclerotic change. As of yet these methods have not been verified as a useful tool in HTN per se; however, they may be especially useful in monitoring response to treatment with medications such as statins because these may act to primarily stabilize the plaque rather than decrease plaque size which alters local metabolic function. Therefore, their efficacy will be underestimated on standard X-ray angiography *(79)*.

In addition to FDG-PET, ^{15}O PET studies have also provided information to categorize those with atherosclerotic occlusion who are at significant risk for future CVA. The presence of an increased oxygen ejection fraction (OEF) on PET in patients with atherosclerotic carotid occlusion correlates with an increased incidence of progression to stroke in these patients, as OEF is an indicator of mismatch between metabolic demand and cerebral blood flow *(74)*.

General Advantages

^{15}O PET, FDG-PET, and SPECT all allow for quantification of various parameters such as rCBF and metabolic rate. This provides indirect information on neuronal and neurotransmitter activity. The information regarding function allows for information not obtained with structural imaging, that is, MRI and CT. In addition, these modalities allow for evaluation of function both at rest and during neuropsychological testing. They also provide information on the efficacy of pharmacologic intervention *(80)*, as in the example mentioned above

with statins and FDG-PET. PET has the advantage of reasonable spatial resolution, approximately 3–4 mm, while the spatial resolution of standard clinical SPECT is approximately 5 mm *(80)*.

General Disadvantages

PET has poor temporal resolution (approximately 1 min) *(80)*. In addition, it is quite expensive and not currently reimbursed for many neurological uses, with the exception of neuro-oncology *(75)*. SPECT and FDG-PET are less expensive and more likely to be reimbursed. The expense and radiation exposure of PET, FDG-PET, and SPECT make them all poor screening modalities, although their mechanism of detection makes them superior in screening for those at significant risk for cerebral ischemia and stroke, as outlined above. Additionally, many of the tracers in PET require a cyclotron nearby due to the half-life of these tracers. FDG-PET gets around these concerns.

SUMMARY AND CONCLUSIONS

Recent advances in neuroimaging, together with the increasing availability of high-field MRI systems at most major medical centers provide the foundation for the expectation that MRI-based measures will allow better quantification and qualification of the effects of HTN on the brain. There is already significant evidence to suggest the role of ASL in monitoring disease progression and medication effectiveness, even though it is a relatively new technique and not yet widely available. Both diffusion and perfusion MRI studies are in their infancy with regard to being used in HTN. Although MRI is clearly superior to CT for studies of brain structure and function, CT still has a role in HTN but for primarily clinical assessment of acute conditions. Further, multimodal MR studies such as the combination of MRS and DTI are essential to the understanding of HTN and its affect on the brain as together they assist in quantification and qualification of structural changes *(68)*. New developments with multislice array systems will potentially allow CT to assume a larger role in the assessment of the effects of HTN on noncerebral targets including the internal organs and especially the heart. These targets are exceptionally difficult to image with MR because of flow and respiration artifacts. As both MRI and PET are expensive to run and maintain, more studies demonstrating the usefulness of advanced neuroimaging techniques are needed to justify their widespread use.

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V   ORGANIZATION OF STROKE CARE

16

The Joint Commission's Initiatives to Improve Stroke Care and What It Means for Acute Stroke Care and Prevention

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CONTENTS

INTRODUCTION

Stroke is the third leading cause of death in the United States with approximately 795,000 new or recurrent strokes each year. About 610,000 of these are first attacks and 185,000 are recurrent attacks *(1)*. The high incidence of stroke worldwide highlights the need for stroke performance improvement and efficiency.

Ensuring that stroke care advances are consistently translated into clinical practice remains a challenge. Fragmentation of services continues due to the lack of an integrated system of stroke care. In late 2003, the Joint Commission (TJC), a nonprofit healthcare accreditation organization, introduced Disease Specific Certification (DSC) for Primary Stroke Center Certification (PSCC) as a means to ensure evidence-based care integration

amongst Emergency Medical System (EMS) providers and hospitals. In this chapter, I provide a brief update on progress of TJC initiatives in stroke, including TJC requirements for stroke performance improvement, and the impact the PSCC has made on acute care and prevention. Additional organizations that designate stroke programs will not be addressed in this chapter.

THE FOUNDATIONS OF STROKE CENTER CERTIFICATION

The approach of quality improvement by hospitals and health systems began with organizations like TJC and the American Medical Association. In 1992, the American Medical Association (AMA) sponsored an assembly to begin to develop the evidence-based medicine concept to improve the quality of care. Their extensive review included a procedural approach to the systematic analysis of the scientific literature evaluating clinical outcomes. They concluded that quality medical treatment is supported by careful and systematic evaluation emphasizing rigorous controlled trials. This idea became the primary criteria of quality care and a core value for medicine in the USA *(2)*.

During the early 1990s, evidenced-based medicine supported designation of stroke units and stroke protocols as ways to improve quality of care. Wentworth and Atkins published a study showing a reduction in charges and length of stay after implementation of a designated stroke unit, medical director, care pathways, and protocols at a community hospital in California *(3)*. In 1995, Gorelick published an article discussing a strategy to reduce stroke cost called the "Time Zero Plan" emphasizing hospital length of stay as a major contributor to inpatient stroke cost *(4)*. Book et al. found that enforcement of care pathways and stroke protocol utilization had a significant impact on reduction of length of stay and improved clinical outcomes in an academic medical center *(5)*.

Published guidelines on hospital stroke center infrastructure were published in the Brain Attack Coalition's article, Recommendations on the Establishment of Primary Stroke Centers *(6)*. As published, Primary Stroke Centers have specific staffing and infrastructure to first stabilize and then treat acute stroke patients. Primary Stroke Centers are designed to evaluate acute stroke patients for emergent treatment such as intravenous (IV) thrombolytic therapy, stabilize vital signs, and provide acute brain imaging *(7,8)*. In 2003, the American Stroke Association, a division of the American Heart Association, and TJC convened and agreed on a PSCC process for stroke using the Recommendations on the Establishment of Primary Stroke Centers *(6)* as a foundation.

PRIMARY STROKE CENTER CERTIFICATION ELEMENTS

TJC provides two types of credentials: accreditation and certification. Accreditation has long been the foundation for TJC, and includes accreditation for hospitals, home health agencies, and staffing agencies. TJC publically provides the organization's accreditation decision, the date that accreditation was awarded, and any standards that were cited for improvement. Organizations deemed to be in compliance with all or most of the applicable standards are accredited. In the USA, accredited organizations are deemed by the Centers for Medicare and Medicaid Services (CMS) to meet the Medicare and

Medicaid certification requirements necessary for gaining reimbursement from Medicare and managed care organizations. The accreditation surveys comprise the majority of TJC regulatory division and are designed for organization-wide evaluation of care processes and functions *(9)*.

In contrast, DSC programs were designed for products or service-specific evaluations of care and outcomes. Certification is voluntary and Medicare reimbursement is not based on the certification decision. There are two categories of DSC: (1) Core DSC programs (level 1) and (2) Advanced DSC programs (level 2). TJC applies similar certification standards to over 60 diseases in Core and Advanced programs. Advanced DSC programs like Primary Stroke Center, inpatient diabetes, chronic obstructive pulmonary disease, ventricular assist device, and chronic kidney disease are all categorized by TJC as Advanced DSC programs due to the increased complexity of treating the disease. As they do with accreditation, TJC publically provides the organization's certification decisions, the date that certification was awarded, and any standards that were cited for improvement *(9,10)*.

There are three major elements to PSCC. These elements include (1) process, which measures compliance with use of evidence-based guidelines; (2) structure, which measures implementation of the Joint Commission consensus-based standards; and (3) outcome, which measures clinical outcomes *(10)*.

First, compliance with use of evidence-based guidelines includes adherence to nationally accepted guidelines such as the American Stroke Association or other equivalent evidence-based guidelines. TJC requires that patient care be based on guidelines and evidence-based practice. It also requires an organizational assessment of implementation of clinical practice guidelines and a sound rationale for selection or modification of clinical practice guidelines. Compliance with evidence-based care includes compliance with BAC primary stroke center recommendations *(7,10)*.

Second, TJC requires compliance with DSC Standards. There are five overarching DSC Standards that include Program Management, Delivering and Facilitating Clinical Care, Supporting Self Management, Clinical Information Management, and Performance Improvement and Measurement *(10)*.

The third and final component of PSCC is compliance with the standardized clinical outcome measure set. The ten clinical outcomes required by TJC are commonly referred to as harmonized measures. The diagnosis reviewed for PSCC may include ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage. In 2008, an expert panel at TJC recommended excluding TIA patients for reporting purposes based on vagueness or difficulties classifying TIA *(10)*.

The process of applying for initial PSCC includes 4 months of data collection on clinical measures. Data are made available to TJC during the initial on-site review. In addition, evaluating perception of care by the patient and family is reviewed during the certification process *(10)*. Finally, a standard process showing consistent implementation of Clinical Practice Guidelines (CPG) should be demonstrated. If certified, a hospital remains certified for 2 years pending an intracycle review by phone 1 year after the on-site review. Re-certification includes consistent data collection and performance improvement planning. Organizations are required to enter clinical outcome data and accompanying quality improvement plans in TJC web-based data repository on a quarterly basis. See Table 1 for details regarding PSCC preparation *(10)*.

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Table 1
Preparation Requirements for the Joint Commission

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Initial PSCC review

- Four months of data for each of the stroke measures along with graphical and/or tabular demonstration of data analysis, and the action plans from performance improvement
- List of physicians who provide care to and/or treat stroke patients, including ED physician (s), neurologist, neuro-interventionalist (if applicable), neurosurgeon, and/or hospitalist
- List of patients for the past 4 months with Ischemic and hemorrhogic Stroke — including age, gender, and ethnic origin, if possible

- List of the program's core stroke team members
- List of ischemic stroke patients who received fibrinolysis
- List of staff that provide care to stroke patients — ER staff, critical care staff, step-down staff, stroke unit staff, PT, OT, SLP; indicate which staff are scheduled to work on the day of the initial review

DATA COMPLIANCE WITH JOINT COMMISSION METRICS

Data entry compliance required by TJC may be achieved in a variety of ways. One database solution is the American Heart Association's Get with the Guidelines-Stroke (GWTG-S) program. As of December 2008, over 1,400 hospitals participated in the GWTG-S database and have entered over 800,000 patient records *(11)*. Clinical outcome trends have improved amongst PSCC hospitals since the GWTG-S official public launch in January 2005. Schwamm et al. found that participation in the GWTG-S initiative was associated with improved adherence to evidence-based guidelines for the treatment of ischemic stroke and TIA. Sustained improvements in stroke care outcomes were seen in all participating hospitals regardless of size, geography, or teaching status *(12)*.

Data collection solutions also include the Centers for Disease Control and Prevention (CDCP) Coverdell Stroke Registry. The Paul Coverdell Registry is designed to track care delivery to hospitalized stroke patients and help monitor improvements in the quality of acute stroke care delivered. A select number of states participate in the Centers for Medicare and Medicaid funded study. In Illinois, Dr. Dilip Pandey led the Coverdell Registry initiative. In one phase of the registry, over 13 hospitals participated and entered over 1,900 stroke patients in the stroke prototype registry. Pandey and colleagues found that providing active feedback to participating sites regarding quality indicators could lead to improvement in stroke clinical outcomes *(13)*.

GROWTH RATE, IMPACT, AND CURRENT STATUS OF PRIMARY STROKE CENTER CERTIFICATION

In January 2004, the first hospitals volunteered for PSCC. By April 2005, TJC reviewed approximately 15 hospitals each month for PSCC. Several states reached greater than 20 Joint Commission certified Primary Stroke Centers by December 2007 *(14)*. Initially,

states with the highest number of certified centers included Wisconsin, Texas, Florida, and California. State legislative influence requiring certification varied amongst the four states. The state of Wisconsin had no state regulations requiring certification; in contrast, the state of Florida passed early state specific legislation that included bypass to designated stroke centers. In 2007, both Wisconsin and Florida had greater than 20 centers certified by TJC (Fig. 1) *(15)*. As of January 2009, TJC has certified over 520 centers in 46 states (Fig. 2) *(10)*. State health departments and other certifying bodies also provide third-party stroke program review. This chapter will not address such alternatives.
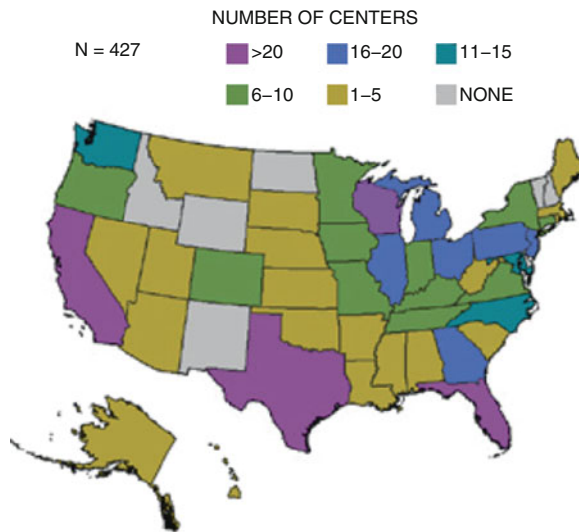
Fig. 1. Primary stroke center certification growth and US distribution 2008 *(10)* with permission.
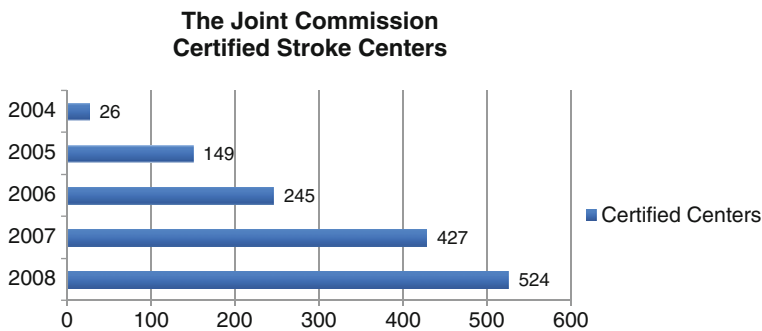
Fig. 2. The joint commission-certified primary stroke centers quality check *(10)*.

IMPACT OF PRIMARY STROKE CENTER CERTIFICATION

The benefits of PSCC have been described in various ways. For the hospital stroke team, PSC may improve the quality of care by reducing variation in clinical processes, or it may provide an objective assessment of clinical excellence by a third-party review. Stroke teams

report cohesiveness amongst team members as part of a culture of excellence across a program or organization. It may also help with external hospital marketing efforts to the consumer and reimbursement *(10)*.

When measured, evidence-based quality improvement allows us to determine the effectiveness of evidence in practice. Michalke and Dunne published a white paper in 2007 which showed survey results of 68 stroke centers in 29 states. Approximately 40 Joint Commission primary stroke center certified hospitals participated in the survey and the remainder of the respondents were not certified or did not plan to certify. Survey results were self-reported and voluntary. Results showed that certified centers are more likely to embrace advanced technology and new treatment options. In addition, certified programs were more likely to use standardized protocols, participate in clinical trials, and administer intravenous tissue plasminogen activator. Finally, certified centers were 50% more likely to track key performance measure and report their findings to consumers (Fig. 3) *(15)*.

Further, PSCC has made an impact on acute stroke treatment clinical outcomes. One such clinical outcome is IV tPA administration for patients presenting to the hospital emergency department within 3 hours of symptom onset. Some 13 years have passed since intravenous
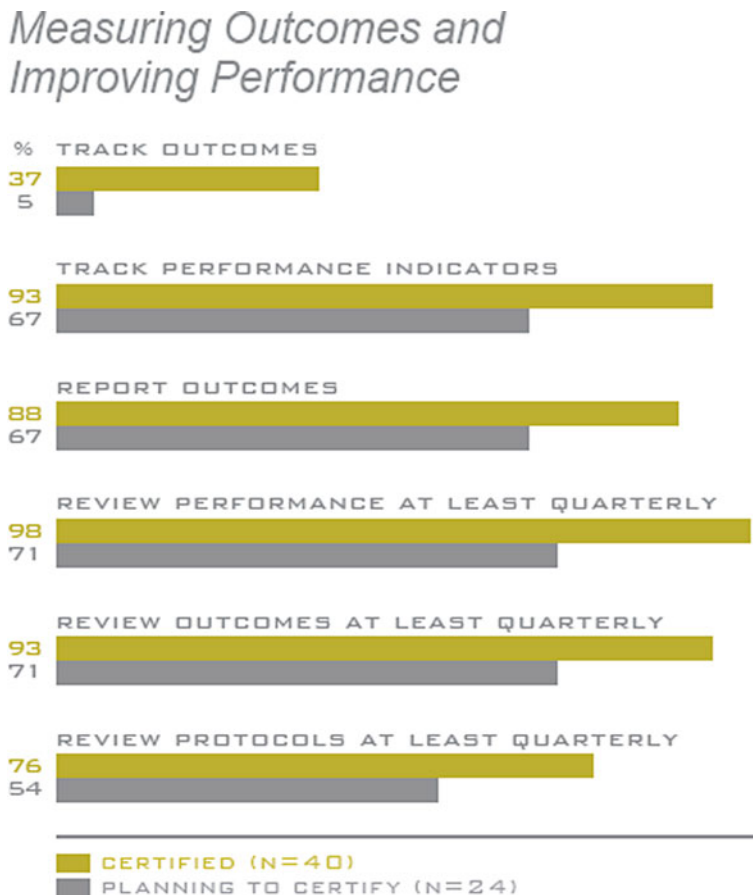
Fig. 3. Adoption of stroke intervention technologies and measuring outcomes and improving performance *(10)* with permission.

tissue plasminogen activator (tPA) was approved by the Food and Drug Administration for treating patients with acute ischemic stroke. In April 2009 Alberts et al. showed that primary stroke center certified hospitals have been slow to implement certification *(16)*. The study found that certified PSCs had a higher rate of tPA administration to eligible stroke patients. In addition, the longer the hospital was in the certification program, the higher its tPA participation rate. Hospitals in their re-certification cycle achieved a 78.6% IV tPA participation rate, and those certified for a third 2-year cycle achieved 94.4% participation. Obstacles, even amongst PSCC persist. Amongst the 4–5,000 hospitals in the United States, less than 600 hospitals are PSCC. TJC also recognizes that tPA may not be used to its fullest potential in eligible patients, as recommended in evidenced-based guidelines, even in certified centers *(16)*.

CURRENT TRENDS

In 2009, TJC established several enhancements in clinical outcome measures. These modifications, integrated throughout the standards, include changes to clinical outcome measures (e.g., Stroke-4) (IV tPA Administered) and Stroke-6 (Discharged on Cholesterol Reducing Medication). Modifications are published in the July 2008 issue of Joint Commission Perspectives and the Joint Commission 2009 Disease-Specific Care Certification Manual and became effective January 1, 2009. Stroke-4, IV tPA Administered, is modified to ensure that the infrastructure for IV thrombolytic therapy administration exists *(10)*.

The focus of the IV-thrombolytic administration measure includes competency of emergency department practitioners, documented exclusion for eligible ischemic stroke patients who did not receive IV thrombolytic therapy, existence of protocols documented in the medical record, 24 h access to a physician consultant with stroke privileges, IV-thrombolytic therapy in the formulary or on a medication list, and in quality improvement for stroke teams to evaluate stroke-specific performance measures on use of IV-thrombolytic therapy *(10)*.

Additional clinical outcome changes include changes to Stroke-6: Discharged on Statin Medication. The measure clarification includes ischemic stroke patients with evidence of atherosclerosis should be discharged on a statin medication *(10,18)*.

Further, standards scoring are modified by TJC. Details are published in the December 2008 issue of Joint Commission 2009 Disease-Specific Care Certification Manual. Changes to TJC scoring are part of the Standards Improvement Initiative (SII). The focus of the SII is on issues critical to patient care or safety. Simply, the more critical the issue, the shorter the time frame the program has to address it. In addition, the Elements of Performance (EOP) will be evaluated as satisfactory compliance, partial compliance, or insufficient compliance. There will be selected EOPs tagged direct impact (tier 3) and indirect impact (tier 4), based on their impact on safety. This information will be scored on-site. The preliminary report will be provided upon closing, but will no longer include a projected decision *(10,18)*.

Certification is typically awarded if the program is in compliance with all standards at the time of the on-site review, or if the Requirements For Improvements (RFI) have been successfully addressed within 60 days of final report posting. If the RFIs are not addressed satisfactorily, an organization may receive (1) Provisional Certification, (2) Conditional Certification, (3) Preliminary Denial of Certification, or (4) Denial

of Certification. Further information regarding scoring will not be discussed in this chapter *(18)*.

In addition to TJC initiatives, the National Quality Forum (NQF) and CMS are leading efforts to evaluate clinical outcome measures. NQF is evaluating national voluntary consensus standards for prevention and management of stroke across the continuum of care. In this project, NQF identifies and endorses measures that address the clinical system and care coordination aspects involved in effective stroke care across the continuum of care *(17,18)*.

In July 2008, the NQF endorsed eight Primary Stroke Center measures. All TJC standardized measures are included with the exception of Smoking Cessation Counseling and Dysphagia screening prior to oral intake *(10)*. Further, the eight performance measures currently used by PSCC hospitals have been approved for use by all hospitals. The measures have been modified to meet national core measure specifications and to better align with CMS. They were implemented in October 2009 *(18)*.

FUTURE DIRECTIONS FOR CARE INTEGRATION: ALEXIAN BROTHERS STROKE NURSE NAVIGATOR PROGRAM

Care integration is an important component of building a system of care for stroke. One way to build a more consistent and streamlined care continuum is through a concept called Patient Navigation. Although the concept was originally developed in oncology, I now introduce a similar concept to stroke.

The future of stroke care is not only providing quality care but also well integrated care. A novel Stroke Nurse Navigator (SNN) pilot program, led by registered nurses at Alexian Brothers Health Network (ABHN), was created in 2008 in an effort to better integrate stroke care from the patients' initial contact with the emergency department to rehabilitation to home. It was observed that patients and families who survive stroke face challenges far beyond the acute care phase of stroke treatment.

The ABHN SNN program integrates neurovascular care from admission to 1 year poststroke. The core responsibilities of the SNN include providing access to community resources, developing patient–physician relationships, assessing the patient's current and future needs, improving patient education, preparing educational materials, and coordinating a second opinion stroke clinic. The SNN also helps track TJC outcome measures, assists with the hospital stroke alert response, and visits survivors in the acute inpatient rehabilitation setting.

Two part-time RNs fill the SNN role to help guide patients through treatment. They serve as a single source for information regarding Stroke Center physicians, programs, and services. The SNN initiates care when the patient first enters the hospital. This may be at a stroke alert or inpatient unit. The SNN then follows patients throughout their inpatient stay. The SNN provides information about stroke-related care and the Stroke Center's programs after discharge. The SNN is also an informational resource for physician referral, information regarding neurologic-related disorders and programs and services. The SNN often triages calls to the appropriate physician, neurologist, neurosurgeon, or interventional radiologist depending on the patients' level of stroke severity in an effort to provide rapid, appropriate triage.

Overall, the implementation of the SNN program attempts to improve the outcomes and efficiency for the patients, physicians, and nurses. This may include improving resource utilization for physicians and better clinical and psychological outcomes for patients. Patients are better informed about their disease, more prepared for their physician appointments, and have better access to psychosocial support programs.

QUALITY IMPROVEMENT OF HYPERTENSION CONTROL IN STROKE PATIENTS

High blood pressure is the most important modifiable risk factor for stroke. Approximately, 1 in 4 or 1 in 3 US adults has high blood pressure. People with blood pressure lower than 120/80 mmHg have about half the lifetime risk of stroke compared to persons with high blood pressure *(1)*. Despite these important statistics, TJC initiatives for Primary Stroke Center Certification do not include clinical outcome metrics for hypertension in relationship to stroke. Efforts should be made to include the management of hypertension control in stroke patients as part of TJC national efforts to improve stroke care. Control of blood pressure after the acute stroke phase is a potent means to reduce recurrent stroke risk.

CONCLUSION

TJC Primary Stroke Center Certification emphasizes the importance of structured stroke care delivery and encourages compliance with nationally published stroke care and treatment guidelines. The initial positive impact of organized stroke care on clinical outcomes has been calculated and published *(12)*. The increasing number of hospitals volunteering to participate in quality improvement programs like GWTG-S and PSCC shows dedication to providing quality stroke care. Further analysis is required to understand the long-term impact of the Primary Stroke Center Certification on the US healthcare system.

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Index