

Flávio Danni Fuchs

Essentials of Hypertension

The 120/80 Paradigm



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The 120/80 paradigm

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*To Sandra, Felipe, Paulo, Laura, Cláudia,
and Therezinha*

Preface

High blood pressure accounts for more than 50% of deaths from stroke and ischemic heart disease worldwide. Hypertensive cardiomyopathy, aortic stenosis, aortic syndromes, and peripheral arterial disease are other consequences of high blood pressure. Millions of people live with clinical manifestations of these diseases, such as heart failure, angina, arrhythmias, chronic claudication, acute limb ischemia, and others. High blood pressure is also a risk factor for dementias, chronic kidney disease, and, possibly, degenerative macular disease.

The discovery of the causes of hypertension, and the development of effective strategies for its prevention and treatment, are among the outstanding achievements of humankind. Nonetheless, doctors and societies are not paying due attention to this evidence and are not taking vigorous attitudes to eradicate the risks of high blood pressure. Clinical inertia is still the prevailing attitude.

Darwin's theory, which most people believe, relies on natural observations and insightful reasoning, without any kind of experimental support. In the case of hypertension, however, experts are still asking for new evidence to set lower thresholds for diagnosis and treatment, which are currently at high and dangerous limits. Many are still dedicated to investigation of the causes of hypertension, methods of measuring blood pressure and of assessing its consequences for target organs, and debating about the more effective therapies to prevent and treat hypertension.

More data will surely come, but those regarding the essentials of hypertension are in. The blood pressure values used for diagnosis of hypertension and as a goal for prevention and treatment should be the same: 120/80 mmHg. Actions for prevention and control should start earlier. Hypertension is not primarily an issue for middle-aged adults and the elderly; it is an issue for children and young adults as well.

Maladaptation of the kidneys to chronic sodium overload explains why blood pressure increases unnaturally with age. Assessment of blood pressure should employ precise options, leaving aside archaic methods such as measurement of blood pressure by doctors with auscultatory sphygmomanometers. Prevention and treatment should rely on effective measures, including preferential use of chlorthalidone with a potassium-sparing diuretic if drugs are necessary.

Studies by our group and participation in many international investigations, associated with continuous updating of the literature, have enabled us to contribute to and get into the topics covered by this book. In four chapters, this book presents the key evidence that lends support for the essentials of the risks of hypertension, goals of treatment, pathogenesis, diagnosis and evaluation, and prevention and treatment of hypertension. Enjoy the reading.

Porto Alegre, Rio Grande do Sul, Brazil

Flávio Danni Fuchs

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To Sandra Costa Fuchs, Leila Beltrami Moreira, Miguel Gus, and Denis Martinez, my senior associates, and to innumerable colleagues from Brazil and abroad, graduate and undergraduate students, and research assistants, who made possible and pleasant the research and learning that resulted in this book.

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Risks of High Blood Pressure and Goals for Treatment

1

In the classic book *The Principles and Practice of Medicine*, Sir William Osler did not mention hypertension or its archaic name, hyperpiesis [1]. He obviously could not address a disease still undiscovered at that time, when the available noninvasive method to measure blood pressure (BP)—the sphygmograph, which measured the amplified radial pulse—was not reliable and practical for clinical use. Scipione Riva-Rocci opened up a new era, presenting the sphygmomanometer in 1896 [2]. Pulse palpation measured only systolic BP. Nikolai Sergeyevich Korotkov, a Russian surgeon, identified diastolic BP by auscultation in 1905 [3]. For many decades, the only novelty in BP measurement was the misspelling of the name “Korotkov,” which was changed to “Korotkoff” in some publications. Chapter 3 discusses the methods used for BP measurement.

Businesspersons were the first people to identify the risks of high BP. In 1911, the medical director of the Northwestern Mutual Life Insurance Company determined that applicants for life insurance should have their BP measured with a sphygmomanometer [4]. Sir William Osler, in a lecture given to the Royal College of Physicians and Surgeons of Glasgow in 1912, proposed that BP over 160 mmHg was high [5]. He did not, however, suspect its importance in the pathogenesis of atherosclerosis.

In the subsequent decades, the recognition of the role of high BP in the causation of cardiovascular disease faced ups and downs. In 1939, Keith, Wagener, and Barker described a cohort of patients with high BP classified into four groups according to different indicators of severity [6]. The criteria included BP values, the presence of symptoms, electrocardiographic abnormalities, albuminuria/hematuria, and optic fundus abnormalities (Fig. 1.1, *top*). Figure 1.1 (*bottom*) shows that most individuals in class IV died within 1 year. They had uncontrolled BP, a poor general state, dyspnea, albuminuria, hematuria, and optic edema. The classes of optic fundus abnormalities became the classic Keith–Wagener (KW) classification (the name “Barker” is not usually included in the eponym) of optic fundus examination—a

KWB classes				
	I	II	III	IV
BP	Slightly high	Higher	Always high	Resistant to treatment
Symptoms	No	No	Dyspnea, headache	Visual disturbances
General condition	Good	Good	Regular	Bad
ECG/Renal function	OK	OK	ECG abnormal/ nocturia	+ Albuminuria / hematuria
Ophthalmoscopy	Mild abnormalities	Moderate abnormalities	Hemorrhages/ exudates	Optical edema

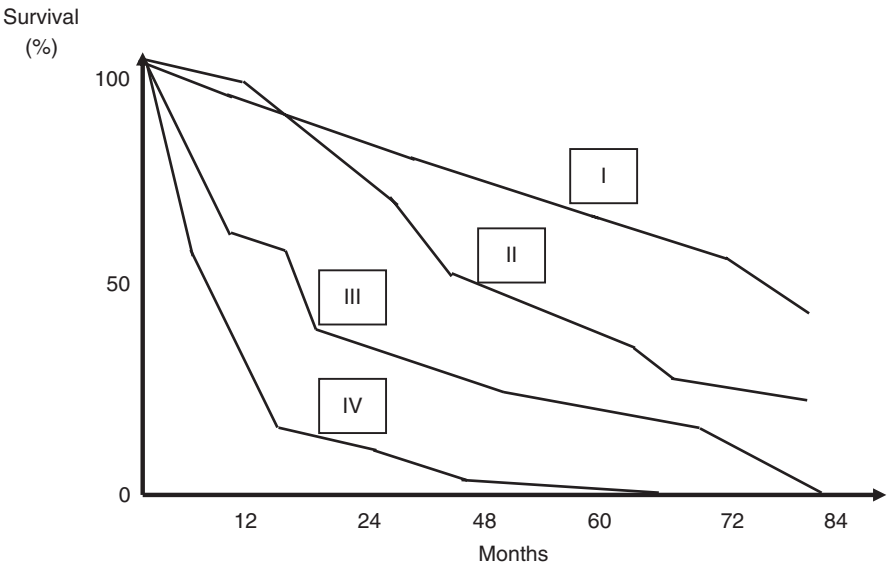


Fig. 1.1 Criteria employed in the Keith–Wagener (KW) classification and survival of patients classified according to KW class [6]

tool still used to estimate target organ damage in patients with hypertension. Classes I and II, however, do not discriminate between different consequences of hypertension for retinal vessels (see Chap. 3) [7].

Many people disdained the role of high BP in the causation of cardiovascular disease. In his classic book *Heart Disease* [8], Paul White stated that

hypertension could be an important compensatory mechanism, which should not be tampered with. Dozens of cohort studies conducted between the fourth and ninth decades of the last century, with large sample sizes, established beyond any reasonable doubt that high BP is the main cardiovascular risk factor.

1.1 Risks for Coronary Heart Disease, Stroke, and Cardiovascular Mortality

Coronary heart disease (CHD) and stroke were the first consequences of high BP to be identified in cohort studies. The authors of the pioneering cohorts put together a group—the Prospective Studies Collaboration—to do meta-analyses of individual data. The first report, in 1990, focused exclusively on the risks of diastolic BP, which was the diagnostic paradigm at that time [9]. This meta-analysis introduced the concept of regression dilution bias in epidemiological studies, which is important not only for epidemiological research but also for clinical practice (see Chap. 3). The authors arbitrarily chose 90 mmHg of diastolic BP as a reference value (Fig. 1.2, *top*). Values below 90 mmHg were, however, already associated with lower risk, anticipating what would be shown in the third meta-analysis. In the second meta-analysis, the Prospective Studies Collaboration demonstrated that relative risks of high BP were higher in younger individuals and that absolute risks were higher in the elderly [10] (Fig. 1.2, *bottom*).

Despite this evidence, isolated and small cohorts reported risks only at higher BP values, when the risks of the previous level were already elevated. The increase in risk with elevation of systolic BP to 140 mmHg was not revealed. In a late analysis of the Framingham Study cohort, the authors concluded that a spline model would better explain the increase in risk [11]. According to this statistical model, which contemplates dynamic changes in the direction of associations, there was no apparent increase in risk below 140 mmHg in men aged 45–54 years, 150 mmHg in the 55- to 64-year age range, and 160 mmHg in the 65- to 74-year age range (Fig. 1.3).

The more extensive and important meta-analysis of the Prospective Collaboration came out in 2002 [12]. It included 61 cohort studies, which identified 56,000 deaths from cardiovascular events in one million individuals followed for 15 years. The risk of elevated BP for cardiovascular events increased steadily from 75 to 115 mmHg of diastolic and systolic BP, respectively, doubling with every 10 mmHg of diastolic BP and with every 20 mmHg of systolic BP (Fig. 1.4a). The baseline risk, on which overlies the risk posed by increased BP, increased every 10 years. In Fig. 1.4a, the absolute risks highlighted on the vertical axis are log transformed—a procedure that rectifies the actual association. In Fig. 1.4b, with real intervals on the vertical axis, the association between increased BP and cardiovascular risk is expressed as exponential curves. Duplication of low risks has less absolute impact, with a more significant increase (inflection of the curve) when the preceding absolute risks are already high.

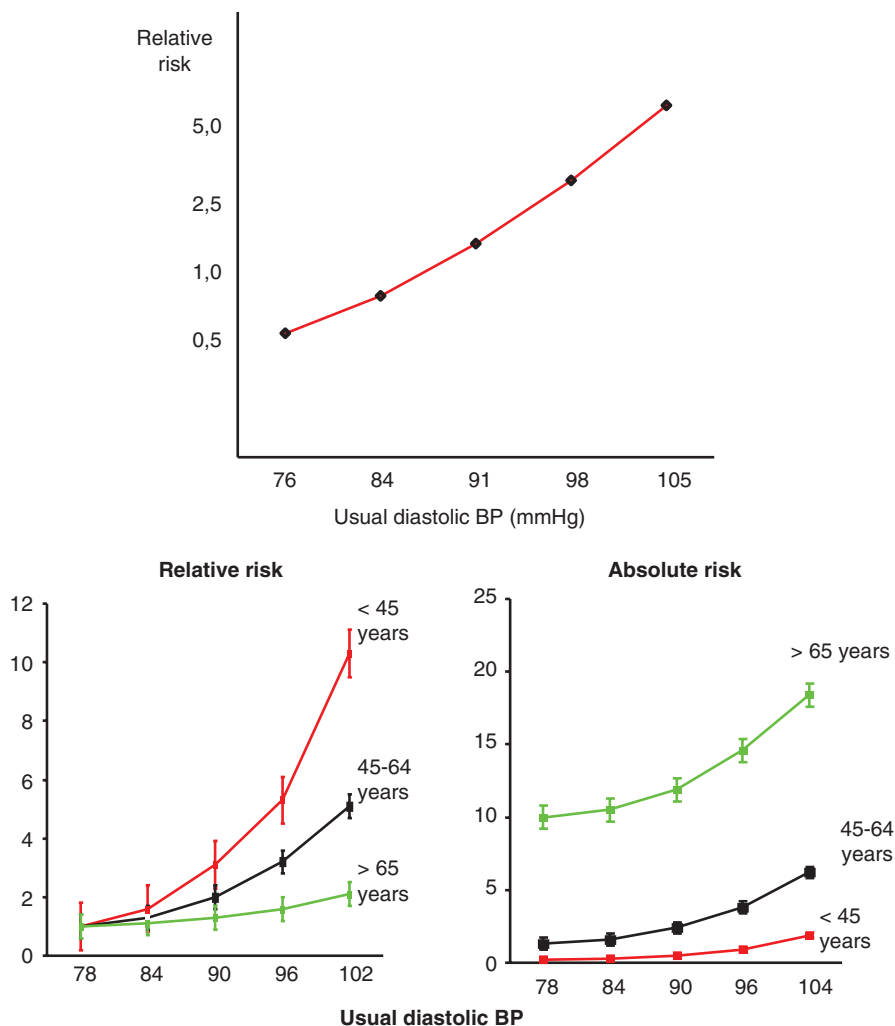


Fig. 1.2 Association between usual blood pressure and incidence of stroke: results from the meta-analyses by the Prospective Studies Collaboration, showing relative risk for the whole sample (*top*) and relative and absolute risk in participants stratified by age (*bottom*). (Modified from MacMahon et al. [9] and the Prospective Studies Collaboration [10], with permission)

Points of higher inflection are employed to define the thresholds for diagnosis of hypertension. This meta-analysis established that the risks arise from systolic or diastolic BP—whichever is high.

The population attributable risks of high BP for incident CHD and stroke were 20% and 40%, respectively, based on a diagnosis of diastolic BP higher than

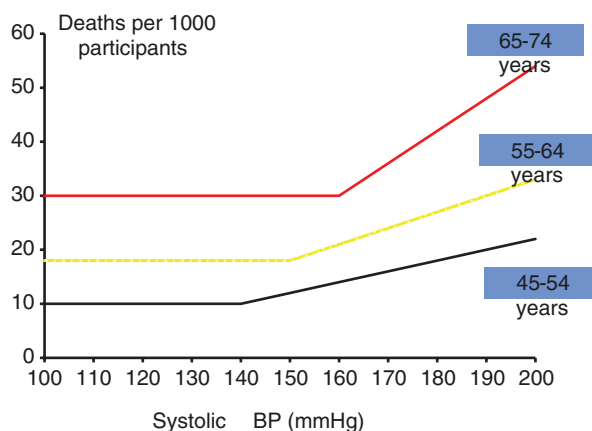


Fig. 1.3 Spline models applied to the Framingham Study cohort data (see text). (Modified from Port et al. [11], with permission)

90 mmHg. Researchers from the World Health Organization recalculated these risks, identifying that systolic BP higher than 115 mmHg or diastolic BP higher than 75 mmHg explain 49% of incident coronary events and 68% of strokes (Fig. 1.5, bottom) [13].

Further observational studies replicated the findings from the Prospective Studies Collaboration. Among them, we demonstrated the risks of high BP for cardiovascular outcomes in a population-based cohort study conducted in our city [14], expanding the findings to developing countries. In this cohort, the attributable risk of hypertension for cardiovascular events was 61%, compared with 10% for diabetes mellitus [15] (Fig. 1.5, top). In China, prehypertension and hypertension account for more than 50% of cardiovascular deaths [16]. Similar population attributable risks were identified in a US cohort of elderly individuals [17]. In a 2014 update report from the American Heart Association, high BP accounted for the highest population attributable fraction of cardiovascular disease mortality (40.6%), in comparison with 13.7% attributable to smoking and lower fractions attributable to other risk factors [18].

Nine risk factors explained almost 100% of the population attributable risk for ischemic stroke in a case–control study conducted at a reference hospital in our state [19] (Fig. 1.6). Hypertension, directly and as a risk factor for atrial fibrillation and left ventricular hypertrophy, was the dominant risk factor. Most of these conditions explained 90% of cases in the Interstroke case–control study [20]. This large worldwide study did not investigate the risks of atrial fibrillation, left ventricular hypertrophy, and carotid bruit. The findings from these case–control studies suggest that the full risk of high BP for stroke may be partially concealed by intermediate risks, such as the risk of atrial fibrillation.

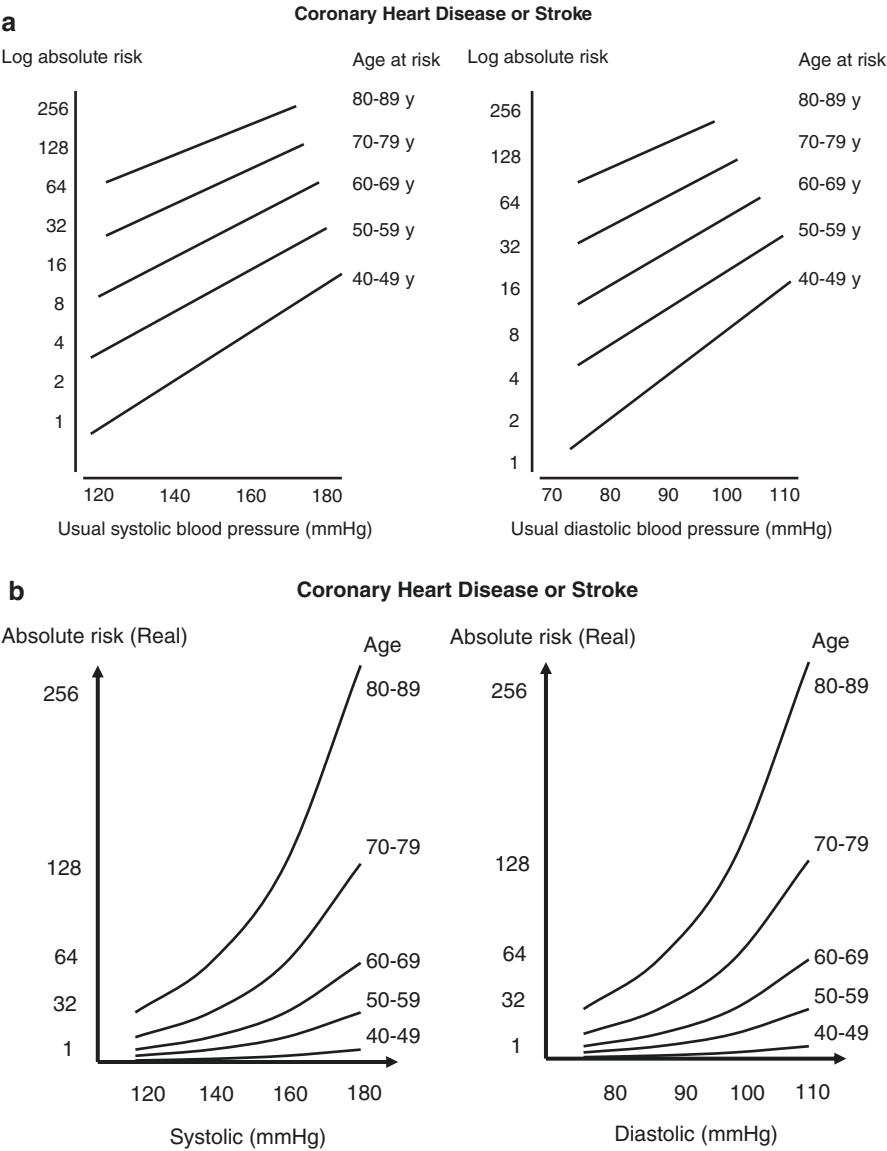


Fig. 1.4 Absolute risk for coronary heart disease or stroke according to blood pressure level, stratified by age group. **a** Log-transformed vertical axis. **b** Real axis. (Modified from the Prospective Studies Collaboration [12], with permission)

Fig. 1.5 Risk attributable to hypertension and diabetes mellitus in the city of Porto Alegre, Brazil (*top* [14, 15]), and estimated by the World Health Organization (*bottom* [13])

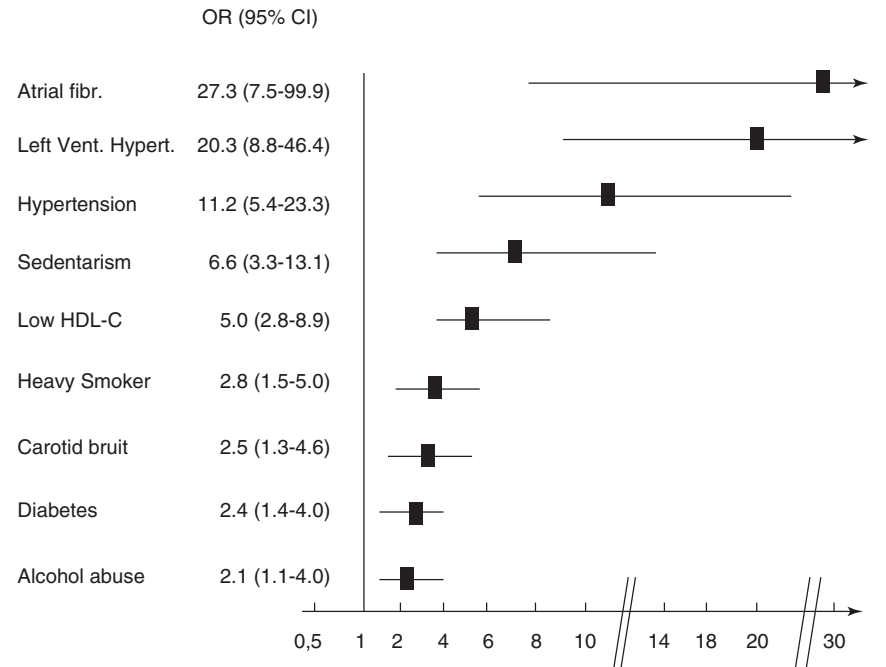
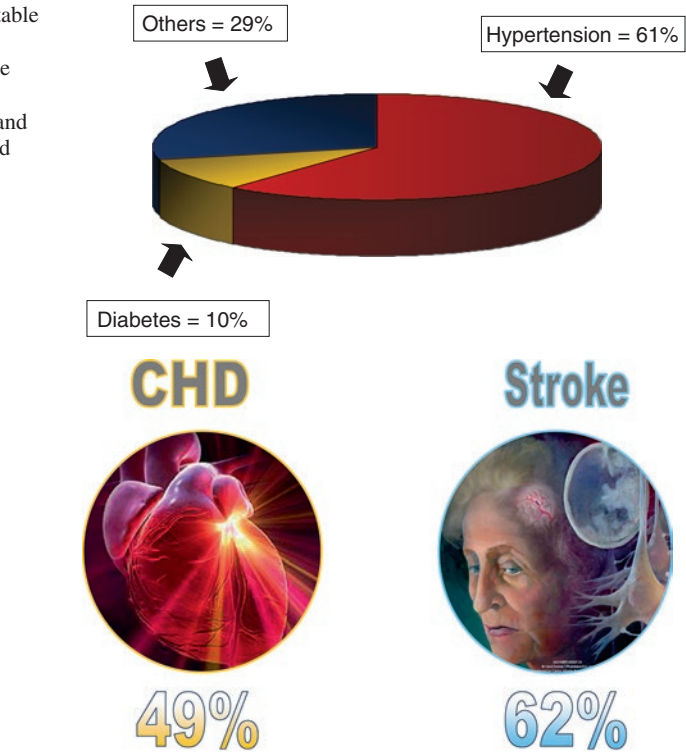


Fig. 1.6 Risk factors for stroke. (Reprinted from Mallmann et al. [19], with permission)

1.2 Other Risks of High Blood Pressure

Besides the risks for stroke and CHD, high BP is a risk factor for other cardiovascular and noncardiovascular diseases (Box 1.1). Usually, CHD and stroke occur earlier in the life-span of patients with hypertension, determining their prognosis. Elderly individuals are still at risk of presenting with these events, but other consequences emerge at this age, such as hypertensive cardiomyopathy (and its consequences, heart failure and atrial fibrillation) and heart valve disease. The lower incidence of CHD and stroke that is occurring in developed countries probably results from the reduction in hypertension. With aging and persistence of elevated BP (even within prehypertension limits), the cardiac and heart valves consequences prevail—a situation that is already happening and probably will be dominant among cardiovascular diseases in the coming decades.

The main consequences of high BP may therefore be classified as those that manifest from young adulthood to very elderly age—death, CHD, and stroke—and those almost exclusive to elderly and very elderly individuals—heart failure with a preserved ejection fraction, aortic syndromes, aortic stenosis, and dementias.

Box 1.1 Consequences of hypertension

Stroke

Coronary heart disease

Hypertensive cardiomyopathy

Heart failure

Aortic valve stenosis and other heart valve diseases

Aortic syndromes

Peripheral arterial disease

Atrial fibrillation

Chronic kidney disease

Dementias

Diabetes mellitus

Age-related macular degeneration

Erectile dysfunction

1.2.1 Heart Failure

Heart failure caused by CHD (myocardial infarction, extensive segmental ischemia), with contractile impairment, is indirectly caused by hypertension (heart failure with a reduced ejection fraction (HFrEF)). On the other hand, hypertension is a direct cause of heart failure with a preserved ejection fraction (HFpEF), as a consequence of hypertensive cardiomyopathy. Its incidence and morbidity are similar to those of HFrEF [21]. Studies have identified various risk factors and pathogenic mechanisms for its development. In all studies, however, hypertension has emerged as a major risk factor.

An international collaboration investigated the causes of the subtypes of heart failure (HFpEF and HFrEF) [22]. In the derivation cohorts, the final predictive model for HFpEF included age, sex, systolic BP, body mass index,

antihypertensive treatment, and previous myocardial infarction. This model had good discrimination for development of HFpEF in the validation cohort (a *c*-statistic of 0.76). Note that all modifiable variables in the model were related to hypertension, besides systolic BP. Antihypertensive treatment identifies the diagnosis of hypertension, and myocardial infarction is in large part attributable to previous hypertension. The main intermediate mechanism linking excessive adiposity to cardiovascular consequences is hypertension (see Chap. 2). In practical terms, HFpEF is a clinical manifestation of hypertensive cardiomyopathy.

The strong benefit of antihypertensive treatment for prevention of heart failure provides proof of concept that hypertension, directly or through intermediate cardiomyopathies, is the major cause of heart failure (see 1.5, proof of concept).

1.2.2 Aortic Valve Stenosis and other heart valve diseases

Aortic valve stenosis is progressively assuming preponderance among cardiovascular diseases in elderly and very elderly individuals. Two reasons explain this fact: the increasingly proportion of elderly people in populations, and long-term exposure of the aortic valve leaflets to sustained blood flow at high pressure in patients with hypertension. Arterial wave reflection due to aortic stiffness and increasing central BP—typical in the elderly—may add an additional burden to the aortic valve [23]. A bicuspid aortic valve is more sensitive to damage, since it divides the overload by two instead of three leaflets.

High BP is the major risk factor for development of aortic stenosis in the elderly [24]. Studies have identified an association of high BP with aortic calcification and stenosis. In a cohort with baseline assessment by ambulatory BP (ABP) monitoring [25], awake and sleeping diastolic BP were independently associated with advanced calcification after adjustment for confounding. In a cohort of 101 patients with aortic stenosis evaluated by computed tomography, systolic hypertension was the strongest risk factor for progression of aortic valve calcification [26]. A risk for aortic valve stenosis and regurgitation [Kazem Rahimi, personal communication, article submitted, 2017], and mitral regurgitation [27] similar to that described for CHD, stroke, and peripheral arterial disease was identified in a cohort of 5.0 million individuals.

1.2.3 Atrial Fibrillation

Atrial fibrillation is closely related to high BP, as another consequence of hypertensive cardiomyopathy or through the intercurrentence of CHD. In a cohort of 4.3 million adults, an increase of 20 mmHg in systolic BP was associated with a 21% higher incidence of atrial fibrillation (relative risk (RR) 1.21, 95% confidence interval (CI) 1.19–1.22) [28].

1.2.4 Aortic Stiffness and Aortic Syndromes

High BP is the predominant risk factor for development of aortic stiffness. On the other hand, aortic stiffness promotes rises in systolic and central BP (see Chap. 3), suggesting there is a bidirectional association between high BP and aortic stiffness,

particularly in elderly individuals. Aging and primary abnormalities in the vascular biology of the aortic wall would be other risk factors for aortic rigidity.

Identification of the predominant pathway linking high BP to aortic stiffness requires studies with a longitudinal design and assessment of aortic properties and BP at baseline. The Bogalusa Heart Study provided an opportunity to evaluate the temporal relationship of elevated BP to arterial stiffness and elasticity [29]. Adults aged 32–51 years were followed for 7 years on average. High BP preceded increases in the aortic–femoral pulse wave velocity and large- and small-arterial compliance, suggesting that the predominant cause of arterial stiffness was high BP.

Aortic syndromes—aneurysm and dissection—are in large part resultant from high BP, surpassing the proportion attributed to medial degeneration [30].

1.2.5 Peripheral Arterial Disease

Using an approach similar to that of the Prospective Studies Collaboration, Emdin et al. showed, in a cohort of 4.2 million adults, that an increase of 20 mmHg in usual systolic BP was associated with a 63% higher risk of peripheral arterial disease [31]. The association between usual systolic and diastolic BP mimics that described for stroke and CHD (Fig. 1.7). In this territory, however, the habit of smoking prevails as a risk factor.

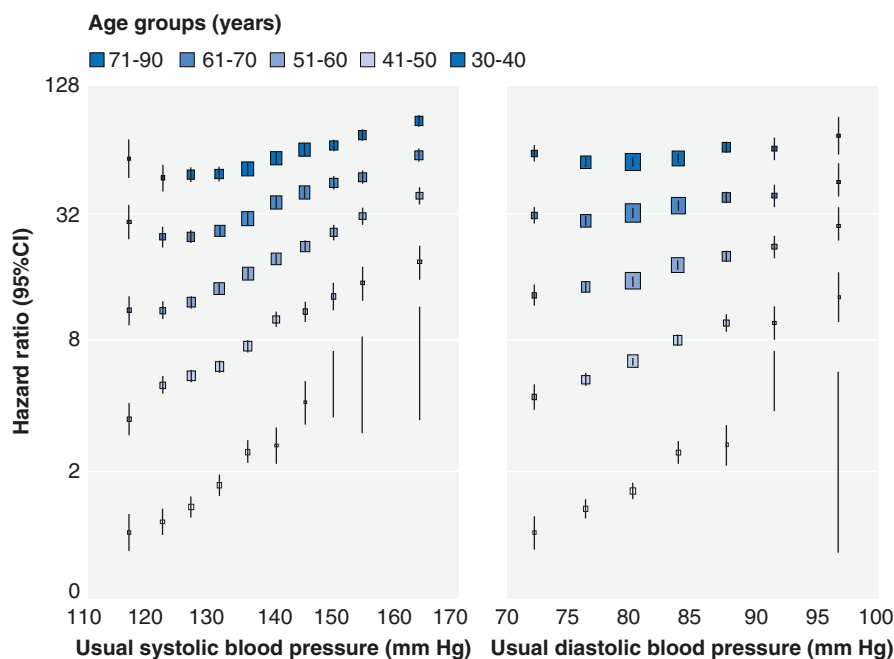


Fig. 1.7 Hazard ratios for incident peripheral arterial disease according to systolic and diastolic blood pressure, stratified by age. (Reprinted from Emdin et al. [31], with permission)

1.2.6 Chronic Kidney Disease

In the past, most cases of chronic kidney disease (CKD) were ascribed to hypertension. The estimates were biased by the cross-sectional design of the studies, which identified that the majority of patients with chronic renal insufficiency had hypertension. In many cases, however, hypertension was secondary to CKD. Longitudinal studies have shown that diabetes mellitus is the major risk factor for CKD, but there is also longitudinal evidence showing the risk of high BP, which ranks as the second biggest cause of CKD.

Klag et al. identified a parallel increase between the risk for end-stage renal disease and the stages of hypertension in the Multiple Risk Factor Intervention Trial (MRFIT) cohort [32], but participants did not have their baseline kidney function assessed. In a cohort of participants in a Kaiser Permanente study, who did not have kidney disease at baseline, the risks for end-stage renal disease increased progressively from 1.62 (95% CI 1.27–2.07) in individuals with prehypertension to 4.25 (95% CI 2.63–6.86) in those with blood pressures $\geq 210/120$ mmHg, in comparison with optimal BP [33]. Risks starting at the prehypertension stage were similarly identified in the Ohasama study (Fig. 1.8) [34]. In the same cohort, nighttime BP on ABP monitoring was a better predictor of CKD than daytime BP [35].

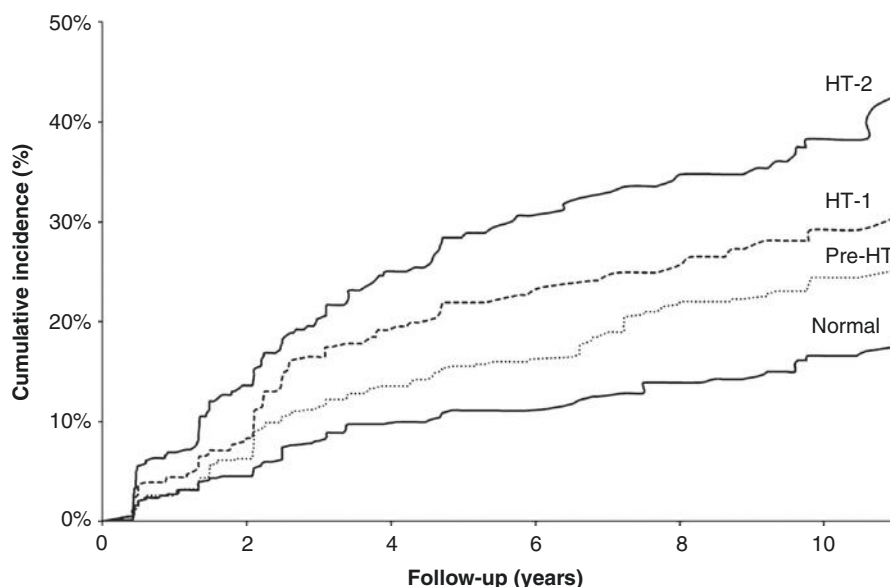


Fig. 1.8 Cumulative incidence of chronic kidney disease in subjects with normotension, prehypertension (Pre-HT), stage 1 hypertension (HT-1), and stage 2 hypertension (HT-2). (Reprinted from Kanno et al. [34], with permission)

1.2.7 Dementias

Dementias are other consequences of high BP. The association between Alzheimer disease and high BP, however, is not fully established. Three meta-analyses did not identify hypertension as an independent risk for Alzheimer disease [36–38]. Studies have shown that high BP in midlife, but not close to the start of the disease, is a risk factor for Alzheimer disease [39, 40]. A statement from the American Heart Association recognized BP in midlife as a strong risk factor for Alzheimer disease [41].

Vascular dementia is more clearly associated with hypertension. Loss of cognitive function after stroke or other manifestations of cerebral ischemia is expected as part of the natural history of cerebrovascular disease. It is still debated whether cognitive decline can happen without documented episodes of ischemia. A cohort study of 4.28 million individuals identified an association between high BP and the incidence of vascular dementia, irrespective of a preceding transient ischemic attack or stroke [42].

1.2.8 Diabetes Mellitus

Diabetes mellitus is a risk factor for development of hypertension (see Chap. 2). Observational studies have suggested that the opposite is also possible. In a cohort study of 4.1 million adults who were free of diabetes at baseline, 20 mmHg higher systolic BP and 10 mmHg higher diastolic BP were associated with 58% and a 52% higher risks of new-onset diabetes, respectively [43]. A systematic review of 30 studies presented in the same report identified similar risks for developing diabetes mellitus. Increases in body mass index (BMI) and age attenuated the risks. Causal and mechanistic links to explain such associations are speculative.

1.2.9 Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is one of the leading causes of blindness in the elderly. Its pathogenesis is complex and not fully understood [44], but that is not essential for the purpose of this book. The association between BP and AMD is controversial. Most epidemiological studies have been of lower quality, particularly in relation to assessment of BP and definition of hypertension. Just a few have had a cohort design, and the statistical analyses may have overadjusted for confounders, such as excessive adiposity. In a meta-analysis, four longitudinal and six cross-sectional studies yielded nonsignificant estimates, while in three case-control studies, there was a 1.48 (95% CI 1.22–1.78) risk ratio [45]. The poor quality of the studies precluded identification of other risk factors for AMD, such as diabetes mellitus [46].

1.2.10 Erectile Dysfunction

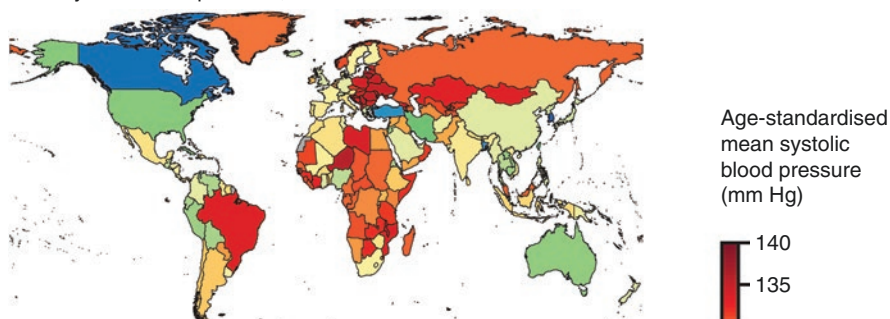
Studies have identified hypertension as a risk factor for erectile dysfunction. In a meta-analysis of 40 studies, including 121,641 individuals, hypertension was associated with a risk of 1.74 (95% CI 1.63–1.80) for the incidence of erectile dysfunction

[47]. The pathophysiological substrate for erectile dysfunction is a decrease in penile blood flow [48]. A low penile peak systolic velocity on Doppler ultrasound is a risk factor for cardiovascular events in patients with hypertension [49].

1.3 Populations at Risk and Trends in High Blood Pressure

Most countries have estimates of their prevalence of hypertension, and reviews presenting worldwide estimates have been published. None have been more comprehensive and extensive than those provided by the Non-communicable Diseases Risk Factor Collaboration (NCD-RisC). The last report covered more than 200 countries, analyzing high BP trends in 19.1 million individuals [50]. The number of individuals with hypertension (according to the 140/90 mmHg criteria) increased from 594 million in 1975 to 1.13 billion in 2015, mostly because of the aging of populations and increases in prevalence in low- and middle-income countries. The mean BP decreased consistently from 1975 to 2015 in high-income countries, with larger uncertainty in Central and Eastern Europe, Latin America, the Caribbean, Central Asia, the Middle East, and North Africa. In contrast, BP increased in East and Southeast Asia, South Asia, Oceania, and sub-Saharan Africa. Figure 1.9 presents the current distribution of BP by country.

Mean systolic blood pressure, men 2015



Mean systolic blood pressure, women 2015

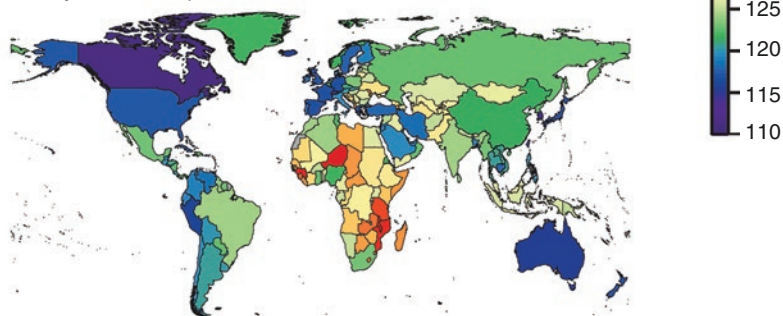


Fig. 1.9 Mean systolic blood pressure in different countries in 2015. (Reprinted from NCD Risk Factor Collaboration [50], with permission)

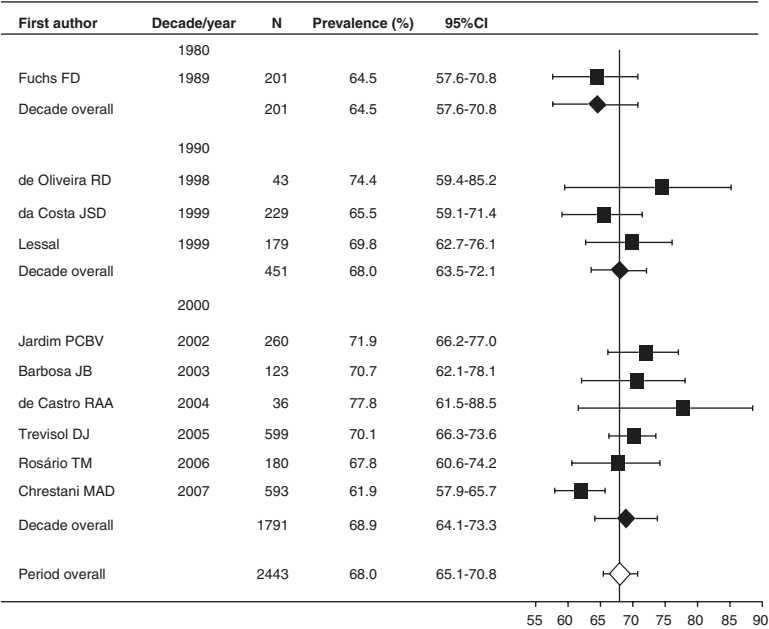
The findings from the NCD Risk Factor Collaboration [50] require scrutiny. Favorable trends in high and some middle-income countries concerning the prevalence of hypertension and BP give the false idea that the burden of hypertension is decreasing, particularly with development of nations. The prevalence of hypertension according to the 140/90 mmHg criterion, however, does not capture the full risk of high BP. The prevalence of prehypertension, which conveys risk for cardiovascular events and target organ damage, is estimated to be between 25% and 50% in adults worldwide [51].

The Global Burden of Disease Study—another collaborative study for investigation of global health risks—identified that high systolic BP moved from being the third biggest contributor to global disability-adjusted life-years (DALYs) in 1990 to being the biggest contributor currently [52]. The same study provided data on temporal trends (from 1990 to 2015) in the prevalence and risks of systolic BP ≥ 110 –115 mmHg and ≥ 140 mmHg [53]. Trends in systolic BP were extracted from 844 studies from 154 countries, totaling 8.69 million individuals. The number of individuals with systolic BP ≥ 110 mmHg increased from 73,119 (95% CI 67,949–78,241) to 81,373 (95% CI 76,814–85,770) per 100,000. The estimated annual death rate per 100,000 people associated with systolic BP ≥ 110 –115 mmHg increased from 135.6 (95% CI 122.4–148.1) to 145.2 (95% CI 130.3–159.9).

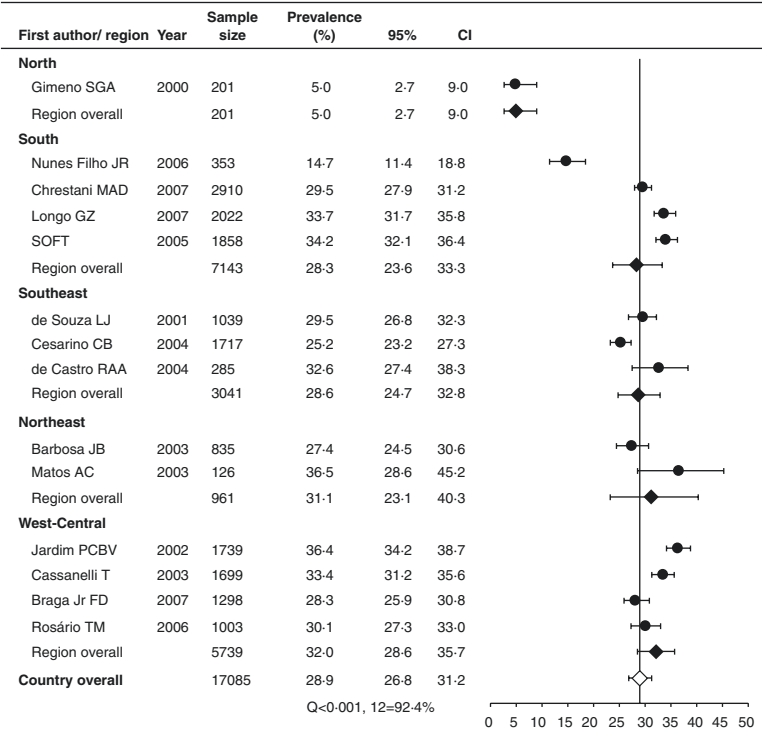
The data from the BP analyses presented above were mostly driven by a low mean BP and a low prevalence of hypertension in young adults. The prevalence among the elderly is more striking and tends to be progressively greater with aging of all populations. Figure 1.10 shows trends in hypertension in adults and the elderly in Brazil. Among all adults, including the elderly, the prevalence was 28.7% (95% CI 26.2–31.4), in comparison with 68.0% (95% CI 65.1–69.4) among elderly individuals [54, 55]. These proportions are similar to those described in other countries, including developed countries with lower average BP. These findings lend support to the interpretation that transition to high BP is still a major problem, even in countries with a trend toward lower average BP.

Fig. 1.10 Prevalence of hypertension in all adults (*top*) and in the elderly (*bottom*) in Brazil. (Reprinted from Picon et al. [54, 55], with permission)

Pooled Prevalence of hypertension among elderly in urban Brazil.



Prevalence of hypertension, according to Joint National Committee* criteria, by Brazilian region in the 2000's.



1.4 Diagnostic Thresholds: Recommendations from Hypertension Guidelines

The continuous risk of BP for cardiovascular events cannot be used for clinical purposes, and a dichotomous definition of hypertension is therefore required. Studies with small samples have identified diagnostic thresholds at BP values associated with a more pronounced shift in the curves of risks. Figure 1.4b shows that the risk inflection associated with increasing diastolic BP is situated between 90 and 100 mmHg, which explains the diastolic BP threshold of 95 mmHg chosen for diagnosis in earlier guidelines. Until the early 1990s, diastolic BP was presumably the only determinant of risk, since the increase in systolic BP was taken as a natural consequence of aging. The benefit of treating isolated systolic hypertension, demonstrated by two large trials [56, 57], refuted this interpretation, and systolic BP of 160 mmHg (initially) and 140 mmHg (more recently) were set as diagnostic limits and goals for treatment.

The report of the first US Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC I) was released in 1973 and published a few years later [58]. In subsequent years, it was updated seven times. Several countries and scientific societies of hypertension have published their own guidelines since then. In its 2003 report (JNC 7), the Joint National Committee coined the concept of prehypertension, corresponding to systolic BP between 120 and 139 mmHg or diastolic BP between 80 and 89 mmHg [59]. The Committee proposed this new classification “to identify those individuals in whom early intervention by adoption of healthy lifestyles could reduce BP, decrease the rate of progression of BP to hypertensive levels with age, or prevent hypertension entirely.” The risk of prehypertension for cardiovascular events was commented on only in relation to the topic of stroke prevention.

In 2014, the JNC 8 report [60] abandoned the concept of prehypertension because there was no trial showing benefits of treatment in this BP range. In addition, JNC 8 proposed higher BP values to diagnose hypertension in patients with diabetes mellitus or CKD, and in the elderly population. Among patients with diabetes, the decision was based on the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [61], which had not shown a statistically significant reduction in the incidence of CHD in patients randomized to a more intensive BP-lowering strategy (120 mmHg) in comparison with a conservative strategy (140 mmHg). The authors of the JNC report ignored the strong benefit of prevention of stroke in the ACCORD trial and the possibility that the absence of a significant benefit in prevention of CHD could have been secondary to a beta error.

The European guideline for the management of arterial hypertension adopted a similar interpretation before the release of the US guidelines [62], increasing diagnostic values for patients with diabetes mellitus and CKD, and for the elderly population, in comparison with the previous guideline [63].

Table 1.1 presents the differences in BP thresholds between the previous and current European and US guidelines. If strictly followed, these guidelines would put millions of people at higher risk for suffering a cardiovascular event. The proportion of elderly individuals in the USA who met BP goals increased to 65.8% according to the JNC 8 criteria, in comparison with 40.0% according to the JNC 7 guideline [64]. This guideline has therefore had an apparent and huge therapeutic effect, because many individuals were classified as having normal BP without changing their treatment.

Table 1.1 Comparison of diagnostic thresholds of blood pressure (BP) in the previous and current US and European guidelines for hypertension

Condition	Guideline	Year	BP threshold (mmHg)
Prehypertension	JNC	2003	120/80
		2014	[Abolished]
High-normal	European	2009	130/85
		2013	130/85
Diabetes/CKD	JNC	2003	130/80
		2014	140/90
	European	2009	130/80
		2013	140/85
Elderly	JNC	2003	140/90
		2014	150/90
	European	2009	140/90
		2013	160/90

CKD chronic kidney disease, JNC US Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure

The American Heart Association and the American College of Cardiology decided to issue their own guideline, which was recently released [65]. It is quite comprehensive and covers almost all aspects of hypertension, similarly to the former JNC guidelines. This guideline established lower BP thresholds to diagnosis hypertension. Normal BP was set at values of systolic BP below 120 mmHg and diastolic BP below 80 mmHg. Systolic BP between 120 and 129 mmHg and diastolic below 80 mmHg was classified as elevated BP. The guideline recommended that the diagnosis of hypertension should be based on systolic BP equal or higher than 130 mmHg or diastolic BP equal or higher than 80 mmHg. This new classification points to the right direction and if implemented will reduce substantially the burden of high BP.

The authors recognized that BP within the elevated BP category is a risk for cardiovascular disease, but recommended only non-drug approaches to prevent the increasing of BP. The use of BP-lowering medications was recommended for patients with hypertension for secondary prevention of cardiovascular disease, including patients with diabetes or chronic kidney disease. Drug treatment was also recommended for individuals with hypertension and estimated 10-year atherosclerotic cardiovascular disease risk of 10% or higher. Individuals older than 65 years without other risks or diseases will likely have cardiovascular risk higher than 10% in ten years. In my view, there is no reason do not offer drug treatment for the individuals who do not have these conditions and do not respond to non-drug therapies. Even with low short-term risk, they will be exposed for longer time to the cardiac and vascular consequences of high BP. And finally, they will be treated with drugs when they commemorate their 65th birthday. The same should be considered for individuals with elevated BP.

1.5 Proof of Concept: Experimental Evidence

The JNC 8 proposal for diagnostic limits and therapeutic targets for BP was based on BP values for which the benefit of treatment had been demonstrated. This assumption is conceptually correct to provide proof of concept of causes of disease. Since it is unethical to experimentally expose human beings to potential

Table 1.2 Beneficial effects of blood pressure (BP)-lowering drugs in patients with normal BP and cardiovascular disease

Clinical condition	Study	Active treatment	Primary outcome	RRR, % (95% CI or <i>P</i> value)
Diabetes mellitus	Micro-HOPE [67]	Ramipril	MI, stroke, CV death	25% (12–36)
Any evidence of atherosclerosis	HOPE [68]	Ramipril	MI, stroke, CV death	22% (14–30)
	EUROPA [69]	Perindopril	MI, CV death, cardiac arrest	20% (9–29)
Recovery from stroke	PROGRESS [70]	Indapamide + perindopril	Stroke	42% (19–58)
Asymptomatic heart failure	SOLVD [71]	Enalapril	CV death	12% (–3 to 26)
Overt heart failure	SOLVD [72]	Enalapril	CV death	18% (6–28)
	SAVE [73]	Captopril		21% (5–35)
Class IV heart failure	CONSENSUS [74]	Enalapril	Total mortality	40% (<i>P</i> = 0.002)

CONSENSUS Cooperative North Scandinavian Enalapril Survival Study, *CV* cardiovascular, *EUROPA* European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease, *HOPE* Heart Outcomes Prevention Evaluation, *MI* myocardial infarction, *PROGRESS* Perindopril Protection Against Recurrent Stroke Study, *RRR* relative risk reduction, *SAVE* Survival and Ventricular Enlargement, *SOLVD* Studies of Left Ventricular Dysfunction

determinants of disease, an experiment should compare the efficacy of antagonists of the presumed cause of disease.

In the case of high BP, however, the authors of the JNC 8 report ignored the benefit of treatment shown by various randomized clinical trials done in patients with BP within prehypertension limits. These studies enrolled patients with CHD, heart failure, stroke, and diabetes mellitus. The drugs employed in those trials were mostly beta blockers, ACE inhibitors, and diuretics. In contrast to the interpretation predominant at that time, the BP-lowering effects of these drugs—and not putative pleiotropic effects—could explain the beneficial effects seen in the clinical conditions presented in Table 1.2 [66].

Two meta-analyses have corroborated this conclusion, showing that the benefit of treatment could be ascribed to the BP-lowering effects of these drugs [75, 76].

A study by Law and colleagues [75] provided proof of concept that high BP was the major cause of cardiovascular disease [77]. The reductions in stroke and CHD incidence rates seen with a 10 mmHg reduction in systolic BP in clinical trials occurred in the same proportion that the Prospective Studies Collaboration meta-analysis [12] had estimated would occur with a similar reduction in BP (Fig. 1.11).

An analysis done in the Pittsburgh cohort of the Systolic Hypertension in the Elderly Program (SHEP) suggested that treatment of patients with systolic hypertension before development of subclinical or clinical disease can be more efficacious in prevention of cardiovascular events [78]. Figure 1.12 shows that the incidence of all-cause mortality and nonfatal cardiovascular events during a long follow-up period was substantially lower in patients who received treatment than in their counterparts who received placebo, and was similar to that in a cohort of patients with normal BP.

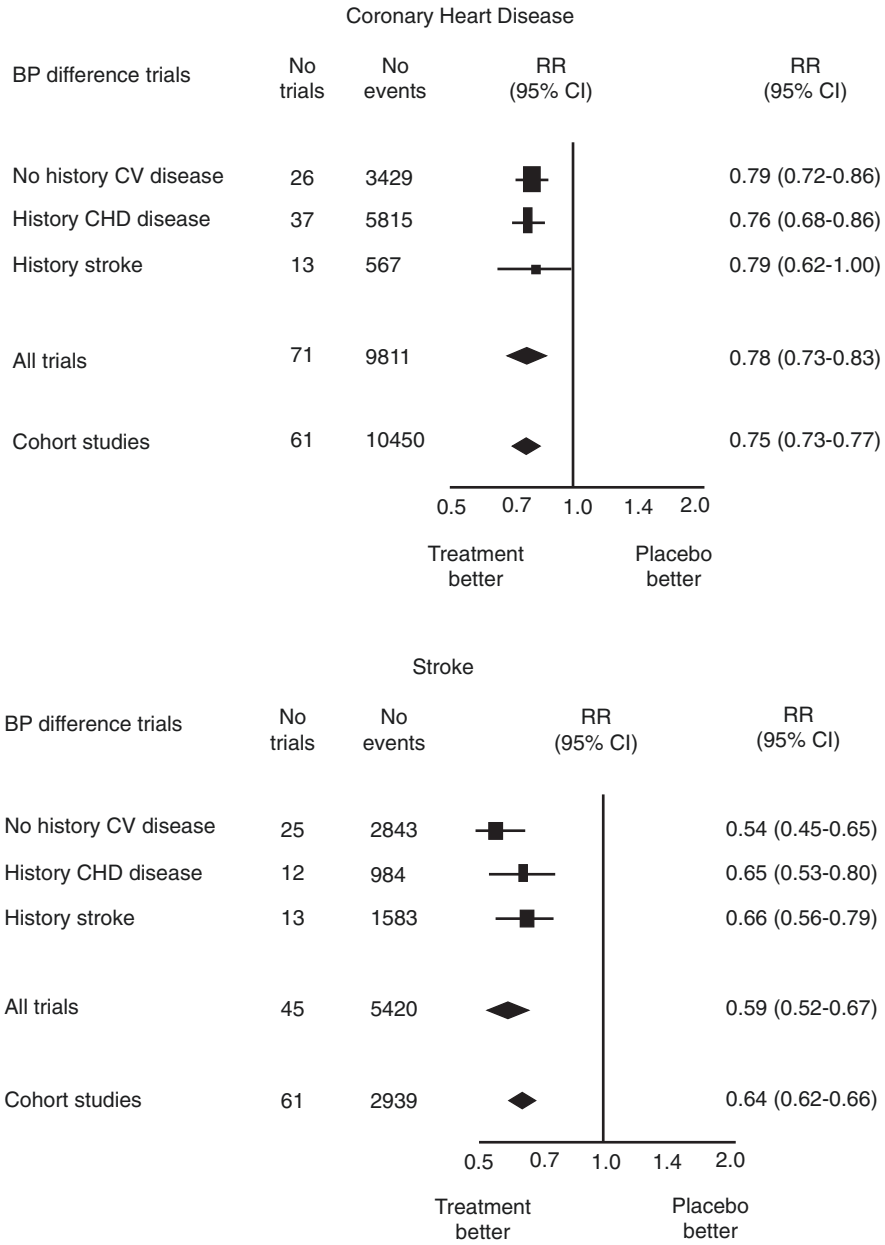


Fig. 1.11 Relative risks for coronary heart disease (*top*) and stroke (*bottom*) according to a standardized 10 mmHg systolic blood pressure difference between clinical trial arms in patients with and without previous cardiovascular disease, and size effect prediction from cohort studies. (Reprinted from Law et al. [75], with permission)

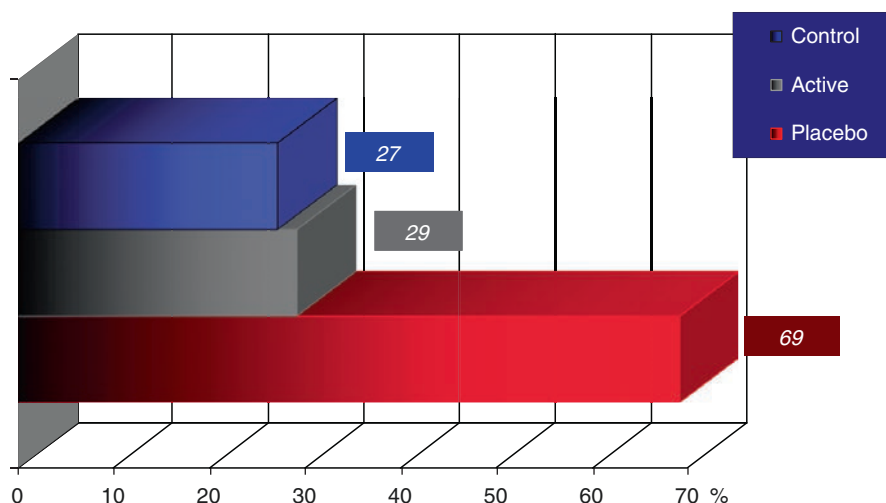


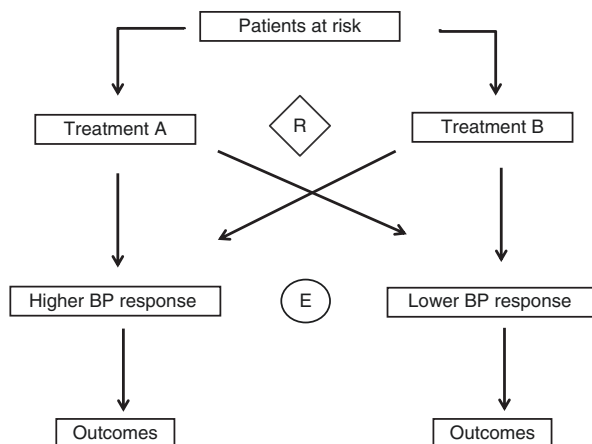
Fig. 1.12 Incidence of all-cause mortality and nonfatal cardiovascular events in participants in the Systolic Hypertension in the Elderly Program (SHEP) [78]

Heart failure is another outcome prevented by BP lowering in a proportion anticipated by studies of risk. Many consider heart failure to be a soft endpoint because the diagnosis depends mainly on symptoms. This interpretation is questionable because the symptoms are their own disease, which is quite limiting. Studies using harder definitions of heart failure have shown strong benefits of BP treatment, such as the incidence reductions of more than 50% seen in SHEP (RR 0.46, 95% CI 0.33–0.65) [56] and more than 60% seen in the Hypertension in the Very Elderly (HYVET) trial (RR 0.36, 95% CI 0.22–0.58) [79]. Patients allocated to the more intensive BP reduction strategy in the Systolic Blood Pressure Intervention Trial (SPRINT) (see Sect. 1.7) had an almost 40% lower incidence of heart failure than their counterparts randomized to a less intensive treatment strategy (RR 0.62, 95% CI 0.45–0.84) [80]. A meta-analysis of 35 placebo-controlled randomized clinical trials has confirmed the effectiveness of BP drugs in preventing and treating heart failure [81].

1.6 Goals for Treatment and the J-Shaped Phenomenon

The evidence that the risk of raised BP starts at 115/75 mmHg has been accepted as a threshold for risk but not as a goal for treatment. Cohort studies and post hoc analyses of clinical trials have indicated that the incidence of cardiovascular events could paradoxically increase if diastolic BP is reduced below 80–85 mmHg. The first description of the risks of excessive lowering of BP for incident myocardial infarction was published in 1979 [82]. Cruickshank et al., who coined the term “J-shaped relation,” reported this phenomenon in a cohort study [83]. In the following years, this phenomenon was described in post hoc analyses of many randomized clinical trials [84] and incorporated by guidelines, becoming a concern in the

Fig. 1.13 Exposure in post hoc analysis of clinical trials: *R* (randomization)—original comparison between groups created by randomization; *E* (exposure)—observational comparison between groups created by post hoc exposure to low and high blood pressure in patients from any of the original groups of randomization. (Reprinted from Fuchs and Fuchs [85], with permission)



management of hypertension. The risk would be higher in patients with CHD, in whom such a BP reduction could be particularly harmful for coronary perfusion.

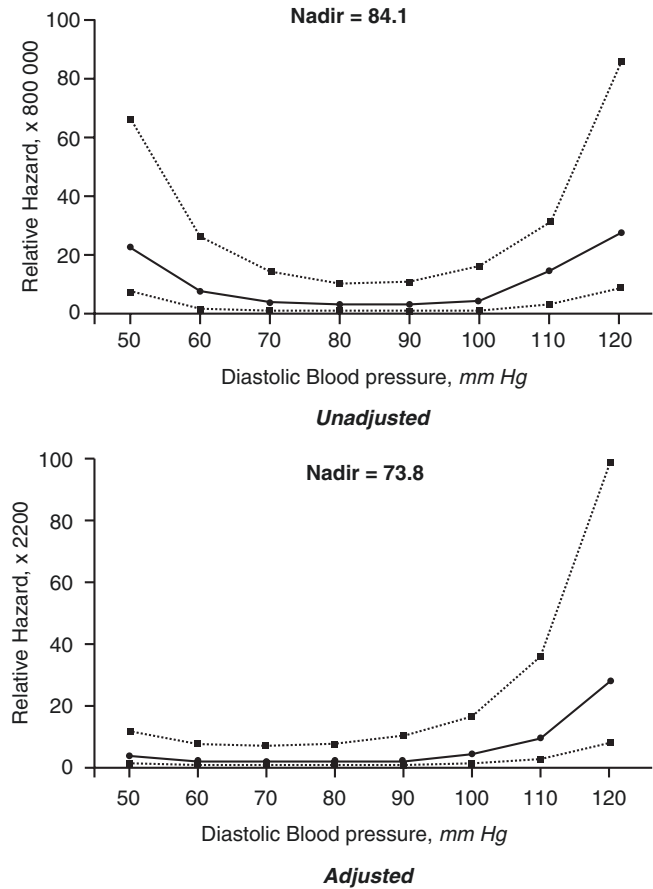
The association of BP with the risk for mortality has a U-shaped format, since below certain BP values, everyone would be dead. The uncertainty concerns the lowest point of the curve (nadir), not its format. We have proposed that the J-shaped phenomenon is an artifact and should not be a reason for concern in treatment of high BP [85]. The higher incidence of cardiovascular events observed at low levels of BP in cohort studies, particularly among the elderly, is attributable to frailty or subclinical disease, particularly heart failure [86]. Post hoc analyses of randomized controlled trials that explored the J-shaped phenomenon have compared the incidence of events in patients with low and high BP achieved during the trials, independently of the original randomized grouping (Fig. 1.13). As in cohort studies, the apparently greater intensity of BP lowering may be secondary to development of subclinical disease or frailty. These patients would benefit from further BP reduction.

A post hoc analysis of the International Verapamil–Trandolapril Study (INVEST) was presented as evidence of the J-shaped phenomenon [87]. Indeed, this analysis showed evidence that health status and other risk factors were confounders of the relationship between treated hypertension and the incidence of cardiovascular events. The nadir of the association between diastolic BP and cardiovascular events in the bivariate analysis was originally 84.1 mmHg and dropped to 73.8 mmHg after adjustment for age and comorbid conditions (Fig. 1.14).

The meta-analysis by Law and colleagues [75] provided sound evidence against the existence of the J-shaped phenomenon. Patients with cardiovascular disease and low BP randomized to further BP reduction had a lower incidence of cardiovascular events than the control group (Fig. 1.15). These trials were those originally planned to demonstrate beneficial effects of BP drugs independently of their BP-lowering effects [66].

New meta-analyses have provided further evidence against the existence of a clinically relevant J-shaped phenomenon. The first included 123 clinical trials with 613,815 participants [88]. The data were analyzed as in the study by Law and colleagues [75], exploring the association between a standardized 10 mmHg reduction in systolic BP and the observed reduction in the incidence of cardiovascular disease. The

Fig. 1.14 Influence of confounding on the association between achieved blood pressure and the incidence of cardiovascular events in the International Verapamil–Trandolapril Study (INVEST). The lines correspond to the relative hazard and 95% confidence interval. (Reprinted from Messerli et al. [87], with permission)



Coronary heart disease events					Strokes			
Pretreatment diastolic blood pressure (mm Hg)	No of trials	No of events	Relative risk (95% CI)	Relative risk (95% CI)	No of trials	No of events	Relative risk (95% CI)	Relative risk (95% CI)
70-74	5	663		0.79 (0.65 to 0.88)	2	284		0.64 (0.50 to 0.80)
75-79	21	3708		0.85 (0.76 to 0.94)	11	1394		0.76 (0.62 to 0.92)
80-84	8	1517		0.86 (0.73 to 1.01)	6	909		0.76 (0.66 to 0.88)
85-89	12	1462		0.84 (0.76 to 0.93)	10	1458		0.78 (0.66 to 0.92)
90-94	6	1358		0.88 (0.79 to 0.97)	7	1030		0.63 (0.56 to 0.72)
>,95	9	255		0.74 (0.58 to 0.94)	9	332		0.54 (0.42 to 0.69)
Not reported	12	848		0.85 (0.75 to 0.97)	2	13		0.63 (0.21 to 1.92)
All trials	71	9811		0.84 (0.81 to 0.88)	45	5420		0.70 (0.64 to 0.76)

Fig. 1.15 Relative risks for coronary events and stroke in patients stratified by blood pressure at the start of randomized controlled clinical trials. (Reprinted from Law et al. [75], with permission)

magnitude of prevention was the same as that predicted by cohort studies, corresponding to 20–30% of cardiovascular events, stroke, and infarction, and 13% of all-cause mortality. The effect was similar in patients who had a wide range of BP values at baseline, including patients with prehypertension. Patients with diabetes mellitus or CKD had reductions in cardiovascular events as well, but of a smaller magnitude.

The second meta-analysis included 19 studies ($n = 44,989$) that compared more and less intensive strategies to lower BP [89]. The more intensive strategy was associated with a reduction in the incidence of cardiovascular disease, myocardial infarction, stroke, retinopathy, and albuminuria. Patients with systolic BP lower than 140 mmHg and previous cardiovascular disease, diabetes mellitus, or CKD had a greater absolute benefit.

The third meta-analysis separately evaluated studies of strategies and studies of BP differences between arms of randomized trials, including those controlled by placebo [90]. The results were similar to those of the previous meta-analyses, with the difference that the absolute benefit was smaller in subjects with the lowest BP at baseline, since the authors excluded studies with patients with cardiovascular disease. This meta-analysis included findings from SPRINT (see Sect. 1.7).

The only meta-analysis that preserved the randomized comparisons within each trial arm showed a more clear benefit of reaching lower BP values with treatment [91]. The relative risk for a reduction of systolic BP to 120 to 124 mmHg in comparison to 125 to 129 mmHg was 0.82 (95% CI 0.67–0.97). In the comparison of BP 120 to 124 mmHg with >160 mmHg the relative risk was 0.36 (0.26–0.51).

Despite this consistent evidence, studies have continued to propose the existence of a J-shaped curve [92], incurring the same errors in analyses that were commented on earlier. A cohort study from the Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) [93] identified a J-shaped association between achieved BP and the incidence of various cardiovascular events. Among them, a J-shaped association with the incidence of heart failure was seen. Occurrence of heart failure due to BP treatment is not biologically plausible, and studies such as the classic Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [74] showed that patients with class IV heart failure and very low BP had 40% lower all-cause mortality when treated with enalapril. Independently of these explanations, the BP nadir values identified in CLARIFY were close to those predicted by observational studies, being around 70 mmHg for diastolic BP and 120 mmHg for systolic BP.

1.7 SPRINT

SPRINT is a milestone in the demonstration of the benefits of more intensive reduction of systolic BP [80]. In total, 9361 individuals older than 50 years, with systolic BP ≥ 130 mmHg and increased cardiovascular risk, but without diabetes mellitus, were randomized to one of two target strategies: reduction of systolic BP to less than 120 mmHg (intensive care) or to less than 140 mmHg (usual care). The presence of one or more of the following characteristics established high cardiovascular risk in participants: clinical or subclinical cardiovascular disease, chronic renal insufficiency (a glomerular filtration rate (GFR) between 20 and 60 mL/min), a Framingham score $\geq 15\%$, and age over 75 years. The choice of drugs was left to the discretion of investigators at the study centers, but there was a recommendation for use of thiazide-like diuretics as

the first choice, preferably chlorthalidone. Patients treated more intensively received, on average, 2.8 drugs versus 1.8 drugs received by those allocated to less intensive treatment. The mean systolic BP during the trial was 121.4 mmHg in the intensive treatment group versus 136.2 mmHg in the control group (a mean difference of 14.8 mmHg).

There was a 25% reduction in the primary composite endpoint (myocardial infarction, other acute coronary syndromes, stroke, heart failure, and cardiovascular disease mortality) in patients randomized to the intensive strategy (Fig. 1.16, *top*). There were reductions of 43% (95% CI 15–62) in cardiovascular mortality and 27% (95% CI 10–40) in all-cause mortality (Fig. 1.16, *bottom*). The benefit was similar in men and women, white and nonwhite participants, different age strata, patients in different systolic BP ranges at entry, and patients with kidney disease or cardiovascular disease.

There were more adverse events in the intensive treatment group: syncope (2.3% versus 1.7%), low BP complaints (2.4% versus 1.4%), and acute renal injury (4.4% versus 2.6%). The incidence of trauma by falling, requiring emergency consultation, was identical in both groups. Postural hypotension, measured objectively, was less common in the intensive treatment group (16.6%) than in the control group (18.3%, $P = 0.01$). The contrast between the higher incidence of complaints in the intensive treatment group and the lower or similar incidence of adverse effects measured objectively suggests that the former was due to the placebo effect, since it was an open study (for a detailed discussion of the placebo effect, see Chap. 4).

Other criticisms focused on the unattended automated BP measurement employed in the trial and the fact that participants treated with the higher BP strategy had BP drugs withdrawn during the trial. The first point is addressed in Chap. 3. The second point was inherent in the trial design, which tested goals for treatment and not drug treatments. If a patient randomized to the higher BP range achieved a BP value in the lower range or vice versa, the treatment strategy should have been changed to reduce the BP below the value planned for the group to which the patient was randomized.

An analysis restricted to participants aged ≥ 75 years (about 25% of the sample) confirmed the overall findings of the study [94]. There were greater reductions in the incidence of the primary composite endpoint (34%) and all-cause mortality (33%). Adverse events occurred in the same proportions of the different treatment arms, with increased incidence rates of some complaints being noted in the whole study among participants randomized to more intensive treatment (difference not significant). Trauma by falling was less frequent in the intensive treatment group (4.9% versus 5.5%), as was postural hypotension (difference not significant), which was measured objectively. The most important finding of this analysis was that intensive treatment was beneficial in the elderly population with and without frailty. This finding contradicts the clinical impression that elderly individuals with frailty are more susceptible to adverse effects of antihypertensive drugs and should therefore be treated with more caution.

1.8 Benefits of Treating Prehypertension

SPRINT provided the first indirect evidence that patients with prehypertension but without major cardiovascular disease should be treated with BP-lowering drugs. Participants who had prehypertension as a therapeutic target (below 140 mmHg) had a higher mortality rate and a higher incidence of cardiovascular events than those

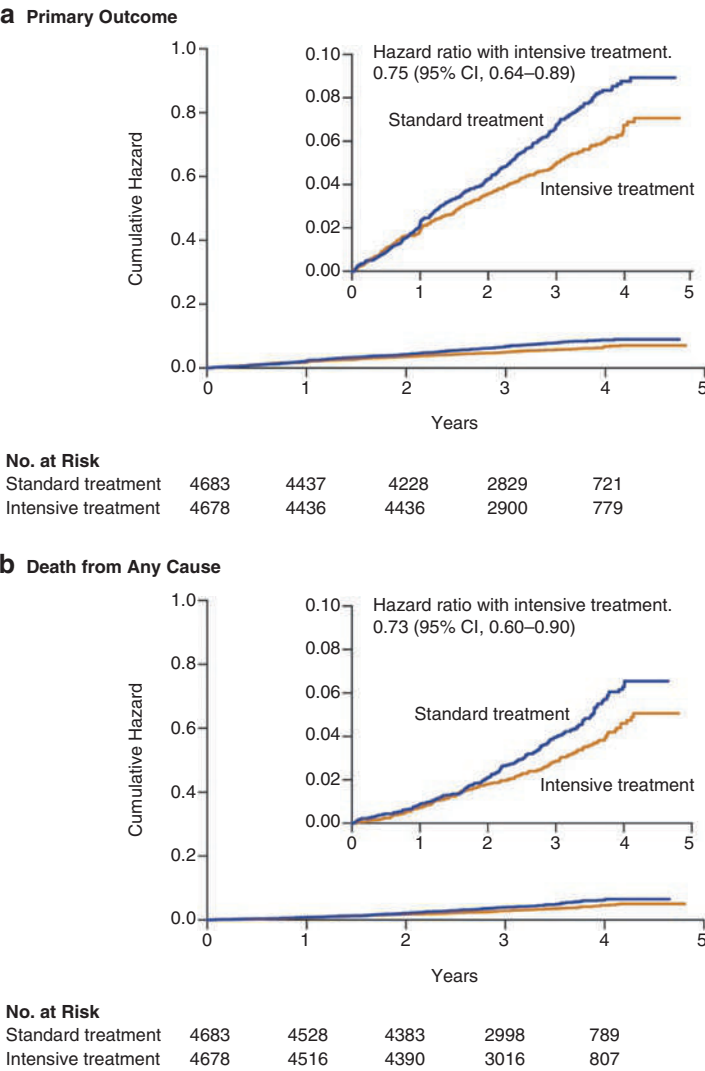


Fig. 1.16 Reductions in incidence rates of the primary endpoint (*top*) and all-cause mortality (*bottom*) in the Systolic Blood Pressure Intervention Trial (SPRINT). (Reprinted from the SPRINT Research Group [80], with permission)

randomized to reach a BP value below 120 mmHg. These findings added another piece to the evidence generated by the meta-analysis conducted by Ettehad and colleagues [88], demonstrating the benefit of reducing systolic BP to values below 130 mmHg.

Besides being a risk factor for cardiovascular disease, prehypertension (designated as “normal and high-normal BP” in the European guidelines) adds two further risks to the well-known risk for cardiovascular disease: development of hypertension and damage to target organs. In a cohort study conducted in Porto Alegre, Brazil, four out of five individuals with prehypertension developed hypertension within 10 years [95] (Fig. 1.17, *top*). Similar incidence rates have

been shown in other populations, such as in a nationwide sample of Japanese workers (Fig. 1.17, *bottom* [96]).

Target organ damage in individuals with prehypertension has been demonstrated in several studies. For instance, in the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) cohort, individuals with prehypertension at baseline who still had prehypertension at the follow-up visit had a risk for increasing left ventricular mass in comparison with individuals who had normal BP [97]. Data from the Atherosclerosis Risk in

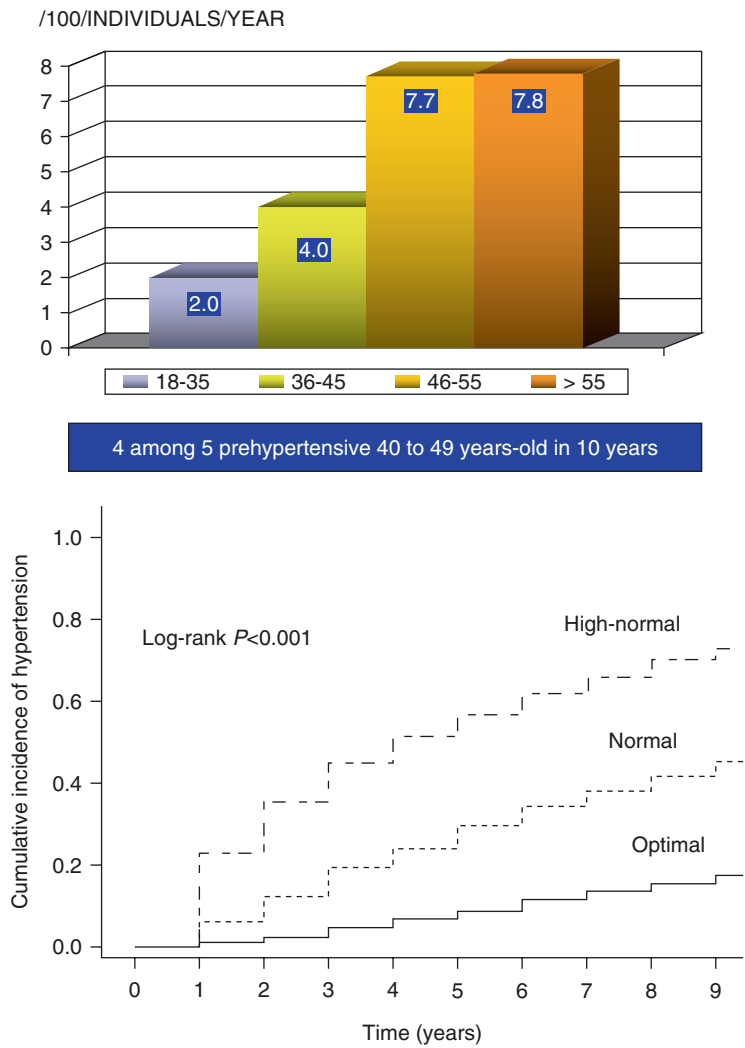


Fig. 1.17 Incidence of hypertension in a population-based cohort study conducted in Porto Alegre, Brazil (*top* [95]), and in a Japanese cohort (*bottom*; reprinted from Kurioka et al. [96], with permission)

Communities (ARIC) study cohort showed that prehypertension was associated with abnormalities in cardiac structure and function in elderly individuals [98].

In view of this evidence, we postulated that drug treatment should be offered to patients with prehypertension [99], on the basis that prehypertension is a window of opportunity to reduce the consequences of high BP [100].

Two clinical trials have demonstrated the efficacy of antihypertensive treatment in decreasing the incidence of hypertension in patients with systolic BP between 130 and 140 mmHg. In the Trial of Preventing Hypertension (TROPHY) [101], occurrence of hypertension over 2 years was prevented in 66.3% of patients treated with average doses of candesartan. This benefit was reduced after discontinuation of treatment. In the Prevention of Hypertension with the Angiotensin-Converting Enzyme Inhibitor Ramipril in Patients with High-Normal Blood Pressure (PHARAO) study, ramipril lowered the incidence of hypertension by 34.4% [102].

The Prevention of Hypertension in Patients with Prehypertension (PREVER-Prevention) trial was the third clinical trial that evaluated the effectiveness of drug treatment to prevent hypertension in patients with prehypertension [103]. We evaluated the effectiveness of low doses of a combined pill of chlorthalidone with amiloride, versus placebo, during a follow-up period of 18 months in individuals who had not had their BP reduced by 3 months of nonpharmacological intervention. The diuretic treatment lowered the incidence of hypertension by 44% (Fig. 1.18, *top*). Unlike the previous trials, the PREVER trial randomized individuals with BP within the full limits of prehypertension. For the first time, we demonstrated that active treatment was more effective than placebo in preventing an increase in left ventricular mass estimated by electrocardiography (Fig. 1.18, *bottom*). Adverse events (musculoskeletal complaints, tinnitus, headache, etc.) occurred in the same proportions of the placebo and active treatment groups, but only 0.5% of participants allocated to the diuretic, versus 2% of those allocated to placebo, reported sexual dysfunction ($P = 0.08$) [72].

The beneficial effects over the prevention of hypertension in the PREVER prevention trial were accompanied by an increase in the proportion of participants who reached optimal BP during the trial (below 120/80 mmHg): 25.6% of the diuretic group versus 19.3% in the placebo group [104]. Despite of these beneficial effects, 74.5% of the participants treated with diuretics remained with BP within prehypertensive levels, suggesting that full doses of BP-lowering drugs may be necessary to reduce BP of individuals with prehypertension to optimal BP values.

1.9 Low Blood Pressure: The Key to a Long and Healthier Life

Study of centenarians is a logical strategy to identify the key to living longer. Genetic background, habits, dietary patterns, family ties, mental stimulation, and other factors are the usual explanations for living for more than 100 years. Nonetheless, many individuals have those factors but do not reach their 100th year of age, and the inverse is also true. The common characteristic shared by very elderly individuals worldwide is low BP.

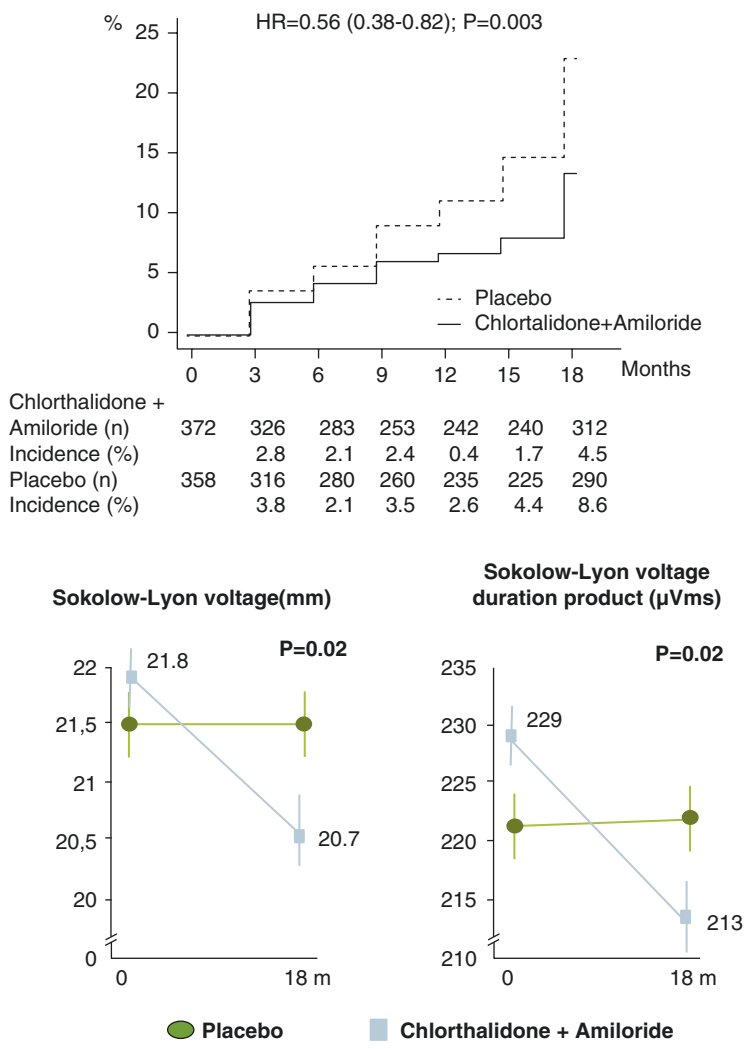


Fig. 1.18 Effects of diuretic treatment on prevention of hypertension (*top*; reprinted from Fuchs et al. [103], with permission) and on electrocardiographic indices of left ventricular hypertrophy (*bottom* [103]) in the Prevention of Hypertension in Patients with Prehypertension (PREVER-Prevention) trial

Geriatricians and other thinkers about longevity consider low BP to be one among several healthier characteristics of very elderly people [105]. Figure 1.19 shows that stroke, cardiovascular disease, dementia, and hypertension occur very late in the lives of centenarians, and that is why those people live long enough to become centenarians. Hypertension, however, is not a consequence of stroke, myocardial infarction, or dementia; it is one of their major causes. These very, very elderly individuals are those who have been naturally able to excrete their dietary sodium load (see Chap. 2) without increasing BP through pressure natriuresis.

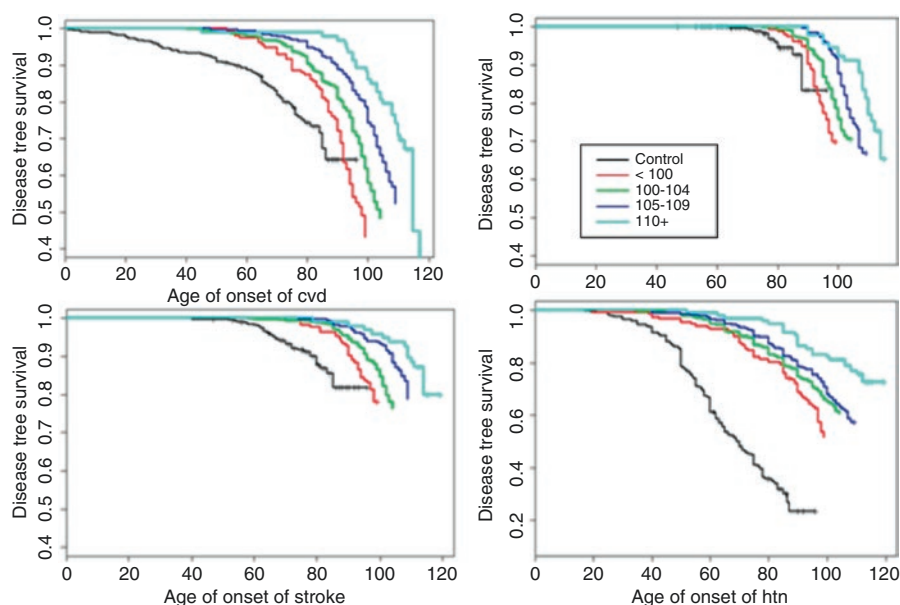


Fig. 1.19 Age at onset of cardiovascular disease, dementia, or stroke, occurring a certain time after development of hypertension. (Reprinted from Andersen et al. [105], with permission)

Therefore, they have real normal BP throughout life and healthier blood vessels, and they do not present with cardiovascular events until very late in life.

Vascular aging underpins the long lives of centenarians. Figure 1.20 shows three theoretical life course trajectories of cardiovascular disease according to BP [106]. The ideal life course presented in the figure is typically associated with low BP and less vascular aging throughout life.

1.10 Misconceptions and Lack of Action

The body of knowledge about the risks of high BP and goals for treatment is robust, supporting the theory that high BP, starting at BP values as low as 115/75 mmHg, is the major cause of cardiovascular disease. Darwin's theory of evolution has strong consistency, but it is supported only by natural observations. The theory of cardiovascular disease causation by high BP has strong consistency as well, but it is additionally supported by a lot of observational and experimental evidence. Many people are still waiting for more evidence and are still discussing J-shaped risks of treatment, the precision of trials, the absence of the perfect study, and other unimportant issues.

Update or position papers from scientific societies have not moved on to establishing lower diagnostic thresholds and aims of treatment. For instance, the leaders of the International Society of Hypertension “think it is premature to advocate such low targets at a global level” [107]. An update of the Canadian guidelines has

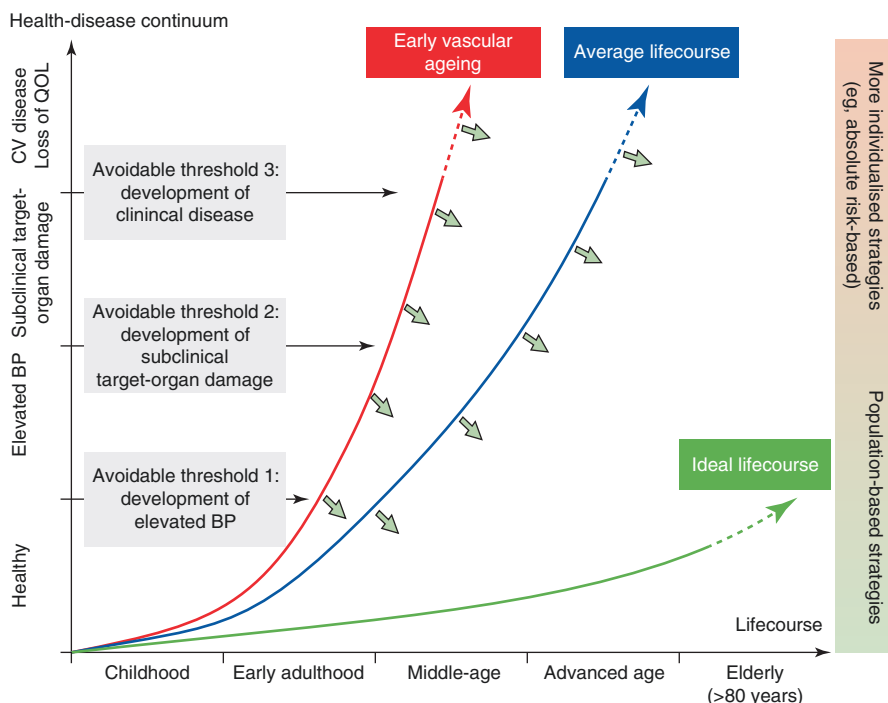


Fig. 1.20 Life course according to blood pressure and vascular aging. (Reprinted from Olsen et al. [106], with permission)

recommended intensive BP reduction to a target systolic BP ≤ 120 mmHg exclusively in selected high-risk patients, similar to the SPRINT participants, but suggests carefully weighing the risks for adverse vascular events and adverse treatment effects [108]. How should a clinician weigh the risks of death and adverse events reported in the SPRINT trial? By withholding treatment in patients treated with the 120 mmHg goal because of complaints of low BP? The American College of Physicians and the American Academy of Family Physicians have surprisingly advocated that the threshold for initiation of treatment and the goal for treatment in adults aged 60 years should be systolic BP ≥ 150 mmHg [109]. The AHA-ACC recently released guideline is the only in accordance with the evidences, presenting lower thresholds for the diagnosis of hypertension [65]. The authors of this guideline could have gone further down in terms of BP recommended for diagnosis and treatment, but the step ahead was relevant in face of the beliefs of many experts and doctors worldwide.

The requirement for evidence that treatment prevents cardiovascular outcomes in a higher range of BP is conceptually correct but impossible to demonstrate. The consequences of high BP have a long period of incubation. The typical patient develops prehypertension from 30 to 40 years of age, hypertension from 40 to 50 years, stage 2 hypertension from 50 to 60 years, a predominance of systolic hypertension from 60 to 70 years and—if he or she doesn't suffer a myocardial infarction or stroke during the journey—aortic stenosis or heart failure from 70 to

80 years of age. A clinical trial covering such a long period is unfeasible, and everyone will be sick or dead before the perfect evidence comes in.

The BP values associated with risks and recommended as the goal for prevention and treatment should be the same: below 120/80 mmHg. Actions for prevention and control should start earlier in life. Hypertension is not primarily an issue for middle-aged adults and the elderly; it is an issue for children and young adults as well. Guidelines should recognize the weight of evidence, and doctors—in their daily practice—should apply this evidence in the care of their patients. Otherwise, we will all miss the window of opportunity to eradicate the risks of hypertension in determination of cardiovascular and other diseases.

1.11 Blood Pressure Classification

The classification of BP to guide public actions and clinical decisions should have only two strata (Table 1.3), which should be used for diagnosis and as the goal for prevention and treatment.

Guidelines have proposed various subclassifications of hypertension within hypertensive levels (stages). The JNC 2 report proposed subclassification of BP within abnormal levels into mild, moderate, and severe strata [110]. This classification was based exclusively on diastolic BP—the paradigm at that time—which persisted in the subsequent JNC reports. The pioneering Veterans trials stratified patients on the basis of similar BP levels (see Chap. 4). Systolic BP was considered abnormal only at values higher than 100 plus the individual's age in years [111]. SHEP is another landmark trial in hypertension that contributed to the establishment of diagnostic limits, demonstrating the effectiveness of treatment of isolated systolic hypertension in preventing cardiovascular events [56].

More recent JNC reports have reduced the stages of hypertension to two, and JNC 8 did not propose any classification of BP [60]. The European guidelines still include three stages within hypertensive BP levels, plus the isolated systolic hypertension stage [62]. Indeed, nobody is classifiable at that stage, because systolic BP defines hypertensive stages in patients with normal diastolic BP. JNC 7 proposed a prehypertension stage [59], which corresponds to the two prehypertension levels in the European guidelines (normal and high-normal). The 2017 AHA-ACC guideline maintained the classification of hypertension in two stages: stage 1: SBP of 130–139 or a DBP of 80–89 mm Hg, and stage 2, all values equal or higher than 140 mmHg for systolic or equal or higher than 90 mmHg [65].

Any arbitrary division of values above 120/80 mmHg would demonstrate a progressive increase in absolute risks. There are substantial reasons, however, to not subclassify BP within abnormal levels.

Table 1.3 Classification of blood pressure in adults of all ages, with and without cardiovascular disease, renal disease, or diabetes mellitus

Classification	Values (mmHg)
Normal	<120/80
Abnormal	≥120/80

First, most individuals at risk in populations are those with low abnormal values. These individuals are not only at risk of presenting with cardiovascular events (even less frequently than at higher BP values) but also at risk of rapidly progressing to higher BP values and to developing subclinical end-organ damage. The final destination of individuals with low or high BP within abnormal values is the same: a cardiovascular event or death, differing only in the time it takes to arrive at the journey's end.

A second reason to not subclassify BP within abnormal values is that treatment is likely easier and more effective at low BP values. Finally, since the pioneering classifications were devised, lower BP values among hypertensive individuals have been classified as mild hypertension. The change to stage 1 did not modify the perception that the severity of disease was not so important at this level, contributing to the inertia in management of hypertension.

Essentials of Risks and Goals for Prevention and Treatment of High Blood Pressure

1. High blood pressure is the major cause of cardiovascular disease.
2. The blood pressure values used for diagnosis and as the goal for prevention and treatment of hypertension should be the same: 120/80 mmHg.
3. These blood pressure values should apply to adults of all ages and patients with cardiovascular disease, renal disease, or diabetes mellitus.
4. Subclassification of blood pressure within abnormal values is unnecessary and may be misleading.
5. Stroke and coronary heart disease are still the typical consequences of high blood pressure, but aortic stenosis and heart failure prevail in elderly individuals who survive the first consequences of high blood pressure.
6. Prevention of an increase in blood pressure with age is the primary action needed to reduce the consequences of high blood pressure and should employ blood pressure-lowering drugs in individuals who do not effectively change their lifestyle.
7. The J-shaped phenomenon is an artifact and should not limit achievement of blood pressure values below 120/80 mmHg in all patients with hypertension.

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The traditional classification of primary and secondary hypertension conveys the concept that hypertension has unknown (primary) and known (secondary) causes. Essential hypertension is another name for primary hypertension. Numerous investigators are still searching for causes of primary hypertension, but the essential cause is known. There are several theories to explain the unnatural increase in blood pressure (BP) with age. Nonetheless, a pool of well-known risk factors explains why BP rises with age in modern civilizations. Among them, the hypothesis that consumption of sodium salts, in amounts that are difficult to excrete by the kidneys, prevails. Besides its coherence, consistency, and support from proof of concept, the hypothesis that excessive salt intake is the key element in the pathogenesis of hypertension satisfies the Occam razor's premise: among competing hypotheses, it is the one with the fewest assumptions to be demonstrated.

The kidneys set the usual BP values of individuals. Other causes of a chronic increase in BP should be expressed only through the kidneys and the balance of sodium, because the increase in BP would lead to renal excretion of sodium and return of BP to usual values. The essentials supporting the role of the salt–kidney interaction in the pathogenesis of hypertension, and the roles of other complementary risk factors for hypertension, are presented in this chapter.

2.1 Maladaptation to Sodium Overload

In the evolution of species, humans and other animals have developed and refined mechanisms to clear undesirable products of metabolism resulting from ingestion of nutrients or inoculation by enemies. The liver decreases the lipid solubility of unwanted substances, enabling their excretion by the kidneys, where hydrophilic molecules do not overcome cellular barriers to tubular reabsorption. Blood filtration by the glomerulus requires filtration of large volumes. Most filtrate is reabsorbed, leaving a small volume of water containing catabolic products in the urine. Water is indispensable in the process, and losses must be replenished to keep humans alive.

Sodium is a central element in this process because it is the main determinant of water balance. The kidneys are very efficient in retaining sodium, filtering blood without losing it. Nonetheless, sodium is inevitably lost in small amounts, in sweat and peeling of mucosa and skin.

In nature, there are few redundant biological systems capable of performing functions similar or complementary to the systems involved in control of the sodium balance. The appetite for salt, the intrinsic efficiency of the kidney, the sympathetic nervous system, antidiuretic hormone (ADH), and the renin–angiotensin system, among others, work together to guarantee supply and maintenance of sodium and, consequently, of water.

Just 2–4 g of sodium per day is necessary to fulfill physiological requirements. For thousands of years, nutritional sodium came exclusively from unprocessed food. The discovery of salt by the Phoenicians was, at the same time, a blessing and a curse. Besides satisfying the daily needs of human beings, salt provided an efficient and inexpensive means of food preservation. The incidence of infectious diseases decreased, and the mobility of humankind increased. Because of salt, Europeans could cross the oceans to live in the New World. According to certain accounts, most of us in the Americas, Australia, New Zealand, and other countries, are descendants of salt. Africans crossed the oceans because of salt as well, during the era of slavery.

The curse of the discovery of salt has manifested in recent centuries, when humans gained control of many causes of disease and started to live longer: causation of hypertension and cardiovascular disease.

2.1.1 Epidemiological Evidence

Several studies have shown that in unacculturated civilizations that did not use salt in preparation and conservation of food, BP did not increase with age. A study conducted in the Amazon forest in the 1950s is an example [1]. Two Brazilian tribes, with similar cultures and habits, differed in their use of salt. Besides catechizing the Mundurucus Indians, Jesuit priests introduced to them the habit of conserving and preparing food with salt. BP increased with age in the Mundurucus but not in the Carajás Indians, who had a similar culture but were not catechized by Jesuits (Fig. 2.1). BP also did not increase with age in Yanomano Indians—another Brazilian no-salt culture [2]. The plasma renin activity of the Indians was elevated, suggesting that normal values observed in acculturated civilizations are depressed by excessive salt intake.

The contributions of Lewis K. Dahl are a landmark in the investigation of the association between salt intake and increasing BP. Among them, he described a linear association between sodium intake and the prevalence of hypertension in several countries [3] (Fig. 2.2).

The Intersalt study was the most extensive cross-sectional study addressing the relationship between sodium intake and BP [4]. The study was carried out at 52 centers in 30 countries. As in the study by Dahl [3], there was a direct intersociety association between the amount of sodium consumed and the prevalence of hypertension. There was, however, a weak association between the amount of sodium consumed and systolic BP in individuals within societies, which was statistically significant at only eight

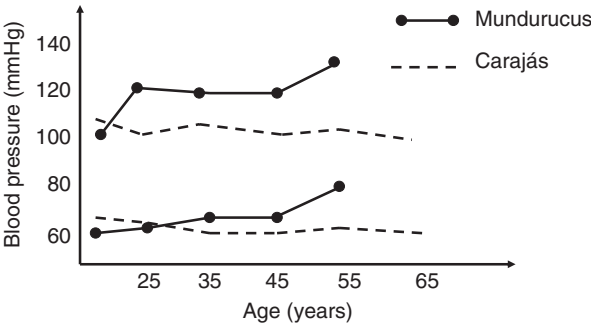


Fig. 2.1 Blood pressure variations by age in Mundurucus and Carajás Indians, Brazil, 1961 [1]

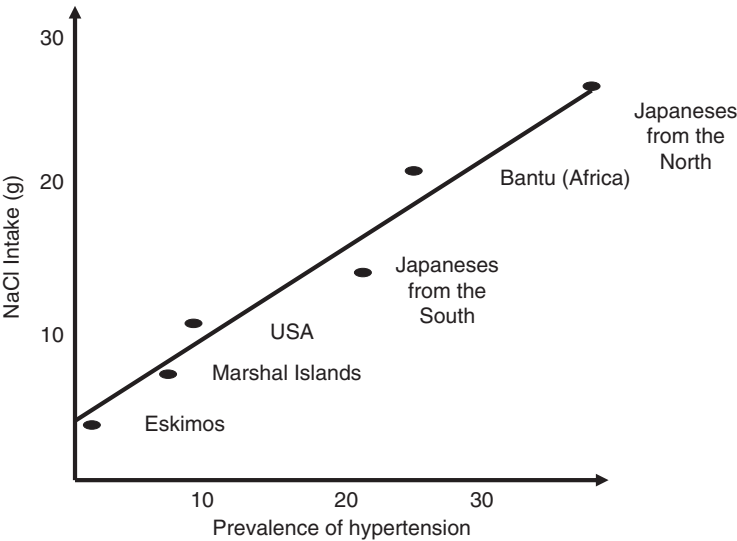


Fig. 2.2 Association between sodium intake and prevalence of hypertension [3]

centers after adjustment for confounding factors. Variable individual sensitivity to sodium loading was the more consistent hypothesis to explain this discrepancy.

Most cohort studies done thereafter have shown direct associations between excessive sodium intake and the prevalence and incidence of hypertension. Moreover, excessive salt consumption has also been directly linked to the incidence of cardiovascular disease. Nonetheless, studies have raised the possibility that a very low intake of sodium (below 2500 mg) would also be associated with a higher incidence of cardiovascular disease. Investigators challenged the existence of a positive association between salt intake and cardiovascular disease. The quality of those studies, however, was low, particularly in relation to the assessment of salt intake and sample selection. Consistent refutation of those studies and detailed revision of the epidemiological evidence were presented in several reports [5–8]. The

interests of industry, represented by the Salt Institute, may be behind the attempt to demystify the cardiovascular risks of salt intake [9].

Epidemiological studies provide only part of the evidence linking the consumption of sodium to hypertension and cardiovascular disease. Other criteria for causality, particularly experimental criteria, offer more robust evidence. The interaction between high intake of sodium and renal ability to excrete this overload explains the increase in BP with age in most individuals.

2.1.2 Salt Sensitivity

Several hypotheses explain the discrepancy of results in different studies within and between societies. Zhu and Psaty proposed that variations in the individual response to sodium overload, secondary to genetic susceptibility, could explain the weak intrasociety association between sodium intake and BP [10]. The proportion of sodium-sensitive individuals would explain the differences in BP between societies that consumed different amounts of salt. Within societies, however, individuals who were resistant to sodium would weaken the association between salt intake and BP.

Figure 2.3 shows the findings of a crossover randomized trial in young volunteers subjected to diets with low, usual, and high intakes of sodium [11]. BP did not differ between volunteers predisposed and those not predisposed to hypertension during 9 days of diets containing low and regular amounts of sodium. During the sodium overload period, systolic and diastolic BP increased during the first days of dietary supplementation exclusively in participants with a parental history of hypertension, returning to the previous values on the ninth day. This phenomenon corresponds to pressure natriuresis as described by Tobian, i.e., necessity to increase BP to excrete excess sodium in individuals with kidneys that are more efficient in retaining sodium [12]. Anticipating the greater

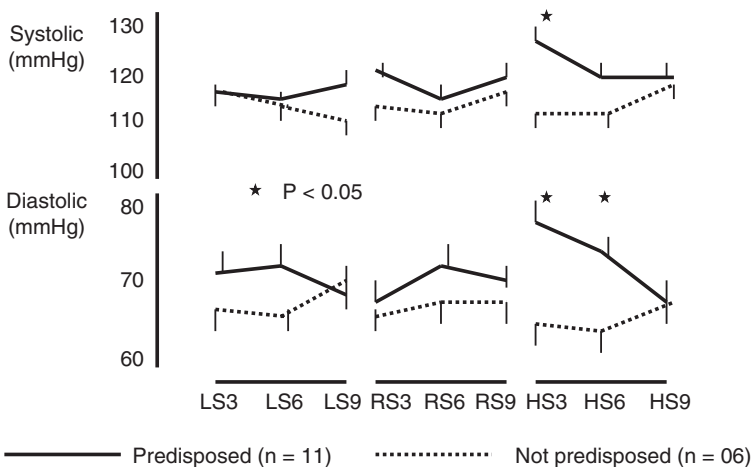


Fig. 2.3 Blood pressure variations during 9 days of diets with variable sodium content [11]. HS high sodium, LS low sodium, RS regular sodium

clinical efficacy of diuretic treatment in prevention and treatment of hypertension, Tobian demonstrated that a thiazide diuretic prevented hypertension in salt-sensitive rats [13].

We demonstrated this phenomenon in free-living individuals as well [14]. We measured BP and overnight urinary excretion of sodium in a subsample of normotensive participants, aged 18–35 years, in a cross-sectional population-based study. There was an interaction between a strong familial history of hypertension (at least two first-degree relatives with hypertension) and sodium overload in determination of BP values (Fig. 2.4). BP was higher in individuals with a strong predisposition to hypertension who consumed large amounts of salt than in individuals with other combinations between salt consumption and familial predisposition to hypertension.

The salt sensitivity hypothesis has been extensively investigated in animal models and humans. In rodents, the trait of sensitivity has been inbred, creating lineages that are sensitive or resistant to salt. Dahl was the pioneer in the development of rats that are sensitive and resistant to salt [15]. Spontaneously hypertensive rats (SHR) are another lineage of salt-sensitive rats inbred by Japanese investigators [16]. These and other strains of rat that are sensitive and resistant to salt have provided proof of concept that salt sensitivity is a genetic trait. Most genetic abnormalities associated with sensitivity to salt involve regulation of natriuresis.

In human beings, however, only breeding between individuals who are prone to developing hypertension would give rise to descendants who are very sensitive to salt. Natural selection of individuals with a predisposition to developing hypertension may have happened in African Americans during their stormy transportation from Africa, according to the “slavery hypertension hypothesis,” which proposes

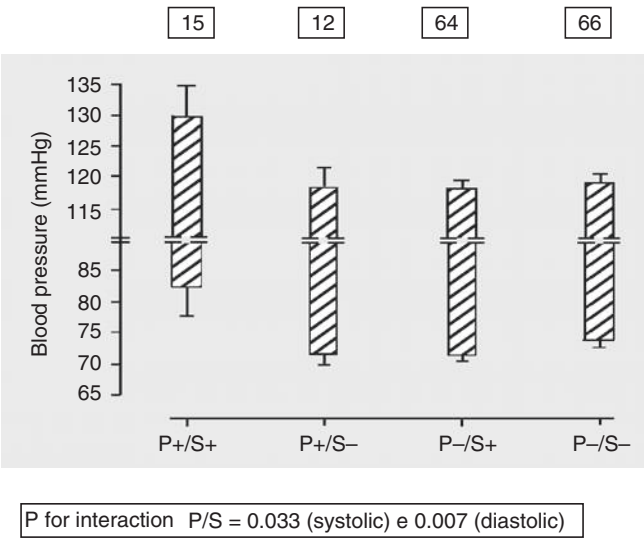


Fig. 2.4 Interactions between strong familial predisposition to hypertension (P+) and sodium overload (S+) in determination of high blood pressure in nonhypertensive individuals younger than 35 years [14]

an explanation for the higher prevalence of hypertension among US blacks. Those who survived the trip could have had an enhanced ability to preserve salt, which protected them from fatal salt-depletive diseases, such as diarrhea and vomiting [17]. Despite being attractive, this hypothesis is hardly demonstrable [18].

The candidate genes to influence sensitivity to salt are related to systems of BP control, such as the adrenergic and renin–angiotensin–aldosterone systems, natriuretic peptides, and tubular regulators of reabsorption of sodium, among others. Studies have been limited by relatively modest sample sizes, investigation of just one or a few polymorphisms, and lack of attention to interactions with others [19]. The publication of many studies with weak associations and fewer studies with negative findings may result from publication bias.

Establishment of a sodium sensitivity phenotype is difficult individually [20]. Protocols with sodium administered orally (PO) or intravenously (IV), with variable amounts of salt, different strategies to measure BP, and different duration of follow-up periods have been proposed. Assessment of the response of hormones, such as aldosterone, and urinary output of electrolytes have been part of some protocols. Individuals defined as being sodium sensitive have a higher risk of developing hypertension or evidence of end-organ damage. Nonetheless, the large number of protocols, lack of standardization among them, and their debatable reproducibility have precluded their clinical use.

These shortcomings, together with biased interpretations of epidemiological studies, have challenged the pivotal role of sodium overload in the pathogenesis of hypertension. Nonetheless, the body of knowledge supporting the primordial influence of salt on the increase in BP with age is strong not only in the pathogenesis of hypertension but as a focus in the prevention and treatment of hypertension [5].

2.1.3 The Central Role of the Kidneys in the Pathogenesis of Hypertension

Here, we face another icon in the investigation of the pathogenesis of hypertension—Arthur Clifton Guyton. He proposed that the kidneys are responsible for chronic regulation of BP through control of the balance of sodium. Figure 2.5 shows the results of his classic experiment in dogs [21]. Removal of approximately 70% of the glomerulus did not change BP. With an overload of sodium, however, there was an increase in BP. The dogs were not uremic.

According to Guyton's theory, other systems would have only acute effects on BP, such as the vasopressor effect of the sympathetic nervous system. If chronically activated, the increase in BP would lead to renal excretion of sodium and a return of BP to the levels set by renal regulation, unless the vasopressor systems influenced renal ability to handle sodium. Secondary hypertension would also result from the action of the primary causes on renal capacity to excrete sodium (Fig. 2.6) [21, 22].

Guyton presented the hemodynamic consequences of the lower capacity for sodium excretion that leads to hypertension. Increases in the extracellular volume and, consequently, in the intravascular volume would be the first consequences, determining the increase in cardiac output. The rise would be transitory because peripheral resistance becomes higher to maintain blood flow adequate for organ

Fig. 2.5 Increasing blood pressure in dogs subjected to sodium overload after removal of two thirds of the glomerulus. (Reprinted from Guyton et al. [21], with permission)

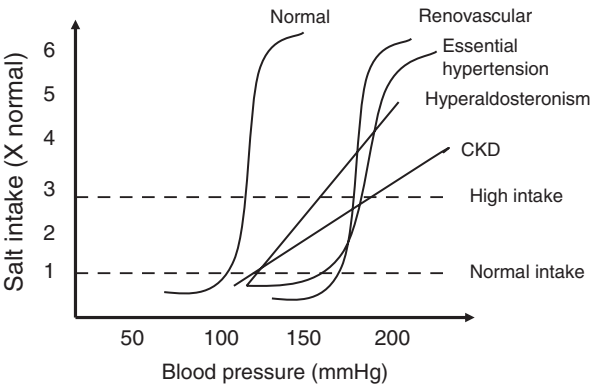
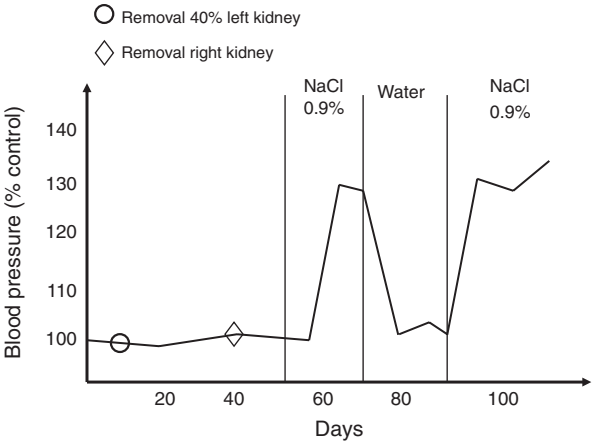


Fig. 2.6 Influence of increasing salt intake on blood pressure (BP) in individuals with normal BP, essential hypertension, or secondary hypertension. *CKD* chronic kidney disease. (Reprinted from Guyton et al. [21], with permission)

necessities. In chronic hypertension, the full hemodynamic pattern arises, with normal cardiac output and high peripheral resistance (Fig. 2.7) [23].

Guyton and colleagues demonstrated the steps in the development of hypertension in their experiments done with dogs [24]. Not all steps in their findings have been replicated in different experimental models, and the idea that there is “essential hypertension kidney” is, at least, questionable. Individual variability in the ability to excrete sodium could be the link between Guyton’s theory and variable salt sensitivity (Fig. 2.8). The variation in sensitivity to salt explains the occurrence of hypertension in most, but not all, individuals and at different ages.

Follow-up of patients with early essential hypertension documented the conversion of a high-cardiac-output state (early hypertension) into long-term normalization of cardiac output with increasing total peripheral resistance (late established hypertension) [25].

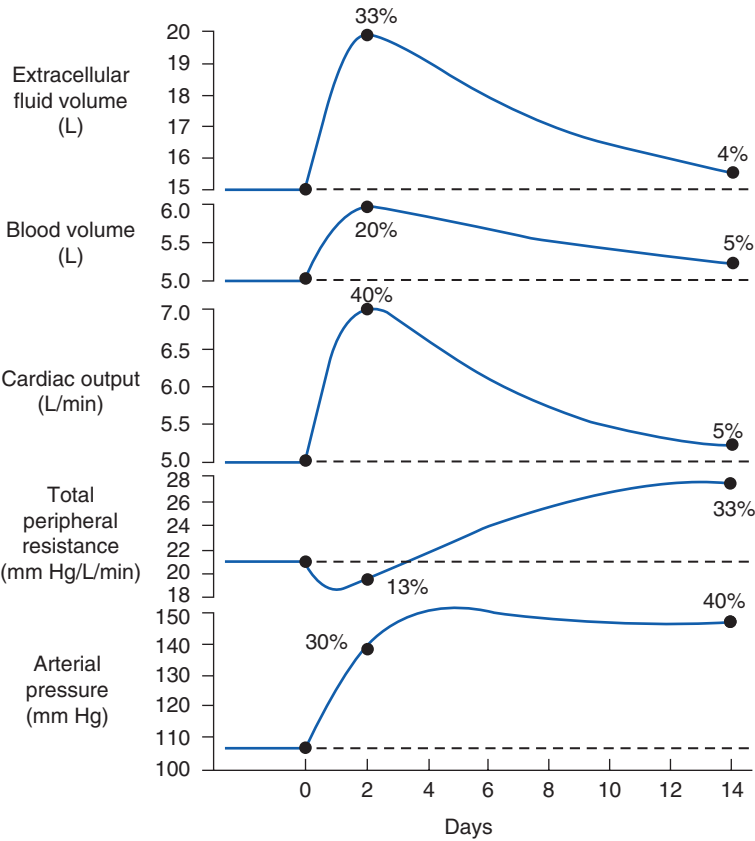
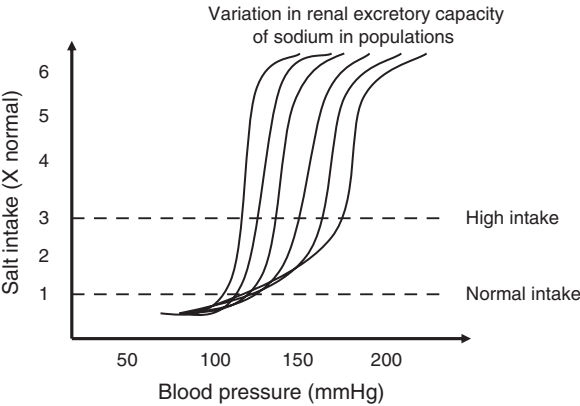


Fig. 2.7 Fluid and hemodynamic consequences of low renal ability to excrete the sodium overload of contemporary diets. (Reprinted from Guyton [23], with permission)

Fig. 2.8 Influence of increasing salt intake on blood pressure in individuals with variable renal ability to excrete sodium



Increasing peripheral resistance has been consistently demonstrated in coarctation of the aorta and in animal and human experiments. In coarctation of the aorta—one of the causes of secondary hypertension—arterioles above the coarctation, which are subjected to chronic pressure overload, develop muscular hypertrophy secondary to the repetitive muscle contractions required to maintain blood flow within the normal range. The arterioles below the coarctation do not present with these consequences.

Folkow and colleagues demonstrated that sustained elevation of BP promotes an increase in the muscular media thickness of arterioles in rats and men prone to development of hypertension [26]. The reduction in the arteriolar lumen area leads to an autonomous increase in peripheral resistance and the chronic hemodynamic state found in patients with hypertension. Moreover, arteriolar hypertrophy increases the response to systemic vasopressors, such as sympathetic catecholamines. Sustained high BP maintains an additional vascular load, promoting vascular damage by increasing circumferential, axial, and shear stresses [27].

2.1.4 Proof of Concept: The Role of Intrinsic Renal Capacity to Handle Salt Overload in the Pathogenesis of Hypertension

Elegant experiments have supported the hypothesis that high BP results from inability of the kidneys to handle an unnatural salt overload. Tobian and colleagues demonstrated a reduction in natriuretic capacity in isolated blood-perfused kidneys of Dahl hypertension-prone rats [12]. Two experiments with cross-transplantation of kidneys between rats from strains that were sensitive or resistant to salt overload showed that sensitivity and resistance accompanied the donor's kidney [28, 29]. The results of the experiment by Bianchi and colleagues are presented in Fig. 2.9.

The observed BP rise secondary to loss of the glomerulus provides further evidence about the role of the kidney in the pathogenesis of hypertension [30].

Clinical trials have provided proof of concept of a salt-mediated increase in BP in human beings. Thirty-four randomized clinical trials ($n = 3230$ participants) showed a modest but consistent BP-lowering effect of low-salt diets, particularly in hypertensive individuals [31]. The lesser than expected efficacy may be ascribed to the stage of development of hypertension—with hypertrophied arterioles—and to poor adherence to low-salt diets in nonfeeding trials.

A singular clinical trial with 15 years of follow-up has provided additional consistent evidence that salt consumption is associated with an increase in BP with age. A total of 245 newborns were randomized to a low-sodium diet (providing less than one third of the usual sodium intake) or a diet providing the usual sodium intake [32]. At the end of the study, systolic BP was 2.1 mmHg lower in participants randomized to the low-sodium diet (Fig. 2.10). The newborns were reassessed 15 years later. Those who had received the low-salt diet for 6 months at the very beginning of life still had significantly lower BP (3.6 mmHg lower, 95% confidence interval (CI) 0.5–6.6) than those who had received the usual-salt diet [33], particularly among those with a higher heart rate.

Fig. 2.9 Development of hypertension in rats subjected to kidney cross-transplantation. The *dashes* indicate hypertensive-prone (H) and normotensive-prone (N) kidney donors. (Adapted from Bianchi et al. [29], with permission)

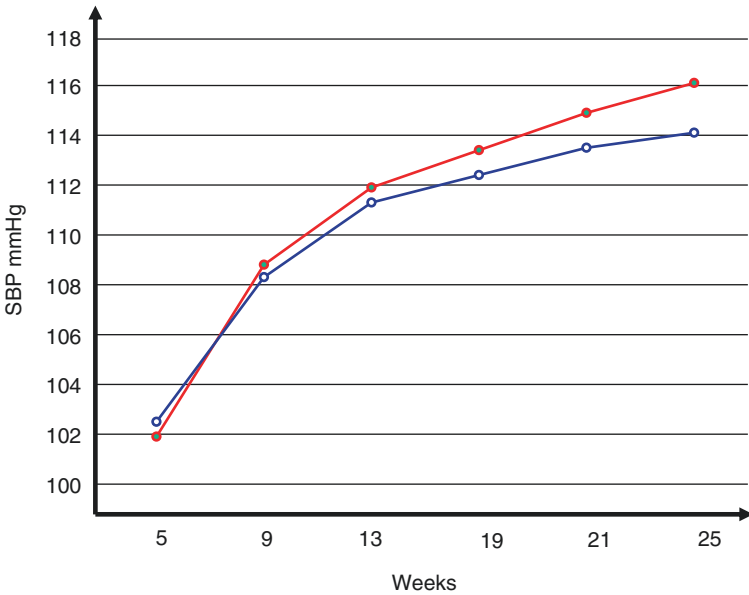
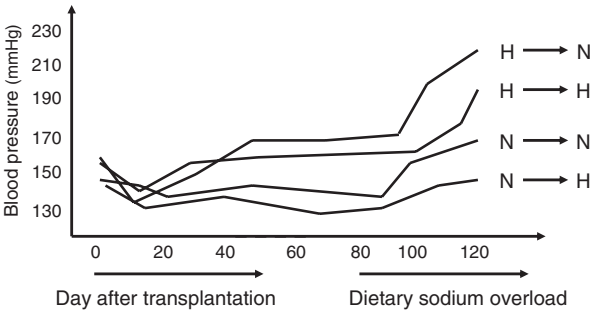


Fig. 2.10 Differences in systolic blood pressure over 25 weeks in newborns consuming diets with low (*dark blue*) and regular (*red*) amounts of sodium [26]

At the other end of the life-span, there is evidence that a low-salt diet in adults diminishes the incidence of cardiovascular events. A meta-analysis of clinical trials of low-salt diets has identified a 20% reduction in the incidence of cardiovascular events [34].

The large volume of evidence summarized herein demonstrates that the interaction between high salt intake and limited renal ability to excrete it is at the root of the rise in BP with age. Many mediators and molecular mechanisms of sodium handling by the kidney have been investigated. They include a wide range of possibilities, from a simple inherited difference in the adrenal response to renin to

complex interactions between systemic mediators, such as the renin–angiotensin and sympathetic nervous systems and intrarenal mechanisms of sodium filtration and reabsorption. Details of these aspects are beyond the essentials of hypertension.

2.2 Excessive Adiposity

The epidemic of obesity is still in progress worldwide. The increase in body mass index (BMI) has slowed in recent years in high and middle-income countries, but has accelerated in other regions [35]. Obesity and overweight are the most evident phenotypes associated with the rise in BP. There have been variable estimates of the population attributable risk of overweight and obesity for hypertension, but all of them are high. A meta-analysis estimated hypertension risks of 32% and 47% attributable to overweight and obesity, respectively [36]. Moreover, hypertension is the more important mediator of the cardiovascular risks of excessive adiposity [37]. Figure 2.11 shows that cholesterol, glucose, and BP levels account for approximately 50% and 70% of the risks of 5 kg/m² higher BMI for coronary heart disease (CHD) and stroke, respectively. BP alone explains most of this risk.

The distribution of excess fat influences the risks for incident hypertension. Central obesity is a risk factor independent of BMI. The waist–hip ratio is a more precise anthropometric predictor of the incidence of hypertension (Fig. 2.12) [38], but the waist circumference alone is easier to measure and captures the risk for hypertension as well [39]. Other cohort studies have demonstrated the association between fat distribution and the incidence of hypertension [40].

Many studies have identified higher risks for hypertension in individuals with increased visceral fat rather than subcutaneous fat. In a cohort of 903 normotensive participants followed for 7 years, visceral fat—quantified by magnetic resonance and proton spectroscopic imaging—was the only fat distribution associated with incident hypertension [41]. The risk of excessive adiposity seems to grow immediately after weight gain [42].

Various mechanisms link hypertension to excessive adiposity. A simple but coherent hypothesis is that in overweight individuals, a positive sodium balance, leading to raising of BP, accompanies excessive caloric intake. Additional requirements to excrete sodium submit nephrons to extra work, since their numbers do not change with an increase in weight. On the other hand, a small proportion of obese individuals have low BP. These individuals are probably those with kidneys that are very efficient in excreting sodium.

The stronger risk due to central adiposity suggests that other mechanisms contribute to its association with increasing BP. Central distribution of fat is associated with greater secretion of cytokines associated with regulation of BP. Systems involved in maintenance of BP may be overactive in persons with excessive adiposity, such as the sympathetic nervous system, renin–angiotensin system, and

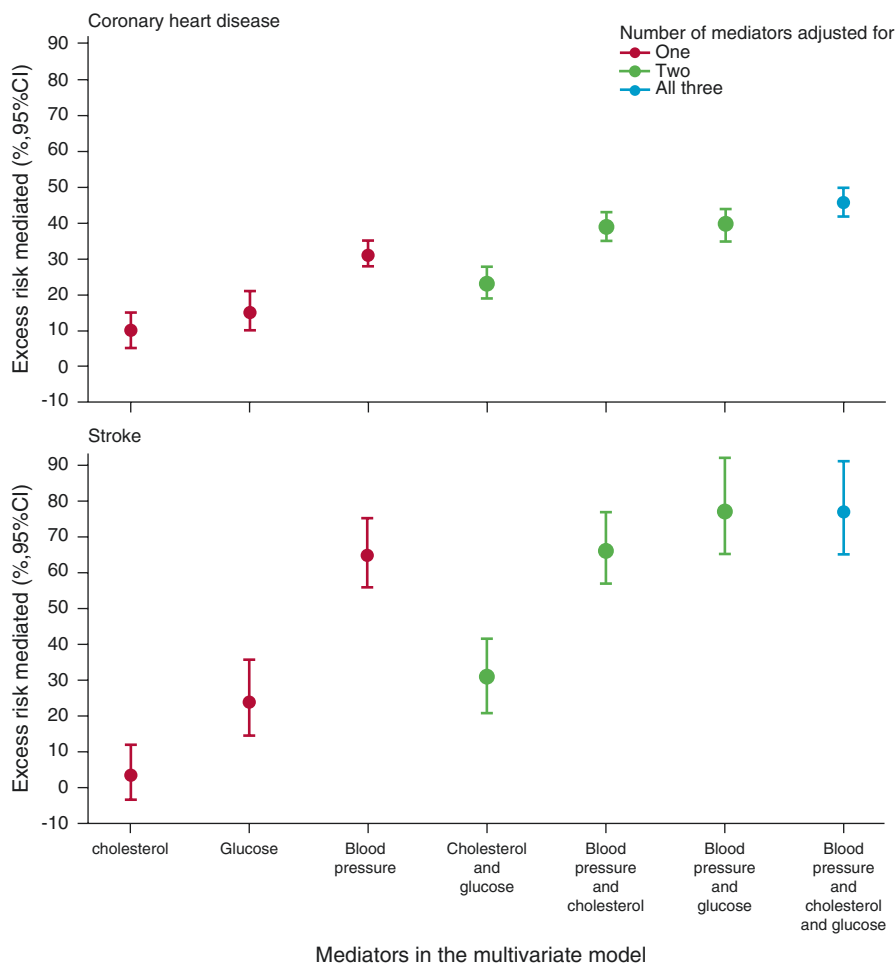


Fig. 2.11 Excess risk per 5 kg/m² higher body mass index mediated by isolated and combined risk factors for coronary heart disease and stroke. (Reprinted from Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration [37], with permission)

endocannabinoid system. Impaired secretion of natriuretic peptides in response to volume expansion may influence the balance of salt and water in obesity-related hypertension. Renal compression by visceral, retroperitoneal, and renal fat could lead to increased intrarenal pressures, impaired pressure natriuresis, and hypertension. This hypothesis is supported by the higher risk of visceral fat than subcutaneous fat for the incidence of hypertension. Further details of the BP-increasing mechanisms of excessive adiposity are beyond the essentials of hypertension and can be found elsewhere [43, 44].

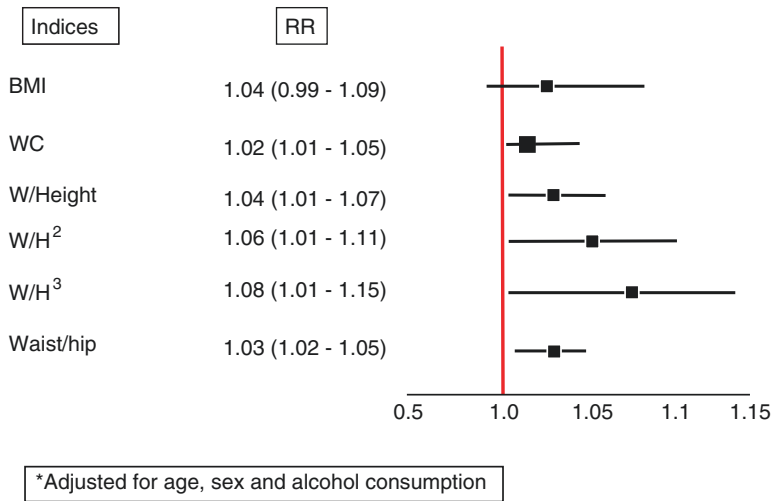


Fig. B.12 Association between anthropometric indices and incidence of hypertension [38]

2.3 Diabetes and Metabolic Syndrome

Diabetes mellitus and hypertension are highly prevalent and share obesity as a risk factor. Therefore, it is difficult to isolate the independent risks of diabetes for hypertension and vice versa. The risk of high BP for development of diabetes was demonstrated in a large meta-analysis [45]. Summary estimates of the risk of diabetes for development of hypertension are lacking.

The concept of metabolic syndrome aimed to unify the mechanisms of the causation of diabetes, lipid abnormalities, and hypertension, attributing them to resistance to insulin, particularly in individuals with abdominal obesity. The agenda of many physiologists and epidemiologists was mainly devoted to the study of this syndrome, which rapidly gained acceptance by clinicians worldwide, who used to see patients presenting with these conditions simultaneously. The pharmaceutical industry was very pleased to have a new disease for which to sell specific treatments. Edwin Gale proposed that the sequence was inverse, i.e., that the syndrome was coined to create an indication for rimonabant—a drug that would specifically reduce waist circumference but was subsequently abandoned because of adverse effects [46].

The concept of metabolic syndrome has faced many criticisms and may be fading away. From an epidemiological perspective, there is no consensus about the definition of the syndrome. Moreover, its prediction of the incidence of cardiovascular disease is equivalent to the sum of its components. From a physiopathological perspective, it was not possible to reproduce the syndrome in experimental models (sodium was not in the models), and the occurrence of isolated

components in many individuals speaks against a common determination. Finally, the presumably specific treatment for the syndrome failed, and prevention and treatment should be directed toward the individual components of the syndrome.

2.4 Potassium and Other Dietary Factors

Sodium and potassium have an interplay in the pathogenesis of hypertension. Modern diets have a high content of sodium and a low content of potassium. Potassium is probably one of the key components of healthier diets, such as the Dietary Approaches to Stop Hypertension (DASH) diet. Bench experiments and clinical trials have shown the BP-lowering effect of supplementation with potassium, which probably minimizes sensitivity to sodium. This and other epidemiological evidence and mechanisms of action have been reviewed [47]. The renal outer medullary potassium channel mediates potassium recycling and facilitates sodium reabsorption [48]. A novel diuretic, which inhibits this channel, has been reported to prevent BP elevation in Dahl salt-sensitive rats and improve renal and vascular function [48].

The DASH diet—based on fruits, vegetables, and dairy products—consistently lowers BP (see Chap. 4). As an analogy, diets with fewer components of the DASH diet (computed as a score in cohort studies) could be a risk for hypertension. Lower DASH scores have been associated with hypertension in some [49] but not all studies [50].

2.5 Alcohol, Hypertension, and Cardiovascular Disease

Alcohol abuse is listed among the causes of hypertension. The association between alcoholic beverage consumption and high BP was first reported in epidemiological studies. A Kaiser Permanente study was among the first longitudinal studies showing this association [51]. In the Atherosclerosis Risks in Communities (ARIC) study cohort, the risk for increased BP and incident hypertension was mostly present in black participants who consumed moderate to large amounts of ethanol (Fig. 2.13) [52]. The same phenomenon was identified in free-living individuals in a cohort study done in Porto Alegre, Brazil [53]. Alcoholic beverage consumption is also a risk factor for development of hypertension in patients infected with HIV [54].

Many putative mechanisms explain the vascular effects of ethanol [55]. There is, however, a paradox concerning the BP-increasing effect of ethanol, i.e., how could an acute vasodilator chronically raise BP? We proposed that the effect could be secondary to BP rebound after the depuration of alcohol. We examined early and late hemodynamic effects of acute administration of water and of 15, 30, and 60 g of alcohol in 40 normal men aged 19–30 years, assessing BP by 24-h ambulatory BP (ABP) monitoring [56]. There was an immediate BP reduction accompanied by a high heart rate after alcohol intake. During sleep, there was a dampening of BP dipping (Fig. 2.14). We proposed that alcohol promotes a short-term BP reduction due to its vasodilatory effect and a later increase in BP due to a rebound effect. In another experiment, we demonstrated an immediate BP-lowering effect of red wine

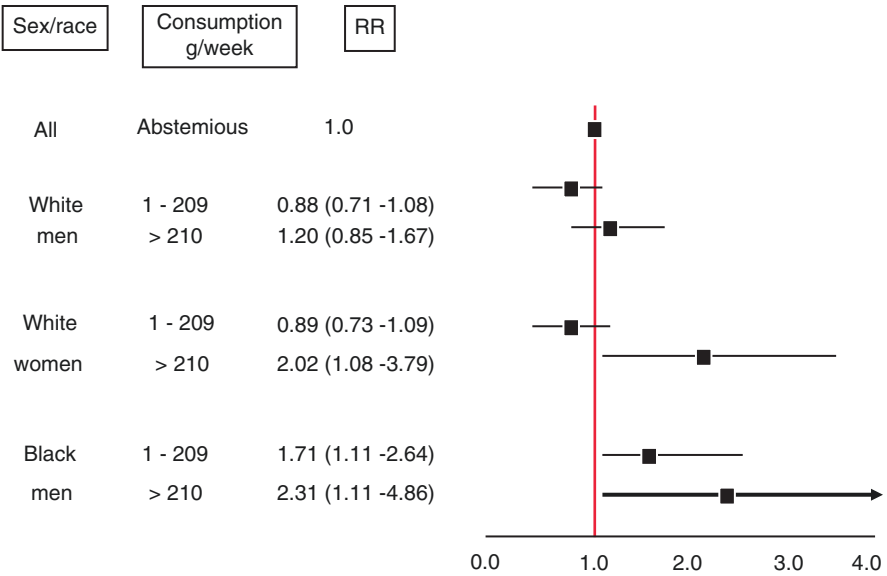


Fig. 2.13 Alcohol consumption and risk for developing hypertension by race and gender in the Atherosclerosis Risk in Communities (ARIC) study [52]

taken with the noon meal in centrally obese hypertensive patients, reproducing the short-term effects of ethanol demonstrated in normal volunteers [57].

Other experiments have shown late pressor effects of ethanol. Abe et al. demonstrated a biphasic effect of ethanol on BP [58]. In a crossover trial, Zilkens and colleagues demonstrated that BP increased during periods of consumption of wine or beer in comparison with periods of consumption of dealcoholized wine or abstinence [59]. The rise in BP was higher during nighttime ABP monitoring. The same group demonstrated a clear biphasic effect of ethanol on BP in individuals with diabetes who drank wine with their evening meal [60]. This posteffect is probably mediated by the central nervous system (CNS) because exclusively peripheral vasodilators do not have a rebound effect. Vagal inhibition and sympathetic activation, which increase heart rate variability after acute ingestion of ethanol [61], may be the mediators.

In a cross-sectional study [62], we identified that BP increased progressively after cessation of alcohol consumption (Fig. 2.15), reproducing the posteffect demonstrated in experiments.

Another ARIC report challenged the almost consensus understanding that low to moderate consumption of alcoholic beverages protects against the incidence of CHD [63]. Alcohol consumption was associated with a lower incidence of CHD among white men (hazard ratio (HR) 0.88, 95% CI 0.79–0.99), but was associated with higher risk among African American participants (HR 1.13, 95% CI 1.01–1.28). Figure 2.16 stratifies this risk by ethnicity/gender and pattern of consumption. The ethnicity difference in the response to ethanol is probably due to lifestyle characteristics of drinkers, since it is unlikely that biological differences could lead to opposite

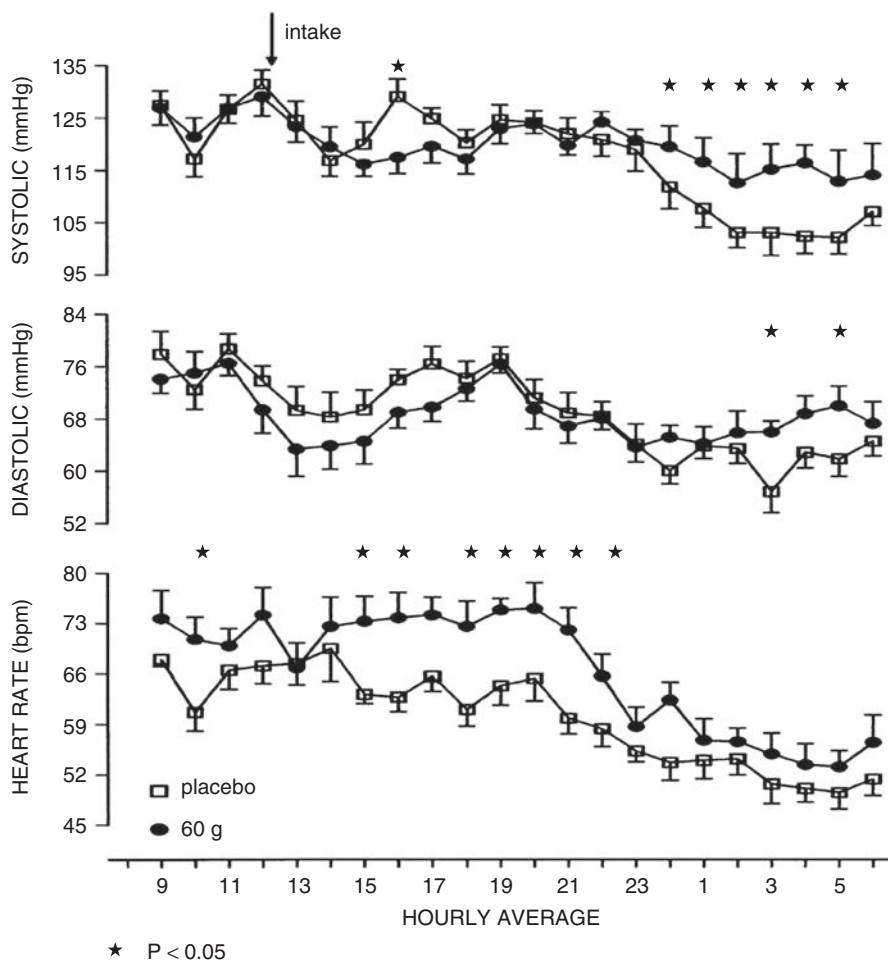


Fig. 2.14 Effects of acute alcohol intake (60 g) on blood pressure and heart rate in normal volunteers (see text). (Reprinted from Rosito et al. [56], with permission)

effects of ethanol on the causation of CHD in white and African Americans. A similar pattern was identified for total mortality in the US population [64]. Alcohol abuse, in particular, is a strong risk factor for the incidence of atrial fibrillation, myocardial infarction, and heart failure [65].

The apparent cardioprotective effects of alcoholic beverages may be attributed to the health cohort effect [66]. People who drink moderately have better health outcomes because of healthy habits, not because they drink a glass of wine (or any other beverage) per day.

In summary, moderate to large amounts of alcohol consumption increase BP—an effect that is probably mediated by a rebound to the depressor effects of ethanol on the CNS. The magnitude of the effect is not large, however, and may be explained in part by other lifestyle factors, particularly in prevention of cardiovascular disease.

Fig. 2.15 Association between number of alcoholic beverages consumed per day and blood pressure (BP) in women and men; behavior of BP in the hours following the last drink [62]

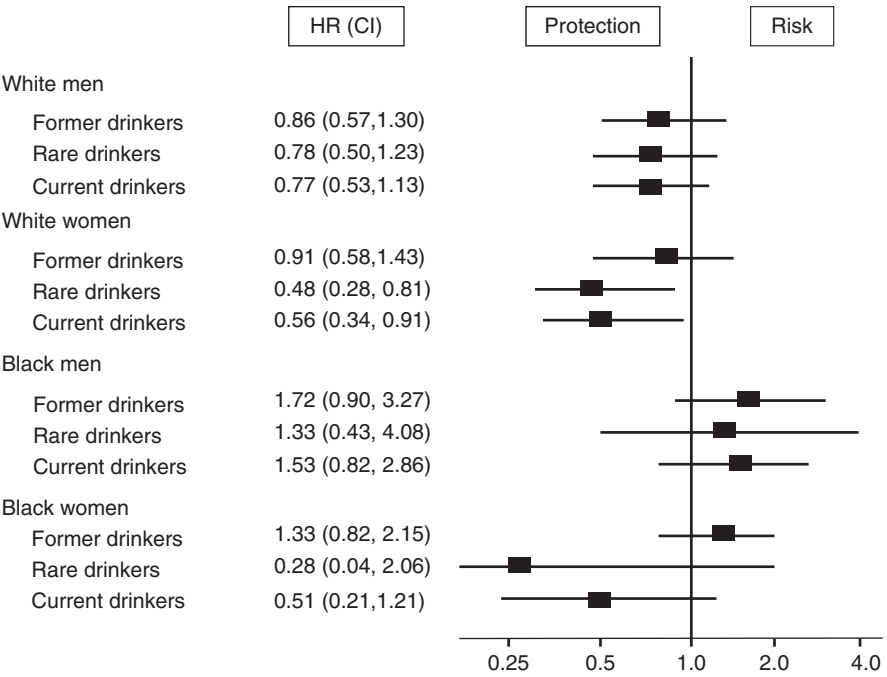
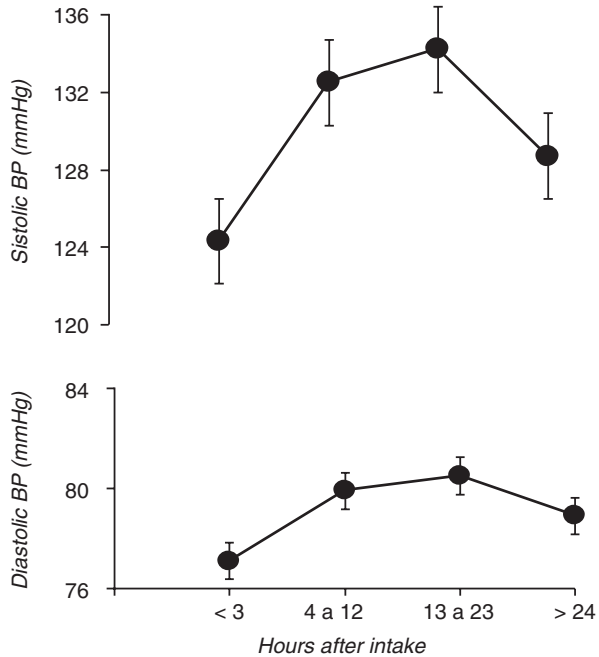
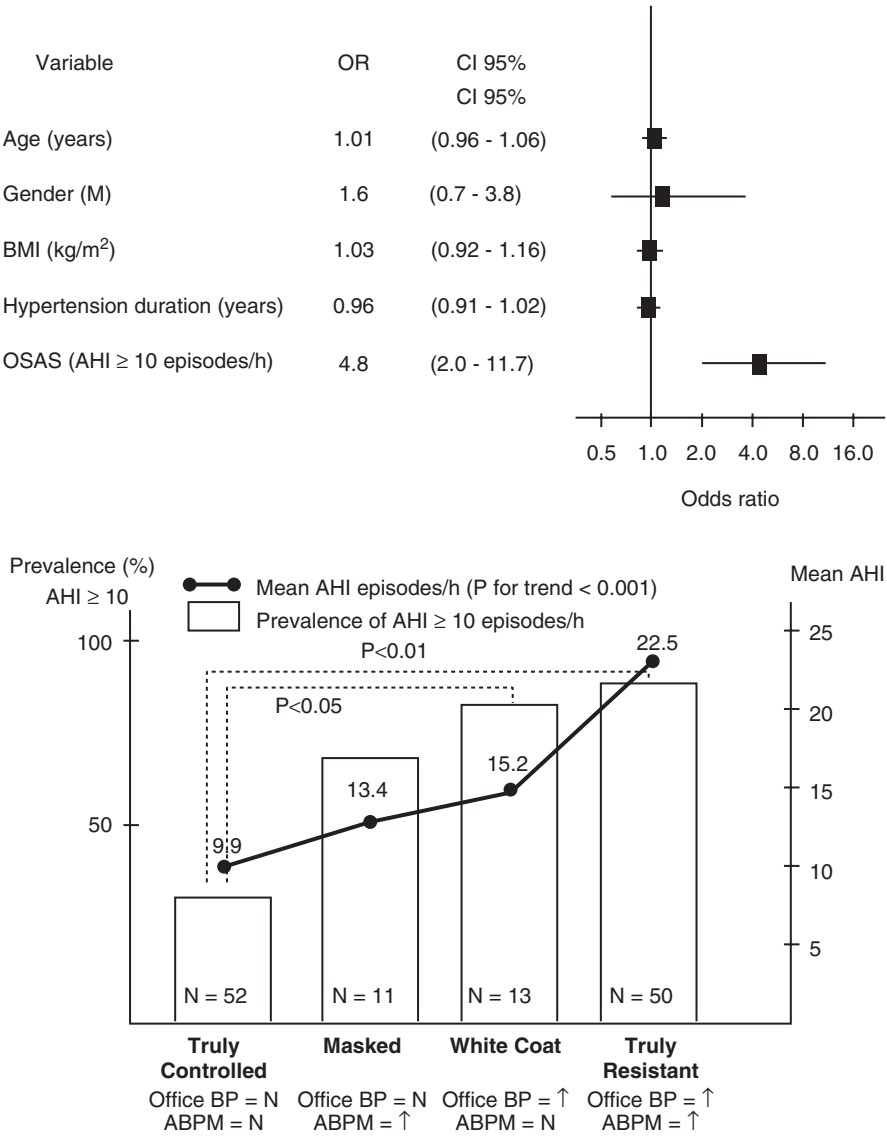


Fig. 2.16 Incidence of coronary heart disease by ethnicity/gender and pattern of consumption of alcoholic beverages. (Reprinted from Fuchs et al. [63], with permission)

2.6 Sleep Disorders

Obstructive sleep apnea (OSA) is listed in guidelines as being among the causes of secondary hypertension. The evidence of a causal association between OSA and mild to moderate hypertension is, however, weak [67].

On the other hand, the risk of OSA for resistant hypertension is consistent. In a case–control study, individuals with resistant hypertension had a risk for presenting with OSA almost five times that of controls [68] (Fig. 2.17, *top*). The mean Apnea–Hypopnea Index (AHI) and the proportion of patients with at least moderate OSA



increased from truly normotensive individuals to truly hypertensive individuals (Fig. 2.17, *bottom*). OSA was assessed by a validated portable device for use at home [69]. The Berlin Questionnaire captured a similar risk [70].

OSA has been associated with CHD [71] and BP variability [72]. In the face of hypertension and other cardiovascular consequences, OSA should be deemed a cardiovascular disease [73]. Treatment of OSA as a means to treat hypertension is presented in Chap. 4.

2.7 Stress

Stress has been a priori responsible for countless ailments. Hypertension is among these ailments. Doctors and laypeople used to attribute high BP to stress, but the evidence is weak. Acute stress (e.g., due to fear, emotion, or anxiety) does raise BP, but the question is whether those moments translate into chronic hypertension. Observational studies—preferably cohort studies—are more adequate to address this question than acute experiments.

In a systematic review of observational studies [74], we identified that chronic stress and a nonadaptive response to stress were associated with chronically raised BP, but the quality of the studies was insufficient for us to calculate summary estimates (Fig. 2.18, *top*). In a population-based cross-sectional study [75], we found that current psychological distress was associated with reported hypertension but not with objectively determined hypertension (Fig. 2.18, *bottom*).

New studies have been of better quality than those included in the above systematic review. In a large cross-sectional study, current perceived stress was not associated with high BP after adjustment for occupational status [76]. In a follow-up of this study, perceived stress was positively associated with high BP only among women, particularly among those with medium or low occupational status [77]. In a German cross-sectional study [78], perceived stress was inversely associated with BP, while exposure to objective stressors was unrelated to BP.

Taken together, these pieces of evidence suggest that chronically stressful conditions may be associated with high BP, but the magnitude of risk is low.

2.8 Other Risks for Hypertension

Numerous conditions are associated with essential hypertension, and some may be part of the causal pathway. Age and family history are unmodifiable risks, but they can have a lesser impact with control of other risks, such as excessive salt consumption.



Fig. 2.17 Obstructive sleep apnea (OSA) as a risk factor for resistant hypertension (*top*), and association of true normal blood pressure, white-coat hypertension, masked hypertension, and true hypertension with intensity of OSA (*bottom*). (Reprinted from Gonçalves et al. [68], with permission)

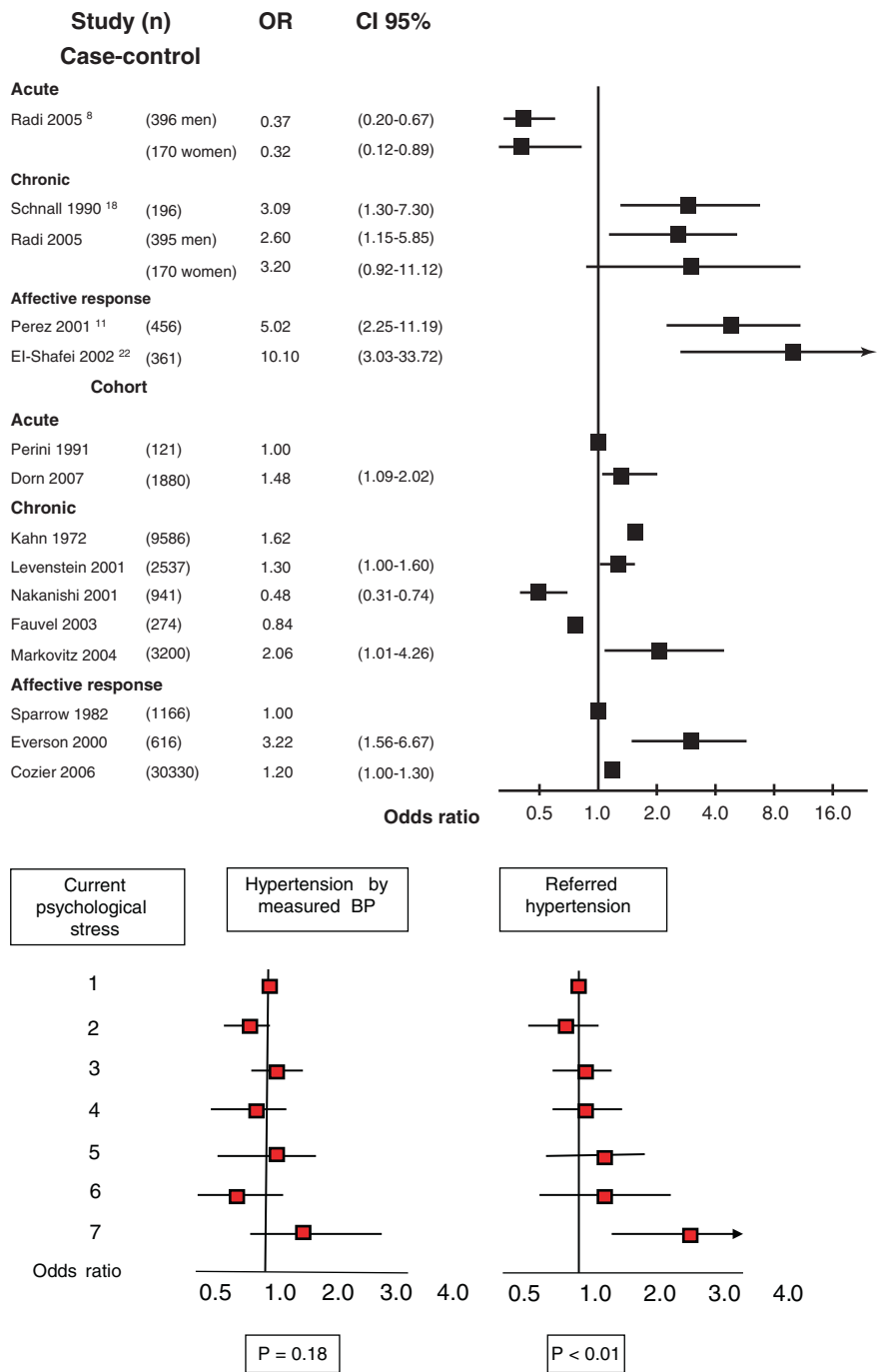


Fig. 2.18 Associations between stress and risk for hypertension in a systematic review (*top*; reprinted from Sparrenberger et al. [74], with permission) and in a cross-sectional study (*bottom*; reprinted from Sparrenberger et al. [75], with permission). Current psychological distress was measured from 1 (less) to 7 (more), using a scale of facial expressions

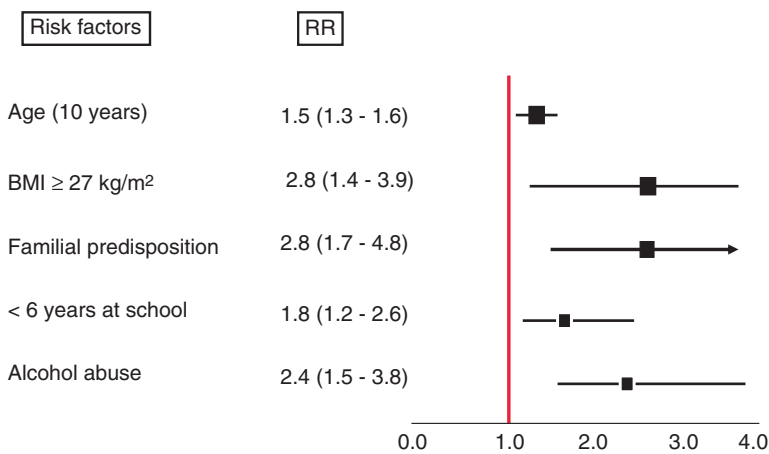


Fig. 2.19 Fewer years at school are associated with higher risk for hypertension, independently of other traditional risks for hypertension [80]

2.8.1 Socioeconomic and Educational Risks

People with fewer years of formal education and lower income are at higher risk of developing hypertension [79]. Fewer years at school are associated with a higher prevalence of hypertension independently of other traditional risk factors for hypertension (Fig. 2.19) [80]. High BP is better explained by socioeconomic position in society than African genomic ancestry [81].

Low education and socioeconomic status are surrogates for various nutritional and behavioral risks for hypertension, which are not fully represented in individual studies.

2.8.2 Depression

The high prevalence of hypertension and mood disorders—mainly anxiety and depression—facilitates coexistence of both conditions in the same patient [82]. Depression is more commonly referred to as a cause of hypertension. In a population-based cross-sectional study [83], depression and hypertension were not associated after adjustment for confounding factors (Fig. 2.20).

Nine cohort studies were selected for a meta-analysis of the risk of depression for the incidence of hypertension [84]. Overall, the risk of depression for the incidence of hypertension was 1.42 (95% CI 1.09–1.86). Some studies had low quality (including studies that included reported hypertension, which is susceptible to measurement bias), and the heterogeneity was high. In a cross-sectional study of psychiatric morbidity in a sample of more than two million people in Stockholm County, Sweden [85], depression was more frequent in

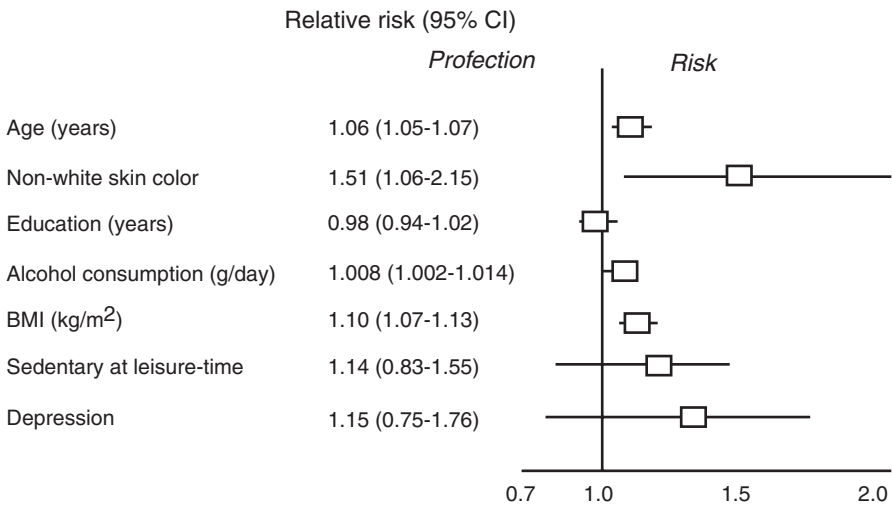


Fig. 2.20 Absence of an association between hypertension and depression after adjustment for confounding. (Reprinted from Wiehe et al. [83], with permission)

patients with hypertension (RR 1.29, 95% CI 1.26–1.33)—a directionality that has not been suggested for this association (i.e., hypertension as a cause of depression). The possible causality of the association of hypertension with depression or vice versa requires demonstration in better-designed longitudinal studies.

2.8.3 Oral Contraceptives

The first oral contraceptives, with high doses of estrogen, were definitely associated with higher BP. The mild anabolic effects of estrogens promote a positive balance of sodium. Pills with low doses of estrogen have lower risk. There have been few contemporary studies investigating this association. A cross-sectional Korean study identified a risk ratio close to 2 for hypertension and prehypertension in users of oral contraceptives for more than 24 months [86].

We identified an association between oral contraceptive use and uncontrolled hypertension at an outpatient clinic [87]. This adverse effect was reversed with suspension of the medication (see Chap. 4).

2.8.4 Shift Work

Shift work may have deleterious consequences for circadian rhythms. Diabetes and hypertension are among these consequences. In a prospectively planned cross-sectional study [88], we investigated 493 nursing personnel from a large hospital. There was no association of shift work with the prevalence of hypertension or prehypertension. A cross-sectional study, with almost 60,000 participants, identified a risk of nondaytime shift work for hypertension in African American people, especially with short periods of sleep [89]. On the other hand, a large cohort did not find any association between shift work and changes in systolic and diastolic BP [90]. Studies have in general been low quality, presenting positive and negative associations. It is unlikely that shift work has a relevant role in the pathogenesis of hypertension.

2.8.5 Endothelial Dysfunction

Impairment of the intrinsic vasodilatory properties of resistance vessels is a questionable cause of hypertension. Abnormalities related to synthesis and activity of nitric oxide are the main mechanisms associated with a vasodilatory deficit [91]. Lack of standardization in the evaluation of endothelial function is a shortcoming in demonstrating this hypothesis. The main limitation, however, is the absence of consistent evidence that abnormalities in endothelial function precede the rise in BP. Most abnormalities are present in patients with hypertension or prehypertension, and they can be secondary to high BP.

2.8.6 Oxidative Stress and Inflammation

Oxidative stress and inflammation are putative causes of numerous diseases. Hypertension is naturally among them. Oxidative stress and inflammation would be mediators of other risks, promoting endothelial dysfunction. Even their role as intermediate mechanisms is questionable, since there is no evidence that anti-inflammatory and antioxidant drugs have any BP-lowering effect; on the contrary—some have been implicated in increasing BP.

2.8.7 Other Risks

Uric acid, caffeine, vitamin D, nutrients, environmental temperature, air pollution, and low birth weight, among other factors, are risks cited in the literature. Not all studies have reported positive associations. The quality of studies and the potential

population attributable risks are low, showing that they are not essential to explain the incidence of hypertension.

Essentials of the Pathogenesis of Hypertension

1. An increase in blood pressure with age is unnatural and is mostly caused by kidney maladaptation to a dietary sodium overload.
2. Excessive adiposity, particularly if distributed centrally, explains around 50% of the incidence of hypertension; a positive sodium balance, associated with high caloric intake, is likely the cause of increasing blood pressure.
3. Low intake of potassium increases the deleterious effects of higher sodium intake.
4. The concept of metabolic syndrome is useless to explain the incidence of hypertension and cardiovascular disease.
5. Alcohol consumption increases blood pressure and is not associated with cardiovascular protection.
6. Obstructive sleep apnea is a major risk factor for resistant hypertension but probably not for less severe hypertension.
7. Chronic stress may be a risk factor for hypertension, but the magnitude of risk is low.
8. Low socioeconomic status and low educational status are surrogate risks for hypertension.
9. Endothelial dysfunction, oxidative stress, and inflammation are not primarily associated with the pathogenesis of hypertension.
10. Other proposed causes of hypertension, if real, have low attributable risks.

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3.1 Blood Pressure Measurement

The first description of intra-arterial measurement of blood pressure (BP) dates from 1733, in an experiment performed by Reverend Stephen Hales. In the second half of the nineteenth century, many scientists developed noninvasive methods to measure BP, but none was practical for clinical use. Scipione Riva-Rocci improved a German prototype and presented the first mercury sphygmomanometer in 1896 [1]. It exclusively measured systolic BP by palpation of the radial pulse. In 1905, Korotkov, a Russian surgeon (whose name is spelled as “Korotkoff” in some publications), described the sounds associated with the pulse wave [2].

Chapter 1 presents the application of these landmark discoveries to identification of the risks of hypertension. The auscultatory method has been used to diagnose and manage hypertension in clinical practice since the studies performed by Korotkov. The development of the aneroid manometer was the only evolution for many years, which was more practical to measure BP and eliminated the environmental risks of mercury. The effectiveness of the auscultatory method to assess the risks of high BP occurred despite its intrinsic limitations, such as the impossibility of measuring BP repeatedly, errors in measurement due to digit preference, and patient anxiety induced by doctors during the measurement process, among others.

Some of these limitations have been circumvented in recent decades. Clinical use of oscillometric devices has eliminated errors due to digit preference. Investigators developed this method before the auscultatory method in the nineteenth century. Instead of hearing the sounds of the turbulence provoked by the arterial occlusion, this method registered the cuff oscillation induced by the arterial occlusion. A gauge transmitted the oscillation to a smoky cylinder, which was obviously not practical for clinical use. Methods to electronically register the signal coming from the cuff oscillation allowed development of devices for clinical use. The mean BP corresponded to the lowest cuff pressure with the highest oscillation, and algorithms were used to derive the values of systolic and diastolic BP.

The European Society of Hypertension [3], the British Hypertension Society [4], and the Association for the Advancement of Medical Instrumentation [5] validate oscillometric devices, mostly through comparison with the auscultatory method, following standardized protocols. The real validation of devices, however, came from the results of cohort studies using ambulatory BP (ABP) and home BP (HBP) monitoring, which employed oscillometric cuffs and electronic registering of BP. These studies captured the risks of high BP with greater precision than studies done with office BP measurement (see Sect. 3.3).

The auscultatory method is outdated. There have been numerous reports of errors in measurement of BP using that method. A systematic review identified 323 studies that reported at least one source of inaccuracy among 29 possibilities related to the patient, device, procedure, or observer [6]. Korotkov and Riva-Rocci would be astonished to see that more than a century after their seminal studies, screening and stratification for hypertension treatment would still be dependent on clinic-based measurement of seated BP [7].

Routine measurement of BP should move to electronic devices. These are at least equally precise and dispense with most procedures used to measure BP by the auscultatory method. This method requires a combination of manual disinflation of the cuff, hearing of Korotkov sounds, and visual identification of the points at which the sounds start and finish on the dial of the gauge. With automatic devices, it is just necessary to push a button and use only one sense—sight—to determine BP. Moreover, oscillometric methods permit recording of unwitnessed and repeated BP measurements. Automatic devices to register Korotkov sounds have been developed in the past and are currently being investigated, mainly to circumvent difficulties in capturing oscillations in fatty arms.

3.2 Daily Blood Pressure Load and the Concept of Casual and Usual Blood Pressure

Each systole generate a distinctive pulse wave and BP value, which results from a fine balance between venous return, cardiac inotropism and chronotropism, and peripheral resistance. These parameters are influenced by exercise, meals, sleep, physical stimuli, and emotional stimuli, among other things. The daily vascular load is theoretically a result of the sum of beat-to-beat BP over a 24-h period (around 100,000 beats per 24 h).

Casual BP measurements can hardly estimate the daily vascular load. Besides measuring only two cycles of BP at each measurement (one for systolic BP and the other for diastolic BP), casual measurement is influenced by the procedures employed in the measurement, and their effects, such as the alertness reaction—a phenomenon exacerbated by measurement of BP by doctors. Despite these limitations, the registering of BP generated by few heartbeats identified the risks of high BP in pioneering cohort studies. New methods of BP measurement have improved the precision of estimates of the 24-h BP load by increasing the number of measurements and by not requiring an observer to measure BP. The average of these

measurements has diminished the influence of spurious values and provided BP values closer to the usual BP of the individuals (the 24-h load).

The concept of casual BP and usual BP is not new. In the mid-1940s, Horace Smirk proposed the concept of basal (i.e., usual) and casual BP [8]. In order to measure basal BP, he recommended an extensive protocol, which included periods of fasting and resting, and several BP measurements.

The methods currently used to get closer to the usual BP of individuals are presented in Box 3.1.

Box 3.1 Methods of blood pressure (BP) measurement

- Repeated measurements in the office
- Automated office BP measurement
- Ambulatory BP monitoring
- Home BP monitoring

3.3 Precision of Methods Used to Estimate Risks of High Blood Pressure

Participants enrolled in the classical cohort studies that established the risks of high BP had their BP measured by the auscultatory method. In some studies, BP was measured a few times and only on 1 day. These BP values corresponded to a casual assessment and tended to be higher than usual BP. If the BP values actually measured in the cohort studies had been included in meta-analyses, the real risks would be diluted, because the participants tended to have lower usual BP outside the clinic evaluation. This phenomenon was referred to as “regression dilution bias.” From the time of their first report [9], the investigators from the Prospective Studies Collaboration adjusted their data for regression dilution bias, through correction of BP variation based on age at baseline and in two subsequent cycles of evaluation of the participants of the Framingham Heart Study cohort. In a more recent report [10], they corrected BP for more measurements, with information on a total of 286,000 BP remeasurements done in individual studies.

BP measured in the office with the auscultatory method is still the most widely used method for diagnosis and management of hypertension, despite the aforementioned limitations. Some procedures may improve the quality of clinic BP measurement. The technique for measurement should be followed strictly, with adequate maintenance of devices. Repeated measurements of BP, particularly on different days, may help to lessen the effects of white-coat hypertension and masked hypertension. Figure 3.1 shows that BP decreased by 10/5 mmHg over the course of six measurements taken on three different days at our clinic, before treatment was started [11].

Estimation of the risks of high BP by ABP and HBP monitoring eliminates the need for adjustment for regression dilution bias, because these methods measure BP repeatedly. Cohort studies employing these methods have reported risks of BP at

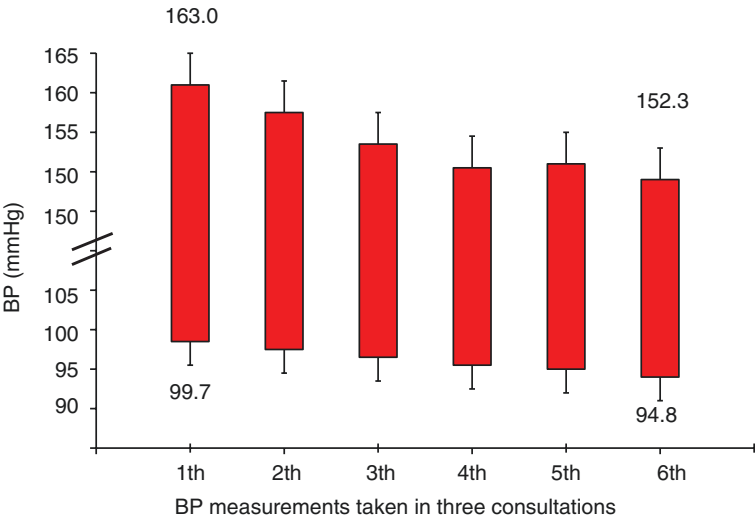


Fig. 3.1 Blood pressure behavior over the course of six measurements taken during three consultations [11]

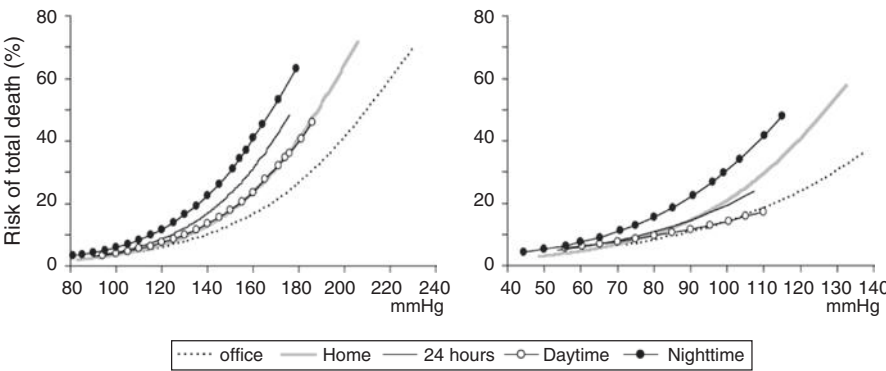


Fig. 3.2 Risks of high blood pressure assessed by different methods in the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) cohort study. (Reprinted from Segal et al. [12], with permission)

lower values than those using office BP, with less dispersion of data and greater precision. Therefore, several cohorts with fewer participants than the studies using the auscultatory method have demonstrated risks of increasing BP, such as the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study [12]. Figure 3.2 shows that the risks identified by HBP monitoring and ABP monitoring at different times of day started at lower BP values and had a sharper inclination than those identified using office BP. Risks of high nighttime BP, which is less influenced by physical and emotional stimuli than daytime BP, were noted. A meta-analysis of individual data showed that the risks of high nighttime BP were independent of 24-h BP [13].

The number of 24-h measurements and the possibility to measure BP during sleep are advantages of ABP monitoring over other methods, particularly conventional office BP measurement. A direct comparison of office BP, ABP, and HBP measurements demonstrated the superiority of ABP in predicting the incidence of cardiovascular events [14]. The superiority of ABP monitoring to establish the prognosis of patients was also demonstrated in patients with resistant hypertension [15].

Morning HBP measurements had better prognostic performance than office BP measurements in patients receiving treatment for hypertension [16]. Devices for HBP monitoring that are programmable to measure BP during sleep have recently been developed. BP assessments by nighttime HBP and ABP monitoring have shown similar averages and associations with target organ damage [17]. Nighttime BP measured by these methods had similar associations with the echocardiographic left ventricular mass index, carotid intima-media thickness, urine albumin excretion, and the ankle-brachial index (ABI) [18].

Protocols for HBP monitoring diverge in terms of the number and periods of BP registration. We demonstrated that a protocol with more measurements taken on fewer days had higher accuracy to diagnose hypertension, taking ABP monitoring as the gold standard [19].

Automated office BP (AOBP) measurement is a strategy that employs the method of out-of-office BP measurement in the office [20]. It uses automatic devices to record multiple BP readings without the presence of a doctor or medical staff. Different protocols use different numbers of measurements, but their averages are similar to the daytime BP average measured by ABP and HBP monitoring. A Canadian cohort used this method for baseline evaluation, which identified an achieved systolic BP (after treatment) between 110 and 119 mmHg as the nadir for the incidence of cardiovascular disease [21] (Fig. 3.3). These values are similar to those used in the intensive BP-lowering treatment arm in the Systolic Blood Pressure Intervention Trial (SPRINT) [22].

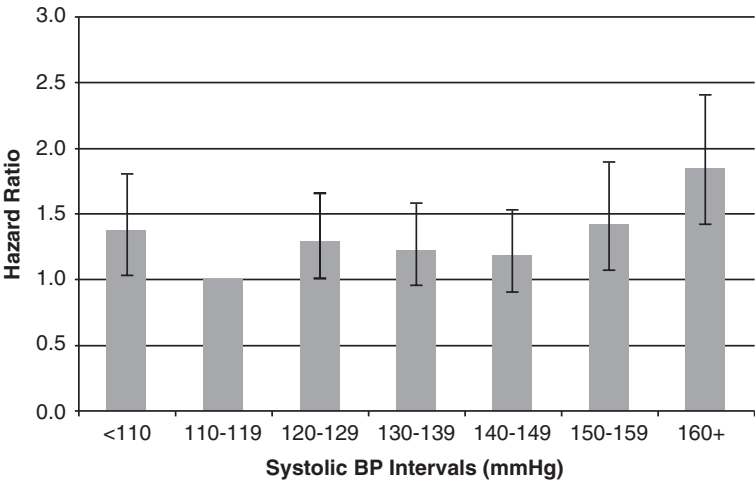


Fig. 3.3 Hazard ratio for incident cardiovascular disease, based on systolic blood pressure (BP) assessed by automated office BP measurement. (Reprinted from Myers et al. [21], with permission)

The search for the usual BP of individuals is likewise important for treatment of patients with hypertension. SPRINT [22] has been criticized because the investigators did not use the common methods to measure office BP [23]. Instead, the patients had unwitnessed BP measurement, done with an automatic device (AOBP measurement), in order to minimize the white-coat hypertension effect. This strategy could underestimate casual BP values by between 5 and 16 mmHg [24]. The critics seem to advocate in favor of an inaccurate method of measuring BP.

In some old cohorts that identified the risks of high BP, BP measurement sometimes did not follow the standards for BP measurement. In clinical trials, however, BP was measured meticulously, frequently with repeated measurements and with discarding of the first measurements. In the seminal Veterans-I trial [25], diastolic BP ≥ 115 mmHg for enrollment in the randomized phase of the study needed to be sustained from the fourth to the sixth day of hospitalization and during the phase of assessment of adherence to treatment, with an inert substance detected in the urine of participants. BP was approximately 9/6 mmHg lower in the clinical trials than on routine office BP readings [26]. BP measured in previous clinical trials were accepted as valid by guidelines and consensus, and nobody sought to adjust for sloopy BP measured in clinical practice.

Anyway, regardless of the repercussions of the automated method of BP measurement employed in SPRINT with respect to the results, the same method should be used in the daily care of patients. The Canadian guidelines for management of hypertension have proposed AOBP measurement as the preferred method to measure BP in the office [27].

3.4 White-Coat and Masked Hypertension

The poor precision of BP measurement by the conventional auscultatory method in the office has led to a mismatch with BP measured outside the office by ABP or HBP monitoring. Most commonly, BP measurements are higher in the office than outside the office in a proportion of patients, because of the alertness reaction. The expression “white-coat hypertension” was coined to describe this condition. Patients already on treatment may present with this discordance as well, which is known as the white-coat phenomenon. The opposite is also true: individuals may have normal BP in the office and high BP at home—this is known as masked hypertension (in individuals not on treatment) or the masked phenomenon (in individuals on treatment). Figure 3.4 shows the diagnostic possibilities arising from BP measurement in the office and out of the office (ABP or HBP monitoring).

White-coat and masked hypertension are part of a continuum for identification of risks of high BP for incident cardiovascular disease. Figure 3.5 shows the risks of these conditions for cardiovascular death in the PAMELA study cohort [28]. In a follow-up period of more than 18 years, the risks of white-coat hypertension were evident for total and cardiovascular mortality [29].

Greater numbers of BP measurements in different conditions permit identification of different responses of individuals to determinants of alertness. Moreover, masked and white-coat effects (in patients on treatment for hypertension) may reflect variable adherence to treatment at home and on the day of a medical consultation. AOBP

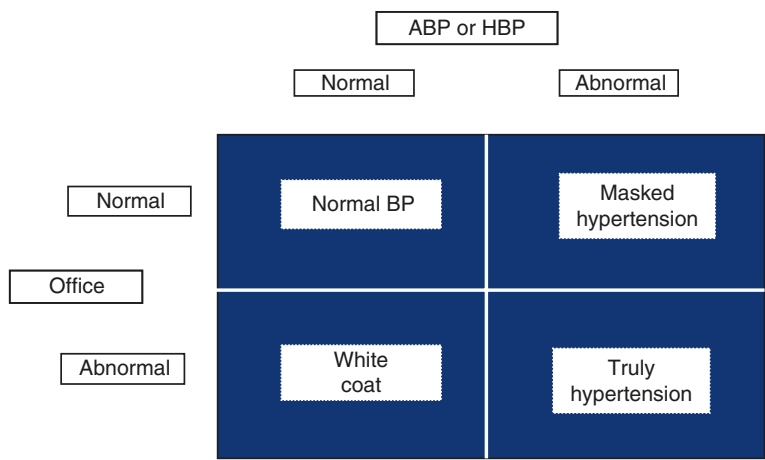
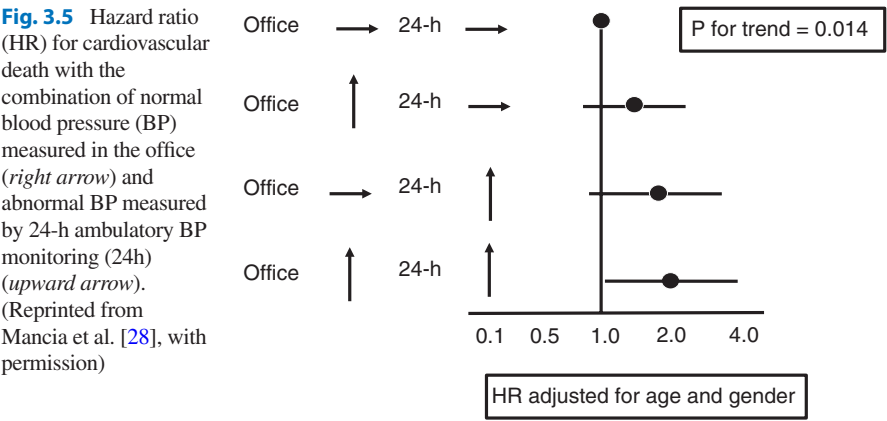


Fig. 3.4 Diagnostic possibilities arising from measurement of blood pressure (BP) in the office and during a daytime period of out-of-office ambulatory BP monitoring



measurement is another method to lessen white-coat and masked hypertension effects. This method should therefore be preferred to measurement of BP in the office [20].

The statistically borderline association of white-coat hypertension with incident cardiovascular events in individual cohorts may be due to insufficient statistical power. Even with aggregate analysis of 11 cohorts by the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators, just 653 individuals with white-coat hypertension were compared with a similar number of individuals with normal BP (using the 140/90 mmHg paradigm) [30]. On the other hand, a systematic review of 23 cohorts, totaling 20,445 individuals not treated for hypertension, identified a risk of 1.38 (95% confidence interval (CI) 1.15–1.65) for incident cardiovascular disease in individuals with white-coat hypertension in comparison with true normotensive subjects [31]. The risk was not significant in cohorts of participants treated for hypertension.

The risks of white-coat hypertension obviously do not derive from higher BP measured exclusively during a medical consultation. In fact, this phenomenon captures the higher usual BP of individuals with white-coat hypertension, versus individuals with true normal BP. Even with BP within normal ABP limits, patients with white-coat hypertension or the white-coat phenomenon have higher BP than their counterparts with true normal BP [32]. In practical terms, however, detection of white-coat hypertension or the white-coat phenomenon draws attention to the higher risk to patients. Since the benefits of treatment have been demonstrated mostly in studies using office BP measurement (including individuals with white-coat hypertension), treatment of white-coat individuals is justifiable.

Estimates of the prevalence rates of white-coat and masked hypertension have been variable, depending on the populations studied. The prevalence of white-coat hypertension has been reported by old studies and in specific populations, and is probably around 25% [33]. Pooling data from a study of the prevalence of masked hypertension in a community sample and data from the nationally representative US National Health and Nutrition Examination Survey (NHANES), investigators estimated that 12.3% (95% CI 10.0–14.5) of the adult US population with normal office BP have masked hypertension, corresponding to 17.1 million persons aged ≥ 21 years [34].

3.4.1 Diagnostic Thresholds for Out-of-Office Blood Pressure Measurement

The bases on which to classify office BP $\geq 120/80$ mmHg as abnormal are presented in Chap. 1 and are likely applicable to AOBP measurement. Current guidelines for HBP and ABP monitoring propose diagnostic values lower than those recommended for office BP (Table 3.1) [33, 35]. These values have come from meta-analyses of cohort studies that measured BP by these methods, which showed cardiovascular risk at lower BP values than office BP. The current diagnostic thresholds are probably not valid anymore, given recent developments regarding the risks and benefits of treating high BP.

The correlation of BP values on AOBP measurement, as employed in SPRINT [22], with those measured by daytime ABP monitoring and HBP monitoring [36, 37] suggests that the threshold of 120/80 mmHg on daytime ABP and HBP monitoring may be used to diagnose hypertension. The values for nighttime and 24-h ABP should be proportionally lower. The recently released 2017 ACC-AHA

Table 3.1 Diagnostic thresholds for high blood pressure (BP) measured by ambulatory BP (ABP) and home BP (HBP) monitoring, according to current guidelines

	ABP (mmHg)	HBP (mmHg)
Daytime BP	$\geq 135/85$	$\geq 135/85$
Nighttime BP	$\geq 120/70$	
24-h BP	$\geq 130/80$	

Table 3.2 Proposal for new diagnostic thresholds for high blood pressure (BP) measured by ambulatory BP (ABP) and home BP (HBP) monitoring

	ABP (mmHg)	HBP (mmHg)
Daytime BP	≥120/80	≥120/80
Nighttime BP	≥100/65	
24-h BP	≥115/75	

guidelines [38] recommended the values presented on Table 3.2. The value proposed for systolic BP during sleep (100 mmHg) exceeds the expected 10% dipping of BP in relation to the value proposed for daily BP, and is rarely seen in ABP exams in the daily practice. Probably these values will be discussed by other scientific societies, but in general the values of the table are those expected for the diagnosis of hypertension with BP measured out of office.

3.5 Clinical Evaluation

Accurate measurement of BP is obligatory in any medical consultation. BP measurement is an essential component of periodic medical examination of adults at all ages [39]. Moreover, consultations in any specialty and visits to emergency rooms should include measurement of BP. Unfortunately, this is not the practice in many medical services worldwide.

The aims of clinical evaluation of patients with high BP are to evaluate the consequences of high BP and to stratify the risks to patients.

3.5.1 Headache

Measurement of BP is the exclusive method used for diagnosing hypertension. Laypeople, doctors, and some medical textbooks still believe that suspicion of hypertension increases in the presence of certain symptoms, mostly headache. Even in the absence of an association between BP levels and headache, some people recommend not dismissing people’s belief in it, since it will make them more likely to seek medical assistance to treat this symptom, increasing the chances of diagnosing hypertension. If there were no association, however, this recommendation would impede diagnosis of hypertension in individuals without symptoms.

We performed ABP monitoring in patients with hypertension who complained of headache [40]. The hourly averages of systolic and diastolic BP did not differ between patients who did and those who did not complain of headache during BP monitoring. BP did not increase before the episode of headache in patients who presented with this symptom during BP monitoring (Fig. 3.6).

In a population-based cross-sectional study, we found no association between hypertension and several types of headache (Fig. 3.7). The complaint of migraine was inversely associated with hypertension after adjustment for confounding (risk

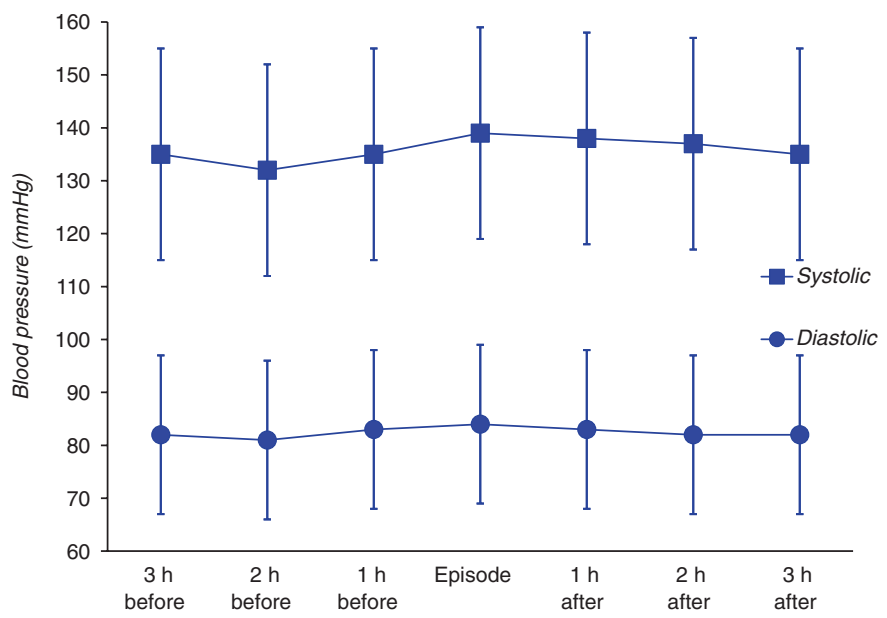


Fig. 3.6 Behavior of blood pressure surrounding an episode of headache. (Modified with permission from [40])

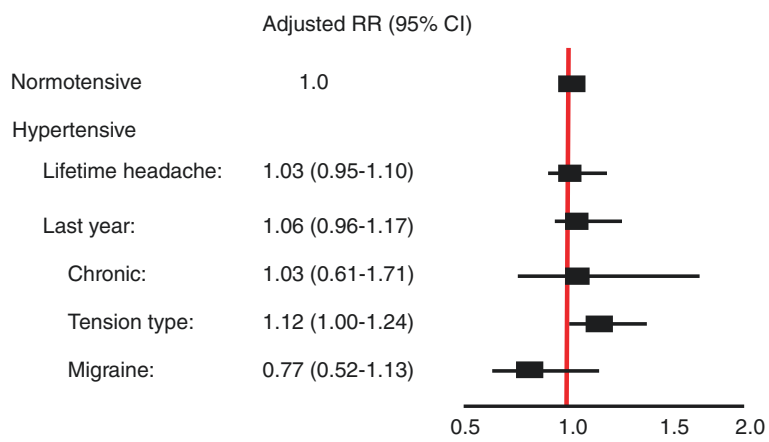


Fig. 3.7 Association between complaints of various types of headache and hypertension [41]

ratio (RR) 0.56, 95% CI 0.41–0.77) [41]. Such an inverse association between BP and migraine has been reproduced in most [42–44] but not all studies [45]. Additionally, we found no association between headache and severe hypertension at our outpatient clinic [46].

Most observational studies have shown no association between BP and headache. Two large longitudinal studies identified an inverse association between BP and the incidence of headache [44, 47].

Secondary findings of randomized trials comparing BP-lowering drugs with placebo have contradicted the findings of observational studies. Compiling 94 small to moderately sized trials (totaling 240,000 participants), a meta-analysis by Law and colleagues [48] found that the prevalence of headache was approximately 30% lower in the active treatment group than in the placebo group (8.0% versus 12.4%). The four classes of BP drugs (diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers) were associated with reductions in the prevalence of headache, with a stronger association being seen for beta blockers. The effect was closely related to diastolic BP reduction.

The findings of the observational and experimental studies are hardly reconciled. Except for diuretics, the other drug classes evaluated in the meta-analysis had beneficial effects on headache in other trials, particularly beta blockers. The trials included in the meta-analysis had high heterogeneity, and headache was one among other adverse events of treatment for which data were collected secondarily. Only around 10% of patients complained of headache. Finally, the absolute reduction was low, corresponding to a number needed to treat (NNT) of 30 patients treated for prevention of one case of headache. Anyway, the question is still open but is unlikely to be investigated in new and large trials.

Even if there is an association between certain types of headache and BP, or if BP drugs lower the prevalence of headache, patients and doctors should not rely on headache as a symptom of hypertension. Diagnosis of hypertension requires active screening through BP measurement.

3.5.2 Epistaxis

This is another condition commonly attributed to hypertension, although most episodes of bleeding come from the venous circulation. Local factors are the likely causes of epistaxis. The frequent association between these conditions in emergency rooms may be a consequence of reverse causality. In two studies at our outpatient clinic, there was no association between a history of epistaxis and BP [49, 50]. In a population-based study, we did not find an association between BP and epistaxis [51] (Fig. 3.8).

3.5.3 Quality of Life

Hypertension may impair the quality of life. Studies addressing this possibility have been heterogeneous, limiting their external validity. We investigated this question in a meta-analysis and in an original population-based study. The meta-analysis of six studies that fulfilled our criteria for selection identified lower quality of life in eight domains [52]. Figure 3.9 presents the estimates for four domains. Only three studies

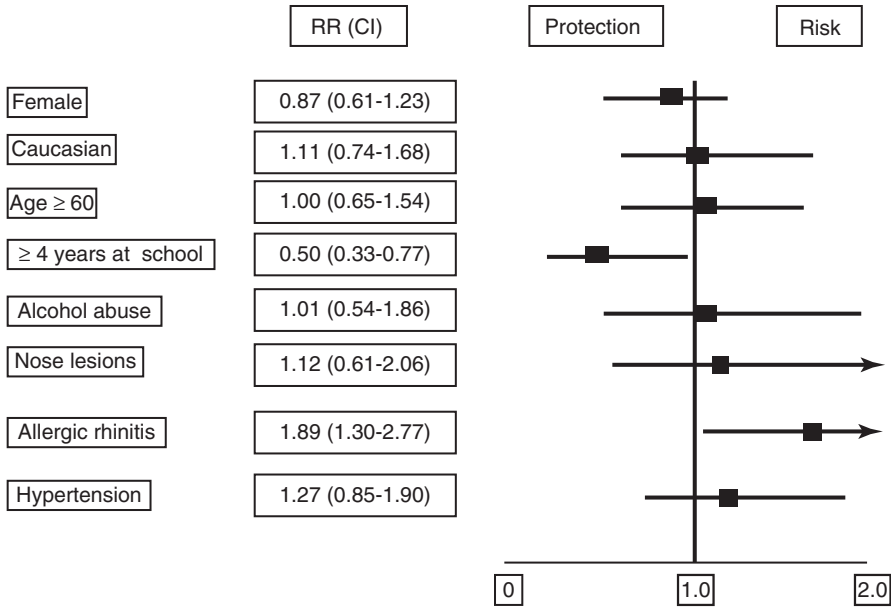


Fig. 3.8 Risk factors for epistaxis in a population-based study. (Reprinted from Fuchs et al. [51], with permission)

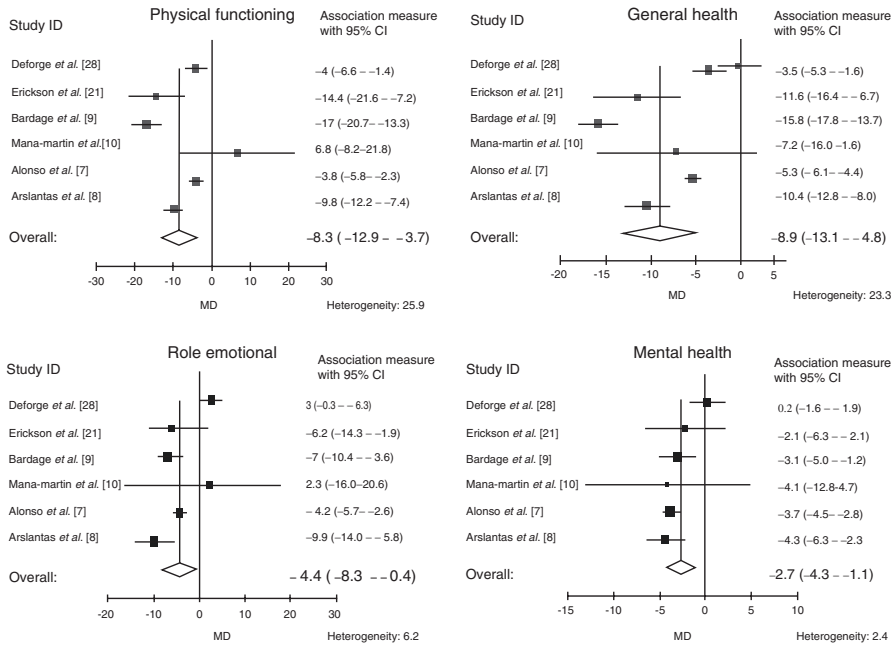


Fig. 3.9 Four domains of quality of life assessed by the 36-Item Short-Form Health Survey (SF-36) were worst in patients with hypertension. (Reprinted from Trevisol et al. [52], with permission)

actually measured BP, but the estimates did not change substantially in relation to other studies. The association with awareness of the diagnosis of hypertension was investigated in only one study.

In a study of 1858 adults selected at random from the community [53], there was an association between hypertension and lower quality of life, particularly in patients receiving treatment with controlled BP. The potential association of high BP with lower quality of life is rational a priori, since individuals tend to feel worse when they are sick. The association with awareness of the diagnosis of hypertension lines up with this interpretation. The identification of lower quality of life in hypertensive patients with controlled BP requires replication. Anyway, if this association is true for patients with hypertension, it may influence adherence to treatment.

3.5.4 Musculoskeletal Complaints

Chronic musculoskeletal complaints are among the more frequent ailments of human beings. Since hypertension is quite common as well, it is natural that many individuals present with both conditions. Moreover, these conditions both have obesity and age as risk factors. Some old studies suggested that hypertension induced hypalgesia, but others did not identify an inverse association between pain and hypertension. In one of our population-based studies, we looked at this possibility [54]. Curiously, chronic musculoskeletal complaints were more frequent in individuals with uncontrolled hypertension under drug treatment, like our findings about quality of life. The association was confined to men, which reduces its consistency. Taken together, the findings from different studies show that the evidence is inconsistent and probably irrelevant to the clinical scenario.

3.5.5 Other Findings in the Medical History

Aspects closely related to hypertension include a family history of hypertension, the duration of hypertension, previous treatments, use of drugs associated with risks for hypertension (such as alcoholic beverage consumption and oral contraceptives), and other cardiovascular risk factors, among others. Clues for diagnosis of secondary hypertension are presented in Sect. 3.9. Symptoms and a history of cardiovascular disease are important for risk stratification.

3.5.6 Physical Examination

Accurate measurement of BP is the focus of the physical examination, which should be complemented by an out-of-office measurement (see Sect. 3.4.1).

Clinical skills for clinical assessment of the consequences of hypertension are still useful, despite the current availability of laboratory tests, electrocardiography (ECG), and echocardiography.

Greater intensity of the aortic valve closing in the second heart sound, in comparison with the pulmonary component, is probably the first manifestation of hypertension on physical examination. Hearing of a fourth heart sound denotes impairment of left ventricular diastolic function. The presence of a sustained apex beat (ictus cordis) is a sign of more advanced and chronic pressure overload. Deviations and an increase in the extension of the apex beat are rare in uncomplicated hypertension.

Abdominal examination includes a search for renal masses and bruits over the aorta or renal arteries. Probably, most suspicious findings will not be confirmed on imaging and Doppler examinations, but clinical examination is safe and inexpensive.

The search for signs of clinical disease resulting from hypertension is important, particularly if there have been symptoms in the medical history. A large and deviated apex beat, a third heart sound (S3), atrial fibrillation, rales, abnormalities in the carotid or peripheral pulses, and neurological deficits, including deficits in cognitive function, are among them.

3.5.7 Laboratory Data

The routine laboratory evaluation is simple (Box 3.2).

Box 3.2 Routine laboratory tests for patients with hypertension

- Glycated hemoglobin
- Lipid profile
- Creatinine and urinalysis
- Electrolytes (potassium)

Tests of glycated hemoglobin and the lipid profile aim to identify other cardiovascular risk factors. A creatinine test is used to estimate the glomerular filtration rate to identify the presence of chronic kidney disease—a cause of secondary hypertension. Urinalysis, particularly for proteinuria, seeks signals of chronic kidney disease as a cause or consequence of hypertension. A serum potassium test assesses adverse events of diuretics and is a preliminary screening test for hyperaldosteronism. Further laboratory investigations are dictated by specific clinical suspicions.

3.6 Risk Stratification

Evidence of subclinical end-organ damage may refine risk stratification of patients with hypertension. Other cardiovascular risk factors potentiate the risks of high BP, requiring specific control measures. Finally, other BP-related conditions might influence the prognosis of patients, such as optic fundus abnormalities, BP variability, and high central BP. Investigations into these conditions have been extensive. It remains to be demonstrated if they add additional prognostic precision to isolated

peripheral BP measurement and, more important, if there is evidence that they should be a focus of specific therapies. For now, they serve mostly to provide better understanding of the consequences of BP but do not fulfill the criteria for choosing specific treatments in patients with hypertension.

Electrocardiography, echocardiography, and other examinations used in risk stratification of patients with hypertension are shown in Box 3.3.

Box 3.3 Findings for risk stratification of patients with hypertension

- Electrocardiographic abnormalities
- Echocardiographic abnormalities
- Development of clinical disease
- Optic fundus abnormalities
- Aortic stiffness and peripheral arterial disease
- Blood pressure variability

3.6.1 Electrocardiography

This old companion of clinicians and cardiologists still has a place in evaluation of patients with hypertension and prehypertension. Besides its utility for detecting arrhythmias, ischemia, and other abnormalities, ECG is useful for estimating the consequences of high BP for left ventricular mass (LVM).

The performance of the voltage and voltage–duration Sokolow and Cornell indices to rule out left ventricular hypertrophy (LVH) is satisfactory in terms of specificity, but the sensitivity to screen for LVH is insufficient. In this regard, echocardiography and other imaging methods surpass ECG in the estimation of LVH. Nonetheless, a strain pattern on ECG predicts morbidity and mortality in patients with hypertension independently of echocardiographic parameters [55, 56]. Regression of LVH assessed by ECG has been associated with a better prognosis in patients with mild [57] and resistant hypertension [58]. Moreover, the variation in LVM indices captures differential effects of BP treatment in patients with hypertension [59] and prehypertension, as was recently shown in the Prevention of Hypertension in Patients with Prehypertension (PREVER-Prevention) trial [60].

The presence of abnormalities on ECG, however—as with other methods of risk stratification of patients with hypertension—does not influence strategies and goals for treatment, which remain based on BP levels.

3.6.2 Echocardiography

There is extensive literature showing cardiac structural and functional echocardiographic abnormalities in patients with hypertension and prehypertension. Among the structural consequences, LVH is noticeable, including mostly but not only concentric remodeling [61]. Nondilated and dilated concentric hypertrophies and

dilated eccentric hypertrophies are associated with a higher risk of cardiovascular events, but nondilated eccentric hypertrophy is not [62, 63].

The main consequence of LVH is impairment of left ventricular diastolic function. Echocardiography is the preferred method for clinical assessment of diastolic function. The old-fashioned method to evaluate diastolic function—the E/A wave ratio—has been progressively replaced by Doppler tissue imaging. The ratio between the standard mitral inflow maximal velocity (E) and the mitral annular relaxation velocity (E')— E/E' —is currently the standard for evaluation of diastolic function. Diastolic function deteriorates with aging but is strongly influenced by BP. This evolution is the natural history of hypertensive cardiomyopathy (as described in Chap. 1), leading to development of heart failure with a preserved ejection fraction.

In a community-based cohort study, individuals older than 45 years, free of heart failure, were examined by echocardiography 4 years apart and were further followed for 6 years [64]. The incidence of heart failure was higher in participants who had persistent, or progression to, moderate to severe diastolic dysfunction and in those who had persistent, or progression to, mild diastolic dysfunction, in comparison with participants who retained normal, or who normalized, diastolic function (Fig. 3.10).

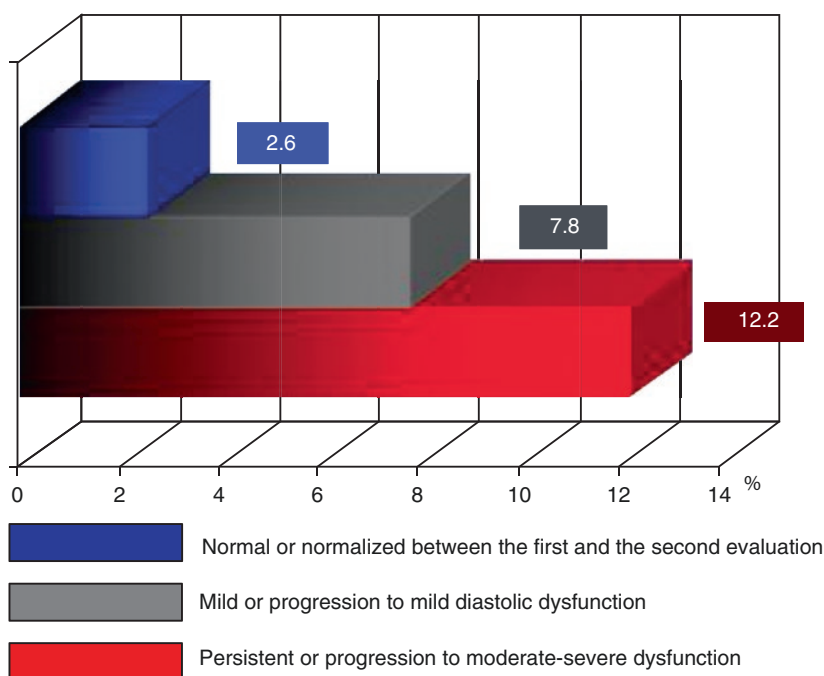


Fig. 3.10 Diastolic function in two evaluations and incidence of heart failure during follow-up for 6 years [64]

Echocardiographic abnormalities occur in individuals with prehypertension as well. Structural and functional abnormalities have been found in nonelderly [65] and elderly individuals [66].

Natural progression of diastolic dysfunction and other echocardiographic abnormalities to heart failure, particularly with preserved ejection fraction, can be stopped with effective BP-lowering treatment. Chlorthalidone has been shown to be superior to amlodipine and lisinopril in this regard [67], reflecting its greater BP-lowering efficacy. Therefore, identification of hypertensive echocardiographic abnormalities is useful to recognize target organ consequences of hypertension and helps to confirm that diuretics are a better option than other treatments for management of hypertension.

3.6.3 Development of Clinical Disease

Development of clinical cardiovascular disease is a striking risk modifier in patients with hypertension and dictates their prognosis. BP eventually reduces after cardiovascular events but still needs to be lowered further, as in survivors of stroke and coronary events (Chaps. 1 and 4). Management of patients with clinical cardiovascular disease requires additional therapies and is out of the scope of this book.

3.6.4 Optic Fundus Abnormalities

Optic fundus abnormalities are the most traditional evidence of target organ damage in patients with hypertension. In the classic cohort study by Keith, Wagener, and Barker [68], participants were classified into four classes based on clinical, ECG, and retinal abnormality criteria. The presence of optic edema characterized class IV. Participants with retinal exudates and hemorrhages were in class III. Mild alterations (mild generalized retinal arteriolar narrowing) and moderate alterations (definite focal narrowing and arteriovenous nicking) on optic fundus examination were part of the criteria defining classes I and II, respectively. Mortality was progressively higher from classes I to IV (see Chap. 1). Other criteria defining the classes were set aside in the following decades, and the Keith, Wagener, and Barker proposition became the classic Keith–Wagener (KW) classification (the name “Barker” is not usually included in the eponym) of optic fundus abnormalities in patients with hypertension.

We were probably the first group to question the performance of KW classes I and II in estimating the severity of hypertensive retinopathy [69]. We examined the distribution of classes I and II in patients with systolic BP higher and lower than 180 mmHg and diastolic BP higher and lower than 105 mmHg. Class I abnormalities were more common than class II abnormalities in patients with high BP by both definitions (Fig. 3.11).

The performance of the KW classification to predict the incidence of coronary heart disease (CHD) was explored in the Lipid Research Clinics Coronary Primary

Prevention Trial cohort. Arteriolar narrowing was the abnormality denoting higher risk for incident CHD [70] (Fig. 3.12).

As far as we know, we developed the first semiautomated method to measure retinal vessel diameters [71]: the microdensitometric method. Instead of measuring the vessel calibers on a retinography projection, the program estimates the edges of vessel walls through subpixel identification. Figure 3.13 exemplifies the image acquisition process.

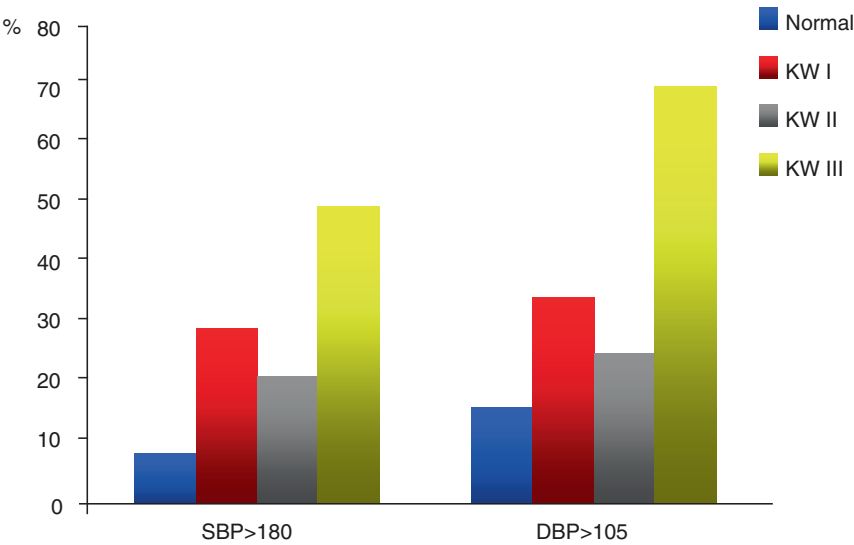
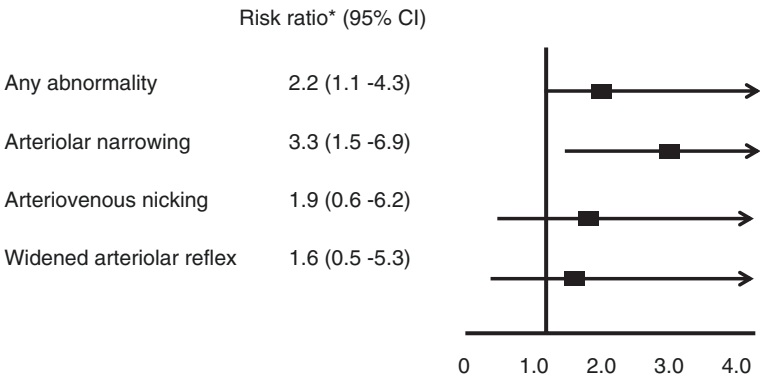


Fig. 3.11 Proportions of normal optic fundus examinations and Keith–Wagener classes I–III in patients with high blood pressure [69]



*Adjusted for BP and other risk factors for cardiovascular disease

Fig. 3.12 Association of retinal vessel abnormalities with incident coronary heart disease [70]

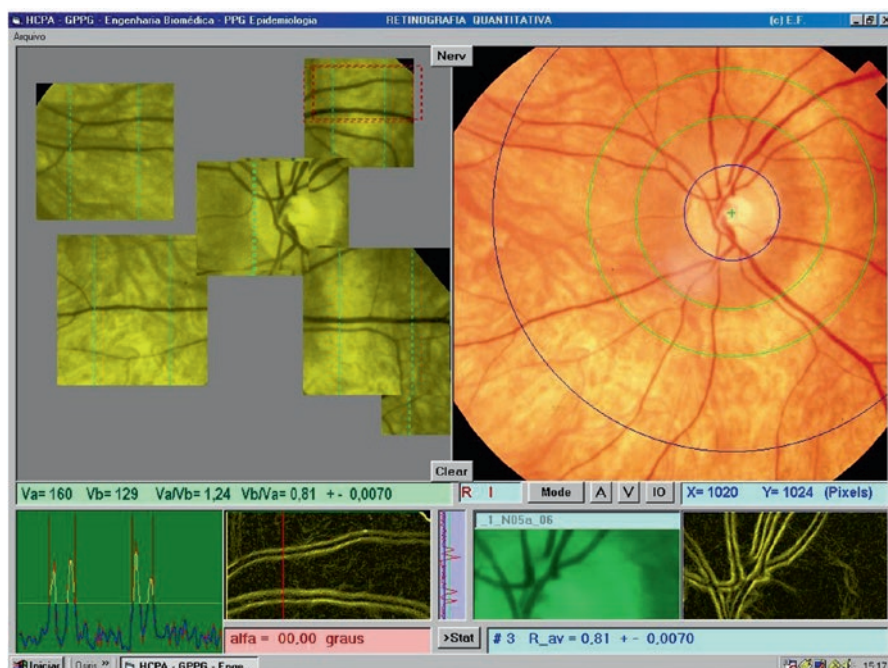


Fig. 3.13 Example of the semiautomated edge detection pixel intensity method to determine retinal vessel diameter; see Pakter et al. [71] for details. (Reprinted from Pakter et al. [71], with permission)

Taking the images from microdensitometry as the gold standard, we demonstrated the poor performance of clinicians and ophthalmologists in assessment of arteriolar narrowing [72]. A study with images obtained simultaneously by use of image-processing software on color fundus photographs and by fluorescein angiographs demonstrated that the microdensitometric method measured the vessel lumen [73]. Differences in vessel diameters measured by the microdensitometric method observed in clinical conditions may therefore be ascribed to variations in wall thickness or vasoconstriction. We explored these possibilities by performing microdensitometric acquisition of images during 24-h ABP monitoring [74]. The mean 24-h, daytime, and nighttime systolic and diastolic BP—but not BP measured at the time of acquisition—were inversely associated with the arteriolar caliber, suggesting that BP measured at the time of retinography acquisition does not influence the diameter of retinal vessels.

Newer methods of assessment of retinal vessels have allowed more precise measurement of the walls and lumens of arterioles [75]. Studies using these methods have demonstrated that remodeling of retinal arterioles seems to include short-term functional and long-term structural changes [76].

Retinal vessels are a window for direct identification of microvascular abnormalities, allowing investigation of target organ damage and physiopathological aspects of hypertension. For example, adiponectin has been inversely associated

with the retinal arteriolar caliber in elderly individuals, suggesting that it is a marker of microvascular damage in this age stratum [77].

Tien Wong led several investigations into the performance of retinal vessel abnormalities for prediction of several cardiovascular outcomes in different cohorts. These investigations consolidated the interpretation that classes I and II of the KW classification do not discriminate between different degrees of retinal vessel damage promoted by high BP. Wong and Paul Mitchell proposed a new classification of optic fundus abnormalities in patients with hypertension, in which they collapsed KW classes I and II of the KW classification [78]. Studies comparing the association of these classifications with target organ damage did not show substantial differences between them—a finding that favors the Wong–Mitchell classification in terms of clinical simplicity [79].

Studies of physiopathological and prognostic aspects of optic fundus abnormalities may help us to understand the pathogenesis of hypertension and improve scores for prediction of cardiovascular events. Despite these findings, retinal vessel examination is not a part of the routine grading of hypertension. Nonetheless, optic fundus examination is obligatory in patients with severe hypertension to exclude optic disk edema.

3.6.5 Aortic Stiffness and Peripheral Arterial Disease

Stiffness of the aorta may be a consequence or a cause of high systolic BP. The possibility that abnormalities in the biology of the aortic artery precede the increase in BP is discussed in Chap. 1. Indeed, there is more evidence in favor of the interpretation that aortic stiffness is predominantly a consequence of chronic elevation of BP.

The natural history of uncontrolled hypertension leads to progressive loss of the elastic properties of large arteries, particularly of the aorta. Clinically, it is easy to recognize the development of aortic stiffness, which promotes the preponderance of high systolic BP over high diastolic BP in elderly individuals, and the consequent high pulse pressure. The pulse wave velocity (PWV) and central BP measurement are the methods used to assess the degree of aortic and arterial stiffness. Methods of central BP measurement provide an estimate of reflection of the pulse wave by the aorta—the augmentation index. There are many reports describing associations of aortic stiffness evaluated by PWV with target organ damage and cardiovascular outcomes [80]. The associations with central BP are less consistent [81].

The ABI is an estimate of the magnitude of peripheral arterial disease. It corresponds to the ratio of the BP (measured by echo Doppler) at the ankle to the BP measured in the upper arm. Low values indicate the presence of atherosclerosis and have prognostic implications even in asymptomatic individuals [82].

It is still unknown if risk stratification by measurement of aortic stiffness or peripheral arterial disease by any method has an incremental value over measurement of brachial BP. Moreover, the utility of measuring vascular properties would require demonstration that treatment of hypertension would benefit from stratification by the presence of aortic stiffness or peripheral arterial disease. The Conduit Artery Function Endpoint (CAFE) study, a substudy of the randomized

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [83], suggested that the superiority of amlodipine to atenolol in the main trial could have resulted from a greater decrease in central BP than in brachial BP. Nonetheless, atenolol is a less effective beta blocker (see Chap. 4), and amlodipine probably has a greater BP-lowering effect than atenolol not only on central BP but also on 24-h and night-time BP.

3.7 Blood Pressure Variability

In addition to the biomechanical consequences of high BP, BP variation over time (high BP variability) may lead to additional vascular damage. Experimental studies have demonstrated an association of high beat-to-beat variability with development of endothelial dysfunction and atherosclerosis [84]. The technical barriers to measurement of intra-arterial beat-to-beat variation in BP has limited studies in human beings. BP assessed by ABP monitoring has opened up an opportunity for estimating 24-h variability. This possibility has translated into several methods to assess BP variability: the time rate index (the first derivative of systolic BP over time); the standard deviation (SD) of 24-h systolic BP; the coefficient of variation of 24-h systolic BP; power spectral analysis; the trough-to-peak ratio; the smoothness index; visit-to-visit variability (in some cases with an interval of months); reading-to-reading variability (from 24-h ABP); and day-to-day variability (from 7-day home BP), among others. The indices are divided into short-, mid-, and long-term BP variability. A statement from the European Society of Hypertension has evaluated methods of measuring BP variability [81].

Numerous studies have looked at the association of BP variability with evidence of target organ damage and other parameters. For example, we demonstrated an independent association between the time rate index and the ABI in patients with hypertension [85], but there was no such association with several echocardiographic parameters in patients with controlled and uncontrolled hypertension [86] and in patients with diabetes [87].

There have been many clinical and epidemiological studies investigating the association of BP variability with cardiovascular outcomes. Overall, these studies have shown that BP variability may add some prognostic information to BP. For example, a meta-analysis of studies done exclusively with measurement of visit-to-visit BP variability identified its association with all-cause mortality (Fig. 3.14), cardiovascular mortality, and stroke [88]. Visit-to-visit variability was also associated with a higher incidence of cognitive decline independently of BP [89].

In these and other cohorts, the association of BP variability with cardiovascular outcomes was apparently independent of hypertension or BP. Some indices, such as the SD and coefficient of variation of 24-h systolic BP, are intrinsically dependent on the mean BP. Moreover, the possibility of residual confounding cannot be excluded, particularly in studies that have controlled for hypertension but not for continuous BP. Differences in BP among participants with hypertension, and the risk of prehypertension, may still be underlying confounders of the association

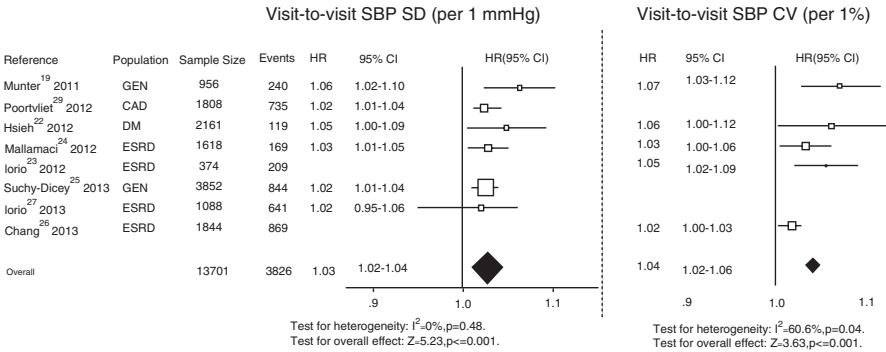


Fig. 3.14 Association of two measurements of blood pressure variability with all-cause mortality. (Reprinted from Tai et al. [88], with permission)

between BP variability and outcomes. Adherence to treatment may influence BP variability, particularly visit-to-visit indices [90].

Many secondary analyses of trials comparing the BP-lowering effects of different classes of BP-lowering drugs on BP variability have been published. The results varied depending on the methods used to assess BP variability, but there were trends toward greater efficacy in reducing BP variability with long-acting calcium channel blockers and diuretics [91–93]. These trends ran in parallel with the greater BP-lowering efficacy of these drugs and their greater efficacy in preventing cardiovascular outcomes.

In summary, it is still unclear if BP variability is independent of BP values in establishment of the prognosis of patients with hypertension, and there is no evidence that it should be a focus of treatment.

3.8 Resistant Hypertension

Patients who do not have BP controlled with three drugs including a diuretic, or who require four drugs to control BP, are categorized as being resistant to treatment [94]. Many cases of resistant hypertension are due to nonadherence to treatment or to the white-coat phenomenon. Resistance due to secondary hypertension can also inflate estimates.

Patients with uncontrolled hypertension taking at least three drugs but without a workup to exclude nonadherence or white-coat hypertension have apparent resistant hypertension, while patients who are resistant after exclusion of nonadherence and white-coat hypertension have true resistant hypertension.

The prevalence of apparent resistant hypertension in the 2005–2008 NHANES was 28% [95]. The prevalence of true resistant hypertension, however, was lower. After confirmation of resistance at a second visit and exclusion of secondary hypertension, poor adherence, and white-coat hypertension, the prevalence of true resistant hypertension was only 3% among sequential patients younger than 65 years at

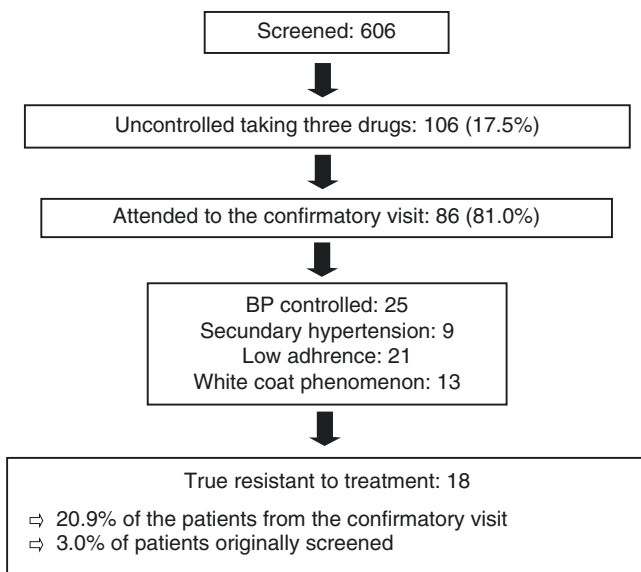


Fig. 3.15 Prevalence of true resistant hypertension in nonelderly patients with hypertension [96]

our outpatient clinic [96] (Fig. 3.15). Since we excluded elderly patients, the true prevalence may have been higher. In 54,590 Chinese patients with hypertension submitted to a systematic five-step treatment program, the final prevalence of resistant hypertension was only 1.9% [97]. Patients with secondary hypertension were not classified as having resistance to treatment in that study. In a Spanish ABP monitoring registry of more than 60,000 individuals, 12.2% had resistant hypertension according to office BP [98]. Approximately one third had white-coat hypertension, resulting in a proportion of 7.6% with resistant hypertension. Adherence to treatment was not checked, suggesting that the prevalence of true resistant hypertension was lower.

The prevalence of resistant hypertension in clinical trials such as the Antihypertensive and Lipid-Lowering and Treatment to Prevent Heart Attack Trial (ALLHAT) [99], ASCOT [100], and the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [101] has been higher than the estimates obtained in clinics. Nonadherence is unlikely, given the controlled nature of the studies. On the other hand, the patients were relatively old and therefore preliminarily prone to resistance to treatment. Moreover, a large proportion of participants in these studies were not treated with diuretics.

The incidence of true resistant hypertension was determined in a cohort of 205,750 participants who had a diagnosis of incident hypertension in the Kaiser Permanente health plan [102]. After excluding participants with pseudoresistance due to nonadherence (defined as those who had less than 80% of the electronically controlled pill refill), only 1.9% developed resistant hypertension within a median

follow-up period of 1.5 years. Participants who developed true resistant hypertension had almost a 50% higher risk of developing major cardiovascular events or chronic kidney disease during a median follow-up period of 3.8 years than those who did not develop true resistant hypertension (hazard ratio (HR) 1.47, 95% CI 1.33–1.62).

Apparent resistant hypertension conveys a higher risk for development of cardiovascular and renal events as well. In ALLHAT, the risks of apparent resistant hypertension were 1.46 (95% CI 1.29–1.64) for cardiovascular disease and 1.95 (1.11–3.41) for end-stage kidney disease [103]. Because of the trial design, use of a diuretic was not a requirement for diagnosis of apparent resistant hypertension. It should be noted that the risks of apparent and true resistant hypertension were similar, denoting that high BP itself entails the risks whether patients do not take their pills or are resistant to them.

Treatment of resistant hypertension, including management of poor adherence to treatment, is addressed in Chap. 4.

3.9 Secondary Hypertension

The search for primary causes of hypertension has been a medical obsession. Investigators and physicians have put a lot of effort into developing and applying methods of screening for primary causes of hypertension. Countless patients have been investigated, but relatively few have had BP controlled through eradication of the primary cause. Besides the low incidence of secondary hypertension, the major cause—chronic kidney disease—usually has no effective treatment other than control of BP and diabetes. The limited effectiveness of surgical or endovascular treatment of renovascular disease has been frustrating. Primary hyperaldosteronism is the primary cause associated with a relatively higher incidence and availability of specific treatment. Box 3.4 shows the most common causes of secondary hypertension.

Hypertension is more frequent in other clinical conditions, such as in Cushing syndrome and other syndromes related to cortisol and mineralocorticoid receptors, congenital adrenal hyperplasia, hypo- and hyperthyroidism, and deficiency of vitamin D, among others. The management of these conditions is oriented by the primary condition.

Box 3.4 Common identifiable causes of secondary hypertension

- Renal parenchymal hypertension
- Primary hyperaldosteronism
- Renovascular disease
- Pheochromocytoma
- Coarctation of the aorta
- Obstructive sleep apnea
- Use of hormonal contraceptives

Studies of the prevalence of secondary hypertension have been done mainly in hypertension clinics, which are not representative of populations. Estimates of between 5% and 10% have commonly been reported, but contemporary studies are rare [104, 105]. The prevalence may be higher in young patients [106]. The proportion of secondary hypertension due to parenchymal kidney disease is highest, but there is evidence that the prevalence of primary hyperaldosteronism may be higher than previously estimated. The use of the aldosterone-to-renin ratio for screening has improved the rate of case detection, which is estimated to be 4.3% in primary care studies [107].

Despite the relatively low prevalence and the preponderance of conditions that are not modifiable to control BP (e.g. chronic kidney disease), primary causes of hypertension cannot be overlooked. Table 3.3 shows clinical conditions that increase the suspicion of secondary hypertension, justifying further workup for confirmation. Resistance to treatment is the clinical condition that most frequently prompts investigation for secondary hypertension.

Table 3.4 presents the initial workup for diagnosis of secondary hypertension in patients with clinical suspicion.

The roles of obstructive sleep apnea (OSA) and use of hormonal contraceptives in the pathogenesis of hypertension are presented in Chap. 2. Detailing of parenchymal kidney disease is beyond the essentials of hypertension. Surgical endovascular treatment of renovascular hypertension has yielded frustrating results (see Chap. 4) [108], but the diagnosis still need to be made.

Table 3.3 Clinical clues for diagnosis of secondary hypertension

Clinical clue	Primary cause
Absence of family history, resistance to treatment	Any primary cause
Elevated creatinine, marked proteinuria, hematuria	Parenchymal kidney disease
Hypertension onset after age of 55 years, abdominal bruit, acute pulmonary edema, impairment of renal function by drugs that block the renin–angiotensin system	Renovascular disease
Moderate hypokalemia without diuretics and severe hypokalemia with diuretics	Primary hyperaldosteronism
Snoring, daytime sleepiness, obesity	Obstructive sleep apnea
Diminished femoral pulses, abnormal chest X-rays, lower BP in limbs	Coarctation of the aorta
Acute fluctuation in BP, accompanied by facial flushing, sweating, and palpitations	Pheochromocytoma

BP blood pressure

Table 3.4 Workup for diagnosis of primary causes of hypertension

Diagnosis	Examination
Chronic kidney disease	Creatinine and estimated glomerular filtration rate, urinalysis
Renovascular disease	Doppler ultrasound of the renal arteries, angio-CT, or magnetic resonance angiography
Primary hyperaldosteronism	Aldosterone-to-renin ratio (see text)
Pheochromocytoma	Plasma metanephrine
Coarctation of the aorta	Doppler echocardiography, followed by magnetic resonance imaging or CT

CT computed tomography

The search for primary hyperaldosteronism is a more challenging condition in clinical management of patients with hypertension. Current guidelines recommend screening for the aldosterone-to-renin ratio, followed by a test of suppression of aldosterone secretion by an oral or intravenous salt-loading test. Adrenal venous sampling usually enables diagnosis of unilateral or bilateral adrenal secretion [109]. Younger patients with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions on an adrenal computed tomography (CT) scan may be treated by unilateral adrenalectomy without adrenal venous sampling.

An outcome-based randomized diagnostic clinical trial evaluated the control of BP and the number of BP drugs used 1 year after testing by CT or adrenal venous sampling [110]. The intensity of BP treatment and other outcomes did not differ between treatment arms, suggesting that the decision to treat could be based on the imaging examination.

Essentials of Diagnosis and Evaluation of Patients with Hypertension

1. Measurement of usual blood pressure—an estimate of the daily blood pressure load—is the primary objective of blood pressure measurement.
2. The oscillometric method has fewer errors than the auscultatory method, permits recording of unwitnessed blood pressure measurements, and should be preferred for measurement of blood pressure.
3. Ambulatory blood pressure monitoring is the gold standard method to estimate usual blood pressure.
4. Home blood pressure monitoring is another efficient method to estimate usual blood pressure.
5. Automated office blood pressure measurement avoids the white-coat phenomenon and should be preferred for measurement of blood pressure in the office.
6. Blood pressure $\geq 120/80$ mmHg measured by automated office blood pressure measurement, home blood pressure monitoring, and daytime ambulatory blood pressure monitoring is the threshold for diagnosis of hypertension and should be the goal for prevention and treatment.
7. Subclassification of blood pressure within abnormal values is unnecessary and potentially misleading.
8. Uncomplicated hypertension is not accompanied by symptoms, and the diagnosis should rely on active screening with accurate blood pressure measurement.
9. Risk stratification of patients with hypertension is markedly influenced by development of clinical disease, which assumes dominance in the prognosis of patients.
10. Electrocardiography, echocardiography, optic fundus examination, and evaluation of aortic stiffness, peripheral arterial disease, and blood pressure variability may further stratify the risks to patients with hypertension

but do not influence the choice of therapeutic options, which should rely on adequate measurement of peripheral blood pressure.

11. Most patients who have uncontrolled blood pressure while using at least three drugs have apparent resistant hypertension. Nonadherence to treatment and the white-coat phenomenon should be excluded to diagnose true resistant hypertension.
12. Patients with apparent or true resistant hypertension have an approximately 50% higher risk for presenting with a cardiovascular event than those without resistant hypertension.
13. Modifiable causes of secondary hypertension are infrequent but should not be overlooked.
14. Extensive investigation into causes of secondary hypertension is not recommended. The most common trigger for investigation of primary causes is true resistant hypertension.

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The thresholds for diagnosis of hypertension, goals for treatment, the J-shaped phenomenon, proof of concept about the risks of high blood pressure (BP) and benefits of treatment (including treatment of prehypertension), and analysis of current guidelines for management of hypertension were addressed in Chap. 1. Here, we present evidence to support selection of nonpharmacological interventions and drug treatment to prevent and treat hypertension. These treatments were studied under the 140/90 mmHg paradigm for diagnosis and the goal for treatment of most patients. The findings of these studies will likely, by analogy, be applicable to a more strict goal for prevention and treatment (120/80 mmHg).

4.1 Nonpharmacological Therapies

Nonpharmacological strategies to prevent and treat hypertension mostly consist of advice to adopt healthier nutritional and behavioral attitudes. They are therefore recognized as recommendations to change lifestyle.

4.1.1 Reduction of Salt Intake

4.1.1.1 In Populations

Reduction of excessive sodium intake by populations would prevent the rise in BP with age. The major limitation for implementation of low-salt diets—in addition to humans' appetite for salt—is that sodium salts are the most cost-effective food preservatives. Food industries have been reluctant to reduce the amount of salt in processed foods but are now moving to methods of food processing with less addition of salt.

An initiative by US scientists and leaders of industry identified many barriers to this transformation, such as potential effects on health, need for investment in

research and development, the quality and taste of reformulated foods, supply chain management, customer acceptance, and cost [1].

Nonetheless, there are joint actions between governments and industry in progress in many countries to reduce the amount of salt in food [2]. Canada, Finland, France, Japan, and the UK, among others, have implemented more advanced propositions, leading to reduction of the amount of salt added to industrialized foods. A salt reduction program in England led to a decrease of 15% in consumption of salt over 10 years. BP, the incidence of stroke, and coronary heart disease (CHD) mortality decreased in parallel with this reduction in salt intake (Fig. 4.1) [3]. The design of this observation is ecological, and therefore less robust for establishment of causality, but reinforces

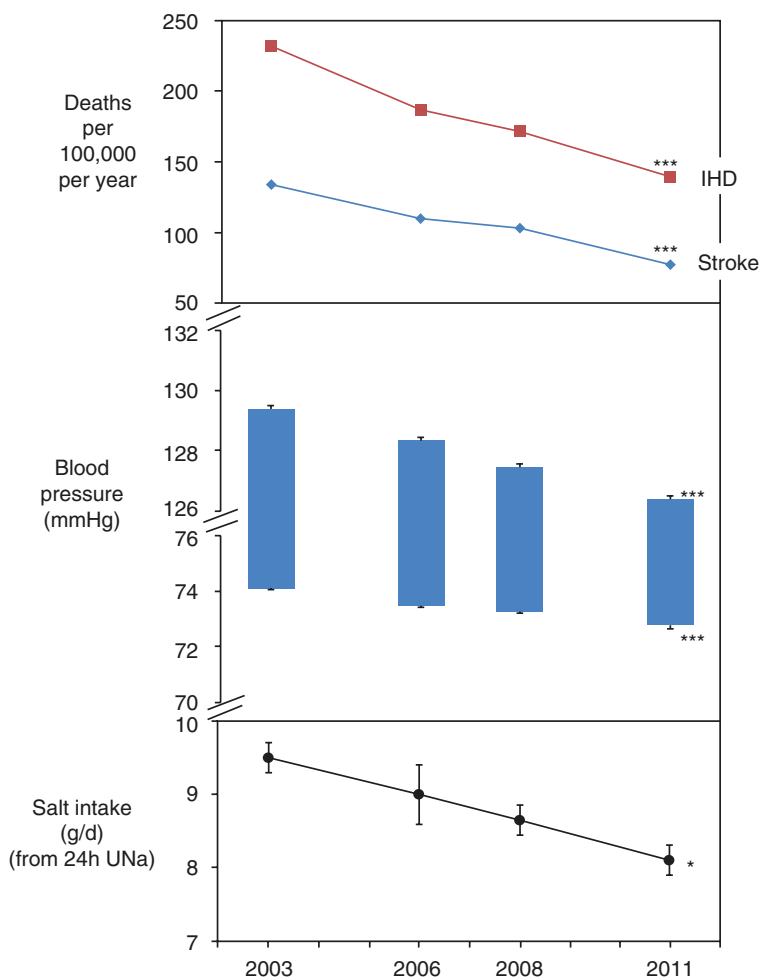


Fig. 4.1 Reductions in salt intake, blood pressure, stroke, and ischemic heart disease mortality in England from 2003 to 2011. (Reprinted from He et al. [3], with permission)

the expansion of these programs worldwide. In Brazil, government and industry have signed an agreement to reduce the amount of salt added to food by the year 2020 [4].

4.1.1.2 In Individuals with Normal and High Blood Pressure

Prescription of low-sodium diets for individuals is a rational approach to prevent and treat hypertension. Dozens of randomized controlled trials have investigated the effects of low-salt diets on BP. The effectiveness was higher in the short-term but tended to disappear after 6 months [5]. A meta-analysis included 34 clinical trials (*n* = 3230) of variable duration and moderate heterogeneity [6]. There was a modest fall in BP, which was higher in hypertensive individuals (5.4 mmHg, 95% confidence interval (CI) 3.2–6.6). In a meta-analysis restricted to six studies, there was a substantial reduction in urinary sodium [7]. The studies were heterogeneous and had varying quality and duration. There was a BP reduction of 4–7 mmHg. Some trials provided the meals for participants to consume at home, which is not feasible for communities.

In a cohort of patients at an outpatient hypertension clinic, we investigated the effectiveness of nonpharmacological recommendations prescribed by doctors to control BP. In the first analysis, involving 637 patients followed for 3.5 months on average, adherence to a recommendation to lose weight was the only nonpharmacological prescription associated with BP lowering [8]. In an analysis involving more than 800 patients followed for 2 years, we identified a BP-lowering effect associated with compliance with diets that were restricted in sodium and calories (Fig. 4.2) [9]. Adherence to the practice of physical exercise was not associated with a BP-lowering effect.

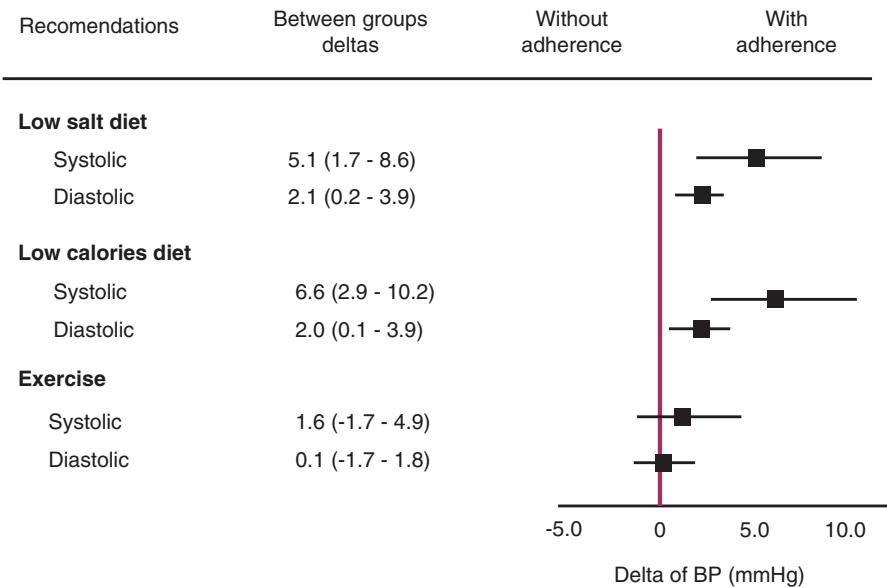


Fig. 4.2 Effects of adherence to nonpharmacological recommendations for blood pressure: results of a cohort study with 2 years of follow-up [9]

The effects of low-sodium diets have also been investigated in studies with cardiovascular outcomes. A meta-analysis of seven studies, totaling 6489 normotensive and hypertensive participants, showed a trend toward benefit [10]. This meta-analysis was criticized for including a trial with patients who had heart failure, who had a trend toward increased mortality. A meta-analysis restricted to patients without heart failure identified a 20% reduction in the incidence of cardiovascular events [11].

A new systematic review, which included cohort studies, evaluated the effects of restricted-sodium diets on BP and primary outcomes [12]. There was a significant BP-lowering effect in adults (a reduction of approximately 3.4 mmHg in systolic BP) and children (a reduction of around 0.8 mmHg). In the cohorts that were included in the meta-analysis, high sodium intake was associated with a higher incidence of stroke and coronary artery disease.

4.1.2 Hypocaloric Diet

Weight reduction is another rational nondrug intervention, because excessive adiposity is a major risk factor for hypertension. Clinical trials evaluating the efficacy of weight reduction to lower BP have been few and very heterogeneous. A systematic review—which included eight trials, nine quasiexperimental studies, and eight cohort studies—showed no association between weight loss and reduction in diastolic BP [13]. For systolic BP, there was a 1 mmHg decrease for each kilogram of weight lost.

The Look Ahead Study was designed to evaluate the effectiveness of a low-calorie diet and practice of exercises in preventing cardiovascular outcomes in patients with diabetes mellitus [14]. Patients with systolic BP >160 mmHg or diastolic BP >100 mmHg were excluded. The mean baseline systolic BP was approximately 128 mmHg on average. The study included more than 5000 patients, who were followed for more than 9 years, at which point the study was interrupted because of futility. Body weight was reduced by 8.6% in the intervention group versus 0.7% in the control group. Despite this important effect, there was no tendency to prevent cardiovascular events. Systolic BP was reduced by only 1 mmHg more in the group treated intensively than in the control group.

Among the drugs that have been used for management of obesity, sibutramine promoted an increase of 3.2 mmHg (95% CI 1.4–4.9) in diastolic BP in a Cochrane meta-analysis [15]—an effect that probably explained the increase in cardiovascular events in patients treated with sibutramine.

In our study of the effectiveness of nonpharmacological interventions [9], the reduction in systolic BP was 6.6 mmHg (95% CI 2.9–10.2) greater in patients who reported adherence to a hypocaloric diet than in those who did not follow the recommendation.

4.1.3 DASH Diet

The BP-lowering effect of the Dietary Approaches to Stop Hypertension (DASH) diet—which is rich in vegetables and dairy products, with restriction of saturated

fats—created new perspectives for management of hypertension [16] (Fig. 4.3). The BP-lowering effect was the greatest seen among dietary interventions. In this study, most meals were provided for the participants. The effect was increased by salt restriction [17]. Nonetheless, in conditions closer to the real world, the Trial of Lifestyle Interventions for Blood Pressure Control (PREMIER) showed that a recommendation to follow the DASH diet, without supplying meals, was less effective [18].

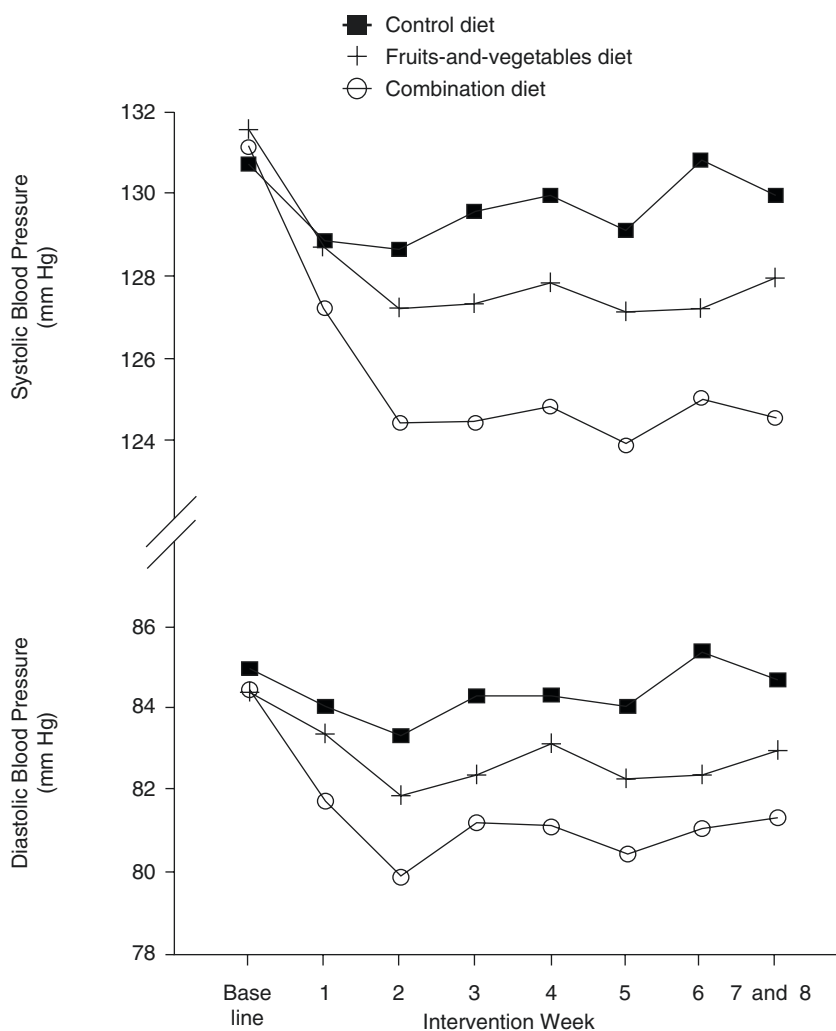


Fig. 4.3 Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure in the original trial. (Reprinted from Appel et al. [16], with permission)

4.1.4 PREDIMED Diet

The Prevention with Mediterranean Diet (PREDIMED) study compared the Mediterranean and low-fat diets for primary prevention of cardiovascular disease. Additionally, participants allocated to the Mediterranean diet were randomized to receive either an additional 50 g of extra-virgin olive oil per day or 30 g of nuts and seeds (15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts) per day. In a substudy with 235 participants, with a follow-up period of 1 year, there was a decrease of 2.5 mmHg in 24-h systolic BP on ambulatory BP (ABP) monitoring in patients on the active diets in comparison with the control group [19].

4.1.5 Supplementation of Potassium, Calcium, and Magnesium

Diets enriched in sodium, which are associated with the pathogenesis of hypertension, are partially deprived of potassium. Diets that are poor in potassium with high sodium-to-potassium ratios are associated with an increased incidence of hypertension. Among the DASH diet components that may explain its effectiveness are greater amounts of potassium, calcium, and magnesium, coming from increased intake of dairy products, fruits, and vegetables.

Diets with supplementation of potassium or a recommendation to increase its intake have been evaluated in several clinical trials. A meta-analysis of 15 studies (with a moderate degree of heterogeneity) in normotensive and hypertensive individuals showed a reduction of 4.7 mmHg (95% CI 2.4–7.0) in systolic BP [20]. The effects were greater in hypertensive patients.

The idea of replacing part of the sodium chloride in dietary salt with potassium chloride (25%, with 10% magnesium sulfate), taking advantage of sodium reduction and increased potassium intake, was investigated in two clinical studies conducted in Chinese rural communities. The first, lasting 1 year, included patients with previous cardiovascular disease or systolic BP higher than 160 mmHg [21]. There was a reduction in systolic BP (3.7 mmHg, 95% CI 1.6–5.9; $P < 0.001$). In the second study, with a 2-year duration, there were systolic BP reductions of 2 mmHg (95% CI 0–4) in normotensive participants and 4 mmHg (95% CI 2–6) in hypertensive patients [22].

Isolated manipulations of calcium and magnesium intake have had no clear effects on BP. Meta-analyses of older studies, with low quality and high heterogeneity, have shown no substantial effects [23, 24]. A meta-analysis [25] of 16 clinical trials ($n = 3048$ normotensive participants) demonstrated a small effect of calcium supplementation: systolic BP was reduced by 1.4 mmHg (95% CI 0.7–2.2) and diastolic BP by 1.0 mmHg (95% CI 0.5–1.5).

4.1.6 Comparative Effectiveness of Dietary Interventions

A meta-analysis of all interventions described above found overall pooled net effects of dietary intervention of -3.07 mmHg (95% CI -3.85 to -2.30) on systolic BP and -1.81 mmHg (95% CI -2.24 to -1.38) on diastolic BP [26]. All of the diets had a BP-lowering effect, but the DASH diet was the most effective (Fig. 4.4).

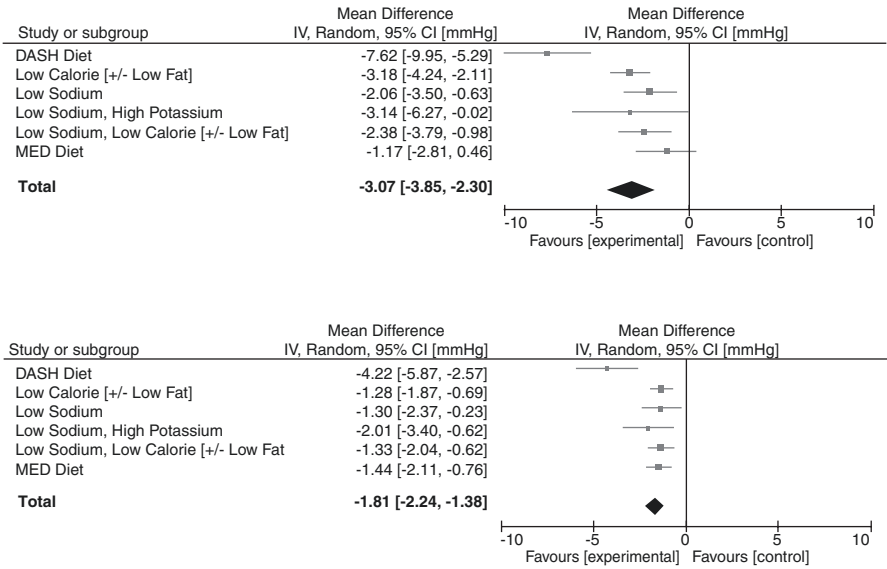


Fig. 4.4 Effects of dietary interventions on systolic blood pressure (*top*) and diastolic blood pressure (*bottom*). (Reprinted from Gay et al. [26], with permission)

4.1.7 Other Nutritional Interventions

4.1.7.1 Alcoholic Beverage Consumption

The effect of abstinence or a reduction in alcohol consumption in 2234 patients with hypertension was evaluated in a meta-analysis of 15 old randomized controlled trials of varying quality [27]. There were reductions of 3.3 mmHg (95% CI 2.5–4) in systolic BP and 2.0 mmHg (95% CI 1.5–2.6) in diastolic BP.

4.1.7.2 Chocolate and Other Cocoa Products

A meta-analysis [28] of ten randomized trials ($n = 297$) identified reductions of 4.5 mmHg (95% CI 3.3–5.9) and 2.5 mmHg (95% CI 1.2–3.9) in systolic and diastolic BP, respectively, with supplementation of cocoa products. The studies were very heterogeneous and had varied interventions. The balance between calories and the potential BP-lowering effect should be taken into account.

4.1.7.3 Other Nutraceuticals

Utilization of the BP-lowering activity of phytochemicals (nutrients with pharmaceutical activity) present in fruits, vegetables, and cereals has been advocated. Garlic, arginine, vitamin C, and carrot juice are those most frequently referred to. There have been few comparative studies with placebo, and virtually all were low quality. A better-quality double-blind placebo-controlled study using different doses of aged garlic showed a dose-dependent effect [29].

In Brazil, there have been numerous reports of plants with alleged hypotensive effects, but the evidence has come almost exclusively from studies done with

laboratory animals. In an old randomized clinical trial involving normotensive volunteers, we did not identify any hypotensive effect of chayote tea, which is commonly used by people to lower BP [30].

4.1.7.4 Probiotics

Microorganisms with presumed therapeutic effects, such as those present in yogurts, have been tested in various clinical conditions, including hypertension. A meta-analysis of nine randomized controlled trials ($n = 543$), with variable types of control groups, identified a decrease of 3.6 mmHg (95% CI 0.7–6.5) in systolic BP in studies done predominantly with yogurts [31].

4.1.8 Physical Activity

Regular physical activity is associated with multiple health benefits, including a reduction in the incidence of cardiovascular disease. Similarly, greater fitness or regular physical activity are associated with lower BP and a lower incidence of hypertension. These associations, however, may be confounded by other healthy characteristics of individuals who exercise.

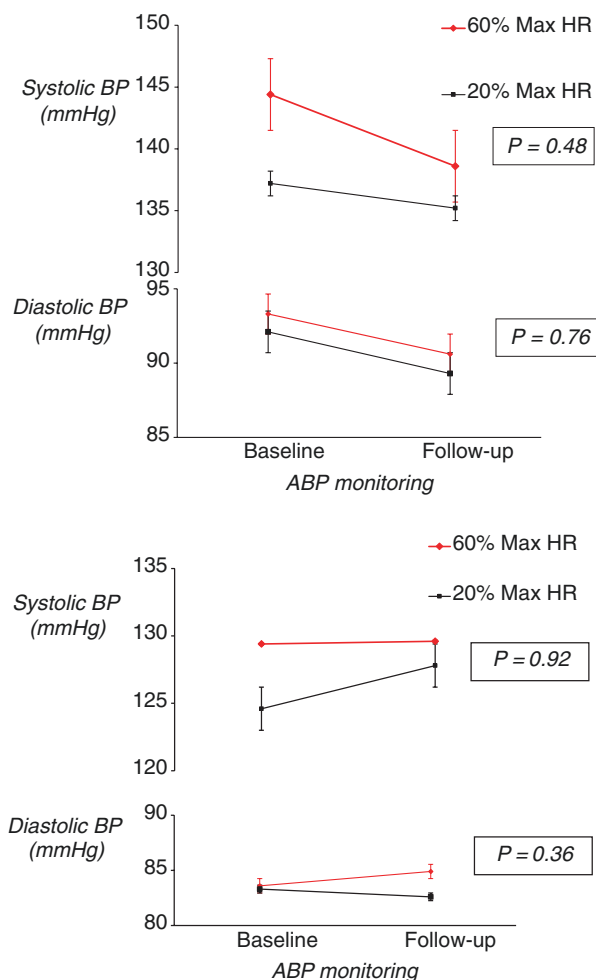
The Look Ahead Study [14] evaluated the efficacy of moderate physical activity prescription for at least 175 min/week, as part of a multifactorial intervention, in preventing cardiovascular outcomes in patients with diabetes. The participants were predominantly normotensive. There was no benefit of the intervention in preventing any cardiovascular event.

Many clinical trials and meta-analyses have evaluated the effect of exercise on BP. A meta-analysis addressed different forms of exercise, separately and together, in 93 studies with more than 5000 participants [32]. Most studies employed dynamic exercise (walking, jogging, cycling, and swimming—also called aerobic exercise); 14 studies explored the efficacy of dynamic resistance exercise (strength training with movement, such as weight lifting); and four studies used only static (isometric) resistance exercise (strength training maintained for some time, with no or little displacement). Systolic BP was reduced by 3.5 mmHg (95% CI 2.3–4.6) after dynamic exercise; 1.8 mmHg (95% CI 0–3.7) after dynamic resistance exercise; and 10.9 mmHg (95% CI 7.4–14.5) after isometric resistance exercise. Combined programs had effects only on diastolic BP. In most trials, there was no control for cointerventions corresponding to the context that surrounded the exercise prescription (routines, orientation, monitoring, etc.).

We conducted a randomized clinical trial with a control group who exercised at a low load, as an attempt to control for cointervention [33]. BP was measured by ABP monitoring. There was no difference in the variation in BP measured in participants allocated to the high and low exercise loads (Fig. 4.5). Nighttime BP did not change in either group.

There have been large clinical trials with good quality and negative results. A trial with 464 postmenopausal, obese, and sedentary women evaluated the efficacy of three exercise intensities in comparison with a group that did not exercise for

Fig. 4.5 Effects of two intensities of aerobic exercise on blood pressure (BP) measured by ambulatory BP monitoring: 24-h BP (*top*) and nighttime BP (*bottom*) [33]



6 months. Functional capacity increased, but the reduction in BP did not differ between the control and intervention groups. [34] In the Early Activity in Diabetes (Early ACTID) study in 593 participants with newly diagnosed diabetes, exercise documented by a pedometer was not associated with a reduction in BP [35]. A meta-analysis of 14 randomized studies, with 3614 young adults, evaluated the effectiveness of advice to exercise in lowering BP. Systolic and diastolic BP decreased until the sixth month of follow-up, but this effect was not present at 12-month follow-up [36].

In our study of the BP-lowering effectiveness of lifestyle change recommendations given at our outpatient clinic [9], there was no difference in the reduction in BP between patients who did and those who did not reportedly follow the recommendation to undertake physical activity.

4.1.9 Treatment of Obstructive Sleep Apnea as a Means to Treat Hypertension

A meta-analysis [37] of 16 randomized controlled trials ($n = 1166$), which evaluated the effect of continuous positive airway pressure (CPAP) in comparison with placebo or subtherapeutic CPAP, identified a discrete BP-lowering effect in office-measured systolic BP (3.2 mmHg, 95% CI 1.7–4.7). The greatest effect was observed at night mean BP (about 5 mmHg for systolic BP).

We demonstrated that obstructive sleep apnea (OSA) is a major risk factor for resistant hypertension [38]. Five randomized controlled trials evaluated the effect of CPAP in this condition—three of them conducted in Brazil. In one of these studies, conducted in our service [39], there was a placebo-controlled sham CPAP. In the 24-h ABP monitoring period, systolic BP decreased by 9.3 mmHg (95% CI 0.4–17.9). This effect was similar to that identified in a prior meta-analysis (7.2 mmHg, 95% CI 5.4–9.0, in 24-h systolic BP). This meta-analysis included secondary clinical trial data and two observational studies [40]. Another Brazilian study of good quality (but without a sham control) did not identify a therapeutic effect—only a trend toward BP lowering during sleep [41].

A descriptive review of five clinical trials explored potential reasons for the discrepancy between studies [42]. The author noted that daytime sleepiness, different fees for treatment, and modification of drug treatment during the study could be the reasons. The most likely explanation, however, was the origin of the patients. In the study by Muxfeldt and colleagues [41], participants were selected from a long-standing cohort of patients with resistant hypertension, with the participants being more vigorously treated (half with use of spironolactone). Because of the open nature of the study, participants in the control group may have improved their adherence to drug prescription.

4.1.10 Oral Contraceptives and Hormone Replacement Therapy

Old studies have shown an association between use of oral contraceptives and high BP. The risk diminished with the decrease in the amount of estrogen in pill preparations. Nonetheless, use of oral contraceptives was associated with poorer BP control at our outpatient hypertension clinic [43]. Patients who substituted their oral contraceptive (under supervision) with another contraceptive method had their BP reduced in comparison with those who did not [44]. This finding in an observational study is obviously untestable in randomized clinical trials.

Contrary to the view of many doctors, hormone replacement therapy in menopause is not accompanied by increased BP [45] but has no beneficial cardiovascular effects.

4.1.11 Surgical Treatment of Hypertension

Resection of adrenal tumors in patients with primary aldosteronism and pheochromocytoma, and correction of aortic coarctation, can be curative if the diagnosis is made before development of myocardial and vascular trophic changes secondary to long-standing hypertension.

4.1.11.1 Renovascular Hypertension

Young patients with renovascular hypertension caused by intimal fibrodysplasia have a good response to percutaneous revascularization, but there have been no clinical trials conducted exclusively in these patients. There was high expectation about the benefit of percutaneous or surgical treatment of renovascular hypertension secondary to atherosclerosis of renal arteries, both to control BP and to preserve renal function. A clinical trial with a large sample and good quality showed no superiority of revascularization to medical treatment alone in preventing primary outcomes, including progression in the loss of kidney function [46]. There was a slight reduction in systolic BP. A meta-analysis of this and seven other clinical trials of moderate quality identified a discrete effect on diastolic BP and a reduction in the number of BP-lowering drugs used by patients [47].

4.1.11.2 Renal Sympathetic Denervation

Ablation of renal innervation by an endovascular approach was proposed as a novel intervention to treat hypertension. The theoretical background was attractive, in the face of the well-known dominance of the kidneys in long-term control of BP. Afferent denervation would increase renal ability to eliminate the overload of sodium, and efferent denervation would decrease systemic sympathetic activation. Indeed, objective evidence of renal denervation and decreased sympathetic activation has never been provided in animal and human studies. Despite this, the method was promptly investigated in patients with resistant hypertension.

Three sequential Symplicity studies investigated the effectiveness of renal ablation. In the first—a case series addressing the feasibility of the intervention—there were promising findings [48]. The second—an open randomized clinical trial [49]—apparently showed great effectiveness of the method, which quickly spread worldwide as a therapeutic option for patients with resistant hypertension. Dozens of original articles (series of a few cases and small open clinical trials) and review articles were published, suggesting that this approach contributed to control not only of hypertension but also of other diseases, such as diabetes and OSA.

US regulatory authorities required a clinical trial with control by a sham intervention to approve the method. The Symplicity-3 double-blind trial, with a sham intervention (arterial catheterization and angiography) and a large sample, did not show a BP-lowering effect of the intervention [50]. Another randomized study comparing denervation with spironolactone [51] was stopped after publication of the results of Symplicity-3. The changes in BP did not differ by group.

Two further trials were negative as well. In one small parallel randomized clinical trial, patients treated with spironolactone (50 mg daily) had a systolic BP reduction of 17.9 mmHg (95% CI 30.9–4.9)—greater than that of patients treated with renal denervation [52]. In a clinical trial with a sham intervention, the BP reductions were almost identical in the renal denervation group ($n = 36$) and the control group ($n = 33$) [53].

Just one randomized study reported after Symplicity-3 identified a borderline-significant adjusted systolic BP-lowering effect of renal denervation on 24-h ABP (a between-group difference of 5.9 mmHg, 95% CI –11.3 to –0.5) [54]. This trial, with fewer than one fifth as many participants as the Symplicity-3 trial, did not have a control group submitted to a sham intervention. Adherence to treatment was poor

but did not differ between groups [55]. Editorialists were enthusiastic about these results and even suggested that further trials with sham interventions would be unethical—a view that challenges the foundations of modern medicine.

Despite the solid negative evidence from the best-designed study, corroborated by others, renal denervation is being still used in many centers, assuming that new methods of denervation are effective. Indeed, this therapy should be put back on the track of experimental drugs (or devices), which are compared with placebo only after showing pharmacological (physiological) activity in animal experiments and a small number of human volunteers. Because many patients have already been submitted to the intervention, new devices could eventually be tested against sham interventions in adequately designed clinical trials. Even believers in the potential efficacy of the method support this requirement [56].

4.1.11.3 Bariatric Surgery

This surgery was not primarily planned to control hypertension. Because the surgery reduces body mass index (BMI), there is a reversal of the positive metabolic balance, e.g., a reduction in salt intake. Improvements in cardiovascular risk factors, including high BP, have been reported [57]. There have been many clinical trials conducted in diabetic patients, which also noted effects on BP. For example, in a randomized clinical trial that compared two gastric reduction techniques with clinical treatment [58], the number of antihypertensive drugs used was reduced by more than 50% after 3 years of follow-up in patients treated surgically, without changes in BP. The results of the first randomized clinical trial of bariatric surgery as a mean to treat hypertension, in patients with BMI between 30.0 and 39.9 kg/m², were reported by Brazilian investigators [59] from 48 patients with complete data, 22 (45.8%) randomized to gastric bypass surgery had remission of hypertension in Ambulatory Blood Pressure monitoring at 12 months of follow-up. None of participants allocated to clinical treatment alone had remission of hypertension. These results need to be replicated in other series and be accompanied for longer periods, but point to bariatric surgery as an effective therapy for obese patients with hypertension.

4.1.12 Other Nonpharmacological Treatments

Many therapies with presumed BP-lowering effects have been proposed for management of hypertension. A statement from the American Heart Association, which I coauthored, assessed the degrees of recommendation and levels of evidence for virtually all nonnutritional and nonsurgical interventions [60]. It included evaluation of the effects of physical exercise and reached different conclusions in regard to those presented in this book. I agree with the evaluation of other strategies. There have been a few relevant studies published since the publication of that statement. A summary of those recommendations is presented in the Sects. 4.1.12.1 to 4.1.12.3.

4.1.12.1 Behavioral Therapies

Different techniques of meditation, yoga, stress management, biofeedback, and relaxation have been tested, but most studies have been of low quality and showed only small BP-lowering effects. Many studies evaluated the effect of an intervention

in comparison with nontreated controls, which does not control for the effect of cointerventions (strategies that surround the intervention, such as repetitive contact with the team of investigators). Part of the effect of the intervention may be additionally mediated by lessening the alertness reaction (the white-coat effect), which explains the greater BP-lowering effect measured by office BP than by ABP. A more recent meta-analysis of the effectiveness of meditation showed that the small effect on ABP may be influenced by the type of meditation (transcendental or nontranscendental) and age [61].

4.1.12.2 Acupuncture

There have been moderately sized studies with positive effects, but the best study, with the largest number of participants and control by a sham intervention, was negative [62].

4.1.12.3 Device-Guided Breathing Modulation

Slow and deep breathing produces a slight drop in BP. Various devices for promoting slow ventilation have been developed and approved in the USA. Basically, they induce conscious ventilation through thoracic sensors and sound output (music) to promote frequency control and respiratory amplitude. A review of nonnutritional interventions [60] had a favorable view of the method (graded as IIa), but certainly the quality of the studies did not support such optimism. The devices are not commercially available in most countries.

The prevailing view of these therapies is that even if they are ineffective or less effective, they have no deleterious effects and may provide other benefits, such as improving the quality of life. Given the need to effectively reduce BP to prevent cardiovascular events, the recommendation of interventions with questionable or discrete hypotensive effects should be condemned. Patients may feel treated with inert therapies, neglecting the use of drugs with clear therapeutic effects.

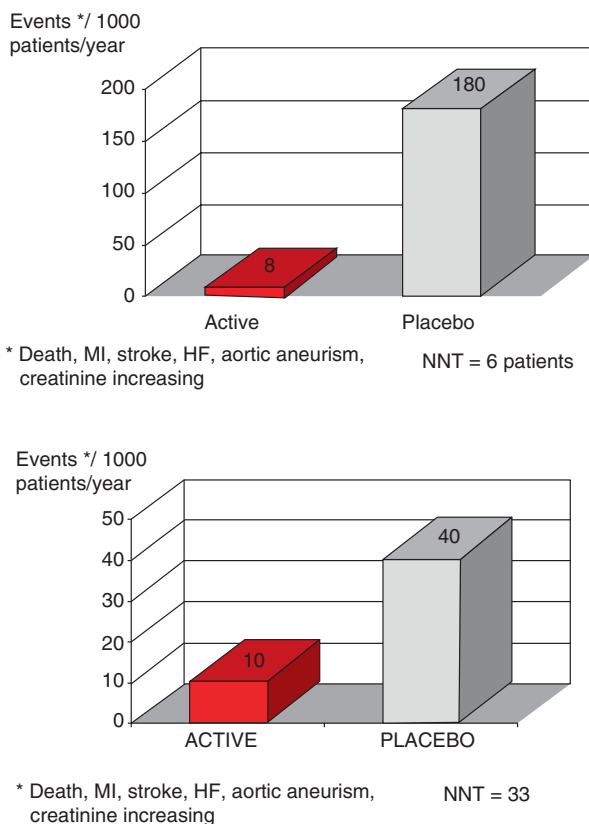
4.2 Drug Treatment

Few diseases have as many options of effective and well-tolerated drugs for treatment as hypertension. Despite this, the rates of control worldwide are far from satisfactory. Herein, we address the comparative effectiveness of drugs to prevent hard outcomes. In addition, we review the evidence on strategies to improve adherence to treatment, treatment of resistant hypertension, and management of high BP in the emergency room. Description of pharmacological properties and dosing schedules for BP-lowering agents is out of the scope of this book.

4.2.1 Pioneering Studies

The first randomized clinical trials done in patients with high BP, assessing the incidence of hard outcomes, established a standard for investigation of the effectiveness of BP drugs against placebo and against each other. Despite the misuse of randomized clinical trials in some investigations, diuretics emerged as the more effective treatment.

Fig. 4.6 Prevention of hard outcomes by pharmacological treatment in the Veterans I trial (*top*) and Veterans II trial (*bottom*) [63, 65]



Treatment based on diuretics was the first to be tested in a randomized placebo-controlled trial [63]. The careful planning of this study—such as its checking for adherence, randomization, blinded allocation of treatments, and evaluation of outcomes—is still a standard for clinical trials. The active treatment consisted of hydrochlorothiazide, reserpine, and hydralazine. This study was selected as one of the classic clinical trials—a collection of studies that changed the way of practicing medicine [64]. After 2 years of follow-up, there was a marked benefit in patients with diastolic BP higher than 115 mmHg, with a number needed to treat (NNT) of only six patients to prevent major cardiovascular events (Fig. 4.6, *top*). A similar relative benefit was demonstrated in patients with diastolic BP between 105 and 114 mmHg (Fig. 4.6, *bottom*) [65], albeit with lower absolute benefit (NNT 35 patients/year). In patients with diastolic BP between 90 and 104 mmHg, recognized as mild hypertension at that time, the active treatment was not superior to placebo. Detailed revision of the historical sequence of trials is out of the scope of this book, unless they influence the contemporary choice of BP agents.

4.2.2 The First Choice

Around 50% of patients respond to monotherapy, especially at less advanced stages of hypertension. For them, and for patients who need two or more drugs, it is

necessary to choose the first option. There is consistent evidence that this choice should be a diuretic, particularly chlorthalidone, accompanied by a potassium-sparing diuretic, such as amiloride.

There was an expectation that some antihypertensive agents, aside from diuretics and beta blockers, would have pleiotropic properties additional to the BP-lowering effect. This was the belief of drug manufacturers, who were interested in a huge market and sponsored several clinical trials comparing new agents with placebo in a variety of clinical conditions. Many studies included inadequate comparisons, and others had biased presentation and interpretation of results. The influence on planning, presentation, and interpretation of studies sponsored by the pharmaceutical industry, aiming to promote their products, was named “corporate bias” [66]. We have identified many shortcomings of these studies in letters to journal editors [67–76] and have addressed these distortions in manuscripts, particularly showing that corporate bias has hidden the evidence that diuretics have unique efficacy and properties in control of high BP [66, 77–82].

The main limitation of the first randomized clinical trials that led to distortion of evidence was comparison of new agents with beta blockers, particularly atenolol, which was ineffective to prevent cardiovascular events in elderly patients [83]. Furthermore, most studies had an open design (with blind evaluation of outcomes—a probe design). In the Captopril Prevention Project (CAPPP) [84], the incidence of stroke was higher in patients treated with captopril—the new treatment at that time. In the Swedish Trial in Old Patients with Hypertension–2 (STOP-2), new and old treatments had similar efficacy in the prevention of cardiovascular events, but more beta blockers than diuretics were used as an old treatment option [85]. In the Nordic Diltiazem (NORDIL) study, diltiazem was as effective as beta blockers or diuretics in prevention of cardiovascular events, but 23% of participants treated with diltiazem abandoned the treatment, in comparison with 7% of the beta blocker group [86]. The Blood Pressure Trialists meta-analyses [87, 88] did not differentiate between diuretics and beta blockers in their comparisons between new and old treatments.

Of the trials published at that time, only the International Nifedipine–GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) [89] compared a slow-release formulation of nifedipine with hydrochlorothiazide associated with amiloride. In the presentation of the manuscript, beneficial effects of nifedipine versus diuretics on blood levels of lipids were highlighted. The higher incidence of myocardial infarction and heart failure in participants treated with nifedipine was almost concealed in the manuscript (Fig. 4.7). Moreover, in an analysis restricted to participants with diabetes [90], the authors apparently summed up cardiovascular and all-cause deaths [74].

In this context, the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)—a landmark trial comparing first antihypertensive options in the management of hypertension—were published [91]. Over 40,000 participants were allocated to receive chlorthalidone (12.5–25 mg/day), amlodipine (2.5–10 mg/day), lisinopril (10–40 mg/day), or doxazosin (2–8 mg/day), in a double-blind fashion. The doxazosin arm was prematurely terminated because patients treated with this alpha blocker had a higher incidence of stroke, cardiovascular events, and heart failure than those treated with chlorthalidone [92].

The incidence of fatal and nonfatal myocardial infarction—the primary outcome—did not differ between participants assigned to chlorthalidone, amlodipine,

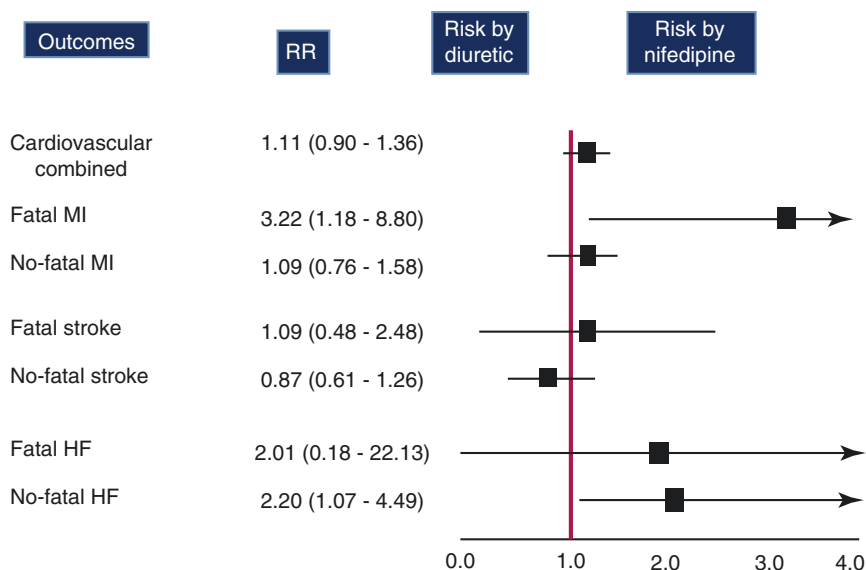


Fig. 4.7 Effects of hydrochlorothiazide/amiloride versus long-acting nifedipine on the incidence of major cardiovascular outcomes [89]. *HF* heart failure, *MI* myocardial infarction

or lisinopril. Other outcomes were defined as secondary outcomes, but the large sample size diminished the possibility that between-group differences arose as a result of an alpha error. The incidence of heart failure, identified by hospitalization or death, was 35% higher in patients treated with amlodipine than in those treated with chlorthalidone. Several outcomes were more frequent in patients treated with lisinopril than in patients treated with chlorthalidone: 15% more strokes, 10% more cardiovascular disease, and 19% more cases of heart failure, among others. Figure 4.8 shows a comparison of the efficacy of chlorthalidone, amlodipine, and lisinopril for prevention of major cardiovascular outcomes.

Systolic BP during the trial was significantly higher in participants treated with amlodipine (0.8 mmHg) and lisinopril (2 mmHg) than in those treated with chlorthalidone. Serum potassium levels at the end of the study were 4.1 mEq/L, 4.5 mEq/L, and 4.4 mEq/L with chlorthalidone, amlodipine, and lisinopril, respectively.

The data from ALLHAT have been scrutinized in several publications; in all, the superiority of chlorthalidone—particularly in comparison with lisinopril—remained. A notable exception was the incidence of stroke, which was similar with lisinopril and chlorthalidone in white patients [93, 94]. In patients with diabetes and a glomerular filtration rate (GFR) between 60 and 90 mL/min, the incidence of end-stage renal disease or a decrement in the GFR of 50% or more from baseline was 70% higher in patients allocated to amlodipine and lisinopril than in those allocated to chlorthalidone (Fig. 4.9) [95].

Participants who developed diabetes during follow-up had a lower incidence of cardiovascular events when treated with chlorthalidone in comparison with other

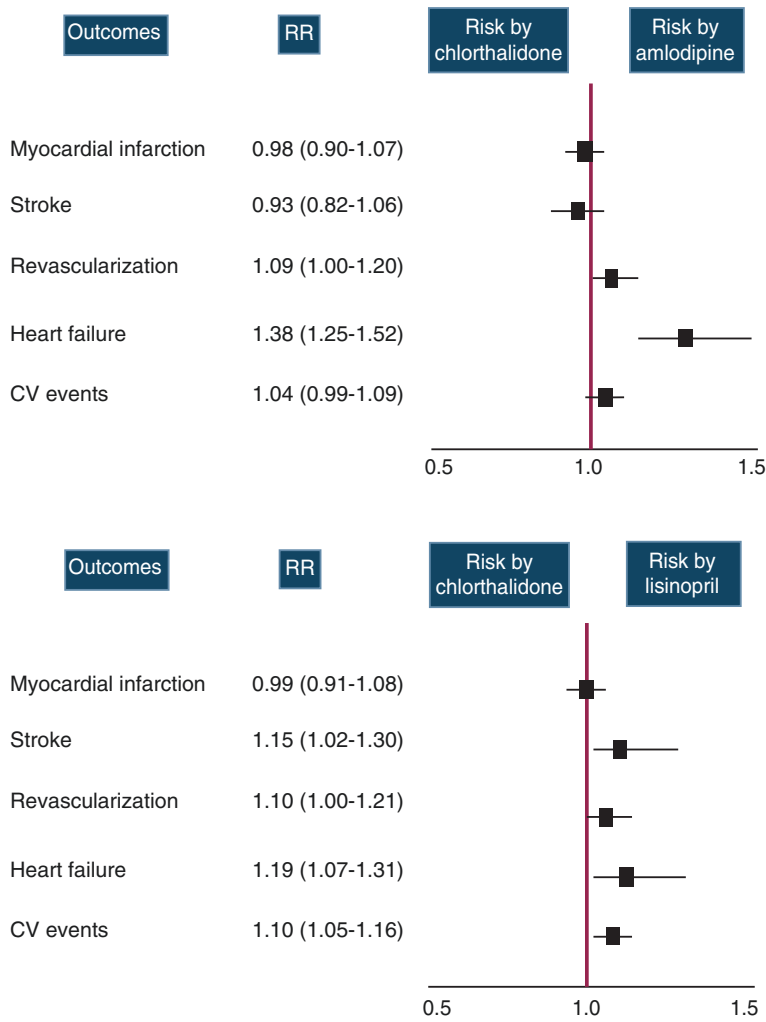


Fig. 4.8 Relative risk (RR) for the incidence of cardiovascular outcomes in patients allocated to chlorthalidone and amlodipine (*top*) and chlorthalidone and lisinopril (*bottom*) in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [91]

treatments [96]. The higher efficacy of chlorthalidone in comparison with amlodipine and lisinopril in prevention of heart failure was noticeable, particularly in patients with a preserved ejection fraction (Fig. 4.10) [97].

The response to chlorthalidone in ALLHAT was faster than those observed with the other drugs (immediate responders) [98]. Nonimmediate responders had a higher hazard ratio (HR) for stroke, combined cardiovascular disease, and heart failure than immediate responders. These findings are complementary to the longer duration of the BP-lowering effect of diuretics. Diuretics not only start to work

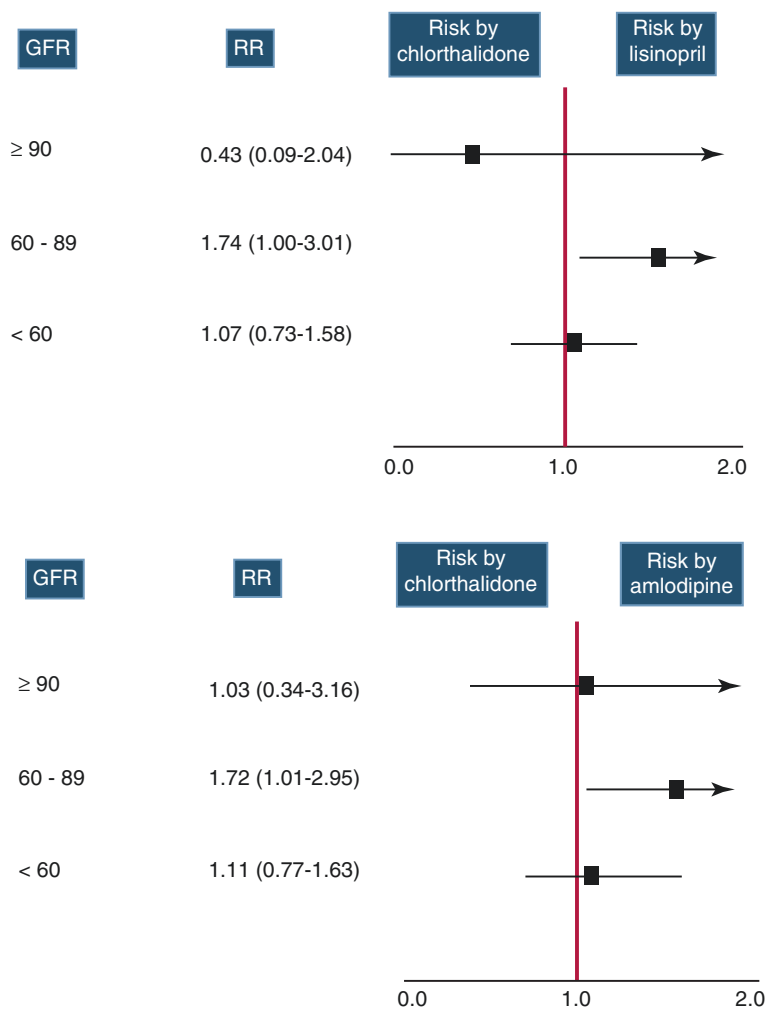


Fig. 4.9 Incidence of end-stage renal disease or a glomerular filtration rate (GFR) decrement $\geq 50\%$ with treatment in patients with diabetes and a GFR between 60 and 90 mL/min in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [95]

earlier but also have long-lasting effects. The duration of the effect was compared in a trial of withdrawal of BP agents in patients with controlled BP [99]. During 1 week of drug omission, systolic BP increased by 7.0 mmHg in participants randomized to bendroflumethiazide, 12.2 mmHg in those randomized to long-acting nifedipine, and 9.7 mmHg in those randomized to enalapril.

ALLHAT identified another superiority of thiazide-like diuretics in comparison with other classes of BP-lowering drugs: prevention of hip and pelvic fractures [100]. Participants randomized to receive chlorthalidone had approximately 21% fewer fractures than participants randomized to amlodipine or lisinopril (HR 0.79,

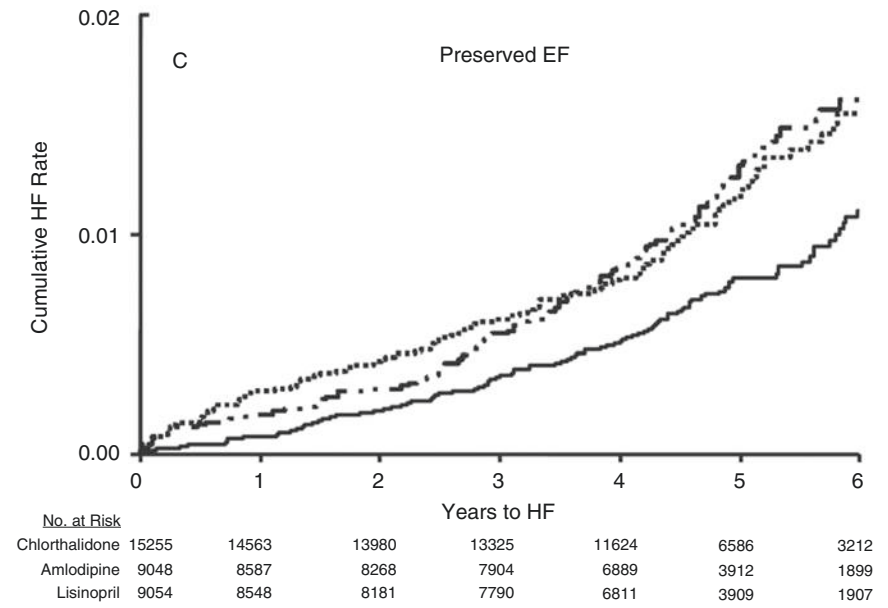


Fig. 4.10 Incidence of heart failure with preserved ejection fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The *solid line* denotes chlorthalidone; the *dashed and dotted line* denotes amlodipine; and the *dotted line* denotes lisinopril. (Reprinted from Davis et al. [97], with permission)

95% CI 0.63–0.98). This experimental demonstration confirmed findings from cohort studies, which showed that thiazide-like diuretics exert a protective effect against osteoporosis [101].

The findings of the Systolic Hypertension in the Elderly Program (SHEP) [102] and the Hypertension in the Very Elderly Trial (HYVET) [103] were aligned with those of ALLHAT. In the first, elderly patients with isolated systolic hypertension treated with chlorthalidone had a marked reduction in the incidence of stroke, heart attack, heart failure, and cardiovascular disease in comparison with placebo. These benefits were reproduced in patients older than 80 years treated with indapamide and perindopril in HYVET, which was the first study to show a decrease in all-cause mortality in patients treated with antihypertensive drugs versus placebo.

Many meta-analyses comparing the efficacy of classes of BP-lowering agents with placebo and with the other drug classes have been published. Several incurred an error in considering beta blockers and diuretics as the same type of treatment (designated as old treatments), comparing them with new agents [73]. More recently, a clear advantage of diuretics over other options was evidenced in a meta-analysis that included almost all relevant studies [104]. Diuretics were superior to other drug classes in prevention of various clinical outcomes and were the only drugs consistently superior to placebo in prevention of various cardiovascular events, cardiovascular death, and all-cause death (Fig. 4.11). It is of note that angiotensin receptor blockers (ARBs) were not directly compared with diuretics in any trial with hard outcomes.

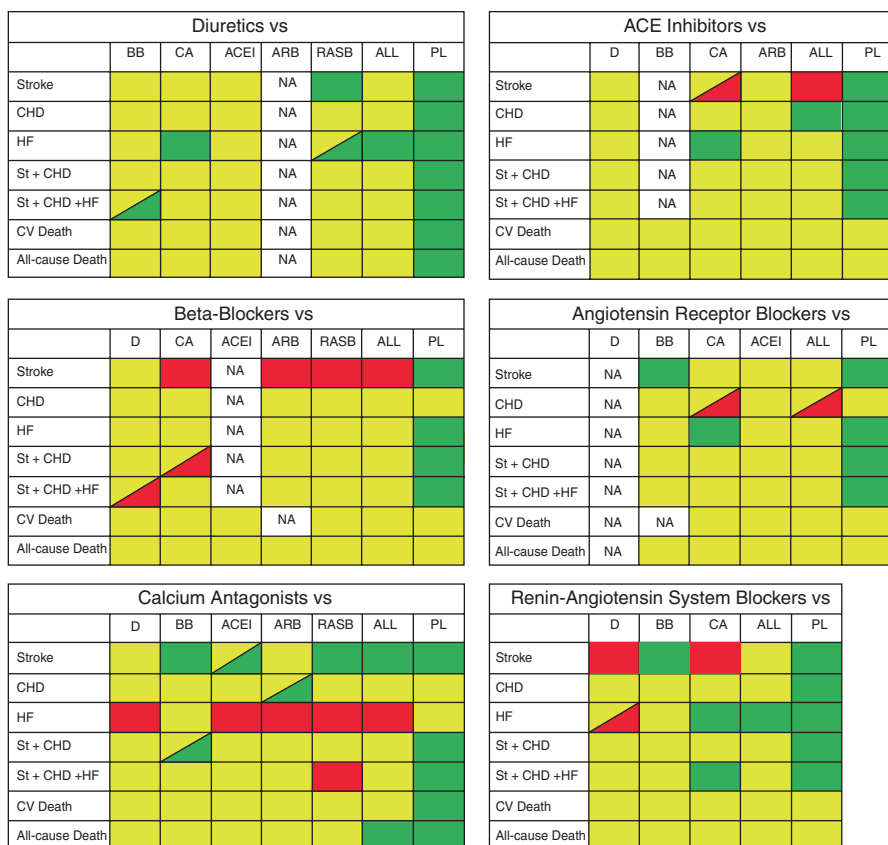


Fig. 4.11 Comparison of antihypertensive classes with each other and with placebo for prevention of stroke, coronary heart disease (CHD), heart failure (HF), combined events, cardiovascular death (CV), and all-cause death. *ACE-I* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *CA* calcium channel antagonists, *D* diuretics, *RASB* renin-angiotensin system blockers. *Yellow* denotes similar efficacy between the heading group and the comparator (*top* of each column); *green* denotes superiority of the heading to the comparator; and *red* denotes inferiority of the heading to the comparator. (Reprinted from Thomopoulos et al. [104], with permission)

4.2.3 Diuretic Preference and Association with Potassium-Sparing Agents

There has been no direct comparison of different diuretics in prevention of cardiovascular events. In the Multiple Risk Factor Intervention Trial (MRFIT), patients randomly allocated to diuretics, among multiple interventions, could be treated (at the discretion of the investigators) with hydrochlorothiazide or chlorthalidone. In a retrospective analysis [105], participants were classified by the periods when they were using chlorthalidone or hydrochlorothiazide or had stopped the diuretic. The incidence of cardiovascular events was lower during treatment with chlorthalidone versus hydrochlorothiazide (HR 0.79, 95% CI 0.68–0.92).

A network meta-analysis showed similarity between the different diuretics, but there were few studies available for comparison [106]. Another attempt to indirectly compare the effects of chlorthalidone and hydrochlorothiazide, using a network meta-analysis, included comparisons of these diuretics with other active treatments, in addition to a comparison with placebo [107]. Chlorthalidone was superior to hydrochlorothiazide in prevention of cardiovascular events despite having similar effects on office-measured BP.

Studies have directly and indirectly compared the BP-lowering effectiveness of chlorthalidone and hydrochlorothiazide. A randomized crossover clinical trial was stopped after the first cycle because of confirmed superiority of chlorthalidone (25 mg) in comparison with hydrochlorothiazide (50 mg) in lowering BP measured by ABP monitoring, especially during sleep [108]. In a meta-analysis [109] of clinical trials of short duration, the BP-lowering efficacy of hydrochlorothiazide was equivalent to that of other antihypertensives only when it was used at a dose of 50 mg. Another meta-analysis compared the BP-lowering effects of hydrochlorothiazide in 26 trials, chlorthalidone in three trials, and bendroflumethiazide in one trial [110]. The estimated dose of each drug predicted to reduce systolic BP by 10 mmHg was 1.4 mg, 8.6 mg, and 26.4 mg, respectively, for bendroflumethiazide, chlorthalidone, and hydrochlorothiazide. This proportional potency was also seen for diastolic BP, serum potassium, and uric acid. The only parallel head-to-head comparison of chlorthalidone (6.25 mg) with hydrochlorothiazide (12.5 mg) was reported in a small trial with ABP monitoring [111]. There was greater efficacy of chlorthalidone, despite the lower dose, particularly during sleep (Fig. 4.12).

The effects of different diuretics on BP, the duration of action, and indirect evidence provided by network meta-analyses point to the superiority of chlorthalidone to hydrochlorothiazide. Nonetheless, the main reason to indicate chlorthalidone as the preferred diuretic in management of hypertension relies on the findings of the major trials discussed earlier, such as SHEP and ALLHAT. Moreover, in the Systolic Blood Pressure Intervention Trial (SPRINT) [112], chlorthalidone was recommended as the preferred

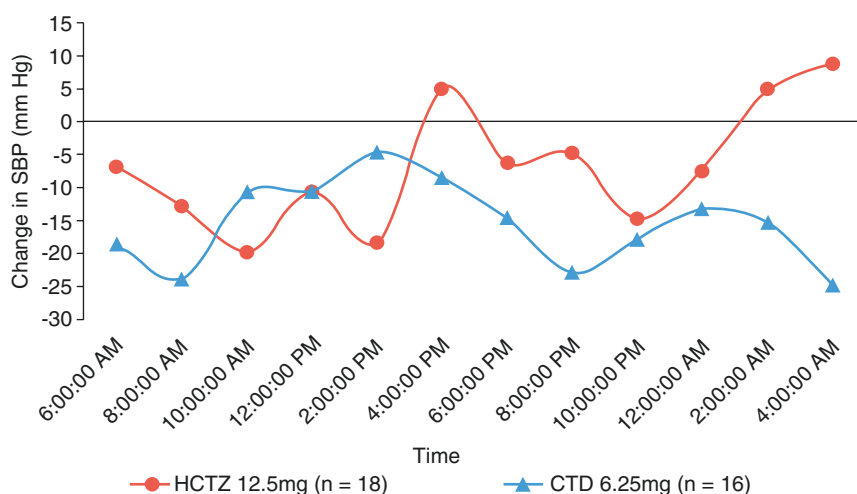


Fig. 4.12 Effects of chlorthalidone versus hydrochlorothiazide on 24-h ambulatory blood pressure monitoring. (Reprinted from Pareek et al. [111], with permission)

diuretic. In the Prevention of Hypertension in Patients with Prehypertension (PREVER-Prevention) trial [113], the combination of chlorthalidone with amiloride had greater efficacy than placebo in preventing progression of arterial hypertension and an increase in left ventricular mass. In the PREVER-Treatment trial [114], chlorthalidone with amiloride was superior to losartan in reducing BP during 18 months of follow-up.

Hydrochlorothiazide associated with amiloride may be considered as an alternative to chlorthalidone with amiloride, based on the results of INSIGHT [89]. Indapamide, which was used in HYVET [102] and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [115], in association with perindopril, is another option, given its consistent effectiveness in reducing the incidence of all-cause mortality and recurrent stroke.

The main adverse effect of diuretics is hypokalemia. When potassium is below 3.5 mEq/L, the benefit of treatment is lost [116]. The reduction in serum potassium also promotes a mild increase in blood glucose in patients treated with thiazide diuretics [117]. These consequences can be prevented with a combination of potassium-sparing diuretics. Amiloride is effective for this purpose [118], preventing an increase in blood glucose by preventing loss of potassium, as was shown in the Prevention and Treatment of Hypertension with Algorithm-Based Therapy-3 (PATHWAY-3) trial (Fig. 4.13) [119].

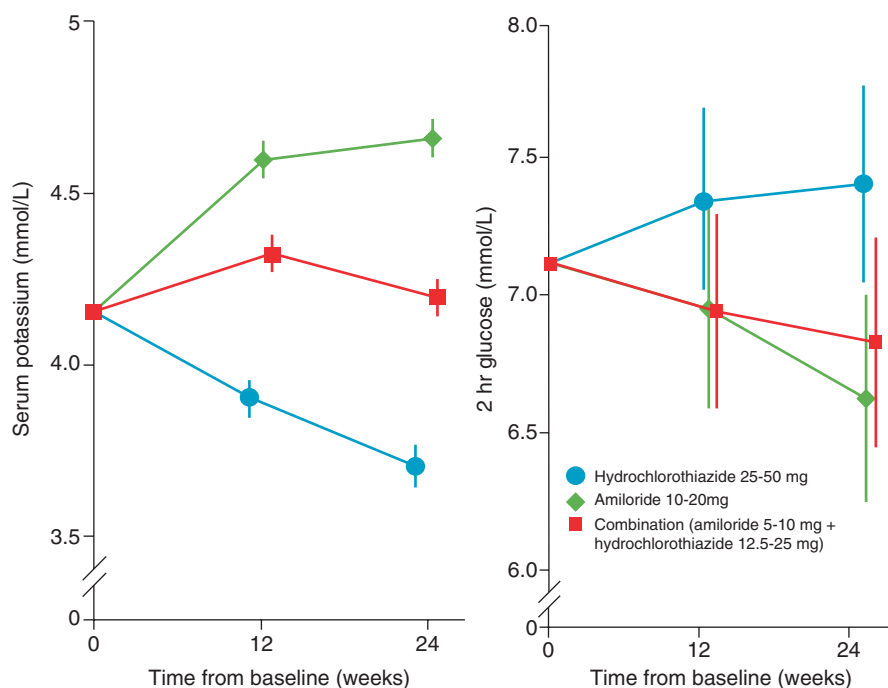


Fig. 4.13 Serum potassium (*left*) and 2-h glucose (*right*) after treatment with hydrochlorothiazide, amiloride, and the combination of the two. (Reprinted from Brown et al. [119], with permission)

4.2.4 Other Options for the First Choice

Nondiuretic BP-lowering drugs have been employed in studies of secondary prevention of cardiovascular disease, on the assumption that they act through pleiotropic mechanisms. Nonetheless, their effectiveness can be explained solely by their BP-lowering effects [120, 121]. Since they were the drugs tested in the studies of secondary prevention, they have a preferential indication in these conditions. In PROGRESS, in patients recovered from a recent stroke, indapamide associated with perindopril promoted a 40% reduction in recurrence of stroke in hypertensive and normotensive patients [115]. Beta blockers had been highly effective in preventing recurrence of infarction [122]. Angiotensin-converting enzyme (ACE) inhibitors are also indicated in patients who have recovered from myocardial infarction, as well as in patients with diabetes [120]. Beta blockers and ACE inhibitors are indicated in patients with heart failure. It is of note that the benefit was demonstrated in patients with prehypertension [120].

ARBs are the worldwide preference of doctors and patients as a first option for treatment of hypertension. Their popularity comes from good tolerability and the presumed existence of cardiovascular protective effectiveness independent of their hypotensive effect. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study [123] is the point of departure for this preference, because of the marginal superiority of losartan to atenolol in prevention of cardiovascular outcomes, particularly stroke. This trial, like the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [124], inadequately employed atenolol as a control—a drug that was inert in preventing cardiovascular outcomes in elderly patients [71, 75]. A meta-analysis of clinical trials showed that atenolol was not superior to placebo and was inferior to comparators in prevention of several cardiovascular outcomes [125]. The advantage of losartan over atenolol in the LIFE study could also be explained by more frequent use of diuretics in patients treated with losartan [126].

In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [127], amlodipine was superior to valsartan in prevention of myocardial infarction and stroke. In an accompanying paper [128], the authors of VALUE presented an inexplicable analysis for a randomized controlled trial, evaluating the efficacy of valsartan exclusively in participants who had a BP-lowering effect similar to that of participants treated with amlodipine. They rightly concluded that when BP is lowered equivalently, the effectiveness is also equivalent. This does not mean, however, that the drugs have the same effectiveness, since many participants treated with valsartan did not have the same BP response as those treated with amlodipine. An analysis restricted to these participants [not presented] would show a higher risk of myocardial infarction in patients treated with valsartan than in participants treated with amlodipine. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [129] did not show any advantage of telmisartan over ramipril in prevention of cardiovascular disease.

More recently, numerous large clinical trials testing the effectiveness of ARBs in various clinical conditions have been published [130–136]. The ethical foundation of many is questionable, because they compared ARBs with placebo in clinical conditions where there was already evidence of benefit from other antihypertensives, such

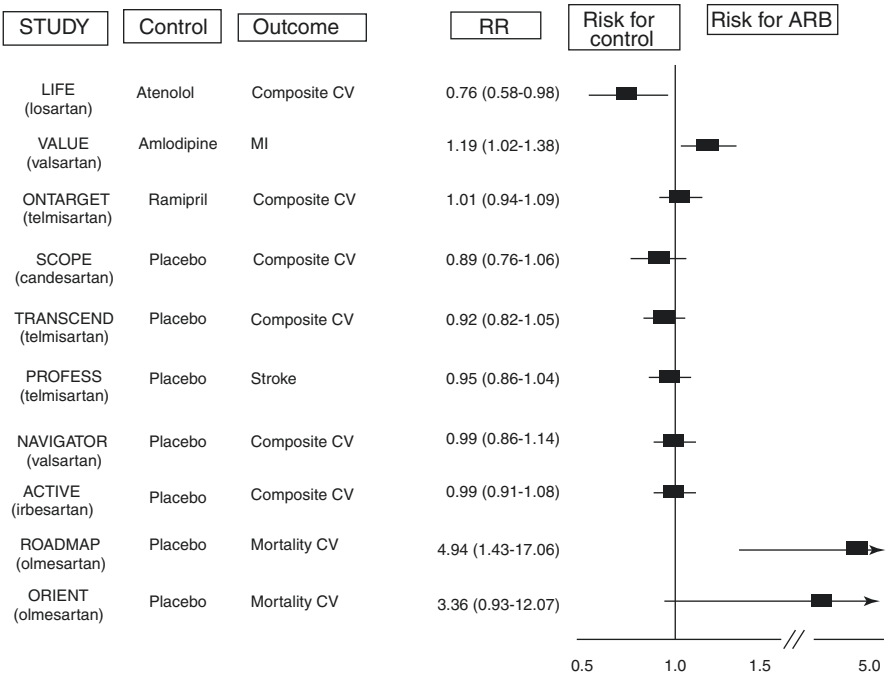


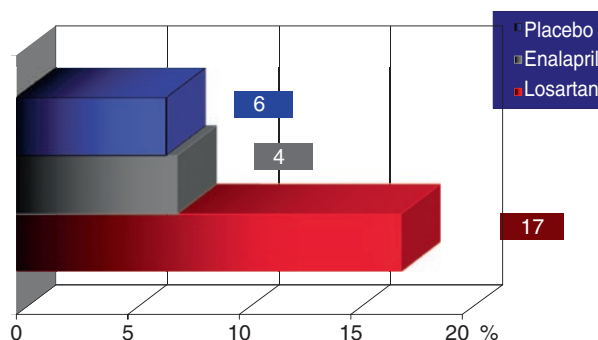
Fig. 4.14 Relative risks and 95% confidence intervals for cardiovascular outcomes in clinical trials comparing angiotensin receptor blockers with other drugs or placebo in patients with hypertension or high cardiovascular risk. (Reprinted from Fuchs [78], with permission; references to the individual studies are cited in the text)

as secondary prevention of stroke. Unexpectedly, in virtually all studies, ARBs were inert in prevention of various cardiovascular outcomes, and in two studies, they were associated with increased cardiovascular mortality (Fig. 4.14).

We analyzed these studies in a descriptive review [78]. In addition to absence of prevention of major cardiovascular outcomes, ARBs had a deleterious effect on renal function. Because renal effects were secondary outcomes in these trials, the play of chance cannot be discounted. One study, however, was specifically designed to compare the effects of enalapril and losartan with placebo for prevention of nephropathy and retinopathy [137]. Participants with uncomplicated type 1 diabetes mellitus underwent two renal biopsies 4 years apart in order to compare the efficacy of losartan and enalapril with placebo for prevention of mesangial proliferation and other secondary outcomes. Retinopathy was prevented by enalapril and losartan in comparison with placebo. There was no effect on mesangial proliferation. The incidence of microalbuminuria was three times higher in patients treated with losartan than in those treated with enalapril and placebo ($P = 0.01$) (Fig. 4.15).

The evidence of untoward renal effects of ARBs in patients free of kidney disease are an unexplained contradiction to the beneficial effects of renin–angiotensin system antagonists in patients with chronic kidney disease (CKD). In a large

Fig. 4.15 Incidence of microalbuminuria in patients with type 1 diabetes after 4 years of treatment with enalapril, losartan, and placebo [137]



meta-analysis exclusively involving patients with CKD, ACE inhibitors were superior to placebo and other treatments in prevention of end-stage renal disease [138]. Nonetheless, ARBs were less efficacious than ACE inhibitors, particularly in prevention of cardiovascular events, suggesting that the latter should be preferred in management of patients with CKD [138].

Several meta-analyses of studies comparing ARBs with placebo and other drugs have been published, confirming that these drugs are less efficacious than other options in prevention of cardiovascular mortality and infarction. The first explored the efficacy of ARBs in prevention of myocardial infarction and other cardiovascular outcomes [139]. Patients had various criteria for enrollment in the trials, such as hypertension, heart failure, diabetes, stroke, atrial fibrillation, and others. In total, 37 randomized clinical trials, with 147,020 participants, were included. When compared with placebo or active treatment, ARBs were inert in prevention of myocardial infarction (relative risk (RR) 0.99, 95% CI 0.92–1.07), death, cardiovascular death, or angina pectoris. The authors of this meta-analysis presented the following bizarre conclusion regarding drugs that are used to prevent cardiovascular outcomes: that ARBs do not increase the risk of myocardial infarction.

The second meta-analysis investigated the efficacy of renin–angiotensin–aldosterone system (RAAS) inhibitors in cardiovascular morbidity–mortality trials [140]. At least two thirds of the participants in these trials should have hypertension. The meta-analysis included 158,998 patients. RAAS inhibition was associated with a 5% reduction in all-cause mortality (HR 0.95, 95% CI 0.91–1.00) and a 7% reduction in cardiovascular mortality (HR 0.93, 95% CI 0.88–0.99). The effect was entirely due to ACE inhibitors (HR 0.90, 95% CI 0.84–0.97). ARB treatment had no effect on prevention of all-cause mortality (HR 0.99, 95% CI 0.94–1.04).

The third meta-analysis augmented the concern about the status of ARBs in prevention of cardiovascular disease [141]. This meta-analysis was restricted to patients with diabetes. In comparison with placebo or other active treatment in 23 studies involving 32,827 patients with diabetes, ACE inhibitors significantly reduced the risk of all-cause mortality by 13% (RR 0.87, 95% CI 0.78–0.98) and cardiovascular death by 17% (RR 0.83, 95% CI 0.70–0.99). ACE inhibitors were effective in prevention of major cardiovascular events, myocardial infarction, and heart failure. On the other hand, ARBs were ineffective in reducing the risk of all-cause mortality

(RR 0.94, 95% CI 0.82–1.08) in 13 studies with placebo or no treatment control, with a total of 23,867 patients. With the exception of a reduction in the risk of heart failure, ARBs were inert in lowering the cardiovascular death rate (RR 1.21, 95% CI 0.81–1.80) and major cardiovascular events (RR 0.94, 95% CI 0.85–1.01). It is of note that studies ascribed to ACE inhibitors in this meta-analysis, such as the Action in Diabetes and Vascular Disease—Preterax and Diamicron Controlled Evaluation (ADVANCE) trial [142], in fact included an association with a diuretic—indapamide—with perindopril. The ADVANCE trial may have incurred an ethical issue, because the active treatment was compared with placebo at a time when the effectiveness of treatment with ACE inhibitors had already been demonstrated [68].

In a meta-analysis restricted to elderly patients, ARBs increased the incidence of all-cause mortality by 3% [143]. Risks for renal damage were identified in this meta-analysis as well, with a risk of 1.6 (95% CI 1.3–2.0) for the incidence of acute kidney injury. A meta-analysis of 24 studies, with 61,961 patients followed up for an average of 3.2 years, explored the effectiveness of renin–angiotensin system inhibitors (RASIs) in comparison with placebo or active treatment in patients with coronary artery disease without heart failure [144]. Treatment with RASIs was more efficacious than placebo in prevention of various cardiovascular events, but was not superior to active controls. The evidence of superiority to placebo, however, was mostly driven by trials with ACE inhibitors.

The lower efficacy of ARBs in current trials than in studies versus placebo—in comparison with the efficacy demonstrated for diuretics in earlier trials—could be in part due to the background treatment of patients. In older trials, patients were not being treated, and the differences in BP between active and placebo treatment were somewhat greater. In recent trials with ARBs, many patients were on treatment, and there was a lesser decline in BP [78]. The absence of a consistent benefit for some outcomes, such as atrial fibrillation [134, 145–147], and the harmful effects on the kidney [131, 134, 135, 137] are hardly explained. The greater BP-lowering effect of diuretics demonstrated in the PREVER-Treatment study [113]—the only head-to-head comparison between these drugs—suggests that the low efficacy of ARBs in trials with hard outcomes is at least in part explained by the lower antihypertensive potency of ARBs.

Another relevant issue that argues against the effectiveness of ARBs is the fraud committed in three major studies done with these agents, which were retracted from the literature [148–150]. The contrast between the numerous experimental studies showing beneficial effects of ARBs on many biological parameters, particularly in bench investigations, and the lack of consistent effectiveness in clinical trials, is apparently unexplainable. There is currently a concern with the huge rate of nonreproducibility of experimental and preclinical studies [151, 152]. I am not an investigator or even a systematic reader of experimental studies, but in at least one such study [153], the statistical analysis was wrong [69].

The original studies and meta-analyses of ARBs herein reviewed demonstrate, beyond reasonable doubt, that these agents do not have a good record of efficacy. Since effective treatments for hypertension are increasingly demanded, it is imprudent to start antihypertensive treatment with ARBs.

4.2.5 Second-Line and Third-Line Drugs for Management of Hypertension

A significant proportion of patients with hypertension need two or more agents for adequate BP control. In ALLHAT [91], which enrolled stage 1 and 2 hypertensive patients, approximately 50% of participants used at least two drugs to control BP—a proportion that has been found in most studies and in clinical practice.

The ideal study to endorse the second (and third) choice of antihypertensive drugs would be a randomized controlled trial comparing different options in patients treated equally with a first-line drug [154]. Most studies, however, have compared pairs of drugs.

The International Verapamil–Trandolapril Study (INVEST) [155] evaluated verapamil and trandolapril versus atenolol and hydrochlorothiazide in preventing primary endpoints, demonstrating similar efficacy. However, it was impossible to isolate the contribution of each agent. The same thing happened in the ASCOT study [124].

Clinical trials comparing the BP-lowering effects of drug associations versus monotherapy, and occasionally comparing second choices on top of a common first choice, are more frequent. Law and colleagues [156] found that six out of ten combinations evaluated in 119 clinical trials had an additive effect on the reduction of BP.

ONTARGET investigated whether double blocking of the renin–angiotensin axis with a combination of telmisartan and ramipril was more effective than either agent alone in prevention of hard outcomes [129]. There was no benefit of the combination versus each agent alone. Both drugs were equivalent to each other. Symptoms of hypotension were more common with the combination. Renal dysfunction occurred in 13.5% of participants treated with the combination versus 10.2% of participants treated with ramipril ($P < 0.001$). This association should therefore be proscribed in the treatment of hypertension.

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study [157] is probably a unique study comparing the effectiveness of the second option with a common companion. Patients were treated with benazepril (an ACE inhibitor) and amlodipine (up to 10 mg/day) or hydrochlorothiazide (up to 25 mg/day). The pairs of drugs were initiated together, and not after lack of response to the first option. The incidence of the composite outcome—death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitated sudden death, and myocardial revascularization—was 19.6% lower in patients treated with amlodipine ($P < 0.001$). The discrepancy between the findings of ALLHAT (which showed superiority of diuretic to amlodipine) and this trial was more likely due to the types of diuretic used [79]—chlorthalidone in ALLHAT and hydrochlorothiazide in ACCOMPLISH.

The preferential drug to be used as a second option in patients on initial treatment with a diuretic, chlorthalidone particularly, has not been investigated in adequately designed clinical trials. Exploration of complementary mechanisms of action, in line with classical recommendations, may be a valid approach, using a beta blocker as a second option and a vasodilator as the third. Among beta blockers, metoprolol has the best record, particularly in comparison with atenolol [158, 159]. Amlodipine is the preferred vasodilator, given its good performance in ALLHAT. Hydralazine

can replace amlodipine, particularly when there is intolerable lower limb edema [154]. ACE inhibitors may replace the beta blocker, taking advantage of its potassium-sparing effect. If chlorthalidone is associated with a potassium-sparing agent, the blood levels of potassium need to be checked periodically.

ARBs were the only agents compared with placebo as the second, third, or fourth option in the clinical trials with hard endpoints that were discussed earlier [77, 78]. The reservation raised by their performance in those studies casts doubt on their utility as part of the association of BP-lowering drugs.

4.2.6 Management of Resistant Hypertension

Many patients with resistant hypertension have OSA. The effectiveness of treatment with CPAP or renal denervation was addressed in Sect. 4.1. Among drugs, spironolactone was superior to bisoprolol and doxazosin as the fourth option [160]. Preliminary results of a Brazilian clinical trial [161] (Personal communication, Eduardo Krieger, 2017) showed equivalence between spironolactone and clonidine.

Treatment based on diuretics (spironolactone, furosemide, and amiloride)—added sequentially to control home BP (HBP)—lowered daytime systolic BP on ABP monitoring by 10 mmHg (95% CI 7–14) more than the association of ramipril with bisoprolol [162]. The treatment with diuretics led to a greater reduction in left ventricular mass [163].

Taken together, the evidence from trials in patients with resistant hypertension—which is defined by resistance to treatment that includes a diuretic—shows that it is necessary to give more diuretic. Spironolactone is the agent with more favorable evidence. Nonetheless, adherence to treatment is particularly critical in this scenario and should be meticulously checked.

4.2.7 Adverse Events, Adverse Effects, and the Nocebo Effect

These concepts are essentials for evaluation of drug-related complaints by patients. Doctors, and even researchers, sometimes misinterpret the origin of those complaints. Adverse events are any occurrences related to administration of drugs. More commonly, adverse events correspond to unwanted effects attributed by patients to drugs. Adverse effects are complaints that are really caused by drugs. The causality of common adverse effects requires demonstration of a higher incidence in the active treatment arm than in the placebo arm of a randomized double-blind clinical trial. It is usual that a proportion of patients from the placebo arm report the same complaint; therefore, the frequency of adverse effects attributable to drugs corresponds to the difference in those reported in the active and the placebo arm, demonstrating that the difference is not due to chance. On the other hand, rare adverse effects are mostly detectable in postmarketing pharmacovigilance.

Common adverse events that are not true adverse effects are attributable to the nocebo effect. The nocebo effect results from common beliefs and expectations of

patients about unwanted drug effects. In practical terms, the placebo effect corresponds to the opposite of the placebo effect.

The popular belief (largely endorsed by health professionals) is that high BP causes headache, epistaxis, and other symptoms. Similarly, there is a perception that antihypertensive drugs, like others in general, cause many adverse effects.

In the PREVER-Prevention study [113], around 50% of patients attributed at least one complaint to treatment during the 2 years of follow-up, independently of having been allocated to the active or placebo arms. The misinterpretation of the occurrence of adverse events in SPRINT [112] is another noticeable example. Some of them were real adverse effects (those assessed in blinded conditions, such as acute renal damage), but the more common ones were typically attributable to the placebo effect. Because of the study's open design, doctors and patients were prone to believing that low BP increased the risk of hypotension and syncope, which were more frequently reported by participants in the more intensive BP-lowering arm. Objective assessment of adverse events, such as injuries and postural hypotension, showed that their incidence was not higher in the intensive treatment arm; on the contrary, objectively assessed postural hypotension was more common in patients allocated to the higher BP goal. The same pattern was observed in analyses restricted to elderly participants [164]. In addition, the higher incidence of adverse events in the more intensive BP-lowering arm in SPRINT may have resulted from the greater frequency of medical visits to adjust treatment in these patients.

We investigated the occurrence of adverse events/effects at our outpatient clinic [165]. About one third of 1366 patients reported an adverse event during a mean follow-up of 1 year. Many complaints were characteristically placebo effects. Patients under treatment with diuretics less frequently reported adverse events with drugs used in monotherapy (Fig. 4.16).

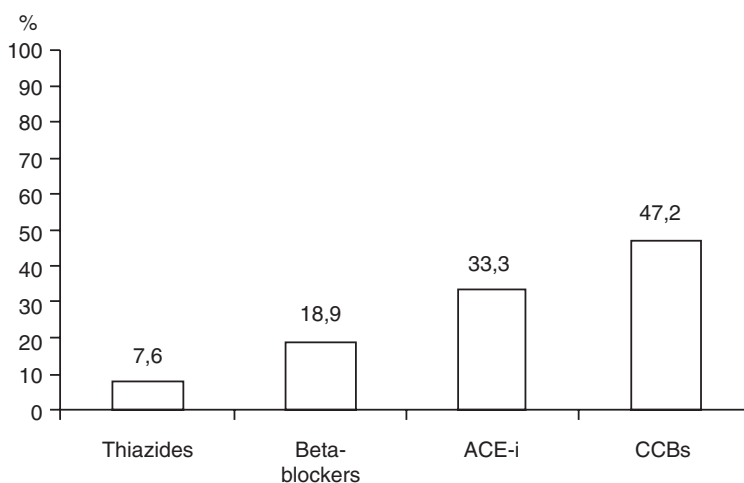


Fig. 4.16 Incidence of adverse events by treatment with monotherapy at an outpatient hypertension clinic. (Reprinted from Gonçalves et al. [165], with permission)

Independently of being true adverse effects, adverse events may influence adherence to treatments. In a meta-analysis of 85 controlled randomized clinical trials of placebo and active treatment (totaling almost 400,000 participants), Thomopoulos and colleagues identified an association between adverse events and discontinuation of treatments [166]. The RRs for discontinuation were significant and around 2 for all classes of drugs, with the single exception of ARBs. We identified the occurrence of adverse events in a population-based study [167]. Participants treated for hypertension reported worse quality of life than those not treated, which can contribute to poor adherence to treatment.

Scientists should provide knowledge about the differences between adverse effects and adverse events, and doctors should implement this knowledge in clinical practice. Experienced physicians know that it is difficult to convince patients to keep taking drugs associated with adverse events, even if they surely are not adverse effects (cough with amlodipine, for example). The risk is not only losing adherence to treatment but losing the patient, who will look for another doctor to reinforce his or her view. Nonetheless, an effort to clarify misconceptions about adverse events that still prevail in clinical practice is worthwhile. It is difficult to control BP in many patients without a diuretic, as the first option or as a rescue drug, but many people believe that they are associated with increased diuresis, sexual dysfunction, and other adverse reactions. In double-blind conditions, however, these complaints are no more frequent in the diuretic arm than in the placebo or other drug arms [113, 114, 168]. Doctors have created this monster; it is time to show that it is not so ugly and may be a friend.

Detailed description of adverse effects of BP-lowering drugs is out of the scope of this book and can be found online from many sources. It should be noted that prescribing information presents a long list of presumably adverse effects of drugs (adverse reactions). These lists are mostly based on reports of adverse events. Dizziness, for instance, is listed as an adverse effect of most BP-lowering drugs. In double-blind trials controlled by placebo, however, the incidence of dizziness in the active treatment arm has been similar to or slightly higher than that in the placebo arm, demonstrating that this complaint was typically a nocebo effect in most patients.

4.2.8 Hypertensive Crises, Urgencies, and Emergencies

Emergency rooms worldwide receive a significant proportion of patients with very high BP. Many have sought assistance because of high BP, but in others, high BP is detected during evaluation of other clinical conditions. For decades, management was guided by the concept of a hypertensive crisis—a sudden elevation of BP presumably associated with immediate risks. This concept resulted from observation of marked elevations of BP during clinical catastrophes, such as stroke. From these observations were derived routines for rapidly reducing BP, which was supposed to be the cause of clinical events.

Subsequently, hypertensive crises were divided into hypertensive urgencies and hypertensive emergencies. In the first condition, there is elevation of BP accompanied by a variable list of clinical conditions, such as unstable angina, anticoagulation, or cocaine or amphetamine intoxication, among others. Isolated and marked elevation of BP ($\geq 180/110$ mmHg) is also usually labeled as a hypertensive urgency. In hypertensive emergencies, the conditions associated with BP elevation are more severe, including hypertensive encephalopathy, pulmonary edema, myocardial infarction, aortic dissection, intracranial hemorrhage, eclampsia, postoperative bleeding, extensive burns, pheochromocytoma crisis, and malignant hypertension.

In many clinical situations, the increase in BP results from reverse causality, such as in the acute phase of stroke, with elevated BP resulting from potent pressor stimuli generated in the ischemic brain. Ischemia in other organs, particularly the heart, also causes large elevations of BP. Less serious conditions, such as headache, may also determine BP elevation.

The prognosis of these conditions is predominantly determined by the underlying disease, and there are no clinical trials showing the effectiveness of immediate BP-lowering therapies. Nonetheless, the elevation of BP exacerbates certain clinical conditions, even if they are the source of the BP elevation. For example, in the presence of myocardial infarction, an adrenergic response due to ischemia and pain may occur, with a consequent elevation of BP. This, in turn, exacerbates the demand for oxygen, intensifying ischemic damage. The same can occur in cases of acute pulmonary edema accompanied by elevated BP.

Thus, lowering BP may be a legitimate therapeutic goal, but it should be done in the context of management of the underlying disease, whose protocols may recommend use of titratable drugs, such as sodium nitroprusside or nitroglycerin. Beta blockers may be particularly useful in aortic dissection. It is more important, however, to institute measures aimed at treatment of the clinical condition—for example, initiating myocardial reperfusion measures in myocardial infarction, with a thrombolytic and acetylsalicylic acid, or with angioplasty. Effective analgesia may also be useful, such as that provided by morphine in the presence of aortic dissection, or for relief of dyspnea in acute pulmonary edema. BP tends to normalize or at least reduce as a result of treatment of the acute condition, requiring no antihypertensive treatment in some situations.

An isolated elevation of BP does not require immediate treatment. Two cohorts of patients treated with this condition demonstrated good prognosis, with rare clinical events, with or without emergency care. The first cohort was followed in Bahia, Brazil [169]. There was no complication in patients with elevated BP alone (designated as a pseudocrisis in the study). The second compared the clinical course of patients with isolated elevation of BP detected in the office ($\text{BP} \geq 180/110$ mmHg), who were referred to the emergency room (426 cases), versus 58,109 patients who were sent home [170]. Major cardiovascular events were rare in both cohorts but more frequent in those managed in the emergency room. Numerous trials have shown BP reductions from treatment with different drugs, but they may be not necessary. For example, just resting for 2 h had the same effect as telmisartan [171].

The diagnoses of hypertensive crisis, hypertensive urgency, and hypertensive emergency should be abandoned. The reasons for the very high BP in patients presenting to emergency rooms should be investigated. Once the diagnosis has been established, protocols for each condition should be implemented. Rapid control of BP is recommended for some clinical conditions. Patients with isolated elevation of BP, who could be classified as patients with uncontrolled BP, should be referred for outpatient hypertension management. Initiation of treatment in the emergency room has no clear justification but may be useful for patient comfort, since many patients are conditioned to being treated in this context. The traditional routine administration of captopril or clonidine tablets is probably safe, but both need to be swallowed, because the oral mucosa does not absorb the tablets. The usual reduction in BP after treatment, however, is largely due to regression to the mean.

4.2.9 Strategies to Improve Adherence to Treatment

Awareness about the risks of hypertension has not yet resulted in adherence of many patients to drug and nondrug prescriptions. Poor adherence is associated with a higher risk of presenting with a cardiovascular event [172]. There are innumerable reports of inadequate adherence to treatment and, consequently, of interventions to improve it. Adherence to BP drugs can be assessed by several methods, such as pill counting, questionnaires, serum dosing, and control of BP.

Some strategies to improve adherence to antihypertensive treatment, particularly with drugs, are reviewed in Sects. 4.2.9.1, 4.2.9.2, 4.2.9.3, and 4.2.9.4.

4.2.9.1 Self-Monitoring of Blood Pressure

Measurement of BP by the patient, informed about the goal for treatment, may help with adherence to treatment. Many trials have tested this strategy. The Efficacy of Home Blood Pressure Monitoring (MONITOR) study, done by our group, demonstrated that awareness of BP measured by the patient at home promoted a greater BP reduction than usual care for BP measured by ABP monitoring, especially during sleep (Fig. 4.17) [173]. The prescription was not modified in response to the BP values measured by the patient, suggesting that the effect resulted from better adherence to treatment. A meta-analysis of this trial and similar studies identified a small but consistent BP-lowering effect with use of HBP measurement [174]. The studies had variable durations and protocols. In many, medication was modified according to the results of the HBP assessment.

4.2.9.2 Telemonitoring

Remote monitoring of BP, sometimes with consultation and orientation by pharmacists, is another approach to improve adherence tested in several clinical trials. A meta-analysis of studies with some similarity showed that the intervention was associated with improvement of BP control, accompanied by increased costs of care [175].

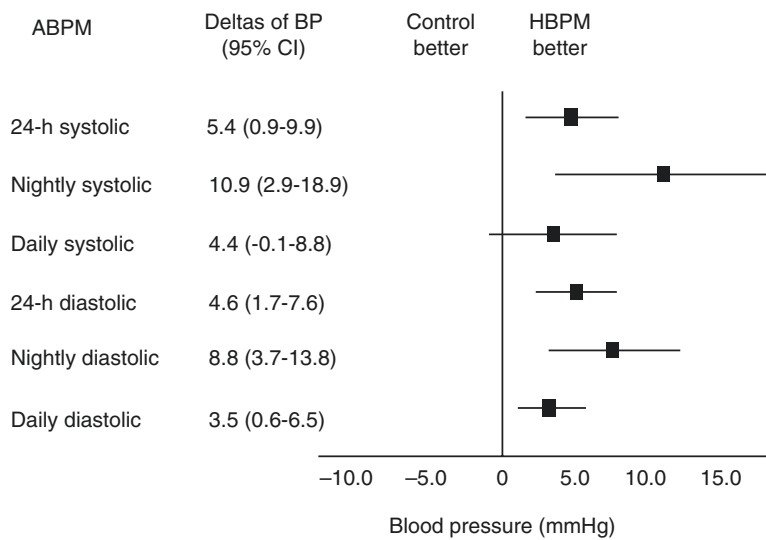


Fig. 4.17 Effect of home blood pressure (BP) monitoring on systolic BP assessed by ambulatory BP monitoring. (Reprinted from Fuchs et al. [173], with permission)

4.2.9.3 Pharmacist Care

The involvement of pharmacists in the care of patients has been associated with improved outcomes in several diseases. In a clinical trial conducted at our outpatient clinic, we demonstrated that pharmacist care augmented the incidence of control of BP [176]. In a secondary analysis of this trial, we identified that cognitive deficit impaired adherence to drug therapy [177]. Among the various meta-analyses that synthesized the benefit of this intervention, one done by Santschi and colleagues identified a 7.6 mmHg (95% CI 6.3–9.0) greater systolic BP reduction in patients receiving pharmacist care in comparison with various types of control [178].

4.2.9.4 Text Messages

The effectiveness of text messages delivered via mobile phones has been widely investigated. Protocols included unilateral or bilateral contact with the patient, besides other differences. A systematic review identified the effectiveness of this method [179]. A large single-blind clinical trial, using interactive messages, showed a slight benefit for systolic BP (2.2 mmHg, 95% CI 0.04–4.4) after 1 year of follow-up [180].

A systematic review of different strategies to improve adherence suggested that self-monitoring, feedback interventions, packaging for controlling the use of tablets, and motivational interviews have some effect [181]. Multiple interventions are probably more effective, obviously at higher cost. Starting treatment of high BP earlier in life—maybe with just one drug at a low dose—may prevent escalation to multiple drug prescription and, therefore, prevent multiple problems. The 120/80 paradigm is the key to eradicating most consequences of increasing BP with age.

Essentials of Prevention and Treatment of Hypertension

1. The blood pressure goal for prevention and treatment of hypertension, at all ages, should be the same: below 120/80 mmHg.
2. Nonpharmacological strategies (lifestyle changes) are preferred for prevention and treatment but have only minor effectiveness.
3. Reduction of salt intake by populations, through a decrease in the amount added for preservation of foods, may have a large long-term impact on the incidence of hypertension and should be pursued by societies. Diets enriched in potassium have a complementary benefit.
4. Long-term weight reduction, as a mean to treat hypertension, seems unattainable for now and has not been improved by medications.
5. The DASH and Mediterranean diets (enriched with extra-virgin olive oil or with nuts and seeds, as in the PREDIMED diet) lower blood pressure. The Mediterranean and PREDIMED diets reduce the incidence of cardiovascular events.
6. Restraint from alcoholic beverage consumption is good for blood pressure control and health overall.
7. The effectiveness of other dietary interventions and of nutraceuticals still requires demonstration in better-designed clinical trials.
8. The blood pressure–lowering effectiveness of physical exercise is debatable, but it may have other health benefits.
9. Treatment of obstructive sleep apnea, as a means to treat hypertension, is more effective in patients with resistant hypertension.
10. Substituting oral contraceptives with other contraceptive methods lowers blood pressure. Hormone replacement therapy does not increase blood pressure but is devoid of any beneficial cardiovascular effect.
11. The effects of percutaneous or surgical correction of atherosclerotic renovascular disease have been frustrating and may have a small blood pressure–lowering effect at best.
12. Renal sympathetic denervation is a therapy looking for evidence that it has biological activity, including a blood pressure–lowering effect in patients with resistant hypertension.
13. Bariatric surgery is likely to reduce blood pressure and the number of blood pressure pills taken, in patients with and without diabetes.
14. The effectiveness of other nondrug and nondietary therapies for hypertension is still unproven.
15. Diuretics are the cornerstone to effectively lower blood pressure and prevent cardiovascular events, and they should be the first option for patients of all ages without cardiovascular disease and for patients who have recovered from a stroke.

16. Blood pressure–lowering treatment, particularly with chlorthalidone, is effective to prevent not only stroke and coronary heart disease but also heart failure, including heart failure with a preserved ejection fraction.
17. Beta blockers and angiotensin-converting enzyme inhibitors have documented effectiveness in certain clinical cardiovascular conditions, such as postmyocardial infarction and heart failure.
18. Chlorthalidone and indapamide have the best record in terms of cardiovascular disease prevention. Addition of a potassium-sparing diuretic, such as amiloride, prevents adverse effects of diuretics, such as hypokalemia and the consequent increase in blood glucose.
19. Chlorthalidone has stronger and more durable blood pressure–lowering efficacy than hydrochlorothiazide.
20. A moratorium on the preference for angiotensin receptor blockers in management of hypertension and prevention of cardiovascular disease is required, in the face of their poor efficacy in prevention of many cardiovascular outcomes.
21. The preferential drug to be used as a second option in patients on initial treatment with a diuretic—chlorthalidone particularly—has not been investigated in adequately designed clinical trials. Complementary mechanisms of action justify a beta blocker—metoprolol preferentially—as a second option, and a vasodilator—such as amlodipine—as the third. An angiotensin-converting enzyme inhibitor may replace the beta blocker, taking advantage of its potassium-sparing effect.
22. Resistant hypertension is more frequently apparent and is due to poor adherence to treatment. In true resistant patients, treatment of obstructive sleep apnea may be useful; among drugs, spironolactone deserves preference as a fourth drug.
23. Complaints about untoward effects of blood pressure drugs are mostly due to the nocebo effect; misconceptions about adverse events with blood pressure drugs hamper the indication for more effective treatments of hypertension.
24. The diagnoses of hypertensive crisis, hypertensive urgency, and hypertensive emergency should be abandoned. Management of patients with very high blood pressure in emergency rooms should follow the protocols for the underlining clinical conditions.
25. Self-monitoring, feedback interventions, packaging for controlling the use of tablets, pharmacist care, and motivational interviews are interventions that improve adherence to treatment; multiple interventions are probably more effective, but at higher cost.
26. Early management of hypertension according to the 120/80 mmHg paradigm would require less drug use and would have a large impact in preventing hypertension-related outcomes.

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