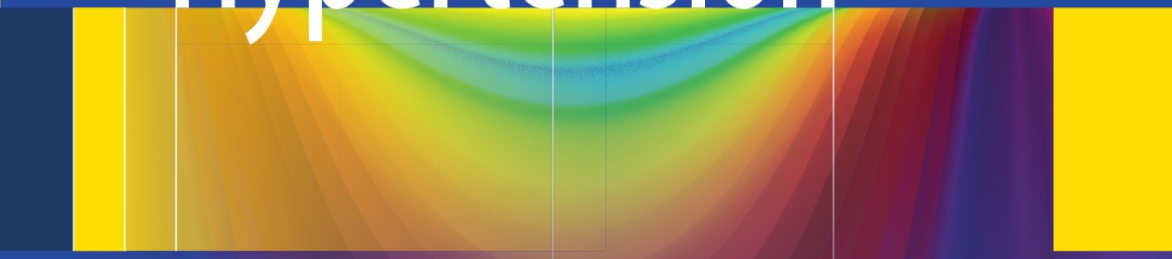
Adel E. Berbari
Giuseppe Mancia *Editors*

Special Issues in Hypertension



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Editors

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Preface

Hypertension, i.e. the single major cause of cardiovascular morbidity and mortality worldwide, has been addressed by a large number of books and monographs which have dealt with this topic in all its multifold epidemiological, diagnostic and therapeutic aspects. The aim of this book, however, is not to add another systematic review to those already available. It is rather to provide a cutting edge on key basic and clinical issues on high blood pressure and its related cardiovascular disorders, which are of greater current interest and sometimes controversial interpretation, either because of conflicting data or because hypotheses, rather than data, are available.

Some of the topics included in the book are well known to students of hypertension, also because they have a prominent place in the scientific programme of all major meetings: the risk involved in high normal blood pressure and the evidence in favour or against extending treatment; to this "prehypertension" condition; whether white coat hypertension is clinically innocent or it carries a higher than normal risk that deserves a close follow-up and treatment; how to identify, within the normotensive population, those with ambulatory or home BP elevations who should be treated; how often hypertensive patients should be assessed for their asymptomatic organ damage, and whether the treatment-induced changes in the damage allow physicians to better appreciate the achieved cardiovascular protection; how to score new effects of antihypertensive treatment that can differ between drug classes such as short-term (within 24 h) and visit-to-visit blood pressure variability; which is our knowledge of the epidemiology and the treatment-dependent benefits of conditions frequently seen in hypertension, such as obstructive sleep apnea, cognitive impairment and dementia, hypertension of the very elderly, and hypertension associated with diabetes or dyslipidemia; how can we deal with the challenge of reducing the high residual risk exhibited by even apparently well treated hypertensive patients and whether this can be obtained by lower blood pressure targets or earlier initiation of treatment.

The above few examples give the reader an idea of the range and scope of the topics included in this book, which in addition deals with problems perhaps less controversial but nevertheless of practical importance, such as hypertension in post menopausal women, the difficult coexistence of antihypertensive treatment with drugs to be given for inflammatory disorders and pain, the sexual dysfunction

accompanying treatment (and leading to treatment discontinuation) and, a topic virtually unaddressed before, the effect of Ramadan fasting on blood pressure control.

We hope this will increase general and specific knowledge of the pathophysiology and clinical aspects of hypertension, and also stimulate not only curiosity but also a critical attitude on issues on which much future research and confrontation of ideas is needed.

We express our deep gratitude and warm appreciation to the experts who kindly contributed to the various chapters of this book.

Beirut and Milan, December 2012

Adel E. Berbari
Giuseppe Mancia

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Part I

1 Prehypertension: Definitions, Clinical Significance and Therapeutic Approaches—To Treat or not to Treat?

Stevo Julius and Carlos A. Feldstein

1.1 Introduction

In 1939, Robinson and Brucer examined longitudinal data from 11,383 life insurance records [1] and reported that in the group with an initial blood pressure (BP) below 120/80 mmHg, BP did not increase with aging. However, BP did increase with age and mortality rates were higher in the *prehypertension* (120–139/80–89 mmHg) and *hypertension* (140/90 mmHg or higher) groups. The data in this seminal paper were undisputable, but the term *prehypertension* did not take root.

About 60 years ago, the first appearance of effective antihypertensive agents generated a renewed interest in BP classification. All first-generation antihypertensive drugs caused serious side effects and it was important to select for treatment patients with reproducible, *sustained*, hypertension. In contrast, patients with occasionally elevated BP values were classified as having *labile* hypertension. This proved to be a semantic mishap, as it implied that patients with labile hypertension have excessive BP variability. In a review of papers published prior to 1971 [2], we found no solid evidence for increased BP variability and reactivity in labile hypertension and proposed to replace *labile* by the term *borderline* hypertension.

In the USA, the term *high-normal blood pressure* (HNBP) first appeared at the fifth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 5). In this and in the sixth [3] JNC report (JNC 6), the BP range for HNBP was set at a value of 130–139/85–89 mmHg. The World Health Organization (WHO), the International Society of Hypertension [4], and the

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European Society of Hypertension (ESH) guidelines [5] also use the term HNBP and define it as in JNC 6. Obviously, world opinion leaders preferred not to use the word *hypertension* for people with HNBP. Indeed, the semantic difference between *high-normal* blood pressure and *borderline* hypertension is huge; the former is a variant of normalcy, whereas the latter refers to a subform of the disease of hypertension. Particularly worrisome was the likelihood that the term *hypertension* may decrease an individual's chances to obtain health insurance or to secure employment.

Against this background, it came as quite a surprise that the 2003 JNC 7 report [6] reintroduced the term *prehypertension* for people with marginal BP elevation and widened the prehypertension range to 120–139/80–89 mmHg. This range is so wide that it becomes meaningless. In 347,978 middle-aged men screened for the Multiple Risk Factor Intervention Trial (MRFIT) [7], only 18.2 % had normal BP. The rest had either prehypertension (46.7 %), stage 1 hypertension (25.9 %), or other stages of hypertension (9.2 %). Using the new prehypertension definition, physicians would be obliged to manage the BP in 80 % of all patients. Worldwide, practitioners are urged to be cost-effective and see more patients. Under such circumstances, clinicians are likely to focus on patients with *serious* hypertension and neglect the sea of people with prehypertension. Based on the National Health and Nutrition Examination Survey (NHANES) of a representative sample of the USA population, we calculated [8] that approximately 83 million US people have prehypertension as defined by the JNC 7. If the selection is narrowed down to a HNBP range of 130–139/80–89 mmHg, the number of people with a *hypertension problem* decreases to 31 million. However, as it is the case with other *pre* conditions (precancer, prediabetes), the term *prehypertension* is appealing and is often used. Consequently, we proposed that the group within the HNBP range be alternatively named as *stage 2 prehypertension* and argued that the BP in this group should be diligently managed.

Since nomenclature changes frequently, this chapter focuses on studies of HNBP as defined by the JNC 6, the ESH, and the WHO guidelines and uses the term *prehypertension* for studies that investigated marginal BP elevations but did not abide by the HNBP definition.

1.2 The Public Health Impact of High-Normal Blood Pressure

In a number of longitudinal studies, the group with HNBP [8] was 2–3 times more likely to develop hypertension than normotensive individuals. In the placebo group of the Trial of Preventing Hypertension (TROPHY) [9], 52 % of subjects with HNBP developed hypertension over a period of 4 years. Whereas the frequent transition of prehypertension to stage 1 hypertension increases the cardiovascular (CV) risk, there is evidence that HNBP per se is also deleterious. In six longitudinal studies [8], data were adjusted for progression to hypertension and compared to the normotensive population. The hazard ratio of a CV event in 10 years in the HNBP group ranged from 1.42 to 2.33.

To further assess the public health impact of HNBP in this review, we used the cumulative incidence, spanning 15 years, of CV events in 347,978 men aged 35–57 years screened for the MRFIT trial [7]. The prevalence of HNBP in this population was 22 % and the cumulative incidence of deaths from coronary heart disease (CHD) and strokes was 2.9 %. We adjusted [8] the prevalence of HNBP and the incidence of events for age and gender to extrapolate the 15-year cumulative incidence of events to the total adult (35 years or older) USA population. According to our rather conservative projection, at least 2,000,000 persons with HNBP may have died from CHD or stroke over a period of 15 years.

The increasing use of out-of-office BP measurements introduced a new element in the field of prehypertension. These measurements invariably detect subgroups with *white coat* (high in office/normal at home) and *masked* (high at home/normal in the clinic) hypertension. In the population-based Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study [10], 14.5 % had masked hypertension with ambulatory blood pressure (ABP) and 15.5 % by home BP monitoring. In a further analysis of that study [11], after 12 years of follow-up, the total and CV deaths increased in a stepwise fashion from normotension to white coat, masked, and sustained hypertension. This pattern was detected both with ABP and home BP measurements. In a recent meta-analysis of eight studies with a follow-up ranging from 3.2 to 12.8 years [12], the odds ratio of CV events in the masked hypertension compared to normotensive group was 2.09.

The widely used ABP and home BP monitoring are bound to detect more cases of white coat and masked hypertension. Since in such patients the risk of total and CV mortality is increased, it is likely that physicians will manage masked hypertension in the same manner as they manage HNBP. This, in turn, will further expand the number of patients with prehypertension.

1.3 Association of Prehypertension with Other Cardiovascular Risk Factors

Most guidelines take note of the association of prehypertension with other CV risk factors and, based on the presence of these predictors, recommend different levels of therapeutic vigilance. In the study of a representative section of the middle-aged inhabitants of Tecumseh, Michigan [13], 822 subjects were normotensive and 124 were prehypertensive. The prehypertension group had significantly higher than normal percentage of obesity, thicker skinfolds, and increased waist-to-hip ratio. Furthermore, cholesterol, glucose, insulin, and triglyceride levels were significantly higher in the prehypertension group whereas high-density lipoprotein (HDL) levels were significantly lower. The resting heart rate, a recognized coronary risk factor [14], and hematocrit [15], another known CV risk factor, were increased in the Tecumseh prehypertension group [16]. When we grouped the total study population in tertiles of hematocrit levels, the clinic, home, and work BP values increased significantly in a stepwise fashion from low to medium to high hematocrit brackets. Furthermore the

cholesterol, glucose, insulin, and triglycerides levels and the percentage of overweight persons were significantly elevated in the highest hematocrit group.

The close association of HNBP with CV risk factors was again demonstrated in patients with HNBP enrolled in the TROPHY trial [9]. When all anthropometric (overweight or obese), hemodynamic (BP, tachycardia), metabolic (dyslipidemia), and rheological (hematocrit) risk factors were considered, 96 % of TROPHY participants had at least one, 81 % had two or more, and 13 % had five or more additional risk factors [17]. Consequently assessment and management of CV risk factors must become an integral part of the clinical approach to prehypertension.

1.4 Natural History of Marginal Blood Pressure Elevation

In clinical practice, HNBP is usually detected in the third or fourth decade of a patient's life. However, adults with prehypertension have higher than normal BP already as children and young adults. This *tracking phenomenon* has been verified in a systematic meta-regression analysis of 50 cohort studies [18]. In the Tecumseh study, we used records of earlier medical exams [13] to reconstruct previous BP trends in subjects who, at 32 years of age, were normotensive or prehypertensive. Adult subjects with prehypertension had significantly elevated BP levels already at 6 and 21 years of age. There was little or no BP increase between the ages of 6 and 21. However, this pattern dramatically changed from 21 to 31 years of age. In the third decade of life, the average BP increased in both cohorts but the increase in the prehypertension group was nearly three times as steep as in normotensive subjects (Fig. 1.1).

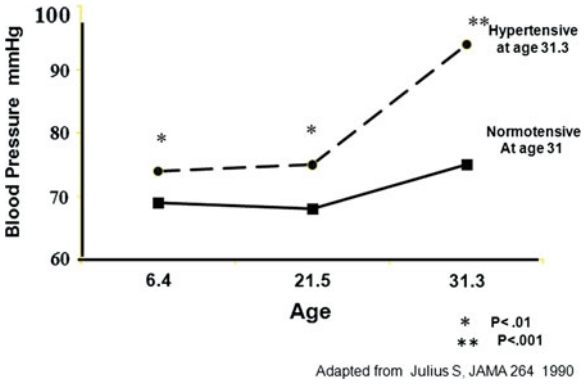

Fig. 1.1 Diastolic blood pressure (BP) trends in the Tecumseh, Michigan study. Participants were classified as normotensive ($N = 563$) of prehypertension ($N = 78$) at the average age of 32 years. BP levels at a younger age were retrieved from previous Tecumseh health exams

The nonlinearity of the BP increase was also demonstrated in 26,980 teenagers recruited to the Israeli army and followed over an average period of 14 years [19]. In men the relative risk of developing hypertension was 51 % and in women 48 % higher in the baseline HNBP group than in the normotensive groups. At the beginning of the follow-up, the difference in cumulative incidence of new onset hypertension was only slightly higher in the baseline HNBP. However, as time

passed, the cumulative incidence of hypertension in the HNBP group increased in an exponential fashion and the gap between the originally normotensive and HNBP groups substantially increased.

1.5 Pathophysiology of Blood Pressure Acceleration in Subjects with High-Normal Blood Pressure

1.5.1 Primary Mechanism of Blood Pressure Acceleration

BP acceleration in the course of prehypertension is associated with structural and functional changes in resistance arteries [20]. A hypertension-related increase of regional vascular resistance in various human organs and tissues has been reported [21]. Advanced hypertension [21–23] is commonly associated with structural arteriolar abnormalities. Whereas the morphology of reported changes in arteriolar structure may vary, all authors agree that the observed changes are physiological responses to higher BP levels. According to Folkow [23], a sustained BP elevation causes a hypertrophy of the vascular wall. Due to this adaptive process, the same degree of vasoconstriction (the same shortening of vascular smooth muscle cells) elicits a smaller intravascular diameter as the thickened wall encroaches into the vascular lumen. This, in turn, exponentially increases vascular resistance and the morphological changes in resistance vessels act as a *structural BP amplifier*. Crucial to Folkow's concept are two assumptions: (1) that thickening of the muscular layer (media) in resistance vessels alters the wall-to-lumen ratio and (2) that the thickening is due to smooth muscle hypertrophy in the vascular wall. An altered wall-to-lumen ratio of small arteries was found in histological examinations of autopsy or biopsy materials from essential and secondary hypertension [24, 25].

Another form of arteriolar restructuring called *eutrophic inward remodeling* has also been reported in hypertension [26]. Such arterioles show an increased media thickness, a slightly reduced lumen diameter, and a decreased external diameter with subsequent increased media-to-lumen ratio [27]. It is not known whether this type of remodeling contributes to BP acceleration in untreated hypertension.

Structural vascular alterations also decrease the range of arteriolar vasodilation. In part this is due to mechanical factors; the thicker wall protrudes more into the lumen even when arteriolar smooth muscles are maximally relaxed. Maximal vasodilation can be assessed in humans after a period of anaerobic forearm exercise by measuring blood flow immediately after the tourniquet has been released. With that technique, we found a higher than normal forearm vascular resistance, compatible with thickening of the vascular wall in stage 1 hypertension [28] and prehypertension [13]. Furthermore, endothelium-related dilation is also decreased in hypertension [29]. It is likely that a reduced capacity of arteriolar vasodilation contributes to BP acceleration in the course of hypertension.

1.5.2 Secondary Mechanisms of Blood Pressure Acceleration

Stimulation of the sympathetic nervous system and excess activity of the renin–angiotensin system (RAS) promote vascular hypertrophy by a direct action on smooth muscle cells. This, in turn, suggested that sympatholytic and RAS blockers may be particularly effective in interrupting the vicious cycle of BP acceleration. A short period of treatment with angiotensin-converting enzyme inhibitors [30, 31] altered the natural history in rats with spontaneous hypertension (SHR). In untreated SHR rats, the BP continued to increase to ever higher levels. However, in the treated group, one short burst of BP lowering arrested a further BP increase. This conversion from accelerated to *mild* hypertension in rats [31] was associated with favorable morphological changes in small renal arteries. A lifelong reduction of BP after a short period of treatment was seen only if the treatment was given to young SHR rats. Apparently, there is a *point of no return* after which the BP can be lowered but the natural history of the disease cannot be altered. These studies suggest, but do not prove, that RAS inhibition may have a better effect than other antihypertensive agents. In all SHR studies, RAS inhibitors were compared to hydralazine. Vasodilation with hydralazine elicits compensatory increases of sympathetic and renin–angiotensin activity which by itself may negatively affect arteriolar structure and function.

Schiffrin and colleagues used serial gluteal biopsies to assess the effect of prolonged antihypertensive treatment on the structure of small arteries [32]. Treatment with different antihypertensive drugs induced regression of vascular remodeling, but treatment with atenolol was not associated with such an effect. However, treatment with atenolol may have deleterious side effects. BP lowering with atenolol is associated with increased vascular resistance and higher central (aortic) BP [33]. These hemodynamic features may negatively affect vascular structure in the atenolol group.

Another possible secondary mechanism of transition to hypertension relates to increased BP variability and reactivity in prehypertension. It has been suggested that hypertension evolves through a summation of repeated bouts of excessive BP increases. In Ann Arbor, Michigan we did not find signs of hyperreactivity in young people with prehypertension [34]. However, Flaa and colleagues [35] found that hyperresponsiveness to mental stress in young subjects with prehypertension predicts future BP trends. Furthermore, BP response to exercise proved to be a predictor of CV mortality. However, animal experiments do not support the notion that repeated BP increases lead to a permanent increase in BP [36, 37].

1.6 Therapeutic Approaches to Prehypertension: To Treat or Not to Treat?

Current USA and European guidelines recommend lifestyle modifications (LSMs) for the management of prehypertension. In USA guidelines, LSMs are the only option, whereas European guidelines suggest initiation of pharmacological treatment in HNBP patients with three or more CV risk factors, metabolic syndrome, diabetes mellitus, or subclinical organ damage.

The 8-week-long Dietary Approaches to Stop Hypertension (DASH) study reported a −6/−3 mmHg BP decrease with life style modification (LSM) in prehypertension [38]. In the DASH study, all patients were trained and motivated by experts in specialized study centers and all meals were prepared in the centers and handed to the participants. In the 6-month-long PREMIER: Lifestyle Interventions for Blood Pressure Control (PREMIER) study [39], specialized teams intensively facilitated behavioral changes. At the end of the trial, the BP in the prehypertensive group was reduced by −3.1/−2.0 mmHg more than in the control group. There is no information whether participants in these studies continued to practice LSMs after the study ended.

In most weight loss studies, an early decrease of weight was followed by a later gain of weight which erased the initial results. A recent 2-year-long study [40] of weight loss in clinical practice reported a 4.6 kg weight loss throughout the study. The study offered weight loss support via telephone, a dedicated website, and encouragement by email. It is questionable whether these new techniques will be widely implemented. Presently, in USA and worldwide, the population weight and the percentage of obesity are inexorably and exponentially increasing.

It is conceivable that population-based measures to increase physical activity and restrict sodium intake may prove effective. However, the current focus is on LSMs in individual patients. Clinical experience tells us that the majority of overweight patients fail to alter lifelong habits. Consequently, in real life LSMs are not an effective treatment strategy and the recommendations to manage prehypertension with LSMs amount to an invitation to failure.

The treatment goal in established hypertension (decreasing the incidence of CV events) is different from the goal in prehypertension (decreasing the incidence of established hypertension). In SHR rats, a short period of early antihypertensive treatment suppressed the transition to the advanced stages of hypertension [31, 32]. However, treatment must be given early; the same bout of BP lowering in older animals fails to change the course of the disease. Observations in SHR rats of a point of no return after which the natural history of hypertension cannot be altered are in line with clinical experience. Withdrawal of treatment in established hypertension is invariably associated with a return to previous high BP levels. Another argument for earlier treatment relates to the steep increase of BP [13] and the incidence of hypertension [19] in middle-aged subjects with prehypertension. This steep BP rise is a reflection of a vicious cycle in which the slight initial BP elevation elicits a restructuring of arteriolar resistance vessels which, in turn, renders them hyperresponsive to all vasoconstrictive stimuli. In parallel, anatomic restructuring and the ensuing vascular endothelial damage limit the capacity for vasodilation.

Given the limitations of the LSM approach and encouraged by the SHR results we initiated and completed the 4-year-long TROPHY trial [9]. Participants with HNBP were randomized to either candesartan ($N = 391$) or matching placebo ($N = 381$). In the first 2-year long, double-blinded phase the participants received either placebo or candesartan, and in the second 2-year phase placebo was given to all participants. The main outcome variable was the rate of developing

hypertension. In the first report new hypertension was defined as BP $\geq$ 140 and or 90 mmHg occurring three times during the study. In the second report [41], we used the more strict JNC 7 definition of new hypertension. The results with that definition are shown within parentheses.

In the first two years, there was a 26.8 % (28. 9 %) absolute and a 64 % (68 %) relative reduction of the risk of new hypertension in the candesartan group. In this study phase we demonstrated that antihypertensive agents can be safely used in patients with HNBP and that concerns of symptomatic hypotension or dizziness were not justified. The safety of antihypertensive treatment of HNBP was confirmed in the Prevention of Hypertension with the Angiotensin-Converting Enzyme Inhibitor Ramipril in Patients with High-Normal Blood Pressure (PHARAO) study, a prospective, randomized, controlled prevention trial of the German Hypertension League [42], where gradual increase of ramipril up to 5 mg/day was not associated with excessive side effects. Taken together, the TROPHY and PHARAO studies have opened the doors for future studies of pharmacological intervention in prehypertension.

In the second 2-year phase of the TROPHY trial, when patients previously treated with candesartan were switched to placebo, we evaluated whether active treatment postponed or prevented the development of hypertension. Two years *after discontinuation of active treatment* there was a 9.8 % (9.5 %) absolute and 16 % (18 %) relative risk reduction in the group previously treated with candesartan. While highly significant from a statistical viewpoint, the suppression of new-onset hypertension was modest. Participants in our study were relatively old (48.5 years) and the antihypertensive treatment period was 2 years. Whether the results would be different in younger subjects or if the period of treatment was extended remains an open question. Furthermore, TROPHY did not test whether other antihypertensive agents would be equally beneficial.

In summarizing the TROPHY results [9], we recognized the study limitations and did not suggest initiation of pharmacological treatment of HNBP. However, we did express our hope that further research may resolve some outstanding questions. We also underscored that potentially positive outcomes in larger trials of prehypertension may have a large impact on public health.

In conclusion, the *treat or not to treat* question in prehypertension has not yet been answered. Present USA guidelines encourage the use of LSMs for the management of prehypertension. European guidelines state that pharmacological antihypertensive treatment should be initiated in patient with HNBP who have three or more CV risk factors as well as in those who are diabetic, have metabolic syndrome, or have subclinical organ damage. I strongly support this approach.

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Clinical Significance and Treatment Requirements in White Coat and Masked Hypertension

2

Jean-Michel Mallion

2.1 Introduction

The phenomena of white coat hypertension (WCHT) and masked hypertension (MH) were first identified once blood pressure (BP) measurements became possible outside of a clinic/office setting. Ambulatory blood pressure (ABP) or home blood pressure (HBP) measurements have really changed the way we interpret the significance of BP data. Thus, four BP categories can be measured: MH, true normotension (NT), sustained hypertension (SH) and WCHT ([1]; see Table 2.1).

Generally, clinic/office BP is defined as normal when <140/90 mmHg and out-of-office BP, ABP, or HBP are defined as normal when <135/85 mmHg (daytime or home BP) [1]. The question then is whether these entities are clinically unimportant or whether they are associated with an increased cardiovascular (CV) risk.

2.2 White Coat Hypertension

2.2.1 Terminology

WCHT is the most commonly used term for describing patients with elevated BP in a clinic or office setting but not in other settings [2, 3].The term *isolated office hypertension* is also used.

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Table 2.1 Diagnostic possibilities with reference to ambulatory blood pressure or home blood pressure

	Office BP	
HBP or ABPM	<140/90 mmHg	≥140/90 mmHg
<135/85 mmHg	NT	WCHT
≥135/85 mmHg	MH	SH

ABPM ambulatory blood pressure monitoring, *BP* blood pressure, *HBP* home blood pressure, *MH* masked hypertensive (normal office but high out-of-office BP), *NT* normotension (office and out-of-office BP), *SH* sustained hypertension (high office and out-of-office BP), *WCHT* white coat hypertension (high office but normal out-of-office BP)

2.2.2 Definition

The criterion originally used by Pickering and colleagues [2] to define WCHT was a clinic or office BP that remained above 140/90 mmHg, together with a daytime ABP or HBP below 134/90 mmHg. The threshold values generally used are >140/90 mmHg within an office setting and <135/85 mmHg outside the office [1]. Most investigators have used both systolic and diastolic BP to make a diagnosis of WCHT. WCHT should be distinguished from the white-coat effect, which is the difference between clinic BP and daytime ABP.

2.2.3 Prevalence

The prevalence of WCHT depends on the definition and on the demographic features of the population being surveyed.

Authors of early studies suggested that WCHT occurs in 20 % or more of the hypertensive population [2, 4–6]. Not surprisingly, it is more common (33.3 %) among patients with the mildest hypertension (from 140/90 to 159/99 mmHg) and virtually nonexistent among those with the most severe hypertension (above 210/120 mmHg) [7–10]. The prevalence of WCHT does not appear to increase with age [11], nor does it differ for sex or weight from SH.

2.2.4 Metabolic and Biochemical Features

Weber and colleagues [12] reported that patients with WCHT had higher levels of total and low-density lipoprotein (LDL) cholesterol than normotensive patients. Levels of high-density lipoprotein (HDL) cholesterol and triglycerides did not differ between the WCHT and normotensive groups. Even though several studies have been performed in this area, the authors did not confirm their initial findings.

Cavallini and colleagues [13] and Pierdomenico and colleagues [14] reported that all three groups (NT, SH, and WCHT) had the same levels of total cholesterol,

HDL cholesterol, and triglycerides. Pierdomenico and colleagues [14] also found no difference in the level of LDL cholesterol among groups. In a third study, Marchesi and colleagues [15] reported that, of 84 newly diagnosed hyper-tensive patients, 24 % who were classified as having WCHT had glucose and lipid blood levels that were similar to those in SH patients, though the WCHT patients had lower insulin levels. Pierdomenico and colleagues [16] observed that the LDL of WCHT patients does not exhibit greater than normal propensity toward oxidation.

In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, Mancia and colleagues [17] reported that a prevalence of diabetes (≥126 mg/dL or use of antidiabetic drugs), impaired fasting blood glucose (≥110 to <126 mg/dL), and hypercholesterolemia (total serum cholesterol ≥240 mg/dL or 200 mg/dL) increased progressively from *optimal* to *normal*, *high-normal*, and then *elevated* office systolic or diastolic BP. Fasting blood glucose and total serum cholesterol also increased progressively from the first to the fourth group, with HDL cholesterol values showing a concomitant progressive decrease. Even if the majority of the results show that there is no specific metabolic abnormality associated with WCHT, a unanimous consensus has not been reached.

2.2.5 Target Organ Damage

Verdecchia and colleagues [4] reported that there was no correlation between the magnitude of the white-coat effect and left ventricular mass (LVM). A similar finding was reported by Guida and colleagues [18].

Kuwajima and colleagues [19] performed an echocardiographic study of 67 patients aged 60 years and older: 17 patients with WCHT, 34 patients with ST, and 16 NT control subjects. The patients with WCHT had a moderately increased left atrial mass and LVM in association with a tendency for disturbed diastolic function. These findings suggest that WCHT in older patients may not be unharmful. Cavallini and colleagues [13] found that intima-medial thicknesses (IMT) of the carotid artery in the NT group (0.76 mm) and WCHT group (0.84 mm) were similar, whereas the IMT in the SH group was greater (0.98 mm). Pierdomenico and colleagues [14] compared 50 SHs with 25 sex-matched and age-matched WCHTs and 25 NTs, using a comprehensive battery of tests for target organ damage, including both echocardiography and carotid artery ultrasonography. WCHT subjects did not differ from NT subjects in any of these measures. Cuspidi and colleagues [20], whose study involved 82 patients, reported that the prevalence of left ventricular hypertrophy and cardiac remodeling was significantly more frequent in SH patients (51 %) than in WCHT patients.

Soma and colleagues [21] investigated left ventricular function in 26 subjects with WCHT. They discovered that the arterial pressure response in subjects with WCHT was associated with increased left ventricular external work, increased end-systolic wall stress and alterations of left ventricular filling, though they recorded normal ejection fraction and mean velocity of circumferential fiber shortening. Ormezzano and colleagues [22] did not find cardiovascular alterations

in WCHT subjects with reference to the left ventricular mass index (LVMI), carotid IMT, and aortic stiffness (pulse wave velocity). The results obtained by Sega and colleagues [6] from the PAMELA study did not match with the previous data reported by Ormezzano. In these subjects, LVMI was greater than in subjects with normotension both inside and outside the office setting.

Another sign of target organ damage is microalbuminuria. Hoegholm and colleagues [23] evaluated microalbuminuria in 411 subjects who were NT subjects, SH subjects, or WCHT subjects. The ratios for the NT and WCHT subjects were the same, while those for the SH subjects were greater [9]. Pierdomenico and colleagues [14] and Martinez and colleagues [8] also found lower levels of microalbuminuria in WCHT subjects than they did for SH subjects.

2.2.6 Morbidity and Mortality

Verdecchia and colleagues [24] were the first to propose the hypothesis that WCHT is associated with a relatively low risk of morbidity, with an intermediate level of morbidity for NT and SH subjects. Following up a group of 1,187 NT and HT individuals over 3 years, they reported an event rate of 0.49 per 100 patient years for WCHT subjects (similar to the rate of 0.47 for NT subjects), and rates of 1.79 among hypertensive dippers, who constituted the majority, and 4.99 among non-dippers.

In the Self-Measurement of Blood Pressure at Home in the Elderly: Assessment and Follow-up (SHEAF) study, Bobrie and colleagues [25] reported that even when the characteristics of patients with isolated office hypertension were similar to those of patients with controlled hypertension, patients with isolated office hypertension had fewer previous cardiovascular complications.

In a subsequent report, Bobrie and colleagues [26] performed a multivariable analysis and found that the hazard ratio of cardiovascular events was almost the same in patients with elevated office BP and normal HBP than in patients having normal home and office BP.

After a 10-year follow-up study of 420 patients with grade 1–2 hypertension newly diagnosed by their general practitioner and 146 NT controls for which ABP monitoring was performed at baseline, Gustavsen and colleagues [27] concluded that there was an increased CV risk in WCHT patients compared to NT controls. Ohkubo and colleagues [28] followed 1,332 subjects by means of ABP for a mean duration of 10 years and showed that the CV risk in WCHT subjects does not differ significantly from that of NT subjects.

In the PAMELA study, Mancia and colleagues [29] did not confirm their previously obtained results and, like Gustavsen and colleagues [27], found that WCHT and MH, when identified by office and ABP or by office and HBP, are not prognostically innocent in term of CV risks. Fagard and Cornelissen [30], by means of a meta-analysis, concluded that the outcome of CV events in WCHT does not significantly differ from NT.

A more recent meta-analysis study carried out by Pierdomenico and Cuccurullo [31] confirmed that CV risk is not significantly different between WCHT and NT, regardless of normotensive population type and follow-up length. However, it is noteworthy that during follow-up, drug therapy was more frequent in WCHT than in NT subjects and thus its possible impact on the outcome should be evaluated in future studies. Consequently, when WCHT is identified at an office setting and presents a normal ambulatory blood pressure monitoring (ABPM) and a normal HBP is not perhaps completely innocent.

2.2.7 Management and Treatment

The most controversial issue about the management of WCHT is whether treatment with antihypertensive drugs should be prescribed. Authors of several studies have analyzed the effects of anti-hypertensive medications on patients with SH and WCHT. Pickering and colleagues [32] reported that administration of doxazosin mesylate, a long-acting α-blocker, lowered clinic BP for subjects in both groups and to the same extent, but lowered ABP only in those with SH.

Two other groups, both using calcium antagonists, found that the effects of medication on clinic BP in patients with high and normal ABP were similar. However, when ABP was normal to begin with (i.e., in the case of WCHT), the drug did not lower it further [33, 34]. Herpin and colleagues [35] compared patients treated with a variety of calcium antagonists with treatment with angiotensin-converting enzyme inhibitors, and confirmed that these two drug classes had similar effects on clinic BP. However, calcium antagonists had little effect on ABP if this was low to begin with (i.e., WCHT), whereas angiotensin-converting enzyme inhibitors lowered it irrespective of whether ABP had started out low or high. Kristensen and colleagues [36] found that treatment with benazepril lowered ABP in WCHT patients more than did treatment with felodipine. This finding raises the interesting possibility that there might be differences among the various classes of antihypertensives in terms of the degree to which they affect WCHT.

The other major issue regarding WCHT is patient follow-up. Authors of at least three studies have investigated this by repeating ABPM. Bidlingmeyer and colleagues [37] re-examined 81 patients with WCHT after an average period of 5 years and found that ABP in 60 of them had increased to more than 140/90 mmHg, although no similar change in clinic BP had been recorded. Verdecchia and colleagues [38] followed 83 patients for 2.5 years and found that for two patients, the classification had changed from WCHT to SH. Polonia and colleagues [39] followed 36 patients with WCHT and 52 NT patients for 3.5 years and found that 11 and 6 %, respectively, developed ambulatory hypertension.

In a third study performed by White and colleagues [40], only 12.5 % of WCHT patients became truly hypertensive. The apparent transition of a patient from WCHT to SH could have several explanations. The most widely advocated hypothesis is that WCHT is a prehypertensive state, though an equally plausible

hypothesis is that the transition is nothing more than a regression to the mean. So, it is reasonable to suggest a treatment plan based on lifestyle recommendations in patients with WCHT in the absence of comorbid conditions and target organ damage and monitor them on a regular basis. It is clear that all patients diagnosed with WCHT should be followed up indefinitely, either with both clinic and HBP or with ABPM.

2.3 Masked Hypertension

2.3.1 Definition

Subjects with MH have a normal clinic BP of <140/90 mmHg and an abnormal, out-of-office (ambulatory or at home) daytime systolic BP >135 mmHg or daytime diastolic blood pressure >85 mmHg [1]. MH has also been known as *white coat normotension*, *inverse white coat hypertension*, *isolated clinic normotension*, *isolated home hypertension*, *isolated ambulatory hypertension* and *reverse white-coat effect*.

2.3.2 Prevalence

The use of different BP limits affects the prevalence of MH and MH is certainly often underestimated. Prevalence can be different according to different studies, the range being between 10 and 40 % [5, 6, 22, 26, 28, 29, 41, 42]. According to Eguchi and colleagues [43], prevalence is higher in diabetic patients (47 %), whereas Baguet and colleagues [44] have reported a 30 % prevalence in sleep apnea syndrome.

2.3.3 Target Organ Damage

The first study that looked at the issue of target organ damage in MH was carried out by Liu and colleagues [45], who examined 295 clinically normotensive individuals and 64 patients with SH. They found that individuals with MH had greater LVM and higher prevalence of carotid IMT atherosclerosis than those with normal BP.

Sega and colleagues [6], with reference to the PAMELA study, observed that MH presented higher LVMI and structural cardiac alterations. Bjorklund and colleagues [46] investigated 578 untreated 70-year-old hypertensive men and reported a higher LVM and relative wall thickness for MH patients.

In a population of 688 subjects, Silva and colleagues [47] observed an increased LVM with MH. Ormezzanno and colleagues [22] observed that cardiovascular alterations, such as LVMI, carotid IMT, aortic stiffness, and pulse wave velocity are found in association with MH. These data were confirmed by Lurbe and

colleagues [48] in younger patients. Consequently, we can suggest that subjects with MH have more extensive target organ damage than true normotensive individuals.

2.3.4 Morbidity and Mortality

The clinical significance of MH is based on five longitudinal studies and two meta-analyses. First, individuals with MH are at increased risk of developing SH. In the Hypertension and Ambulatory Recording Venetia Study (HARVEST) [49], 35 % of participants with MH had persistent SH when followed up over 6 years whereas only 19 % of those with true NT at baseline developed SH. This has been confirmed by Mancia and colleagues [29] in the PAMELA study where subjects with WCHT and MH were at increased risk of developing SH. However, Messerli and Makani [50] concluded that for undetermined reasons, some patients are able to remain in the same BP category or are even able to go back to a category that confers reduced morbidity and mortality.

The prognostic value of MH was assessed by Bjorklund and colleagues [46] in a cohort of 70-year-old men followed for 8.4 years. They found that MH was as great a predictor of CV events (relative risk: 2.77) as SH (relative risk: 2.94).

In a cohort of treated hypertensive patients followed up for a mean of 3.2 years, Bobrie and colleagues [26] found that individuals with controlled office BP but uncontrolled HBP were doubly at risk of developing CV events in comparison with patients having their BP controlled both at home and in the office.

The composite risk of cardiovascular mortality and stroke morbidity was calculated for 1,332 subjects from the town of Ohasama, Japan, who were followed up for a period of 10 years [28]. The risk was significantly greater for subjects with MH or SH than for those with NT or WCHT.

Lurbe and colleagues [48] investigated the prevalence, persistence and clinical significance of MH in 592 children and adolescents. They concluded that in children and adolescents, MH is a precursor of SH and LVM.

Finally, in the PAMELA study, Mancia and colleagues [29] discovered that WCHT and MH, when identified by office and ambulatory measurement or by office and HBP, are not prognostically innocent.

Hara and colleagues [51] demonstrated in the Ohasama study that CV risk is higher with MH and similar to that for SH. Taking into account 11 studies and 11,502 participants, Fagard and colleagues [30] established, by means of meta-analysis, that the incidence of CV events is more important in patients with MH. More recently, in a meta-analysis of six cohort studies reporting quantitative data for MH prognosis, Bobrie and colleagues [52] showed that subjects with MH have a higher risk of CV incidents [hazard ratios: 1.92 (1.51–2.44)] than normotensive subjects or subjects with controlled hypertension. Consequently, we suggest that MH and SH subjects have the same CV risk.

2.3.5 Identification of Patients with Masked Hypertension

For practical and financial reasons, ABPM and HBP monitoring cannot be performed in all individuals with normal office BP. The decision to carry out such measurements should be taken according to specific criteria. In the French SHEAF study involving almost 5,000 treated hypertensive patients (mean age 70 years, 49 % men), Mallion and collegues [53] found that three variables at inclusion identified a MH profile: age >60 years, office systolic BP >130 mmHg, male sex. Rasmussen and colleagues [54] showed that a higher daytime than clinic BP was a much more frequent event among men aged 42 years (82 %) than among men aged 72 years (51 %). Thus, MH is expected to be more frequent in men. Recent results from the PAMELA study, however, do not support this hypothesis [55]. In this study, 40.1 % of women and 39 % of men showed a reversed white-coat condition.

Lifestyle factors, and smoking in particular, have been shown to largely influence the relationship between clinic and ABP [56]. Drinking alcohol [57], contraceptive use in women [58], and being sedentary [59] are other lifestyle factors that have been shown to selectively raise ABP. According to some investigators [60], obesity is another determinant of higher daytime BP, but this association has not been confirmed by others [49].

Moreover, MH should be diagnosed in patients who are at increased risk of CV complications, including patients with coronary, cerebrovascular, or kidney disease, patients with diabetes and other individuals with a high CV risk profile.

2.3.6 Management and Treatment

In the absence of randomized trials, treatment recommendations might be premature. However, the existence of MH in a patient with CV risk or sign of CV damage must be an incentive to promote lifestyle recommendations and changes and even to start treatment. In any case, these patients should be closely monitored.

2.4 Conclusions

From a practical standpoint, it is much easier to suspect the diagnosis of WCHT, because patients will usually state that their BP is normal at home. In contrast, MH needs to be looked for, and there are very few clinical hints as to its presence.

A normal BP in the clinical setting does not mean that a patient is not at risk from an elevated BP, which can occur at other times of the day. This is particularly true in patients who are treated with antihypertensive drugs that do not include a full 24-h period. Because most patients take their medication in the morning, BP values in the physician's office are often normal, though they may be substantially elevated at the end of the dosing interval (i.e., during the night and early morning hours). Thus, in many hypertensive patients, clinic BP may be seemingly well controlled, but early morning BP, before the patients takes the medication, may be

elevated thereby increasing the risk of CV events. For both patient and physician, MH may become a blind spot in the antihypertensive regimen. Pickering and colleagues [60] have suggested that, for the detection of MH, home BP monitoring is likely to prove more cost-effective than ABPM.

As to the therapeutic approach, we should remember that WCHT has a benign prognosis and may often be overtreated; therefore, a conservative approach is probably justified. Conversely, MH has a more serious prognosis and is often undertreated; it deserves, therefore, a thorough evaluation and a more aggressive therapeutic approach.

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Resistant Hypertension: Epidemiological and Evolving Therapeutic Concepts

3

Guido Grassi

3.1 Introduction

Despite the emphasis given by current guidelines for the diagnosis and treatment of hypertension on the importance of blood pressure (BP) control in treated hypertensive patients, the achievement of target BP values in current clinical practice remains an unmet goal of therapeutic intervention [1, 2]. Epidemiological studies carried out in different European and extra-European countries show that no more than one-quarter or, at best, one-third of treated hypertensive patients display BP values <140/90 mmHg [3–8]. The situation is even worse when hypertensive patients require the achievement, according to the guidelines [1], of a tighter BP control, i.e., of BP values close to 130/80 mmHg. This is the case for subjects in which high BP is associated with renal insufficiency, diabetes mellitus, or metabolic syndrome, or when the cardiovascular risk profile of the patient is very high [1]. In all of the previously mentioned conditions, even when the data come from clinical trials, i.e., when both clinicians and patients are highly motivated to follow therapeutic recommendations, no more than 20–25 % of subjects display BP values in the well-controlled range [1].

Among the various conditions potentially responsible for poor BP control (Table 3.1), one is represented by the so-called *resistant hypertensive state*. According to the definition jointly provided by the European Society of Hypertension/European Society of Cardiology guidelines published in 2007, resistant hypertension is a clinical state in which "a therapeutic plan that has included attention to lifestyle measures and prescription of at least three drugs in adequate doses (including a diuretic) has failed to lower systolic and diastolic BP at goal [1]."

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Table 3.1 Factors responsible for poor blood pressure control

• Poor treatment compliance
• Insufficient use of lifestyle modifications and/or significant alcohol consumption
• Use of substances with a prohypertensive effect (cocaine, liquorice, nonsteroidal anti-inflammatory drugs, steroids)
• Sleep apnea syndrome
• Undetected causes of secondary hypertension
• Irreversible target organ damage
• Volume overload due to insufficient diuretic therapy, worsening renal failure, high dietary sodium intake and/or hyperaldosteronism

The concept of resistant hypertension has been recently modified with the introduction in the medical literature of the term *apparent treatment-resistant hypertension*, based on the notion that a poor compliance to treatment (which by definition excludes the presence of resistant hypertension) is difficult to be monitored in clinical practice and thus the word *apparent* has to be added to the term [4].

The present chapter, after briefly summarizing some general information related to the pathophysiology, prevalence, and diagnosis of resistant hypertension, focuses on the therapeutic strategies for this condition, with particular emphasis on two new promising interventional procedures, i.e., carotid baroreceptor stimulation and renal denervation.

3.2 Resistant Hypertension: Pathophysiology, Associated Clinical Factors, and Prevalence

Although there is no unequivocal interpretation of the main pathophysiological aspects of resistant hypertension, key factors appear to be a blood volume overload, triggered by excessive salt intake or, more probably, by the stimulation of aldosterone secretion, and the activation of the renin–angiotensin system (RAS) [9]. Other pathophysiological features which have received special attention in the past have included: (1) an increase in brain natriuretic peptides (2) elevated levels of atrial natriuretic peptides (3) insulin resistance, and (4) activation of the sympathetic nervous system, with the resulting increase in vasoconstrictor tone, heart rate and, in some instances, cardiac output [9, 10]. Interestingly, many of the clinical conditions linked to apparent resistant hypertension (Table 3.2) are indeed characterized by one or more of these pathophysiological alterations. This is the case, for example, when an overweight or an obese state is present, and in the case of obstructive sleep apnea, diabetes mellitus, and chronic kidney disease [1, 9].

Data on the prevalence of the disease are often different from one study to another. This heterogeneity can be explained not only by the clinical setting but also, and to a greater extent, by the inclusion in the definition of patients who are *false resistant* due to a lack of adherence to antihypertensive drug treatment, to the

Table 3.2 Clinical conditions associated with resistant hypertension

• Inadequate therapeutic approach
• Scarce use of combination treatment
• Secondary hypertension
• White coat hypertension
• Ineffective drug regimen
• Treatment compliance
• Combined conditions

incorrect use of agents at inadequate daily doses (particularly diuretics), or to medication intolerance [1, 11]. According to recent surveys, performed in European and extra-European countries, the prevalence of resistant hypertension is reported to be between 5.0 and 15.0 % [4, 9, 11–13]. This is the case for the 2003–2008 National Health and Nutrition Examination Survey in which a careful assessment of the data available identified the prevalence of resistant hypertension in about 9.0 % of patients examined [12]. This is also the case for data collected in the USA between 1988 and 2008 [4] and for the findings of the Blood Pressure Control Rate and Cardiovascular Risk Profile (BP-CARE) study carried out in Central and Eastern European countries on more than 8,000 treated hypertensive patients [14]. As it frequently happens in the diagnosis of hypertension, availability of home and ambulatory BP values allows investigators to obtain more consistent epidemiological data on the prevalence of the disease. This has been recently shown in a substudy of the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study in which the examination of clinic, home, and ambulatory BP data quantified as approximately 10 % the percentage of people with apparent resistant hypertension [15].

3.3 Diagnosis and Management of Resistant Hypertension: General Principles

Guidelines and scientific statements emphasize the importance of a correct diagnosis of resistant hypertension by excluding (1) possible causes of secondary hypertension (2) white coat or masked hypertension, and (3) poor treatment compliance [1, 11]. This can be achieved by performing an accurate collection of the patient's clinical history, by carrying out appropriate diagnostic examinations (including ambulatory blood pressure monitoring), and by accurately checking for patient adherence to the prescribed drug regimen/s [1, 11]. A further diagnostic step involves the need to accurately assess the cardiovascular risk profile. This can be performed by assessing the patient for the possible presence of concomitant cardiometabolic disease, kidney disease, and target organ damage, particularly that associated with the heart, carotid arteries, and kidney [1]. This latter approach is

particularly important for the assessment of the total cardiovascular risk profile and thus for the likelihood of developing a cardiovascular event in the future. Important prognostic information on this specific issue can be achieved by home and 24-h ambulatory BP measurement, which has been shown to be a better predictor of future cardiovascular events than clinic BP measurement [16].

The management of patients with resistant hypertension may involve a variety of interventions, such as lifestyle changes, an increase in drug dosage and/or frequency, the use of synergistic drug combinations, and the addition of diuretics and/or aldosterone antagonists. Aldosterone antagonists have been known to be effective in the treatment of hypertension for nearly half a century and their use has also long been suggested in refractory hypertension [1], though until recently they have not been used widely or recommended in standard medical texts. More recently, however, there has been increasing interest in the role of aldosterone antagonists, particularly spironolactone, in patients with refractory hypertension [17]. The data collected so far emphasize the drug's efficacy, which in some studies appears to be greater in magnitude than that achievable with the double pharmacological blockade of the renin–angiotensin–aldosterone system. In addition, in resistant hypertensive patients, spironolactone may (1) exert end-organ protection throughout BP (BP)-dependent and -independent (so-called *ancillary properties*) effects and (2) reduce the severity of sleep-apnea syndrome, which has been thought to be involved in the development of resistant hypertension. Other drugs which have been proposed for the treatment of resistant hypertension are the endothelin receptor antagonists which, although effective, may be associated with a reduced compliance to treatment and a significant side effect profile [18]. This is represented by volume retention in a large percentage (approximately 30 %) of treated patients and possibly, throughout this mechanism, exacerbation of a pre-existing heart failure state [18].

3.4 New Therapeutic Approaches

As previously mentioned, over the past two decades significant evidence has accumulated suggesting a causative or ancillary role of sympathetic neural factors in the development and progression of essential hypertension and hypertension-related cardiometabolic alterations [19]. This finding, coupled with the previously mentioned evidence that adrenergic activation is potentiated in resistant hypertension as compared to the non-resistant high BP state [10], led to the suggestion that suppression of sympathetic activity should represent one of the major goals of antihypertensive treatment [19]. Continued refinements in medical technologies have recently led to the developement of two innovative approaches aimed at obtaining an inhibition of the sympathetic cardiovascular drive, i.e., carotid baroreceptor stimulation and renal denervation [20].

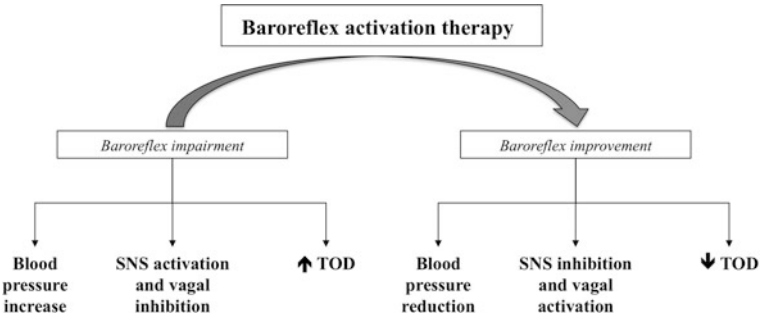

Fig. 3.1 Scheme illustrating the effects of baroreceptor stimulation. *SNS* sympathetic nervous system, *TOD* target organ damage (↑ increase ↓ reduction)

Carotid baroreceptor stimulation is based on the notion that carotid baroreceptors exert a physiological inhibition of the sympathetic drive [19], and thus that their electrical stimulation via a programmable impulse generator (the so-called Rheos device), positioned bilaterally at the level of the carotid sinuses, may reduce BP via an inhibition of the sympathetic cardiovascular drive [20]. Following some promising results obtained in three pioneering studies involving a small number of patients, two recent trials, the Device Based Therapy in Hypertension (DEBUT) and the Rheos Pivotal trial [21, 22], enrolling 45 and 265 patients with resistant hypertension, respectively, have provided conclusive evidence on the long-term effectiveness of the procedure. At the 6-month follow-up, about 40–45 % of implanted patients displayed satisfactory BP control, allowing these patients to reduce the number and/or daily dosage of the antihypertensive drugs used prior to implantation. In addition, as shown in Fig. 3.1, the procedure has been shown (1) to improve vagal control of the heart with a resulting reduction in heart rate (2) exert sympathoinhibitory effects, as documented by the decrease in directly recorded sympathetic nerve traffic, and (3) favor a regression of target organ damage, particularly that associated with the heart. These favorable results should be balanced against the evidence that the procedure is invasive and that about one-fifth of the implanted patients experienced some side effects, most of them related to the surgical and/or anesthetic intervention necessary for the implantation procedure. Future refinements in the technique will likely allow to perform a unilateral implantation of the device and thus reduce the side effect profile related to the procedure.

The other innovative approach for the treatment of resistant hypertension involves the denervation of the bilateral neural afferents and efferents innervating the kidneys [23]. Although introduced several years ago by means of a surgical approach involving total thoracic sympathectomy and splanchnicectomy for the cure of malignant hypertension, the procedure was then abandoned due to its invasiveness and an elevated number of serious side effects and even fatal events. Only in the past few years the procedure received a renewed interest due to the development of a far less invasive approach based on a radiofrequency catheter

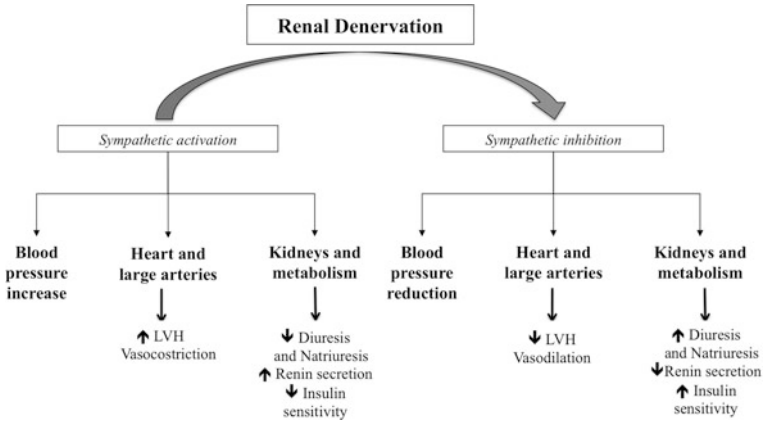

Fig. 3.2 Scheme illustrating the effects of renal denervation procedure. *LVH* left ventricular hypertrophy (↑ increase ↓ reduction)

which is capable of denervating both afferent and efferent renal nerves at the level of both kidneys. Two major clinical trials have been published so far, namely the Symplicity HTN-1 (with the so-called proof-of-principle cohort study) and the Simplicity HTN-2 [24–26]. Their principal results can be summarized as follows (Fig. 3.2). First, the procedure is safe and is not associated with any major short- or long-term complications. Second, at the 18-month follow-up, renal denervation allows to achieve BP control in about 40 % of recruited patients with documented resistant hypertension, with a substantial reduction in the total number and/or daily dosage of antihypertensive drugs used. Third, the intervention allows to reduce sympathetic activity while also ameliorating the metabolic balance of glucose and insulin sensitivity values and favoring regression of left ventricular hypertrophy [27, 28]. As in the case of carotid baroreceptor stimulation, renal denervation has a number of open questions that need to be addressed in the near future. These refer to the long-term efficacy of the intervention, the possible (though unlikely) process of kidney reinnervation and the efficacy of the procedure when the data are based on ambulatory rather than clinic BP. It is also noteworthy and worth investigating why only a subgroup of resistant hypertensive patients benefit from the procedure in terms of BP reduction and control.

3.5 Conclusions

Although overemphasized in its epidemiological aspects, resistant hypertension represents an important and not uncommon clinical state associated with an increased cardiovascular risk. Promising new pharmacological and nonpharmacological interventions will, in the near future, achieve an improvement in BP control in this condition, with favorable consequences for the overall risk profile.

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4 Primary Aldosteronism: Rare or Common Condition in Hypertensive Patients and Normotensive Individuals?

Gian Paolo Rossi, Teresa Maria Seccia and Paola Caielli

4.1 Introduction

A syndrome characterized by high blood pressure (BP), hypokalemia with metabolic alkalosis and periodic paralysis, which is corrected by the removal of an adrenal gland harboring an adrenocortical adenoma, primary aldosteronism (PA) was first described by Lityński in a Polish journal in 1953 [1], but was totally neglected by the scientific community. In 1955, Jerome Conn, an endocrinologist at the University of Michigan in the USA published a similar case in the English literature. His groundbreaking work thereafter led to the full characterization of PA, which classically entails arterial hypertension, suppressed plasma renin activity, elevated plasma aldosterone concentration (PAC), and ensuing hypokalemia [2]. Hence, the credit for the discovery of the syndrome is generally attributed to Conn [3].

An increased secretion of aldosterone that is held to be autonomous of the renin–angiotensin system (RAS) in that the secretion of renin is suppressed, characterizes PA. In the presence of a high or normal sodium intake ($\geq$6.3 g NaCl/day), hyperaldosteronism not only results in sodium and water retention and potassium loss, with ensuing hypertension, suppression of renin and hypokalemia, but also in detrimental consequences for the cardiovascular system [4–21]. These effects

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ultimately cause a high rate of atrial fibrillation, ischemic and hemorrhagic stroke [22, 23], *flash* pulmonary edema and myocardial infarction [24]. Consequently, an early and timely diagnosis of PA and its subtypes, only some of which are curable with surgery [reviewed in (25)], is of paramount importance since adrenalectomy can cure hyperaldosteronism in many patients. When surgery is not indicated, a specific drug treatment is needed to avoid the harmful consequences of PA.

Conn himself reported that PA often "masquerades as essential hypertension" and contended that he had discovered a common cause of arterial hypertension. In contrast to this, others, however, held the view that PA was extremely rare, thereby triggering a long-standing debate [2]. This debate was fueled for years by the publication of retrospective studies on highly selected cohorts, who showed a high, albeit heterogeneous, prevalence of PA, and of some epidemiological studies suggesting a very low prevalence [26]. Evidence is now available that PA is a common, albeit markedly underdiagnosed, cause of curable arterial hypertension as it will be herein reviewed.

The purpose of this chapter is to review the available information on the prevalence of PA in different populations of hypertensive patients and to briefly outline the strategy for identifying patients with PA. The approach to be exploited for the subtype differentiation of PA is beyond the scope of this chapter and has recently been described in detail elsewhere [27].

4.2 Prevalence of Primary Aldosteronism

Normokalemic PA was described by Conn as early as 1965 [28–30]; notwithstanding this, most doctors still assume that hypokalemia is a prerequisite for suspecting the disease. As a consequence of this, most doctors will search for PA only in hypertensive patients who are hypokalemic. Therefore, many normokalemic hypertensive patients who might have PA and almost all normotensive patients do not undergo any investigations to detect the disease. Accordingly, in patients with high BP, PA has probably been considerably underdiagnosed; therefore, its prevalence has been either overlooked and/or heterogeneously estimated [31]. According to a previous meta-analysis of the literature, the prevalence of PA was, in fact, reported to range from 1.4 to 32.0 % [4, 32], a very wide range of estimates, which indicates that the exact prevalence of PA was actually unknown. By contrast, among experts, the opinion that PA could be far more prevalent than usually held was diffuse [33–48]. In line with this contention, a survey carried out in the general population by general practitioners documented a high aldosterone–renin ratio (ARR) a hallmark of PA, in a proportion of hypertensive patients [49].

In 2006 the results of the largest prospective survey designed to provide solid data on the prevalence of PA, the Primary Aldosteronism Prevalence in Hypertensives (PAPY) study, were published [50]. Using a thorough workup to establish the presence of PA and to identify the PA subtype with a rigorous set of diagnostic criteria [32], the study showed that PA was present in at least 11.2 % of the 1,125

consecutive, newly diagnosed patients who were referred to hypertension centers. More importantly, the PAPY Study showed that 4.8 % of patients had a surgically curable subtype of PA. Therefore, PA was held to entail the most common curable endocrine form of hypertension in referred patients with hypertension. The high prevalence of PA documented in the PAPY Study [50] was confirmed in other surveys of selected cohorts [33, 35–45, 47–49]. Moreover, a large retrospective survey of patients with drug-resistant hypertension in Greece, who were screened for PA [51], showed that about 21 % of these patients had elevated ARR, and that at least about half of these patients unequivocally had PA as determined with several confirmatory tests, thus confirming that the syndrome is highly prevalent also among resistant hypertensive patients.

In 2008, based on the contention that an *unrecognized epidemic of PA* could be ongoing and considering the cost-effectiveness of screening, the Endocrine Society in the USA released practical guidelines for the case detection, diagnosis, and treatment of PA [52]. According to these guidelines, screening should be undertaken in some categories of hypertensive patients, including those with unexplained hypokalemia (*spontaneous* or *diuretic-induced*), drug-resistant, and grade 2 or 3 hypertension, early-onset (juvenile) high BP and/or stroke (<50 years), incidentally discovered apparently nonfunctioning adrenal mass (*incidentaloma*), and first-degree relatives of a PA patient.

This list focused exclusively on patients with severe hypertension because they are generally held to be at higher risk of having this curable cause of high BP, thus implying that patients with milder forms of hypertension and normotensive subjects should be neglected from the screening.

4.3 Primary Aldosteronism in Normotensive Subjects

In 2011, a study from Japan challenged another misbelief concerning PA, the fact that it pertains exclusively to patients with high BP and particularly those with the most severe forms [53]. Ito and colleagues found that vast proportion (18.5 %) of consecutive adult subjects undergoing a general health screening had an ARR above 20 suggesting *probable PA*. To confirm the presence of PA, they used a captopril challenge test (CCT) and claimed an overall prevalence of 3.8 %. The study also showed that the prevalence of PA was 6.8 % in prehypertensive subjects versus 3.3 % and 3.1 % in stage 1 and 2 hypertension subjects, respectively. Hence, the prevalence of PA was almost twofold higher in those with prehypertension than in those with hypertension. Even though this difference was not statistically significant, likely because of the small number of patients, these findings suggest that PA is not confined to hypertensive patients, but might be common among those with mild hypertension and even more so in subjects without hypertension, e.g., with *prehypertension*. After Conn challenging the views that PA is exceedingly rare and occurs only in hypokalemic patients, these provoking findings raise the following questions:

(1) Does normotensive PA exist also outside Japan?
(2) Given that aldosterone excess has well-known pressor effects, why is BP not raised in some patients with PA?

With regards to the first question, after the first description in 1972 of a patient with normotensive PA caused by an adrenocortical carcinoma, at least 26 other cases of normotensive PA have been reported, 85 % of which occurred in Eurasians [54]. Overall, the patients were middle-aged and predominantly (81 %) women. Although cases of normotensive PA have been described among individuals with familial hyperaldosteronism type I [54], no other familial cases of normotensive PA have been described, thus rendering a major gene effect unlikely. Severe hypokalemia and/or the presence of an adrenal tumour were suggested as clues to the diagnosis of PA in normotensive subjects. However, according to a recent report, hypokalemia would be present only in one-third of patients [54]. Since the screening was not systematically undertaken in normotensive, normokalemic subjects, the association with adrenal mass and hypokalemia might just derive from a selection bias. This implies that the disease could likely be markedly underdiagnosed because it would not even be suspected in normotensive subjects without an adrenal mass and/or hypokalemia.

The observation of these cases raises a second question: why can patients with PA be normotensive or only mildly hypertensive? A simple explanation could be that normotensive PA just entails a peculiar, possibly early, stage of the disease. Aldosterone is known to rapidly raise BP by increasing afterload via direct vasoconstriction [55], and preload via Na^+ resorption, and Na^+ and water retention. Nonetheless, when normotensive animals are infused with aldosterone, after initial Na^+ and water retention there is a rapid *escape* from these effects, which is likely due to the activation of homeostatic natriuretic and vasodilatory mechanisms, as well as to the suppression of the endogenous renin–angiotensin–aldosterone system (RAAS). In this regard, it should be remembered that the achievement and maintenance of a *normal* BP is a dynamic process: conditions or diseases that cause vasodilation and/or Na^+ wasting can lower BP and/or overcome the pressor actions of aldosterone leading to normotension, even in spite of hyperaldosteronism.

Normotensive PA could therefore be regarded as an interesting model for unraveling the protective mechanisms against hypertension in humans. Genetic susceptibility or, exposure to environmental factors, or both, can conceivably operate with different efficiency across individuals. For example, the exposure to a low Na^+ intake and/or a high consumption of green tea that lowers BP [56] can mask the BP-raising effect of aldosterone. These interactions are best testified by the occurrence of normotensive PA in patients with Bartter and Gitelman syndromes, conditions usually associated with Na^+ wasting and low BP [57]. Hence, genetic and/or environmental factors affecting the pathways through which aldosterone raises BP could explain normotension and mild BP elevation as discussed recently [54].

4.4 Screening Implications

The demonstration that PA is not confined to patients with the more severe or drug-resistant hypertension has important clinical implications in that it suggests that the screening strategy for PA should not be confined to those with severe elevation of BP.

Whether the detrimental changes involving the cardiovascular system [58], and ultimately causing an excess rate of cardiovascular events, also occur in normotensive patients with PA remains unknown. The long-term follow-up of the normotensive PA patients found by Ito and colleagues who did not have adrenalectomy might help clarify these issues. This is obviously relevant to determine if normotensive subjects should be systematically screened for PA. In the lack of this information, a reasonable trade-off between the enormous costs of a widespread screening of normotensive subjects for PA and the uncertain benefits of a timely diagnosis and treatment in normotensive subjects, could be to perform the inexpensive measurement of serum K^+ and to limit the case detection of PA to those normotensive patients who have hypokalemia. This could likely lead to underdiagnosing the normokalemic cases, but will at least allow pinpointing those who need treatment because they can be at higher risk of life-threatening arrhythmias [54]. Available data in fact indicates that in normotensive PA patients, adrenalectomy lowered BP, corrected the hypokalemia, and normalized the plasma levels of aldosterone and renin.

In summary, although it remains uncertain what the real benefits of diagnosing and treating PA in normotensive subjects could be, the acknowledgment of the existence of normotensive PA is important in drawing attention to the fact that this condition is not confined to patients with stage 2 and 3 or resistant hypertension, but occurs also in patients with stage 1 hypertension, borderline elevated BP, and even normotensive subjects.

4.5 Implications of the High Prevalence of Primary Aldosteronism in Hypertensive Patients for the Screening Strategy

The high prevalence rate of PA in referred patients with high BP has a major impact on the strategy to be used in the investigation of patients with high BP. Knowledge of the exact prevalence of the disease in the population at risk, along with the individual patient's clinical history for estimating the patient's probability, is fundamental because the incremental gain of a test is maximized when the patient's pre-test probability of a disease is between 10 % and 30 % [59]. Hence, this estimate is important for a cost-effective use of diagnostic tests: with a prevalence of PA of 11.2 % in patients with hypertension [20] and by selecting the categories of patients to be screened (Table 4.1) [53], one could select a subgroup of hypertensive subjects in whom the PA prevalence is higher and, therefore, make the screening cost-effective.

Table 4.1 Subgroup of hypertensive patients with increased chance of primary aldosteronism

- Resistant hypertension
- Grade 2 or 3 hypertension
- Spontaneous or diuretic-induced hypokalemia
- Incidentally discovered apparently nonfunctioning adrenal mass (*incidentaloma*)
- Early-onset (juvenile) hypertension and/or stroke (<50 years)[a]
- Patients with evidence of cardiovascular damage disproportionate to their BP levels
- Patients with obstructive sleep apnea syndrome
- Patients who are overweight or obese

[a] These patients may have familial type 1 hyperaldosteronism (FH-1), also known as glucocorticoid-remediable aldosteronism

The Endocrine Society guidelines [reviewed elsewhere (59)] based their suggested strategy [53] on these considerations and suggest that the screening tests should be performed only in patients with a higher pre-test probability of PA. However, given the high prevalence of PA [50] and the feasibility of preventing cardiovascular complications with an early diagnosis followed by specific treatment [60], other experts favor a wide screening strategy, such as assessing for PA all newly presenting patients with hypertension. As many clinicians feel that implementation of this broad strategy could be too challenging on the health-care systems of many countries, this remains controversial. Nonetheless, most experts agree that screening for PA is required in some categories of patients (Table 4.1), particularly if patients have resistant hypertension and are candidates for adrenalectomy. Few additional categories could be included in this list: patients with evidence of cardiovascular damage disproportionate to their BP levels, those with obstructive sleep apnea syndrome, and patients who are overweight or obese [61, 62]. Hence, overall, these categories can comprise at least 70 % of all hypertensive subjects, and therefore a wide simplified screening strategy could be exploited.

4.6 A Simplified Screening Strategy for Primary Aldosteronism

The first step for diagnosing PA requires the demonstration of an excess secretion of aldosterone that is autonomous from the RAS. The ARR has been introduced as a straightforward approach to the detection of PA [63], but its proper use requires consideration of a range of issues as discussed in detail elsewhere [27]. In essence, the ARR is a crude bivariate analysis: its value depends on the PAC and on the renin levels. Hence, very different PAC and renin values can produce the same ratio. Accordingly, the ARR will be increased even when the PAC is normal if renin is suppressed. Moreover, the assays that are currently available for measuring plasma renin activity (PRA) and direct active renin (DRA) concentration lose their precision when levels of renin are low. Because of this, to avoid overinflating the ARR when levels of renin are very low, it is common practice to fix the lowest renin value that

can be included in the ratio at a minimum (which is 0.2 ng/mL/h for PRA and 0.36 ng/mL for DRA) [32, 50]. This precaution is crucial in older patients and in people of African origin who usually have low PRA values.

The combination of an increased ARR and a PAC >15 ng/dL should therefore be used to diagnose patients with PA and should be regarded as indicative of this condition instead of using the ARR purely arithmetically. Multivariate approaches based on discriminant analysis strategies have also been proposed to achieve an accurate identification of PA [38]. These strategies use multiple variables at the same time rather than just two variables, consider their absolute values instead of their ratio, and can easily be implemented for use in commercially available worksheets for clinical decision making [38]. They have the additional advantage of providing an estimate of the individual patient's probability of developing PA, which enables clinicians to decide whether or not to proceed with further testing [50].

In the PAPY study, where the diagnosis of aldosterone-producing adenoma (APA) was used as the gold standard and the investigators used receiver operating characteristic curves and Youden's index to determine the diagnostic accuracy of the ARR, the ARR optimal cut-off was 26 [50], which corresponded to a sensitivity of 80.5 % and a specificity of 84.5 %. If the ARR is properly determined, a notably raised value is a strong indication that the patient has PA. Moreover, when repeated under carefully standardized conditions, the ARR was found to have considerable within-patient reproducibility [64]. This implies that even when the ARR values are not noticeably raised, if confirmed to be increased at retesting under proper conditions, they should be regarded as a strong indication of the presence of PA [64].

4.7 Conditions for Testing

Crucial for the success in screening for PA is a careful preparation of the patient [27]. Most antihypertensive drugs affect PAC, renin values, or both; therefore treatment must be properly modified before measuring the levels of aldosterone and renin [for a review, see (27)]. A few agents, such as the α_1 receptor blocker doxazosin mesylate and the long acting calcium channel blockers, have a minimal effect on the RAAS and consequently negligible effects on the ARR [50, 65, 66]. These agents, therefore, can be used alone or in combination to control BP during screening whenever there is a chance that interrupting antihypertensive treatment could be harmful [50], as in patients with severe and/or resistant hypertension, those with evidence of target organ damage or previous cardiovascular events. When the patient needs a stronger treatment than these agents, some hints can assist in interpreting the ARR and making the correct diagnosis, as observed in detail elsewhere [27]. The patients should be tested after they have been kept resting supine, or sitting quietly, for 1 h. A 24-h collection of urine to measure urinary sodium excretion provides an assessment of the electrolyte intake, which is crucial for a correct interpretation of the renin and aldosterone values. Similarly, a measurement of the serum potassium levels is helpful to exclude hypokalemia that, if present, reduces aldosterone secretion and thus can lead to false negative results.

By definition the screening tests must be highly sensitive to avoid missing any patients with PA. This implies that the tests often give false positive results that must be identified and excluded before selecting the patient for adrenal vein sampling (AVS). The oral sodium loading test, the saline infusion test, the CCT, and the fludrocortisone with salt loading test, are available to exclude false positive results [33, 38, 67, 68]. The purpose of these tests is to demonstrate that excess secretion of aldosterone is autonomous from the RAS. However, unfortunately these tests are often unusable, as aldosterone secretion is dependent on angiotensin not only in most patients with idiopathic hyperaldosteronism, but also in many patients with APA [69, 70]. Hence, relying on these tests can lead to missing several patients with curable APA who show suppressible aldosterone excess after blunting the levels of renin. Because of this limitation, once a markedly raised ARR (for example, higher than 100), has been found, we proceed directly with AVS if the patient is willing to pursue a surgical cure [64]. According to the Endocrine Society guidelines, AVS should be performed in all such patients to identify the side of aldosterone excess and therefore the side where to undertake laparoscopic adrenalectomy. A detailed discussion of the limitations of the so-called *confirmatory* tests for PA and for a description of the strategy for the subtyping of PA and the way to perform and interpret AVS, which is beyond the scope of this chapter, has recently been published [27].

4.8 Conclusions

Compelling evidence indicates that PA is far more common than usually perceived and that it can simulate essential hypertension in the majority of cases. This is because the classical physician-alerting sign—hypokalemia—is lacking in most cases. Moreover, recent evidence suggests that PA can be common also among normotensive and prehypertensive subjects. Hence, screening for PA is not undertaken and the diagnosis is overlooked in most cases. Undoubtedly, PA is particularly common in some categories of hypertensive patients (Table 4.1), but it should be kept in mind that it is not confined to those with severe or drug-resistant high BP.

Following a few simple rules, physicians can cost-effectively identify many patients with PA. If a unilateral cause of PA is discovered, hyperaldosteronism and hypokalemia are curable with adrenalectomy in almost all patients, and BP can be normalized or considerably reduced in a substantial proportion of them. Hence, screening for PA is beneficial, particularly when hypertension is severe and/or resistant to treatment, because removal of an APA can bring BP under control even with the withdrawal or a prominent reduction in the number and dosage of antihypertensive medications.

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Hypertension in the Very Old: Special Features, Therapeutic Approaches, and Problems

5

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5.1 Introduction

The prevalence of hypertension markedly increases with age, reaching >60 % after the age of 70 [1]. However, its biological and prognostic significance, as well as the clinical benefits of its treatment, remain complex issues. The most typical form of hypertension in older persons is isolated systolic hypertension (ISH). With aging, there is a continuous increase in systolic blood pressure (SBP), but after the age of approximately 60 there is a progressive decline in diastolic BP (DBP). Pulse pressure, defined as the difference between SBP and DBP, increases in consequence. These changes can be attributed to a progressive increase in the stiffness of large arteries [2, 3]. Pulse pressure in itself becomes a strong cardiovascular (CV) risk factor, whereas the association between mean BP and CV risk diminishes or disappears. Thus, the pathophysiology of ISH differs from that of essential hypertension in younger adults. It follows that the associated CV risks and the benefits of treatment must be verified in older hypertensive persons, and cannot be extrapolated from studies carried out in younger persons.

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Several large population studies have indicated that hypertension remains associated with an increased risk of stroke and coronary heart disease (CHD) even in old age. Key studies carried out in patients with ISH, in particular the Systolic Hypertension in the Elderly Program (SHEP) and Systolic Hypertension in Europe (Syst-Eur) trials, have convincingly shown that antihypertensive treatment decreases the risk of stroke and heart failure, although the reductions in the risk of CHD were disappointing [4, 5]. However, these studies were not performed in very old patients (mean age: approximately 70).

More recently, the Hypertension in the Very Elderly (HYVET) study, performed in patients >80 years old, has confirmed that antihypertensive treatment decreases the risk of stroke and heart failure. The study also demonstrated a reduction in all-cause mortality. This was particularly important, as previous non-controlled trials or subgroup analysis of controlled trials had suggested that antihypertensive treatment increases mortality in patients >80 years old. The results of the HYVET study were impressive enough to lead to the premature interruption of the trial on ethical grounds [6]. Taken together, these results suggest that essentially all patients with hypertension should receive treatment, which represents a formidable challenge in terms of both resource allocation and safety. The aim of this chapter is to discuss some of the issues related to patient selection, safety, and clinical relevance of antihypertensive treatment.

5.2 The Diagnosis of Hypertension

ISH is usually defined by a SBP >140 and a DBP <90 mmHg. However, the measurement of blood pressure is hampered by considerable between-measure variability and by the *artifactual* increase in BP when measured in a medical office, the so-called *white-coat effect*. It follows that many patients with an office SBP >160 mmHg in fact do not present with true hypertension. The problem of white-coat hypertension and therefore possible patient misclassification worsens with age. In a hypertension clinic, we found that the difference in SBP between office measures and ambulatory blood pressure monitoring (ABPM) is considerable at all ages and reaches approximately 40 mmHg in patients >80 years old [7]. A substudy of the Syst-Eur trial investigated clinical outcomes according to BP measured by ABPM. Less than 25 % of patients had sustained hypertension, defined as a mean SBP >160 mmHg by ABPM. Importantly, the benefits of treatment could be demonstrated only in this subgroup [8]. This study suggested that even in large intervention trials many patients included actually present with white-coat hypertension rather than true ISH. These considerations suggest that the diagnosis of ISH should be confirmed either by ABPM or BP monitoring at home, before engaging in a possibly lifelong treatment.

5.3 Blood Pressure Targets in Antihypertensive Therapy

The selection of optimal blood pressure targets in antihypertensive therapy still remains an area of uncertainty. The evidence from randomized controlled trials remains sketchy and different targets may apply in different age groups. A recent US consensus statement proposes a SBP <140 and a DBP <90 mmHg as general targets, while recognizing the arbitrary character of this recommendation [9]. However, as mentioned, the main inclusion criterion in the most relevant clinical trials was a SBP >160 mmHg [4–6]. The SBP achieved with therapy after 1 year was approximately 145–150 mmHg in both the Syst-Eur and the HYVET studies [4, 6]. Thus, the clinical benefits of treatment in these studies were obtained with higher SBP pressure values than recommended in the US consensus statement. It is quite possible that achieving lower SBP values may lead to even better clinical outcomes, but there is little evidence in support of this hypothesis so far. Conversely, intensive treatment targeting lower SBP values is likely to be associated with a higher incidence of side effects. There are few studies on the incidence of antihypertensive drug side effects in geriatric populations. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study in diabetic patients (mean age: 62.2 years) compared standard and intensive BP treatment strategies [10]. The intensive strategy did result in lower SBP values (119 compared to 133 mmHg) and in a somewhat lower incidence of stroke. However, it was burdened by a higher incidence of severe side effects (3.3 vs. 1.3 %), stage 3 chronic renal failure (4.2 vs. 2.2 %), and hypokalemia (2.1 vs. 1.1 %). It is likely that the incidence and severity of complications of intensive therapy would be much higher in frail, geriatric patients. Indeed, patients >80 years of age account for more than half of adverse drug events requiring hospital admission [11]. For instance, the risk of severe hyponatremia due to diuretic therapy is not well known, but may be substantial in patients with multiple comorbidities. While awaiting further evidence, it seems reasonable to propose a SBP value of 150 mmHg both for the diagnosis of ISH, and as a target for therapy in patients >80 years of age. We have insisted on the importance of confirming the diagnosis by ABPM or by BP monitoring at home. Somewhat lower SBP cut-off values for the diagnosis of ISH, 135–140 mmHg, must be applied using these methods.

5.4 The Role of Associated Risk Factors

In young adults, hypertension is often evaluated in the context of metabolic syndrome. Metabolic syndrome represents a cluster of risk factors including diabetes and/or glucose intolerance, dyslipidemia, obesity and/or insulin resistance, and hypertension [12]. The metabolic syndrome concept recognizes that these risk factors are clustered, with obesity as a common denominator. It also emphasizes that weight loss should have favorable effects on associated risk factors, including hypertension [13]. However, several studies have shown that the prognostic

significance of metabolic syndrome markedly decreases with age [14–16]. The prognostic significance of obesity itself actually declines with age [17], and there may even be an inverse association between obesity and mortality in very old populations [18, 19]. It is not surprising that metabolic syndrome is no longer a risk factor in older persons when obesity, its key component, ceases to be one. The interdependence of risk factors composing metabolic syndrome also declines with increasing age [7]. These considerations indicate that metabolic syndrome or its components should not be used to stratify CV risk in older patients, and to *modulate* the indication for antihypertensive therapy. Further, there is neither theoretical support nor clinical evidence for the notion that weight reduction may improve blood pressure in older hypertensive patients.

The interaction between diabetes and hypertension is an important issue. Both the SHEP and the Syst-Eur trials have shown that antihypertensive treatment leads to spectacular reductions in the risk of CV events, in particular stroke, in diabetic patients [20, 21]. Such a subgroup analysis has not been reported for the HYVET study, possibly because of the low number of diabetic patients in this study. Antihypertensive treatment is clearly a priority in the management of older persons with diabetes [22]. However, in view of the data from the ACCORD study discussed previously, we do not believe that the presence of diabetes justifies lower SBP targets than in older nondiabetic patients.

5.5 The Risk of Orthostatic Hypotension

The prevalence of orthostatic hypertension (OH) (−20 in SBP or −10 mmHg in DBP in the upright position) in unselected subjects, aged 65 years or older, has been reported to vary widely between 5 and 30 % [23–25]. In a recent study in a population of 1,100 subjects over 80 years old living in nursing homes, the prevalence of OH was 18 % [26]. This value is similar to those reported for community-living older populations [27], but it is lower than that obtained for older people living in nursing homes, in which a prevalence higher than 30 % was reported [23]. A number of factors account for these discrepancies in prevalence values, including the definition of OH, the characteristics of the population studied (age range, institutionalized, or home-living), the composition of the population, and the influence of medication. Arterial stiffness, which underlies ISH, may also determine poor baroreceptor function and therefore contribute to the pathogenesis of OH [28]. Thus, arterial stiffness may determine both ISH and OH, and OH may be related to ISH rather than to its treatment. Drug-induced OH and a possible increase in the risk of falls is a common concern when treating hypertension in older persons. However, this concern is hard to substantiate.

In a large population study conducted in older British women, the prevalence of OH was elevated in subjects taking three or more antihypertensive drugs compared to those taking none. The association between antihypertensive drug prescriptions and OH was quite weak (hazard ratio = 1.26), and became nonsignificant after

adjustment for other drug prescriptions or comorbidities, the latter being by themselves associated with OH [29]. Recent studies on older patients in the hospital or nursing home setting have shown that antihypertensive treatment is not associated with a higher prevalence of OH [26]. We have recently shown that in older subjects over 80 years old, those who had well-controlled hypertension with antihypertensive medication had lower prevalence of OH when compared to the other groups of subjects [26]. According to a recent meta-analysis, the association between antihypertensive drugs and the risk of falls is weak or even questionable, and certainly much weaker than the risk associated with most psychoactive drugs [30]. Thus, antihypertensive treatment should be closely monitored for OH, especially when multiple or combined drugs are prescribed. However, the risk of OH in itself should only rarely deter from treating hypertension. Parkinson's disease is a special situation (not discussed in this chapter) where frequent, and often severe, preexisting OH is a serious limitation to the treatment of hypertension.

5.6 Hypertension and Cognitive Function

Aging is accompanied by an increasing prevalence of hypertension and cognitive decline and many cohort studies have in effect shown hypertension as a major risk factor for the occurrence of cognitive impairment in the old. The prevention of cognitive decline and dementia has become a major public health challenge in view of the increased longevity of the population. In this context, the discussion about a role of arterial hypertension that is potentially modifiable in the development of cognitive decline is a major issue in both research and clinical practice and a promising target for dementia prevention.

It was shown that hypertension can contribute to several cardiovascular alterations which are associated with impaired cognitive function and dementia. Although hypertension is one of the main risk factors for cerebrovascular disease, the relationship between BP levels and cognitive impairment is controversial. In the Framingham Heart Study, a high BP detected 20 years previously was inversely related with cognitive performance among untreated hypertensive subjects [31]. Since this initial observation, most epidemiological studies have confirmed the relationship between hypertension and cognitive decline. Hence, the Honolulu-Asia Aging Study (HAAS), which followed 3,735 subjects for over 30 years showed that the risk of cognitive decline at age 78 increased with the level of systolic BP measured 25 years earlier [32]. Longitudinal follow-up of patients with hypertension showed that hypertension was associated with a greater number of dementia cases observed 10–15 years later [33]. Even on a shorter follow-up period of 4 years, the Epidemiology of Vascular Aging (EVA) study found the risk of cognitive decline greater among patients with untreated chronic hypertension (odds ratio = 6) compared to a normotensive group [34]. However, this relationship between BP levels and cognitive decline in older populations was

not found in many cross-sectional studies [35–37]. Moreover, hypertension duration, antihypertensive treatment, BP levels, cognitive profile and tests, and differences in the tested population, may contribute to explain the discrepancy about the relationship between hypertension and cognitive decline.

The question whether the treatment of hypertension prevents cognitive impairment and dementia is even more controversial. Some clinical trials demonstrated the beneficial effect of the use of antihypertensive therapy on the incidence of dementia. In the Syst-Eur trial, older people with ISH receiving a calcium channel blocker (nitrendipine) had a lower incidence of dementia [38]. In the 6,105 randomized participants in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), active treatment (perindopril for all and indapamide, a diuretic drug for those with neither an indication for, nor a contraindication to diuretics) was associated with reduced risks of stroke-related dementia and cognitive decline only in those with recurrent stroke [39].

However, the preventive effectiveness of antihypertensive therapy in the development of cognitive impairment remains controversial, since such effectiveness was not found by other studies. No protective effect of a thiazide diuretic on cognitive decline was found in the SHEP study, despite a reduction in blood pressure and a lower risk of stroke [5]. The Study on Cognition and Prognosis in the Elderly (SCOPE) [40] did not find any convincing evidence, in older hypertensive patients, that antihypertensive treatment confers a reduction in cognitive decline during angiotensin receptor blocker therapy, compared with control therapy. Cognitive function was well maintained in both treatment groups in the presence of substantial blood pressure reductions. A meta-analysis including the SCOPE, SHEP, and Syst-Eur studies suggested no convincing evidence that BP lowering in late life prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease [41]. In the first published results from the HYVET study, a double-blind, placebo-controlled trial of indapamide, with or without perindopril, in people aged 80 years and over at enrolment, antihypertensive treatment in older patients did not significantly reduce the incidence of dementia. Nevertheless, a meta-analysis (including the HYVET findings) supported the conclusion that antihypertensive treatment may potentially reduce the incidence of dementia [42]. In the secondary analysis of HYVET, a dynamic model of cognition that allows all outcomes (cognitive worsening, stability improvement, or death) to be categorized simultaneously detected small but significant benefits of the treatment [43].

The relationship between hypertension and cognitive function is probably more complex than a simple linear relationship, leading us to suggest that a midlife BP level is more important as a risk factor for late-life cognitive impairment and dementia than the BP levels evaluated in late life. Moreover, the hypothesis of a vascular involvement independent of BP level has been raised. Although BP levels can be decreased by antihypertensive therapy, vascular alterations (caused in part by hypertension) in a protracted, decade-long process are less sensitive to antihypertensive therapy in late life because they are already too far advanced before such intervention. Some studies show that markers of arterial aging may identify

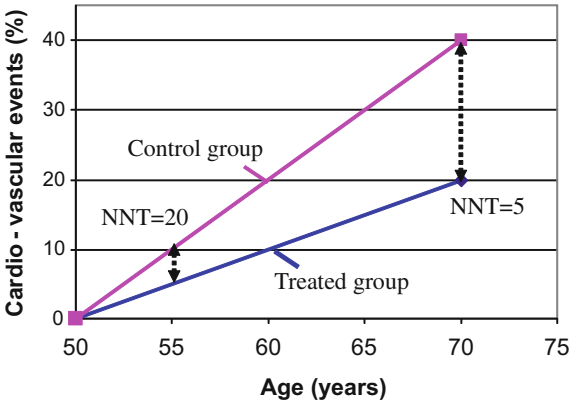

Fig. 5.1 A hypothetical model of the effect of treatment duration on clinical outcomes. *NNT* number needed to treat

subjects at higher risk for cognitive decline, while BP alone does not appear to have a significant predictive value [37, 44, 45].

5.7 The Decision-Making Process in the Initiation and Follow-Up of Antihypertensive Therapy

Many patients may be reluctant to accept treatment, even when its benefits are clearly supported by clinical trials. There are few studies on patient drug observance in old age, but it seems obvious that patients' initial acceptance and long-term observance are management issues that do not get simpler with increasing age. Beyond initial acceptance and implementation, antihypertensive treatment implies follow-up appointments, adjustments in drug schedules, and the burden of possible side effects. It seems logical to assume that patients' observance and even safety are better when they are involved in the treatment and convinced of its benefits. Even when statistically significant, the benefits of a given treatment, in the patient's view, may be insufficient to warrant the effort. Physicians themselves may not always be convinced that the benefits of treatment are clinically relevant.

Evidence from randomized clinical trials (RCTs) is typically based on observations lasting <5 years, whereas treatment is theoretically lifelong. In younger adults, we make the assumption that the benefits of treatment observed in RCTs persist in a linear manner over time. However, although life expectancy in older persons is easily underestimated, it is an inescapable reality that the older the patient, the shorter the available time for treatment. Let us illustrate the issue (see Fig. 5.1) with a hypothetical population aged 50–60 years, with a CV risk of 20 % over 10 years; this risk is reduced by 50 % by treatment. In this case, the number needed to treat is 20 over 5 years. If the treatment is pursued over 20 years

(and assuming linear benefits), the number needed to treat decreases to 5 over 20 years, undisputedly a very significant benefit . Such a benefit is not a realistic expectation in older subjects. Thus, even if the risk reduction afforded by treatment *per time unit* is larger in older subjects, a shortened life expectancy may limit the true benefit of treatment. It follows that the decision to treat hypertension must reach a balance between the evidence from RCTs, the physician's clinical judgment (including priority and safety issues), and the patient's willingness to initiate and continue such a treatment.

We undertook a study to determine patients' willingness to accept antihypertensive treatment and their desire to participate in the decision-making process [46]. Patients received standardized explanations about the outcomes, benefits, and risks of treatment; they were then asked whether they were willing to accept treatment in different scenarios, with varying risks, risk reductions, and incidence of side effects. Only a small minority of patients (4–7 %) clearly refused treatment. The majority of patients seemingly accepted antihypertensive therapy, but in fact appeared uneasy with the complex reasoning about hypertension. Most patients wanted extensive medical information, but only limited, variable participation in decision-making. They appeared to prefer delegating final medical decisions; nonetheless, they wanted to be informed and wanted their general attitudes to be taken into account.

The patients' preferences—and reluctance—must be understood and dealt with before taking the decision to treat—or not to treat. Initial acceptance does not mean that patients understand and accept long-term therapy. A shared treatment plan, which favors safety and compliance, requires detailed explanations not only at initiation but also repeatedly during follow-up.

5.8 Blood Pressure and Reverse Causality

Several studies have challenged the classical association between hypertension and CV or all-cause mortality in the very old, and even observed inverse associations between both SBP and DBP and mortality [47–50]. A Dutch study in a community-dwelling population aged >85 years suggested that the inverse association between SBP and mortality disappears after adjustment for comorbidities [50]. A decline in BP over time in older hypertensive subjects is common and has even been observed in the control group of the HYVET study. This decline has been associated with increased mortality [51, 52]. BP may decrease as a result of incident heart failure or other comorbidities. However, a recent retrospective study in diabetic patients has shown that blood pressure decreases in the 4 years preceding death, more rapidly than in surviving age-matched patients, and that this observation is not accounted for by age, sex, race, medications, and comorbidities [52]. Reduced blood pressure may also be associated with features of malnutrition, such as reduced salt intake or weight loss. Being overweight and/or obese is associated with elevated blood pressure via multiple mechanisms including

hyperinsulinemia or insulin resistance, hyperleptinemia, and activation of the hypothalamic melanocortin system [53]. Weight loss could possibly lower blood pressure by antagonizing these mechanisms. Irrespective of the underlying mechanism(s), when a decreasing BP is a marker of declining health, a high BP may become a marker of good health in a phenomenon of reverse causality. In the presence of arterial stiffness, declining BP may further decrease an already low DBP, which in turn leads to lower coronary perfusion [54]. Patients with *former hypertension* may carry a worse prognosis than those with *stable* hypertension while being classified as nonhypertensive, thus confusing the classical association between BP and mortality. Of particular interest, this reverse relationship between BP and mortality is observed in very old and/or frail and polypathological, polymedicated subjects. Alternative approaches for the estimation of CV risk in these subjects, such as direct measurements of arterial functional properties could actually provide better information [55].

The inverse epidemiological association between BP and mortality should not lead to the denial of the benefits of antihypertensive therapy documented in clinical trials. However, the issues of reverse causality confuse the risk stratification according to BP. The progressive decline in BP over time in older patients also suggests that the requirements for antihypertensive treatment may decrease over time. In our view this issue clearly deserves more attention from both clinicians and researchers. Strategies for verifying whether a given treatment remains appropriate over time would be welcome. For the time being, adhering to blood pressure targets—and avoiding going much lower—is probably the best way to avoid overtreatment, not only at the initiation of therapy, but also during follow-up. Unfortunately, precise guidelines cannot be proposed, as there is no simple lower BP threshold below which treatment reduction should always be attempted. Another important issue is the management of putative drug side effects. If faced with a putative drug side effect, it may be quite rewarding to stop the drug rather than to replace it, and to add a new one only if the SBP rises again above targets.

5.9 Conclusions

The treatment of arterial hypertension is a key strategy for the prevention of stroke and heart failure even in very old hypertensive patients. However, it is a challenging public health task given the sheer number of patients, the complexity, duration, and cost of treatment, and safety issues. To avoid overtreatment, it is important to confirm the diagnosis with ABPM or by BP monitoring at home. A systolic BP of 150 mmHg is an acceptable cut-off value both for the diagnosis of hypertension and as a target for treatment in most patients >80 years old. Avoiding *going too low* is important for treatment safety. Treatment should be initiated and followed up in a shared decision-making process, taking the patients' preferences into account. These strategies will help to ensure treatment adequacy and safety. Conversely, the fear of drug-induced OH should in itself only rarely be

a reason not to treat. The possibility that the prognostic value of high BP and the benefits of antihypertensive drugs decrease in very old and frail subjects must be kept in mind. Such a decrease may render patients more vulnerable to drug side effects. Avoiding *going too low* is important not only at the initiation of therapy, but also during follow-up.

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Part II

Ambulatory Blood Pressure in Clinical Practice: Clinical Relevance of Circadian Rhythm and Nocturnal Dip

6

Josep Redon and Fernando Martinez

6.1 Introduction

Blood pressure (BP) is one of the most important cardiovascular risk factors; a relationship between BP values and cardiovascular and renal risk has been well established [1]. Thirty years ago, the introduction of methods to assess BP automatically during daily life represented a new dawn in the field of hypertension [1]. Today, ambulatory BP monitoring (ABPM) is a tool available not only in specialized clinics but also in many sectors of primary care. A large number of studies have demonstrated the improved reproducibility and the prognostic superiority of BP values obtained using ABPM when compared to BP values obtained from standard clinical/office measurements. The prognostic value of ambulatory BP (ABP) for the general population was then transferred to hypertension in general, as well as for specific conditions such as refractory hypertension, diabetes, chronic renal insufficiency, and pregnancy [2]. Based on outcome and epidemiological studies, reference values for ABP have been recommended, even though limitations about their precision remain and, despite the large amount of research done in the past, some unmet needs and unanswered questions remain.

Beside the average of BP values, the description of the different components of BP variability and their relationship with the presence of hypertension-induced organ damage, their prognostic value, and the possibility of being able to modify antihypertensive treatment have received increased attention. One of the more extensively analyzed components of BP variability is the fluctuation of BP

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throughout the 24-h period, the so-called circadian variability. Terms like *dipper* and *nondipper* are now common in daily practice [3]. In this chapter, BP circadian variability is analyzed in terms of its components and determinants, its impact on hypertension-induced organ damage, and its prognostic value. The controversy about what is most important, either the nondipping pattern or nocturnal BP values, are also addressed.

6.2 Circadian Variability of Blood Pressure

6.2.1 Definition

Under normal conditions, there is a physiological nocturnal BP drop during sleep. The extent of the BP drop achieved is more than 10 of the BP values obtained during the awake period; a significant diurnal BP rhythm is observed in most normotensive subjects and in 80 of stage 1 essential hypertensives. Subjects with a blunted nocturnal drop, i.e., less than a 10 % drop, or those who register even higher BP values during the night than during the day are called *nondippers* and *risers,* respectively.

When defining circadian variability, the correct time period should be considered, as well as the appropriate awakening and sleep time periods. Among the methods used to establish such time periods so as to arrive to the most precise definition for each individual component is obtained by simultaneously recording BP values and the level of activity using an ActiGraph activity monitor (ActiGraph, Pensacola, Florida USA) or similar [4]. Although used in research, it adds complexity to routine application in daily practice. Asking patients to record the time they go to bed and the time they wake up in a mini diary is also frequently used. Restricted time periods that avoid transitional hours, for example, 06:00–08:00 and 22:00–24:00, are frequently used and the results do not differ from when a more precise definition is used [5].

The poor reproducibility over time of the classification of hypertensive patients into dippers and nondippers based on single ABPM has been recognized [6, 7]. In about one-third of patients the dipping pattern is not reliable since dipping status is not confirmed by repeated ABPM monitoring. However, intrasubject *variability* within a variable circadian pattern is lower under certain conditions, with a high prevalence of nondipping patterns, such as chronic kidney disease with reduced glomerular filtration or diabetes. Therefore, classification of the dipping status of hypertensive patients based on a single ABPM recording is more reliable in chronic kidney disease and diabetes than in subjects with normal renal function or nondiabetic subjects [8].

6.2.2 Mechanisms

There are several *mechanisms* underlying the abnormalities of circadian variability. Although BP drops during sleep, this is mainly dependent on a reduction in the *sympathetic drive*. Persistence of sympathetic drive and other factors can contribute to reduce the sharp drop in BP during the nighttime, thereby resulting in the persistence of higher BP values during sleep [9]. Such factors importantly include the reduced sensibility of *baroreceptors* and *volume overload* [10]. Persistence of the sympathetic overdrive during the resting period is observed in a large proportion of hypertensive subjects and as a consequence of several clinical states such as sleep-apnea syndrome [11]. Baroreceptors reduce the sympathetic tone and increase the parasympathetic tone when BP increases [12]. A reduction in parasympathetic tone has been described in subjects where a nocturnal dip is absent. Volume overload, as it is the case with primary aldosteronism, advanced renal failure, or intermittent volume increment after recumbence due to the reabsorption from the extravascular space, may also contribute to keeping BP values high [13]. In addition, primary or secondary *autonomic dysfunction* results in higher BP when in the supine position, thereby also producing a nondipping pattern [14]. The impact of each of the components in an individual subject differs, with the predominance of one or the other mechanism according to the specific clinical condition. Then, the absence of a normal nocturnal dip implies the existence of abnormalities in the regulatory mechanisms of BP, such abnormalities being frequently associated with underlying organ damage. As a consequence, sustained high BP values overload the vascular tree and impact susceptible organs.

6.2.3 Factors Related to Nondipping Status

The amount of nighttime BP drop has been linked to the absolute level of BP elevation, to global cardiovascular risk [15], the presence of *comorbidities* [16, 17], and the type and time of administration of *antihypertensive treatment* [18]. Data from a large database analyzing more than 44,000 subjects, revealed that factors independently associated with *nondipping* status included advanced age, female gender, nonsmoker status, obesity, dyslipidemia, *diabetes*, BP severity, the presence of target-organ damage, and overt cardiovascular disease [19, 20].

A factor that has frequently been missed is antihypertensive treatment. Usually, antihypertensive treatment reduces BP according to pretreatment BP values, therefore, the higher the BP the higher the reduction. Indeed, a reduction in BP when a subject is active is higher than when they are sleep, decreasing the BP differences between activity and sleep and the BP day-to-night ratio, thereby increasing the probability of a nondipping pattern. Therefore, evaluating circadian variability while subjects are receiving antihypertensive treatment does not always have the same significance than the circadian variability observed in untreated subjects. The significance of *nondipping* status in hypertensive subjects under treatment should then be considered separately (see later on in the chapter).

6.3 Abnormalities in Circadian Variability and Hypertension-Induced Organ Damage

Apart from the fact that the nondipping pattern is associated with underlying organ damage in hypertension, persistence of high BP during the resting period contributes to increases in cardiac load, macro- and microvascular wall stress, and renal dysfunction. In some cases, higher BP values during the night time may contribute to the progression of *organ damage*, while in other cases such high values are but a consequence of the underlying damage itself [21].

The kidney is particularly susceptible to sustained levels of high BP during sleep. Glomerular capillary hypertension and hyperperfusion are the important factors leading to glomerular damage and the progressive loss of renal function. The increase in afferent arteriolar resistance is part of a compensatory mechanism which prevents the transmission of increased preglomerular pressure to the glomerular capillary network [22]. This autoregulatory response, when impaired, as in the diseased kidney, allows increased systemic pressure to be transmitted without restriction to the glomerular and peritubular capillaries. Increased glomerular capillary pressure results in an increased glomerular filtration rate for each individual nephron, an increased transglomerular passage of proteins, and an increased influx of proteins and other macromolecules into the mesangium, favoring the development of glomerulosclerosis. Further interstitial damage may result from increased pressure in the peritubular capillaries, due to the impaired autoregulatory mechanisms. This is more evident in the nephrons of the deeper, juxtamedullary regions of the kidney. Elevations in BP have been shown to raise peritubular capillary and interstitial pressure in this region. Increased interstitial pressure would, in turn, be transmitted throughout the renal parenchyma [23].

6.4 The Prognostic Value of Abnormal Circadian Variability

Subjects with a blunted BP drop (<10 %), or even those with an increase in BP at nighttime, are those who present with a worse cardiovascular prognosis. From when an abnormal circadian BP profile was first associated to an increased risk of stroke, subsequent studies of populations and hypertensive cohorts generally corroborated that raised nocturnal BP predicted a higher rate of cardiovascular complications. The prognostic value of abnormal circadian variability was also observed for BP values related to sleep, though discrepancies have been observed among the different studies that have focused on this issue.

6.4.1 General Population

The relationship between a normal nocturnal drop in BP and the risk of cardiovascular mortality in individuals with and without high 24-h BP values was evaluated in 1,542 residents of Ohasama, Japan, who were aged 40 or more

representative of the Japanese general population, during a follow-up period of 9.2 years. There was a linear relationship between a nocturnal drop in BP and cardiovascular mortality. On average, each 5 mmHg decrease in nocturnal systolic/diastolic BP was associated with an approximately 20 % greater risk of cardiovascular mortality. There were no significant interactions for the risk between 24-h systolic/diastolic BP values and continuous values for the nocturnal drop in BP. Even when 24-h BP values were within the normal range (135/80, average 118/69 mmHg), reduced nocturnal drops in systolic/diastolic BP were associated with an increased risk of cardiovascular mortality [24, 25].

6.4.2 Hypertensive Subjects

The stroke events in 575 older Japanese patients with sustained hypertension determined by ABPM were evaluated. They were subclassified according to their nocturnal systolic BP drop (97 extreme dippers, with ≥20 % nocturnal systolic BP drop; 230 dippers with ≥10 % but <20 % drop; 185 nondippers with ≥0 % but <10 % drop; and 63 reverse dippers, with <0 % drop in BP) and were followed prospectively for an average duration of 41 months. Baseline brain magnetic resonance imaging showed that the percentage with multiple silent cerebral infarction were 53 in extreme dippers, 29 in dippers, 41 in nondippers, and 49 % in reverse dippers. There was a J-shaped relationship between dipping status and stroke incidence (extreme dippers, 12; dippers, 6.1; nondippers, 7.6; and reverse dippers, 22 %), and this remained significant after a Cox regression analysis, controlling for age, gender, body mass index, 24-h systolic BP, and antihypertensive medication. Intracranial hemorrhage was more common in reverse dippers (29 of strokes) than in other subgroups (7.7 % of strokes, $p = 0.04$). In the extreme dipper group, 27 % of strokes were ischemic strokes that occurred during sleep (versus 8.6 % of strokes in the other three subgroups, $p = 0.11$). The authors concluded that extreme dipping of nocturnal BP may be related to silent and clinical cerebral ischemia through hypoperfusion during sleep or an exaggerated morning BP surge, whereas reverse dipping may pose a risk for intracranial hemorrhage [26].

Whether or not the benefits of antihypertensive treatment vary according to dipper status was analyzed in 811 asymptomatic older Japanese hypertensive subjects who underwent 24-h ABPM for a mean follow-up period of 41 months. The study found that in established hypertension, antihypertensive therapy using clinic/office BP may be less effective for the groups with extremely abnormal diurnal BP patterns, extreme dippers and reverse dippers, than those with relatively normal patterns [25]. The degree of night BP decline was also associated with reduced prognostic value [27, 28].

6.4.3 Sleep-Apnea Syndrome

A small study of 50 men analyzed the prognostic value of the nocturnal dip in the development of cardiovascular events during a 7–9 year follow-up of men with

mild-to-moderate essential hypertension. During the follow-up, 16 cardiovascular events in 12 patients were documented (three fatal and 13 nonfatal). An insufficient nocturnal drop in systolic BP (<10 %) was an adverse prognostic factor for cardiovascular morbidity in mild-to-moderate essential hypertensive subjects [29].

6.4.4 Chronic Renal Failure in Hemodialysis

Lack of nocturnal BP drop is common among hemodialysis patients, but very little is known regarding its association with cardiovascular disease morbidity and mortality, these being the leading causes of mortality in hemodialysis patients. Although the role of arterial hypertension in the prognosis of cardiovascular disease in hemodialysis patients is not as clear as in the general population, high BP is a contributor. One study demonstrated the importance of BP circadian variability. Compared with dippers, nondippers initially had a higher incidence of coronary artery stenosis ($p < 0.05$) along with left ventricular asynergy (both p values <0.01). The circadian rhythm of autonomic function was impaired in nondippers. The incidence of cardiovascular events and cardiovascular deaths was 3.5 and 9 times higher in nondippers than in dippers [30].

6.4.5 Pregnancy

One study analyzed the prevalence of hypertension during sleep in preeclampsia and gestational hypertension, and whether women with hypertension during sleep have worse pregnancy outcomes than hypertensive pregnant women with controlled normal BP during sleep. In a study of 186 hypertensive pregnant women, maternal and fetal outcomes were compared between women with and without sleep hypertension and the prevalence of sleep hypertension was determined. Sleep hypertension was present in 59, more commonly in preeclampsia (79) than in gestational hypertension or essential hypertension (45 %). Sleep hypertensive subjects had a significantly greater frequency of renal insufficiency, liver dysfunction, thrombocytopenia, and episodes of (awake) severe hypertension ($p < 0.05$), as well as lower-birth-weight babies. Hypertension during sleep is a common finding in women with hypertensive disorders associated with pregnancy, particularly preeclampsia [31].

6.5 Prognostic Value of Nocturnal Blood Pressure

A large number of studies demonstrated that nocturnal BP values have a better prognostic value that their diurnal counterparts or than the day-to-night ratio.

6.5.1 General Population

The Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study of the general population, the placebo arm of the Systolic Hypertension in Europe (Syst-Eur) trial and other studies in hypertensive subjects agreed on the superiority of nocturnal BP over other parameters [32].

6.5.2 Hypertensive Subjects

The prognostic significance of nighttime and daytime ambulatory BP and their ratio for mortality and cause-specific cardiovascular events in hypertensive patients without major cardiovascular disease was analyzed, pooling data from four studies collecting data from 3,468 patients. Daytime and nighttime systolic BP predicted all-cause and cardiovascular mortality, coronary heart disease, and stroke, independently from office BP and confounding variables. When these BP values were entered simultaneously into the models, nighttime BP predicted all outcomes, whereas daytime BP did not add prognostic precision to nighttime BP. The results were similar in men and women, in younger and older patients, and in treated and untreated patients [33]. In the placebo arm of the Syst-Eur trial, nocturnal BP had a higher prognostic value when compared to diurnal BP [34]; this was also found in a population based-study [35].

6.5.3 Chronic Kidney Disease

Amar and colleagues [36] investigated the prognostic role of ambulatory BP in cardiovascular mortality in 57 subjects during a 34-month follow-up period. After adjustment for age, sex, and previous cardiovascular events, the study demonstrated that nocturnal BP and 24-h pulse pressure are independent predictors of cardiovascular mortality in treated hypertensive hemodialysis patients. Likewise, in patients with stage 3/4 chronic kidney disease, we found that nocturnal systolic BP was a predictor of progression to end-stage renal disease or death, with a nocturnal systolic BP $>$ 130 mmHg doubling the risk of the combined endpoint, compared to a nocturnal systolic BP $<$ 120 mmHg [37].

There is currently no clear explanation as to why nighttime ABP would be a better predictor of outcome than daytime ABP, but several factors could be involved. BP is more variable during the day than during the night because of physical and mental activity, so it is possible that intermittent BP measurements may not completely capture the true average daytime ABP. Likewise, nighttime BP is likely to be more stable so that intermittent BP measurements may be more representative of the true nighttime average BP. Moreover, BP during sleep is more closely related to basal BP, which has been shown to predict life expectancy better than casual BP. Finally, nighttime ABP may be influenced by sleep apnea in

some patients, which is associated with a worse prognosis. Another possible explanation for the observed superiority could be the result of a mathematical artifact. Distribution of BP values at night is narrower than that observed for daytime BP values and as a consequence the regression line generated with these can result in a steeper line.

6.6 Nondipping Versus Nocturnal Blood Pressure

The relative importance of circadian variability or nocturnal BP as a prognostic factor raises not only academic interest, but also clinical utility [38]. The potential prognostic value for cardiovascular and renal disease has been outlined. This has been demonstrated also in the earlier stages of organ damage. Both a nondipping pattern and nocturnal BP values have prognostic value with regard to the development of early renal damage [39, 40].

One thing is to assess prognosis while another is to consider which of the two parameters should be considered as a target of antihypertensive treatment: reversing circadian variability or reducing sleep BP values?

The International Database of Ambulatory BP in relation to Cardiovascular Outcome (IDACO) consortium compared the prognostic value of abnormal circadian variability and BP in the different time periods for cardiovascular events [41]. The predictive accuracy of daytime and nighttime BP values and the night-to-day BP ratio were dependent on the outcome under study. For fatal end points, nighttime BP did better than daytime BP and the night-to-day ratio predicted total, cardiovascular, and noncardiovascular mortality. In contrast, for fatal combined with nonfatal outcomes, daytime BP did equally well as nighttime BP, and the night-to-day ratio lost its prognostic accuracy in all participants and in those who were untreated. The findings from the IDACO database suggest that a less pronounced dip in BP might just be a marker of pre-existing or concurrent disease, leading to lower daytime BP, or it might be the result of the antihypertensive drugs used to lower BP during the daytime.

Nighttime BP predicted mortality and nonfatal outcomes, irrespective of treatment status. Daytime BP independently predicted the composite of all fatal and nonfatal cardiovascular events, especially in untreated participants. The findings therefore support that the proposed thresholds for 24-h BP should inform clinical decisions rather than the dipping pattern [42]. Chronotherapy means timing the administration of antihypertensive drugs in such a way that the BP is lowered over the 24-h period, while a normal night-to-day BP ratio is preserved. However, there is no evidence supporting the efficacy of chronotherapy in terms of BP control or outcome. Furthermore, the classification of patients according to the night-to-day BP ratio greatly depends on arbitrary criteria, is poorly reproducible, and has a different prognostic meaning according to the disease outcome under study, the prevailing 24-h BP level, and treatment status.

6.7 Nocturnal Blood Pressure Dip

An excessive BP dip during sleep has been associated with a higher risk of cerebral and/or *retinal ischemia* [43]. A J-shaped relationship of nocturnal dipping status with silent cerebral infarcts can be detected by brain magnetic resonance imaging, and with stroke incidence during the follow-up period. Extreme dippers (with marked nocturnal BP dipping) had a higher prevalence of silent cerebral infarcts and a poorer stroke prognosis than those with normal nocturnal BP dipping (dippers). Extreme dippers tended to have predominantly systolic hypertension and increased BP variability. They might also have increased arterial stiffness with reduced circulating blood volume in addition to an excessive morning surge due to alpha-adrenergic hyperactivity [43].

Recent studies using 24-h ambulatory BP monitoring have shown that the development and progression of nonarteritic anterior ischemic optic neuropathy and glaucomatous optic neuropathy are significantly correlated with nocturnal arterial hypotension, particularly in hypertensive patients receiving oral hypertensive therapy. These studies suggest that several of the optic nerve head ischemic or ocular vascular disorders previously thought to be manifestations of arterial hypertension may, in fact, be due to a combination of systemic arterial hypertension and hypotension, with arterial hypertension acting as a predisposing factor and arterial hypotension actually producing the disorders [36]. The precise role of the nocturnal dip in the risk for ischemic events requires further study.

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Morning Surge in Blood Pressure in Hypertension: Clinical Relevance, Prognostic Significance, and Therapeutic Approach

7

Kazuomi Kario

7.1 Introduction

Hypertension is the most powerful risk factor for cardiovascular disease. The diagnosis of hypertension and the therapeutic target of blood pressure (BP) are based on the average of each BP reading; however, there is a significant variability in BP levels among hypertensive subjects. Previous clinical research using ambulatory BP monitoring (ABPM) clearly demonstrated that increased ABPM variability was significantly associated with target organ damage and poor cardiovascular prognosis [1, 2]. Recently, peak BP and increased variability in clinical BP and self-measured home BP were reported to be associated with hypertensive target organ damage and to be a significant predictor of cardiovascular events independently of the average of BP levels [3–6].

Morning BP surge (MBPS) is one of the components of diurnal BP variability, and normal MBPS is a physiological phenomenon. However, an exaggerated MBPS is a pathological phenomenon. In addition to a 24-h persistent pressure overload, dynamic BP variability from the nadir during sleep to peaking early in the morning would contribute to the cardiovascular continuum from the early stages of subclinical vascular disease to the final trigger of cardiovascular events [7]. Recent studies have shown that an exaggerated MBPS is a cardiovascular risk in both normotensive and hypertensive subjects [8–15]. As advancing age and hypertension augment MBPS, the impact of MBPS should be significant in both medicated and unmedicated hypertensive patients.

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In this chapter, the recent literature on this subject is reviewed, and reference is made to the clinical relevance and prognostic significance of MBPS. Finally, practical therapeutic approaches are examined.

7.2 Prognostic Significance

Recent studies have shown that exaggerated MBPS is a risk factor for cardiovascular disease independently of a person's 24-h BP level. There have been eight prospective studies on both hypertensive outpatients and community-dwelling subjects [8–15]. Seven of these showed that MBPS is a predictor of future cardiovascular events.

The first of these studies, the Jichi Medical University School of Medicine-ambulatory blood pressure monitoring (JMS-ABPM) study was carried out by our team. Wave 1 of the study included 519 unmedicated older hypertensive Japanese patients with a mean age of 72 years [8]. We first identified two MBPSs: (1) a sleep-through surge, which we defined as morning BP [2-h average, consisting of four 30-min BP readings taken just after waking up], minus the lowest nocturnal BP [1-h average of three BP readings centered on the lowest nighttime reading]; and (2) a pre-waking surge defined as the morning BP minus the pre-waking BP [2-h average of four BP readings just before waking up] (Fig. 7.1). The exaggerated morning surge group was defined as the top 10 percentile of patients with sleep-through surge (>55 mmHg), and these patients had a higher stroke incidence than the nonsurge group (19 vs. 7.3 %, $p = 0.004$). After matching for age

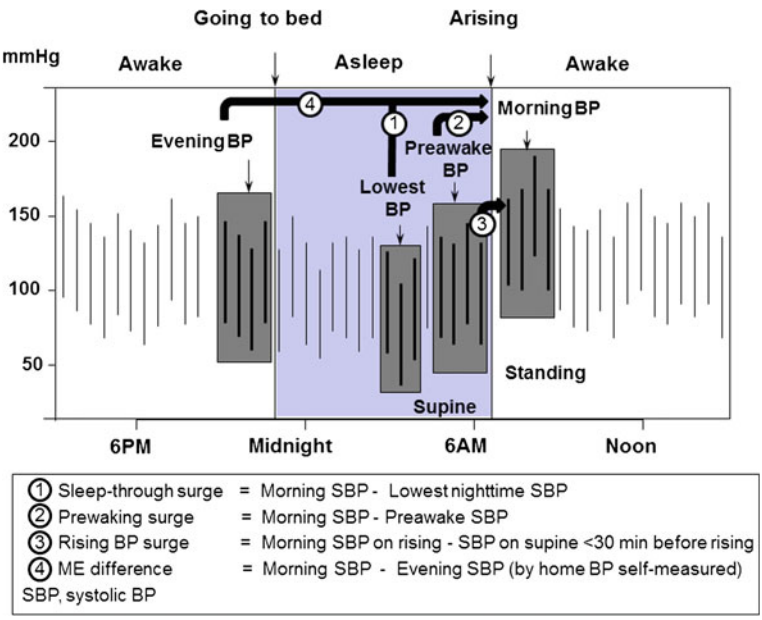

Fig. 7.1 Definition of morning blood pressure surge

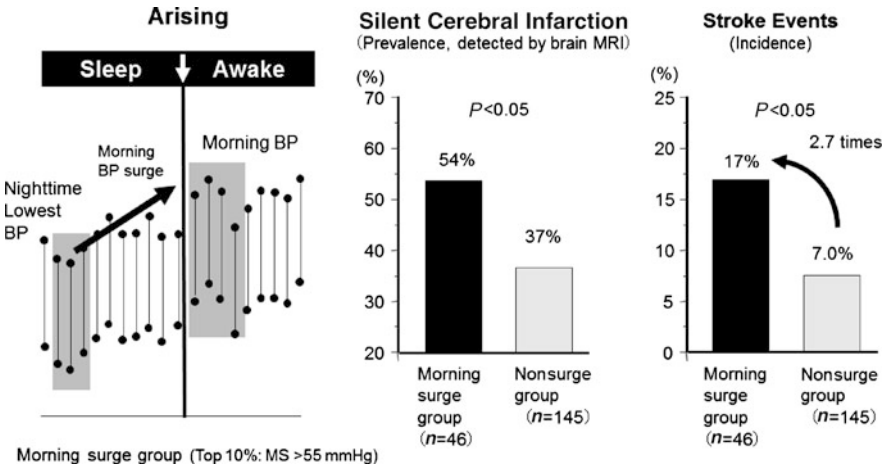

Fig. 7.2 Morning blood pressure surge and silent cerebral infarction and clinical stroke (Jichi Medical University ABPM Study; data were matched for age and 24-h systolic blood pressure)

and 24-h BP, the relative risk of the surge group vs. the nonsurge group was 2.7 ($p = 0.04$) (Fig. 7.2). This association remained significant after adjusting for nocturnal BP dipping status. The pre-waking surge tended to be associated with stroke risk, although the association was not significant ($p = 0.07$).

Similar results were reported by the study carried out by Gosse et al. [9] involving 507 unmedicated hypertensive patients [9]. In this study, the hypertensive patients were classified into quartiles according to the level of rising BP surge (defined as the morning systolic BP measured on rising minus the systolic BP in a supine position <30 min before rising) (Fig. 7.1). Although there were no significant differences in the 24-h BP levels among the groups, the highest quartile group had significantly higher risk for cardiovascular events. In the multivariate analysis, the rising BP surge was significantly associated with cardiovascular risk independent of age and 24-h BP level.

The Ohasama study of 1,430 community-dwelling Japanese people with a 10-year follow-up period also confirmed that both exaggerated pre-waking surge and sleep-through surge were independent risks for hemorrhagic stroke ($p = 0.04$) [10]. In their cohort, MBPS was not a significant risk for ischemic stroke.

In the Dublin Outcome Study of 11,291 referred hypertensive patients (mean age: 54.6 years; 5,326 males), 566 cardiovascular deaths occurred during the 5.3-year follow-up [11]. This large prospective study with sufficient *hard* end points confirmed that a pre-waking surge was a risk for total cardiovascular mortality. A pre-waking BP surge increased the risk for both stroke and cardiac deaths by 37 and 38 %, respectively. Unfortunately, the final results of the study have not yet been published. Thus, the association between the degree of MBPS and cardiovascular risk is not linear, but rather has a threshold.

In the fifth study carried out on 10 normotensive and 32 well-controlled hypertensive older outpatients with 24-h BP < 135/85 mmHg, an exaggerated sleep-through surge was significantly associated with cardiovascular events [12].

The sixth study by Li et al. used the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) study, to analyze 5,645 subjects from eight countries, and provided the definitive results that both types of morning surge (sleep-through and pre-waking) are independent risk factors for total mortality and cardiovascular events [13]. Like our JMS-ABPM study, this study also found that only individuals with MBPS values in the top tenth percentile were at risk of mortality or cardiovascular events, even after controlling for covariates such as age and 24-h BP.

The seventh prospective study of 1,187 patients who had 24-h ABPM performed showed that mild MBPS was associated with peripheral artery disease but not with cardiovascular events [14].

In the eighth study on a cohort of 2,627 patients referred for ABPM, the *1-h* morning surge (the difference between the average BP 1 h before and after awakening) was related to lower mortality. After multiple adjustments including 24-h systolic BP, nondippers ($n = 1{,}039$) in particular had a highly significant morning surge-related decrease in mortality: hazard ratio (HR) = 0.49, 95 % confidence interval (CI): 0.34–0.73, $p < 0.001$, unlike dippers ($n = 1{,}588$), HR = 0.90, 95 % CI: 0.60–1.34 [15].

Among these eight studies, only one, the JMS-ABPM [8], investigated the association between the onset of events and exaggerated MBPS, and demonstrated that the incidence of stroke events in the morning hours was higher in those with exaggerated MBPS than in those without it ($p = 0.05$). However, because the number of events was small in this study, the association between MBPS and the onset of cardiovascular events should be investigated with a larger data set in the future.

7.3 Definition of Morning Blood Pressure Surge

There is no consensus on the definition and threshold value of pathological MBPS. The different definitions on different populations may contribute to the discrepancy of the results. MBPS is usually assessed using ABPM; however, there are several definitions of MBPS, such as sleep-through surge, pre-waking surge, rising surge, and so on (Fig. 7.1). Sleep-through surge is one of the dynamic diurnal surges during the specific period from sleep to early morning [8], when the cardiovascular risk is increased. Thus, it is important to exclude the effects of global diurnal BP variation, such as the dipping status of nocturnal BP, to establish the clinical implications of sleep-through surge.

As expected, sleep-through surge is likely to be associated with extreme dippers with marked nocturnal BP drop, and is less likely to be associated with nondippers with lower dipping of nocturnal BP or with risers with higher nocturnal BP than daytime BP. Even after controlling for the dipping status of nocturnal BP or the mean nocturnal BP level, the risk of sleep-through surge remains significant [8]. Pre-waking surge is the BP change occurring 4 h before and after arising [8].

Although sleep-through and pre-waking surges are defined based on the BP difference, theoretically, the speed of the surge (the slope of the increase in morning BP against time) may be a better indicator of the risk of morning surge [16].

The recently proposed MBPS, derived from the product of the rate of morning surge and the amplitude (day/night difference), giving an effective *power* of the MBPS, may better clarify the cardiovascular risk in the morning [17]. The rising surge (BP increase by arising) may detect only the morning risk just after rising [9], but it may also underscore the MBPS subsequently augmented by physical activity taking place in the morning.

In addition, we consider the association between MBPS and cardiovascular events not to be linear [7]. As the adequate MBPS is physiological, an exaggerated morning surge (top tenth percentile of the study population) seems to be pathological and likely to increase the risk of cardiovascular events or death. Conversely, a sleep-through or pre-awakening morning surge of less than 20 mmHg in systolic BP is probably not associated with an increased risk of cardiovascular events or death [13]. In the JMS-ABPM study, the top tenth percentile of older hypertensive patients was 55 mmHg for systolic BP [8], while that of community-dwelling IDACO subjects was 37 mmHg for systolic BP [13]. Thus, the threshold of pathological MBPS should be identified for conducting clinical practice in the future.

7.4 Target Organ Damage

MBPS is associated with target organ damage such as left ventricular (LV) hypertrophy, carotid atherosclerosis, arterial stiffness, albuminuria, and silent cerebrovascular disease, independent of the 24-h BP level.

7.4.1 Hypertensive Heart Disease

Many previous studies have shown that an elevated MBPS is associated with echocardiographic measures of hypertensive heart disease. MBPS increases cardiac afterload and arterial stiffness, contributing to the progression of LV hypertrophy. Kuwajma et al. first reported that in older hypertensive patients, the rising surge (the change in systolic BP on rising from bed) was significantly correlated with the LV mass index (LVMI) ($r = 0.51$, $p < 0.02$) and the early and late atrial ratio (E/A), which represents diastolic function ($r = 0.70, p < 0.01$) [18]. In the study carried out by Gosse et al. [9] on unmedicated hypertensive patients, the rising surge was a significant determinant for unmedicated hypertensive patients, and the rising surge was a significant determinant of LVMI [9]. In addition, hypertensive patients with an exaggerated MBPS had a prolonged corrected QT (QTc) duration and QTc dispersion in the morning period [detected by Holter electrocardiograph (ECG) recording] compared with those without MBPS [19]. In this study, MBPS was defined as a rise in systolic BP (≥50 mmHg) and/or diastolic BP (≥22 mmHg) during the early morning (06:00–10:00) compared with the mean BP during the night. As increased

QTc dispersion is reported to be associated with LV hypertrophy and cardiac arrhythmia, an exaggerated MBPS appears to be associated with an increased risk of cardiac arrhythmia and sudden death in the morning in hypertensive patients. Another study showed that ST depression, as detected by Holter ECG, was associated with significantly higher BP peaks in the early morning hours [20].

The association between MBPS and LV hypertrophy is also found in normotensive subjects and well-controlled hypertensive subjects. In a study on community-dwelling subjects, the MBPS (sleep-through surge), adjusted for morning physical activity, was significantly correlated with LVMI [21]. In well-controlled hypertensive subjects with a 24-h BP of <130/80 mmHg, MBPS (sleep-through surge) was significantly associated with increases in LVMI and carotid intima-media thickness (IMT) [22].The association found in both studies was non-linear, with a threshold of morning surge. In a recent study on 79 normotensive subjects with clinic BP <140/90 and 24-h BP <130/80 mmHg, sleep-through surge was significantly correlated with LVMI ($r = 0.26, p = 0.019$) [23].

7.4.2 Vascular Disease and Inflammation

A morning surge in BP and an increased time rate of morning BP variation are reported to be associated with carotid atherosclerosis in untreated hypertensive patients [24–26]. This association may be accompanied by increased vascular inflammation, which can induce plaque instability.

Hypertensive patients with MBPS ($n = 128$) had higher levels of carotid IMT and urinary catecholamine excretion ($p < 0.001$), as well as higher levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6, and interleukin-18 ($p < 0.001$), compared with those without MBPS ($n = 196$) [25]. In our JMS-ABPM study on hypertensive patients, MBPS was significantly correlated with the high-sensitivity CRP (hsCRP) level in patients with the highest quartile of MBPS (sleep-through surge), but not in the other quartiles [27].

In addition, a more direct histological study on carotid endarterectomy specimens demonstrated that carotid plaques in those with exaggerated MBPS were associated with vulnerable plaques (higher numbers of macrophages and T cells, increased expression of human leukocyte antigen DR subregion, reduced number of smooth muscle cells, and lower collagen content), increased levels of markers of oxidative stress, and activation of the ubiquitin proteasome system [26]. In that study, the finding that subjects with elevated MBPS had higher levels of the activated subunits (p50, p65) of nuclear factor kappa B—a central transcription factor regulating inflammatory genes—and matrix metalloproteinase-9—an important enzyme involved in plaque rupture—suggests that elevated MBPS is associated with vascular inflammation and plaque instability. These factors were significantly associated with increased oxidative stress and the activation of the ubiquitin proteasome system. Together, these findings suggest that an elevated MBPS accelerates both atherosclerotic plaque formation and plaque instability in relation to vascular inflammation. Clinically, hypertensive patients with carotid

plaques, who are likely to be vulnerable, may receive potential benefit from anti-inflammatory treatment using statins, renin–angiotensin system (RAS) inhibitors, and thiazolidinediones, as well as from treatment to suppress MBPS [28].

In 743 patients with hypertension or diabetes and healthy normotensive subjects, sleep-through rising surges were significantly correlated with pulse wave velocity (PWV) (hypertensive subjects: $r = 0.126$, $p < 0.001$; diabetic subjects: $r = 0.434$, $p < 0.0001$) and LVMI (hypertensive subjects: $r = 0.307$, $p < 0.001$; diabetic subjects: $r = 0.447$, $p < 0.0001$) [29]. In the same study, a rising BP surge was correlated more strongly with these indices of target organ damage than was sleep-through surge or the standard deviation (SD) of daytime BP, independently of nighttime BP and nocturnal BP drop.

7.4.3 Silent Cerebrovascular Infarction

Silent cerebral infarction (SCI) is the strongest surrogate marker of clinical stroke, particularly in those with increased CRP levels [30, 31]. In the JMS-ABPM study, SCI—particularly multiple SCIs—were more frequently detected by brain magnetic resonance imaging in the morning surge group than in the nonsurge group [8]. The odds ratio (OR) for SCI was significantly higher only in patients in the highest quartile of MBPS with higher (above the median) hsCRP (OR 2.74, 95 % CI 1.42–5.30), when compared to those in other quartiles of MBPS and with lower hsCRP (below the median) [27]. This indicates that the relationship between elevated MBPS and the presence of SCI is slightly affected by low-grade inflammation.

While it is well known that sympathetic activity, particularly α-adrenergic activity, is increased in the morning, SCI has been shown to be more closely associated with the exaggerated MBPS related to α-adrenergic activity [defined as the reduction of MBPS by an α-adrenergic blocker (doxazosin mesylate)] than the overall MBPS [32].

7.4.4 Chronic Kidney Disease

Despite the previously described associations between MBPS and cardiac and vascular complications, there have been few studies showing a positive association between MBPS and renal disease. Chronic kidney disease is likely to exhibit a nondipping pattern of nocturnal BP drops [33, 34], and this nondipping pattern might precede microalbuminuria [35]. One cross-sectional study in newly diagnosed type 2 diabetic normotensive patients showed that morning BP levels and MBPS were significantly higher in patients with microalbuminuria than in patients without [36]. This indicates that a systemic BP surge might directly induce a MBPS in intraglomerular pressure under conditions of disrupted autoregulation of the afferent arteriole of the glomerulus, which is typically seen in diabetes. Another study on normotensive subjects and patients with hypertension or diabetes showed only a weak correlation between rising BP surge and albuminuria

($r = 0.126$, $p < 0.05$); however, a sleep-through surge was not associated with albuminuria in that study [29].

The resistive index (RI) in renal Doppler ultrasonography is thought to be a good indicator of renal vascular resistance caused by atherosclerosis. A recent study showed that a MBPS (sleep-through surge) was significantly associated with higher RI in patients, with a concomitant risk of atherosclerosis [37].

7.5 Vascular Mechanism of Exaggerated Morning Blood Pressure Surge

Vascular disease of both the small and large arteries is considered to be not only a consequence, but also the leading cause, of elevated MBPS, a circumstance giving rise to a vicious cycle in the cardiovascular continuum [7, 38, 39].

A recent study which directly assessed small artery remodeling by the examination of biopsy specimens showed that sleep-through surge was significantly positively correlated with an increased media thickness to lumen diameter ratio (a measure of remodeling) of the subcutaneous small arteries in patients with essential hypertension [40]. As shown in Fig. 7.3, the association between contraction of the resistance arteries and vascular resistance is not linear but rather curvilinear, which is in keeping with Folkow's principle [41] and which explains the acceleration of hypertension. Narrowing of the small arterioles has been hypothesized to contribute to the pathogenesis of hypertension [42], but there is little prospective clinical data on this association. Structural narrowing of the small resistance arteries shifts this association curve to the left, compared to the curve for normal arteries. Compared to sleep, when vascular tone is decreased, the difference in vascular resistance between a small artery with remodeling and one without is augmented in the morning when vascular tone is increased.

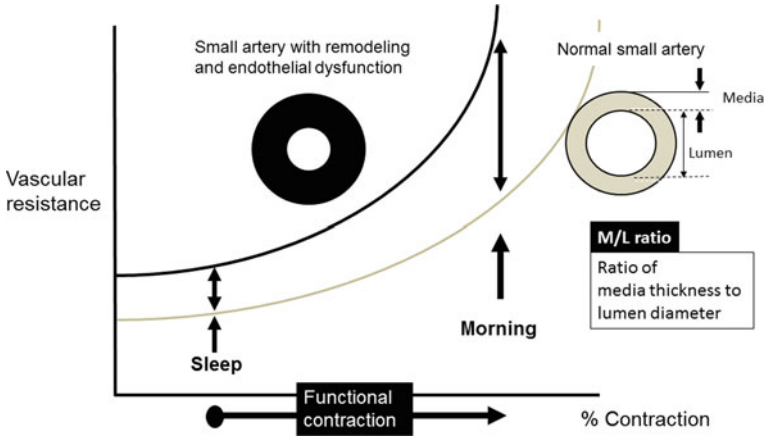

Fig. 7.3 Folkow's principle-based mechanism of elevated morning blood pressure surge in patients with small-artery disease

The activation of various pressor neurohumoral factors, including the sympathetic nervous system and the RAS, occurs early in the morning. Increased sympathetic activity, particularly of the α-adrenergic component [43], increases the vascular tone of the small resistance arteries and may contribute to MBPS. In fact, bedtime dosing of an α-adrenergic blocker was shown to preferentially reduce morning BP levels and MBPS, particularly in those with small artery diseases [32]. The RAS is activated in the morning and could contribute to a MBPS and increase in cardiovascular risk. Plasma renin activity, angiotensin II, and aldosterone levels are all increased before awakening and then further increased after [44]. In addition, a previous experimental study showed that mRNA levels of RAS components in the tissue of the cardiovascular system exhibit diurnal variation, particularly in the hypertensive model, with increases occurring during the awakening period [45]. A recent report showed that a vaccine targeting angiotensin II significantly reduced ambulatory BP throughout a 24-h period [46]. However, the reduction in BP was most prominent in the morning hours. The fact that BP reduction by complete 24-h RAS inhibition was most prominent in the morning indicates that both the RAS and the related pressor effect are highly activated in the morning. In addition, in the morning, endothelial dysfunction is found even in healthy subjects and reduces the capacity for vasodilatation [47]. Thus, the threshold of BP surge augmentation by pressor stimulation may be the lowest in the morning; in other words, the morning is a sensitive period for detecting pathological surge and variability in BP, which reflect vascular status. Thus, using BP surge, the morning may be the best time window to detect the early stages of vascular damage, such as small artery remodeling and endothelial dysfunction.

Considering these facts, even when the mean level of clinic BP is normotensive, masked morning hypertension (isolated morning hypertension) could be considered as *prehypertension* in patients in the early stages of vascular disease (the morning hypertension-prehypertension hypothesis) [39]. Other ambulatory BP surges, such as sleep apnea-related BP surge, orthostatic hypertension, and stress hypertension at the workplace, all of which consist of ambulatory BP variability, could also be considered as forms of *prehypertension*, which may precede *true* hypertension with high clinic and 24-h BP levels. When the duration of pressor conditions persists longer and increases the mean ambulatory BP levels to >133/85 mmHg, these conditions could be considered as masked hypertension before the clinic BP level increases.

In addition to being a consequence of morning surge, increased arterial stiffness in large artery diseases is in itself important as a leading cause of elevated BP variability and MBPS. The PWV, a measure of large artery stiffness, is correlated with sleep-through surge, rising surge, and the SD of daytime BP [21]. Baroreceptor sensitivity (BRS) decreases with an increase in large-artery stiffness, and exhibits diurnal variation with a decrease early in the morning [48]. Thus, reduced BRS in patients with large-artery disease may be insufficient to suppress the BP surge, particularly in the morning. In fact, an impaired dynamic Valsalva-BRS sensitivity has been significantly correlated with an increase in morning BP [49].

7.6 Morning Blood Pressure Surge and Thrombotic Risk

In the JMS-ABPM study, an additive increase of stroke risk was found for MBPS, as well as increased plasma levels of prothrombin fragment 1 + 2 (F1 + 2) and plasminogen activator inhibitor 1 (PAI-1) in hypertensive patients [50]. F1 + 2 is the biomarker of activated coagulation factor Xa while PAI-1 is a well-known inhibitor of fibrinolysis. These biomarkers are known to exhibit circadian variation with elevations in the morning. However, the degree of MBPS per se was not significantly correlated with the plasma levels of these biomarkers when measured in the morning in our study. These results indicate that elevated MBPS additively increases cardiovascular risk when accompanied by hemostatic abnormalities.

In addition, MBPS was significantly associated with increased platelet aggregation, as estimated by laser scattering intensity, to assess platelet aggregation in different sizes of aggregation. In our recent study, spontaneous small-size platelet aggregation was significantly correlated with the degree of MBPS [51]. An association between MBPS and both morning and afternoon platelet aggregation was found, however, the association was stronger with morning platelet aggregation. This indicates a very important aspect of BP variability. High shear stress-induced platelet activation due to increased BP variability in the morning may partly account for this result. Practically, it is important because when hypertensive patients with cardiovascular disease or paroxysmal atrial fibrillation were treated with antithrombotic therapy using either antiplatelet or anticoagulation medications, the hypertensive patients with elevated MBPS were at risk for both thrombotic and hemorrhagic episodes. The Ohasama study demonstrated that MBPS is also a risk for hemorrhagic stroke. Antiplatelet and/or anticoagulation therapy without sufficient reduction of elevated MBPS may increase the risk of hemorrhagic events (Fig. 7.4). The complete reduction of MBPS in hypertensive patients treated with antiplatelet or anticoagulation medications would be clinically important.

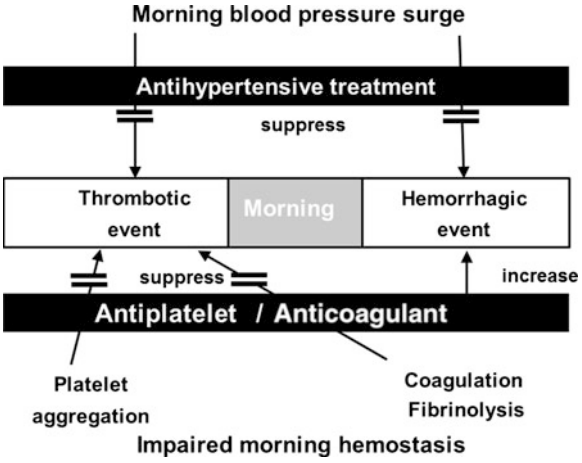

Fig. 7.4 Thrombotic and hemostatic risk in the morning. Antiplatelet and anticoagulation medications reduce thrombotic events but increase hemorrhagic events, while antihypertensive treatment reduces both thrombotic and hemorrhagic events

7.7 Determinants of Morning Blood Pressure Surge

MBPS is increased by various factors, including aging, hypertension, inflammation, glucose abnormality, alcohol intake, smoking, psychological stress, and physical stress [7, 52, 53]. The underlying mechanism of pressor factors, diurnal variation, and the activation of neurohumoral factors that regulate vascular tone and cardiac output, such as the RAS and sympathetic nervous activity, potentially in relation to central and peripheral clock genes, have been thought to be involved in diurnal BP variation and MBPS. These are weekly and seasonal variations in MBPS. MBPS has been shown to be augmented on Mondays [54] and in the winter, particularly in older subjects [55]. Pre-waking MBPS was significantly associated with lower outdoor temperature [56]. These BP variations may partly account for the Monday peak and winter peak of cardiovascular events in older persons [57]. In addition, nocturnal hypoxia or poor sleep quality may augment MBPS, probably through an increase in sympathetic activation and in endothelial dysfunction [58]. In children with sleep apnea, but without any early vascular damage, MBPS has also been shown to be augmented.

A recent study on resting sympathetic outflow assessed by direct measures of intraneural sympathetic nerve activity did not predict MBPS in hypertension [59]. However, this result does not imply that the degree of MBPS is not related to elevated sympathetic outflow, because the evaluation was conducted during the resting sympathetic outflow and in the daytime. MBPS is thought to be composite BP variability associated with orthostatic hypertension and mild exercise-induced BP surge in the morning.

7.8 Practical Use of Self-Measured Home Blood Pressure Monitoring

Clinically, the use of self-measured BP at home is now widely recommended for the management of hypertension [60–62]. There are several potential home BP parameters for assessing the risk of morning hypertension (Fig. 7.5).

Recently, both morning BP—evening BP (= ME difference) assessed by ABPM and self-measured home BP monitoring have been reported to be associated with cardiovascular risk independently of the mean of morning and evening BPs. The ME difference of ABPM was an independent predictor of future stroke events in older hypertensive subjects [63]. In both medicated and unmedicated hypertensive subjects, the ME difference of self-measured home BP was associated with LVMI, a risk for concentric hypertrophy, and increased PWV [64, 65]. Thus, BP-related morning risk of cardiovascular disease may be partly detected by self-measured home BP.

In our recent study, maximum home SBP was significantly associated with an increase in LVMI and IMT, evaluated by carotid echography, and microalbuminuria independently of BP level in unmedicated hypertensive patients [5]. In

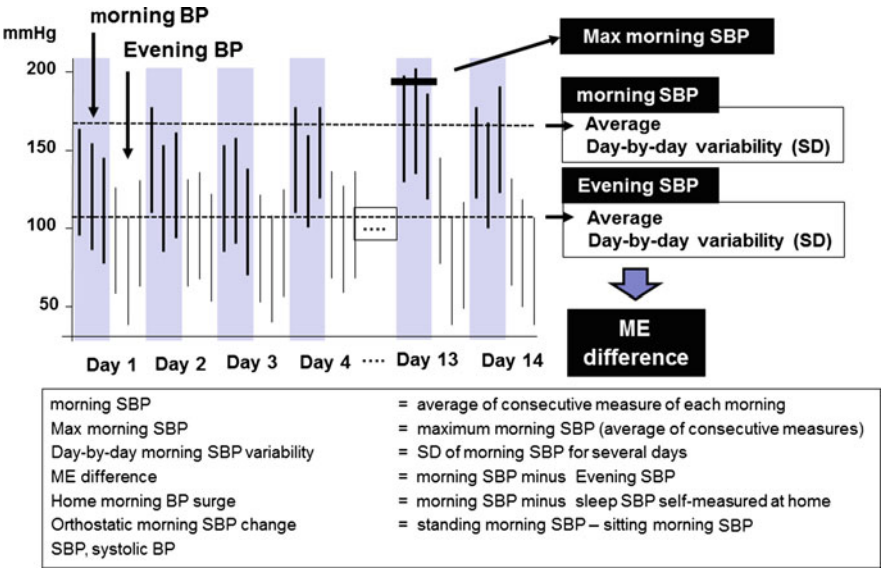

Fig. 7.5 Morning hypertension parameters by self-measured home blood pressure monitoring. *BP* blood pressure, SBP systolic blood pressure, *SD* standard deviation, *ME* morning SBP—evening SBP

this study, even in the well-controlled hypertensive subjects with home BP <135/85 mmHg, the maximum home SBP was significantly correlated with LVMI and carotid IMT. Maximum home SBP was found in the morning BP in 67 % of the total sample.

The Ohasama study also showed that an increase in the SD of home BP self-measured in the morning was an independent risk for future cardiovascular events [4]. In addition, in the recent population-based prospective Finn-Home study, the variability of home BP defined as the SDs of the ME difference, day by day, and first minus second measurements, were associated with future cardiovascular events independently of BP level [6]. The association with cardiovascular risk was stronger with the variability of morning SBP than that of evening SBP. These two studies suggest that BP variability assessed by self-measured home BP has clinical relevance independently of averaged home BP levels.

Thus, in addition to the reproducible elevated morning surge (Fig. 7.6, patient B), an elevated MBPS with poor reproducibility and an increased SD of morning BP may increase the cardiovascular risk (Fig. 7.6, patients c) [7]. As the degree of MBPS in highly reactive patients greatly depends on morning physical activity [66, 67], highly reactive patients would exhibit poorly reproducible elevated MBPS with increased day-to-day variability of morning BP (Fig. 7.6, patient c). Elevated MBPS reactivity may be most risky when physical activity is maximized.

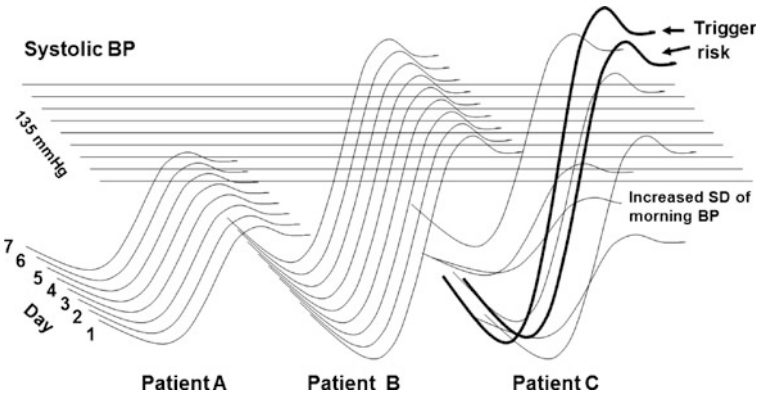

Fig. 7.6 Reproducibility of morning blood pressure surge and cardiovascular risk. Patient A exhibits an appropriate morning surge; patient B exhibits a reproducible exaggerated surge; patient C exhibits an exaggerated variability of morning surge (irreproducible). *BP* blood pressure, *SD* standard deviation

In our recent studies on orthostatic BP changes evaluated by self-measured BP monitoring at home (four BP measures: two measures when sitting followed by two BP measures when standing), both orthostatic hypertension and orthostatic hypotension (two SBP measures when standing minus two SBP measures when sitting) were significantly associated with microalbuminuria and plasma levels of B-type natriuretic peptide in hypertensive patients [68, 69]. In our previous study, orthostatic hypertension, particularly in the morning, was significantly associated with MBPS as evaluated by ABPM [70]. However, home BP self-measured in the morning in a seated position may underscore the risk of ambulatory MBPS, which is augmented by morning physical activity. The simple examination of orthostatic BP change using self-measured home BP monitoring can detect *home orthostatic hypertension* with high reproducibility and without a white-coat effect [71]. Morning BP self-measured at home when standing may be better to detect the risk of MBPS than morning BP self-measured at home while sitting.

Using recently developed home BP monitoring devices, sleep BP could be measured. In our recent Japan Morning Surge Home Blood Pressure (JHOP) study on patients with one or more cardiovascular risk factors, we asked the study subjects to self-measure home sleep BP using the Medinote home BP monitoring device (OMRON HEALTHCARE Ltd., Kyoto, Japan). The sleep BP taken at 02:00, 03:00, and 04:00 was successfully measured by the patients themselves in 65 % of the total 4,019 patients. MBPS and its variability could be more easily and precisely calculated using this or similar device (Kario et al., in preparation).

7.9 Antihypertensive Strategy Targeting Morning Blood Pressure Surge and Morning Hypertension

To our knowledge, there has been no study that has scientifically tested the hypothesis that the selective suppression of elevated MBPS leads to the regression of target organ damage and the reduction of subsequent cardiovascular events. From the viewpoint of perfect 24-h blood pressure control, the kind of BP control which would achieve a more effective protection than conventional antihypertensive treatment based on clinic BP, strict BP control of <130/80 mmHg for 24-h BP, adequate circadian rhythm (dipper type), and suppression of elevated MBPS are key components (Fig. 7.7). As a practical first step, antihypertensive treatment targeting morning home BP <135/85 mmHg is recommended to achieve a strict 24-h BP control.

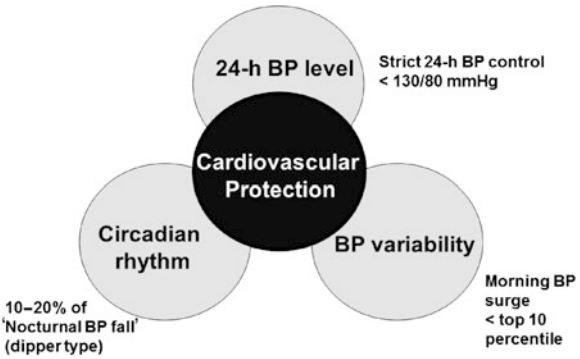

Fig. 7.7 Triad of perfect 24-h blood pressure control. *BP* blood pressure

Nonspecific medications for MBPS include long-acting calcium channel blockers (CCBs), such as amlodipine, which provide continuous BP reduction over a 24-h period to attenuate elevated MBPS [72]. Because the BP-lowering effect of CCBs is dependent on baseline BP, higher ambulatory BP levels decrease more extensively, and the lowest nocturnal BP does not decrease quite as much, thus the MBPS significantly decreases. In contrast, although diuretics also cause the longest duration of the BP-lowering effect, when morning hypertension is treated using diuretics, nighttime BP levels are predominantly reduced compared with daytime BP, and nondippers shift toward becoming dippers [33]. A greater nocturnal drop in BP by means of diuretics may lead to a more exaggerated MBPS. The characteristics of CCBs and diuretics should be considered when using combination therapy with RAS inhibitors [73].

More specific chronological treatment for MBPS may be achieved using antihypertensive medications that reduce the pressor effect of the neurohumoral factors, which is potentiated in the morning, such as inhibitors of sympathetic activity. In particular, bedtime dosing has the most extensive BP-lowering effect in the morning [32]. In addition, an open-label multicenter trial, the Japan Morning

Surge-1 (JMS-1) study, on 611 medicated patients with morning hypertension and self-measured morning systolic BP >135 mmHg, demonstrated that bedtime dosing of doxazosin on top of baseline antihypertensive medication significantly reduced morning BP and albuminuria [74]. In this study, the urinary albumin excretion rate decreased along with a reduction in morning BP.

Another open-label multicenter trial, the Japan Morning Surge-Target Organ Protection (J-TOP) study in 450 hypertensive subjects with self-measured home systolic BP > 135 mmHg, showed that a bedtime dosing of the angiotensin receptor blocker (ARB) candesartan titrated by self-measured home BP was more effective in reducing albuminuria than an awakening administration of an ARB in subjects with sufficiently well-controlled home BP both in the morning and in the evening [75]. This beneficial effect was stronger in subjects with morning-dominant hypertension with an ME difference >15 mmHg for home systolic BP than in those with an ME difference <15 mmHg. In the J-TOP study, even though the morning BP-lowering effect was similar between the bedtime dosing and awakening dosing groups, bedtime dosing of an ARB may be more effective in reducing albuminuria because it may more potently suppress tissue RAS during the sleep–early morning period than awakening dosing [28]. This possibility should be confirmed using a different class of antihypertensive drugs in the future.

The prospective Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC) study of 2,156 hypertensive subjects who were randomized to ingest all their prescribed antihypertensive drugs on awakening or one or more of them at bedtime [76]. After a median follow-up of 5.6 years, subjects ingesting one or more antihypertensive drugs at bedtime exhibited a significantly lower relative risk of total cardiovascular events than those ingesting all medications on awakening [0.39 (0.29–0.51); number of events: 187 vs. 68; $p < 0.001$], as well as a significantly reduced prevalence of nondipping (34 vs. 62 %; $p < 0.001$). In addition, the bedtime dosing of one or more antihypertensive drugs may suppress a surge in hypertensive patients with elevated MBPS, and this may partly contribute to cardiovascular protection.

7.10 Conclusions

Elevated MBPS is the treatable BP variability and is associated with future cardiovascular events independently of the 24-h BP level. Particularly, MBPS is closely associated with vascular damage of both small and large arteries, ultimately leading to target organ damage. Long-acting CCBs either in monotherapy or in combination therapy with RAS inhibitors, and the bedtime administration of antihypertensives to suppress the MBPS would achieve more effective cardiovascular protection in clinical practice for hypertensive patients. In future studies, the threshold of morning BP should be determined.

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Short-Term and Long-Term Blood Pressure Variability

8

Giuseppe Mancia

8.1 Introduction

It has long been known that over the short- and long-term, blood pressure (BP) is characterized by large spontaneous variations [1]. That is, its values vary markedly within the 24-h period due to BP changes between the day and night, but also between hours, minutes, and even adjacent beats. BP also shows large variations over more prolonged time periods because of differences between days, months, and seasons [2] with, in addition, a trend to an age-related, yearly increase [3].

Whether some or all of the features of BP variability mentioned above have clinical significance has been, and still is, the object of intensive research. This chapter will review the most important evidence so far available that short- and long-term BP variability represents a risk for cardiovascular morbidity and mortality and thus merits clinicians' attention.

8.2 Twenty-Four-Hour or Short-Term Blood Pressure Variability

8.2.1 Overall Twenty-Four-Hour Blood Pressure Variability and Organ Damage

Because BP values within a 24-h period have a normal or near normal distribution [1], the overall magnitude of BP variability during this period can be quantified by the standard deviation or the coefficient of variation (standard deviation normalized for mean BP) of the 24-h mean value [1]. Using this approach, Parati et al. [4]

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showed that for each quintile of 24-h mean intra-arterial BP, hypertensive patients in whom systolic and diastolic BP variability was above the median value had a greater score for organ damage [calculated from electrocardiogram, chest X-ray, ocular fundus, and patient history] than hypertensive patients with a variability below the median value (Fig. 8.1, upper panels). Similarly, in a much larger study in which 24-h BP was monitored noninvasively, Mancia et al. [5] found that for each quintile of 24-h mean BP, hypertensive patients with a greater than median BP variability had a greater carotid artery wall thickness than that of patients with a lower than median BP variability (Fig. 8.1, lower panels). Although their cross-sectional nature did not allow for a cause and effect relationship, these observations raised the possibility that 24-h BP variability could be a factor that adversely affects the appearance and progression of organ damage with recognized prognostic significance [6–8].

This finding has received support from longitudinal studies. In a 7.5 year follow-up of hypertensive patients, Frattola et al. [9] observed a relationship between initial 24-h BP variability (intra-arterial monitoring) and the subsequent progression, measured by means of echocardiography, of the left ventricular mass to greater values and left ventricular hypertrophy. Likewise, in a 3-year follow-up study, Sander et al. [10] showed that, in hypertensive individuals with an initially greater standard deviation of 24-h mean BP, the subsequent increase of carotid artery wall thickness was more pronounced than in individuals with a smaller initial standard deviation of 24-h mean BP. Thus, a greater tendency for BP to vary within 24 h seems indeed to favor the development of cardiac and vascular damage over a period of years.

8.2.2 Overall Twenty-Four-Hour Blood Pressure Variability and Cardiovascular Morbidity and Mortality

Longitudinal studies in which 24-h BP was measured noninvasively also found a relationship between overall BP variability and cardiovascular morbid and fatal events [10–14]. To provide some examples, in the study by Sander et al. [10], hypertensive patients with a greater BP variability not only showed a greater 3-year carotid artery wall thickening, but also an increased incidence of cardiovascular events. Kikuya et al. [11] showed that, in a Japanese population, subjects with a daytime standard deviation of systolic BP <15.8 mm Hg had a lower incidence of cardiovascular mortality than subjects with a 24-h standard deviation of systolic BP above this value, irrespective of the concomitant value of daytime heart rate variability, which had a protective effect. Finally, in the long follow-up (approximately 12 years) of the general population of the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, cardiovascular mortality showed a positive relationship with a magnitude of the erratic diastolic BP changes that could be detected by eliminating the most important cyclic components (day and night, and postprandial BP variabilities) by Fourier analysis of the 24-h BP

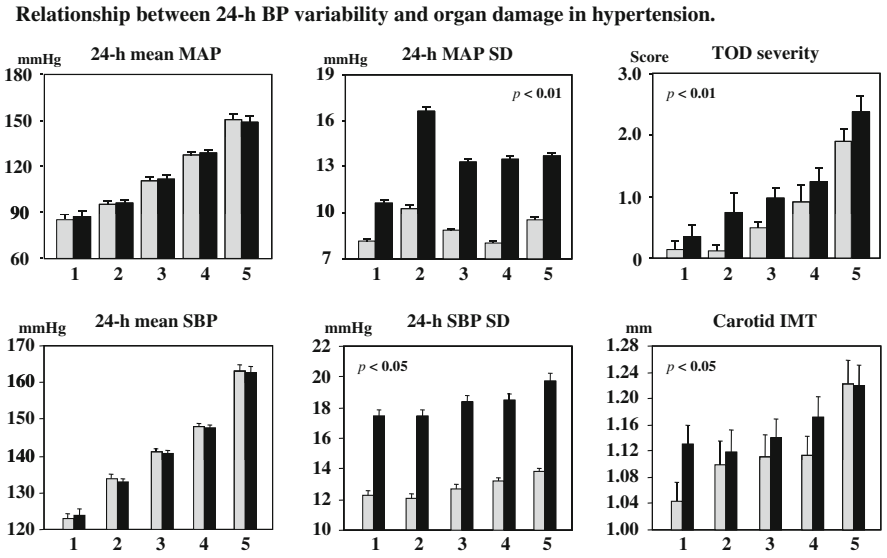

Fig. 8.1 The upper panels show the quintile values of the 24-h average mean arterial pressure (MAP), 24-h MAP variability, and the score of target organ damage (TOD). The lower panels show the quintile values of 24-h average systolic blood pressure (SBP), SBP variability, and carotid artery intima-media thickness (IMT). For each quintile, data are shown for subgroups with a BP variability above and below the median value. *P* refers to the quintile trend. Variability is shown as the standard deviation (SD) of the 24-h SBP mean. The data shown in the upper panels were obtained by intra-arterial BP monitoring. Obtained from Refs. [4] and [5], by permission of the authors

tracing [12]. The relationship was independent of the concomitant 24-h mean BP values as well as of other potentially confounding demographic and clinical cardiovascular risk factors (Fig. 8.2, left and central panels) [12]. Indeed, as shown in Table 8.1, erratic BP variations were found to be a predictor of cardiovascular fatal events more important than the difference in day–night BP values, whose relationship with cardiovascular mortality was of an inverse type (see later in the chapter). They were also found to exceed the importance of 24-h mean BP, suggesting its nonmarginal participation in the array of phenomena that make BP a cardiovascular risk factor of paramount importance.

8.2.3 Clinical Relevance of Specific Components of Twenty-Four-Hour Blood Pressure Variability

Several BP changes that occur regularly during a 24-h period have been reported to have prognostic significance. In particular, the magnitude of the physiological BP difference between day and night has been shown to (1) inversely correlate with various measures of organ damage in hypertensive patients [15, 16] and (2) detect both in hypertensive individuals and in the general population a lower risk of cardiovascular

Relationship between components of 24-h BP variability (erratic and daynight BP changes) and risk of cardiovascular death.

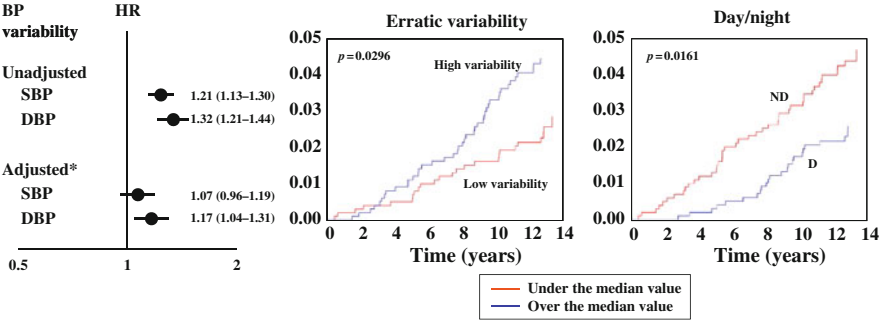

Fig. 8.2 The *left* panel shows the unadjusted and adjusted hazard ratio (HR) for cardiovascular and all-cause death for 1 mm Hg increase in erratic diastolic blood pressure (BP) variability. The numbers in parenthesis refer to the confidence intervals. Adjustment included the variables shown at the bottom of the figure. The *central* and *right* panels show the incidence of cardiovascular fatal events in subgroups with diastolic erratic BP variability and a day–night BP difference above and below the median value. The *p* values refer to between subgroup differences. *D* diastolic, *DBP* diastolic blood pressure, *SBP* systolic blood pressure. Modified from Ref. [12], by permission of the authors

morbidity and mortality [12, 17] (Fig. 8.2, right panel, and Table 8.1). This has favored the classification of patients into dippers and nondippers, i.e., individuals in whom nocturnal BP falls respectively by more and less than 10 % of the daytime mean value; the latter category is regarded as having a higher cardiovascular risk, and even more so if a reduced nocturnal hypotension is replaced by an increase in night BP compared to daytime BP (reversed dippers) [18].

Additionally, evidence has been made available that the physiological reduction in BP that takes place at the time of arousal from night sleep has a relationship with the incidence of stroke [19, 20], thereby being one of the factors (together with increased platelet aggregability, reduced fibrinolytic activity, increased heart rate, and so on) believed to cause cardiovascular fatal and nonfatal events to peak in the early and late morning compared to other times of the 24-h period [21, 22]. There is, on the other hand, no convincing evidence in favor of the prognostic value of another daily BP change, i.e., the BP drop that characterizes the postprandial time, a characteristic of digestion-induced mesenteric vasodilatation and afternoon rest [1]. In the population of the PAMELA study, the cyclic BP change that reflected postprandial hypotension did not show any significant relationship with long-term cardiovascular mortality [12].

8.2.4 Conclusions and Limitations

The evidence summarized in the previous sections provides support to the prognostic importance of 24-h or short-term BP variability. However, additional data are

Table 8.1 Multivariate analysis of the relationship of blood pressure phenomena with cardiovascular and all-cause death in the PAMELA study

DBP[a]	CV death		All-cause death	
	χ^2	p	χ^2	p
Erratic variability	30.80	<0.0001	31.69	0.0001
Day/night Δ	−21.34	0.001	−19.87	0.001
24-h mean	16.11	0.003	16.40	0.002

[a] Adjustment for age/gender/serum cholesterol & glucose/smoking/previous CV events/left ventricular hypertrophy *CV* cardiovascular, *DBP* diastolic blood pressure

needed to turn this support into an undisputable conclusion. In some longitudinal studies, 24-h BP variability was not found to predict cardiovascular morbidity and mortality after correction for confounders [23, 24], which makes further studies desirable, particularly if associated with a high number of events and an appropriate statistical power. Furthermore, 24-h or short-term BP variability has never been studied in treated hypertensive patients, which means that the importance of its treatment-induced changes for the cardiovascular protection associated with BP-lowering interventions is unknown. Thus, collecting data in antihypertensive treatment trials in which all or most patients undergo repeated ambulatory BP monitoring is a real need.

Finally, the quantification of 24-h BP variability by noninvasive ambulatory BP monitoring (the only approach that allows data collection in a large number of subjects) should be made more accurate. Data should ideally be obtained using beat-to-beat monitoring devices, which may allow the study of all the components of short-term BP variability, including a so far neglected phenomenon such as the prognostic importance of the speed of spontaneous BP changes. This speed is greater in hypertensive than in normotensive subjects [25] (Fig. 8.3), and this may have a traumatic effect on the vessel wall and disrupt an instable plaque. Accuracy can also be improved by restricting the time intervals between automatic BP readings to no more than 15 min, beyond which the calculated 24-h BP standard deviation may markedly differ from the real value (Fig. 8.4) [26]. Regretfully, in many previous studies, between-reading intervals longer than 15 min have been used.

8.3 Long-Term Blood Pressure Variability

8.3.1 Visit-To-Visit Blood Pressure Variability

Long-term BP variability has attracted the interest of clinical investigators much more recently, than 24-h or short-term BP variability, and thus fewer studies have addressed the question of its prognostic significance. As mentioned in the Introduction to this chapter, BP shows lower values in summer than in winter [3] (possibly because of the vasodilator effect caused by higher temperatures) [27],

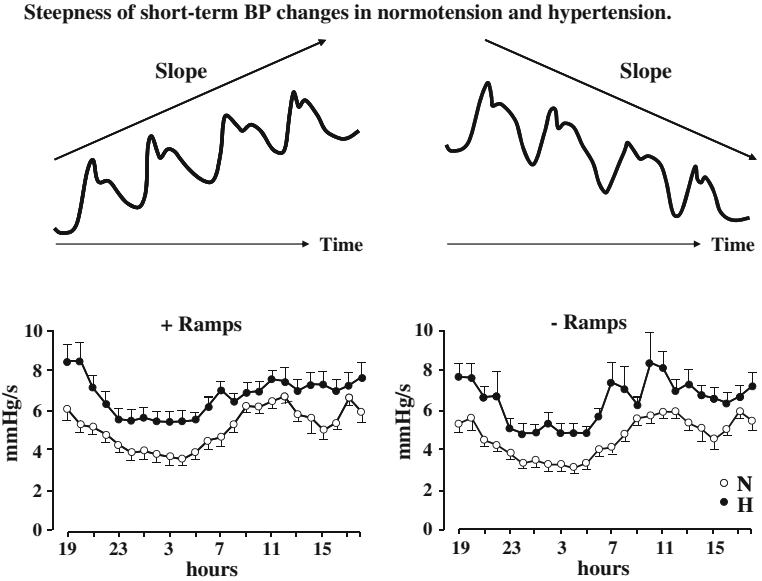

Fig. 8.3 The upper panels show an example of the spontaneous pressor (*left*) and depressor (*right*) BP changes identified on a 24-h BP recording in a single subject. The bottom panels show the slope of the spontaneous SBP changes (ramps) over time, occurring over 24 h in normotensive (N, *open circle*) and hypertensive (H, *closed circle*) patients. Data were obtained using beat-to-beat BP monitoring. Circles represent mean ±SD. Modified from Ref. [25], by permission of the authors

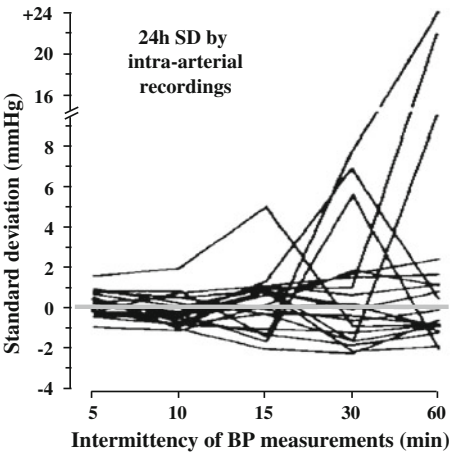

Fig. 8.4 Influence of between-reading intervals on the estimate of 24-h BP standard deviation (SD). Data from 40 subjects in whom 24-h ambulatory BP was measured intra-arterially. The 24-h SD was calculated first by considering all values (*horizontal reference line*) and then by considering BP values spaced from 5 to 60 min intervals. Modified from Ref. [16], by permission of the authors

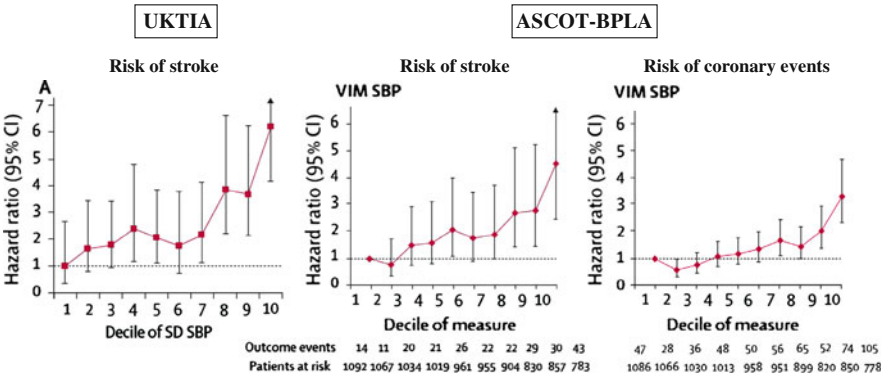

Fig. 8.5 Relationship between visit-to-visit BP variability and hazard ratios for stroke and coronary events in the United Kingdom transient ischaemic attack aspirin trial (UKTIA) and the Anglo-Scandinavian cardiac outcome trial (ASCOT) study. Data are shown for deciles of standard deviation (SD) or of another measure of the variability (VIM) of the mean SBP value throughout the treatment period. Symbols as in preceding Figures. *BPLA* blood pressure lowering arm, *CI* confidence interval, *SBP* systolic blood pressure, VIM BP variation independent of the mean. Modified from [30], by permission of the authors

but whether and to what extent this plays a role in long-term prognosis is unknown. In contrast, Kikuya et al. [28] have recently shown that day-to-day BP variations importantly affect individuals' long-term risk of a cardiovascular outcome because the 10-year incidence of cardiovascular mortality was 4–5 times greater in the quartile in which day-to-day variability was maximal as compared to that in which it was minimal. Furthermore, thanks to the work of Rothwell et al. in Oxford [29], data are available that BP variations between visits spaced by an interval of several months may have prognostic importance. In one study, it was found that in a cohort of individuals with a history of stroke, the risk of stroke recurrence was closely related to the standard deviation or the coefficient of variation of the office mean BP value as calculated from the visits repeatedly performed over a period of several years. In another study [30], Rothwell et al. confirmed this finding in a large cohort of treated hypertensive patients with multiple risk factors or with a cardiovascular event history, adding that (1) although steeper for stroke, the relationship with visit-to-visit BP variability also holds for coronary events (Fig. 8.5) and (2) for both events visit-to-visit BP variations were prognostically more important than mean BP levels during treatment. Thus, during antihypertensive treatment, BP stability may play a clear protective role. This is supported by the results of another large-scale study on treated hypertensive patients with a history of coronary disease in whom calculation was made of the percentage of visits in which BP was found to be reduced to <140/90 mm Hg [31], i.e., the target recommended by guidelines for the general hypertensive population [32]. Over the duration of the study, the incidence and risk of a cardiovascular event, and of stroke in particular, increased progressively as the visits showing BP control decreased from ≥75 to <25 % of all visits. Importantly,

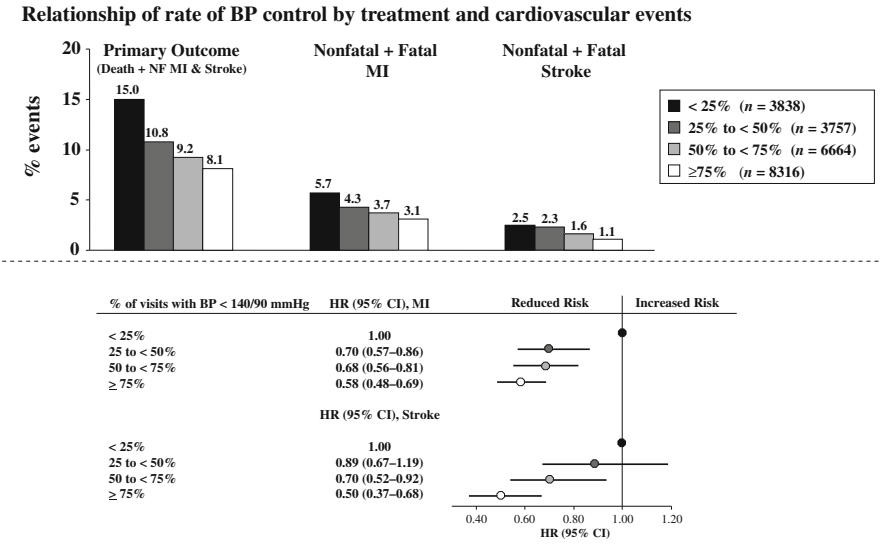

Fig. 8.6 The upper panels show the incidence of the primary end point of cardiovascular events in the International Verapamil SR Trandolapril Study (INVEST) according to the percentage of visits (from <25 to ≥75 %) in which BP was reduced to <140/90 mmHg. The lower panel shows the corresponding hazard ratios (HR) after adjustment for baseline confounders and on-treatment mean BP. Data obtained for the group with <25 % of visits with BP control are taken as reference. *CI* confidence interval; *MI* myocardial infarction, *NF* nonfatal. Modified from Ref. [31], by permission of the authors

this was also the case after the data were adjusted for a variety of confounders, including the lower or higher mean BP values throughout the treatment period (Fig. 8.6).

8.3.2 Implications

The evidence discussed in the previous sections of this chapter supports the conclusion that long-term BP variability may be prognostically adverse. This implies that, during antihypertensive treatment, BP stability at or below the recommended target value may represent an added protective factor as well as a further marker of successful treatment strategies. Currently, instability of BP control is common, as shown by the results of the European Lacidipine Study on Atherosclerosis (ELSA); the percentage of hypertensive patients in whom office or 24-h BP control was achieved at all yearly visits was about three times less than the percentage of BP control at a single yearly visit (Fig. 8.7) [33]. It is reasonable to speculate that this plays a role in the incomplete cardiovascular protection exhibited by hypertensive patients, even when average BP values are on target [34], and that achieving better BP stability during treatment could thus reduce the high residual risk that characterizes treated hypertensive individuals [35].

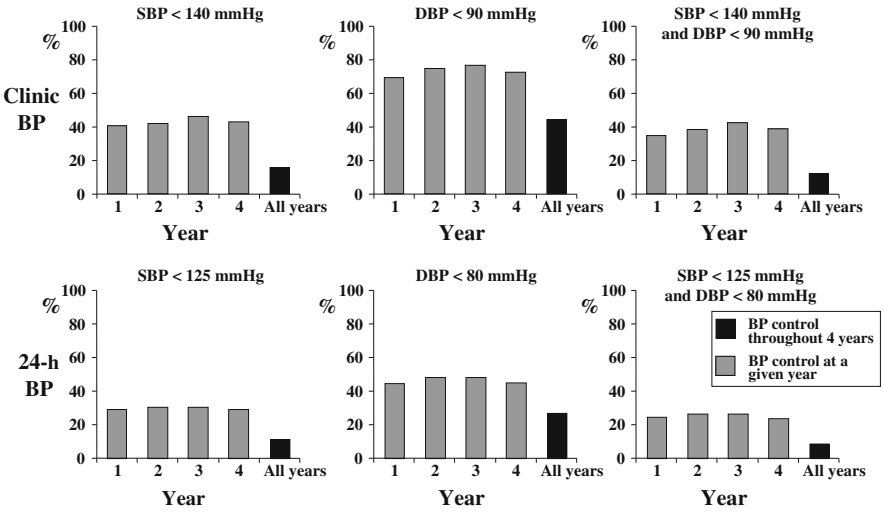

Fig. 8.7 Rate of clinic and 24-h systolic (S) BP and diastolic (D) BP control with treatment in hypertensive patients from the European lacidipine study on atherosclerosis (ELSA) study. Histograms from 1 to 4 refer to the rate of control seen at each yearly visit. The last histogram to the right refers to patients in whom control was seen every year. *BP* blood pressure, *DBP* diastolic blood pressure, *SBP* systolic blood pressure. Modified from Ref. [33], by permission of the authors

This finding supports the recent observation that cardiovascular events are significantly related to the absence of BP control in the visit immediately preceding the event [36].

8.3.3 Conclusions and Limitations

It is important to mention that, the evidence so far available on visit-to-visit BP variability suffers on several limitations. First, data have all been obtained in patients with a high cardiovascular risk profile and it is still to be demonstrated that instability of BP control also plays an important prognostic role in patients with mild-to-moderate hypertension and an overall lower cardiovascular risk, a condition that includes the largest proportion of hypertensive individuals. In the ELSA study on mild-to-moderate hypertensive patients with low cardiovascular risk, the 4-year progression of carotid intima-media thickness (as well as the risk of cardiovascular morbid and fatal events) showed a relationship with the on-treatment average BP but not with its coefficient of variation, suggesting that in these patients temporary BP elevations were less harmful, and thus that BP instability may have different effects in different clinical contexts [37]. Second, data on visit-to-visit BP variability originate from a post hoc approach, which means that comparisons involve nonrandomized groups of patients who may differ for factors

other than BP instability. Furthermore, because the calculation of the BP standard deviation or coefficient of variation needs a number of BP values, patients with an early cardiovascular event are excluded, limiting the data analysis to the latter part of a trial. Finally, while factors involved in the determination of 24-h BP variability are at least in part known [1], no information has so far been obtained on factors responsible for visit-to-visit BP variability. That is, it is not known whether the tendency for BP to be unstable between visits is accounted for by the patients' hemodynamic status or by more general clinical characteristics or whether it is mainly the result of better or worse adherence to the treatment regimen, whose relationship with outcome is well known [38, 39]. This is an important point to clarify to select the therapeutic strategies that may more effectively improve the stability of BP control.

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Home Blood Pressure Monitoring in Hypertension

9

Gianfranco Parati, Juan E. Ochoa and Grzegorz Bilo

9.1 General Considerations

Hypertension is a major risk factor in the development of cardiovascular (CV) events and mortality [1]. Being able to accurately measure blood pressure (BP) then becomes imperative for an early diagnosis of hypertension and for the implementation of appropriate BP-lowering strategies [2]. Measuring office BP (OBP) has long been regarded as the reference standard for this purpose, as most evidence on the CV risk associated with elevated BP levels, as well as on the benefits of BP lowering, comes from studies using this method [3]. However, there is now a general consensus that the adequate management of hypertension cannot be based on isolated office readings only. This is because BP is characterized by a highly dynamic behavior and undergoes continuous changes over time.

An additional reason for the need to combine OBP with information on out-of-office BP levels is the increasing awareness of the limitations that characterize OBP readings, including the inherent inaccuracy of the technique, observer bias and digit preference, variable interference by the *white coat effect*, and the inability of this approach to collect information on BP during the subject's usual activities and over a long period of time. Recently available methodologies for ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) have been proposed as

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useful solutions for a better assessment and management of hypertension when combined with conventional OBP measurements, reducing misclassification of hypertension and better defining the need to start antihypertensive therapy [4].

Although 24-h ABPM is now acknowledged as the gold standard for the diagnosis and management of hypertensive patients [5, 6], this approach is currently recommended in selected groups of patients only [2, 3] because it is costly, it is not easily available everywhere, requires trained clinic staff and specialized equipment, and may interfere with the patient's usual activities and sleep [7]. HBPM shares several of the advantages of ABPM and is less expensive, thus supporting the current recommendation for its extensive use in clinical practice [2, 7–9]. However, unlike ABPM, BP self-measurements by patients through HBPM cannot provide the extensive information on daily life BP behavior available with 24-h ambulatory recordings, thus preventing a dynamic assessment of BP over the day and, in particular, during the night.

Nonetheless, when performed on a regular basis, repeated BP measures obtained by patients at home offer the possibility to obtain accurate and frequent information on out-of-office BP not only during a single day, but also over several days, weeks, or months within a normal life setting. This allows the evaluation of dynamic BP changes over wider time periods, and to quantify the degree of long-term BP variability [7]. HBPM is now being increasingly used all over the world, due to the large availability of accurate, easy-to-use, automated BP measuring devices that are relatively cheap and accepted by both patients and physicians.

Indeed, recent guidelines recommend the routine use of this technique in daily practice [7–9], with a strong agreement in this regard between European and US recommendations [10]. However, despite its multifold clinical advantages and rapidly growing diffusion, HBPM cannot be considered a replacement for ABPM. Although a major common denominator between HBPM and ABPM is the fact that both provide out-of-office BP measurements detecting BP changes in real-life conditions while preventing the nervous reaction associated with OBP monitoring (OBPM) [4], they provide complementary (not interchangeable) information on BP in different living conditions and over different time periods [5, 7, 11]. The main characteristics of the most important methods for BP measurement in humans are comparatively summarized in Table 9.1.

9.2 The Prognostic Value of Home Blood Pressure Monitoring

In most of the available studies addressing the clinical relevance of HBPM, the prognostic value of HBPM has been found superior to that of OBP measurements [12–25]. When averaged over a period of a few days, measurements of BP at home have been shown to significantly predict the development of major CV events (myocardial infarction, stroke, and CV death), all-cause mortality, progression of chronic kidney disease (CKD), and functional decline in older patients.

Table 9.1 Comparison of the features of three main methods for BP measurement

Feature	OBP	ABPM	HBPM
Number of readings	Low	High	Medium
White-coat effect	Yes	No	No
Operator dependency	Yes	No	No
Need of device validation	No[a]	Yes	Yes
Daytime BP	+	+++	++
Nighttime BP and dipping	−	+++	−/+[b]
Morning BP	±	++	+
24-h BP variability	−	++	±
Long-term BP variability	−	±	++
WCH and MH diagnosis	−	++	++
Placebo effect	++	−	−
Reproducibility	Low	High (24-h average values)	High (average of several values)
Prognostic value	+	+++	++
Patient involvement	−	−	++
Patient training	−	±	++
Physician involvement	+++	++	+
Patient acceptance	++	±	++
Monitoring of treatment effects	Limited information	Extensive information on 24-h BP profile, cannot be repeated frequently	Appropriate for long-term monitoring, limited information on BP profile
Hypertension control improvement	+	++	+++
Cost	Low	High	Low
Availability	High	Low	High

[a] Yes if oscillometric device is used

[b] New HBPM devices may perform nighttime BP measures

Modified from [7], by permission. *ABPM* ambulatory BP monitoring, BP blood pressure, HBPM home BP monitoring, *MH* masked hypertension, *OBP* office blood pressure, *WCH* white coat hypertension

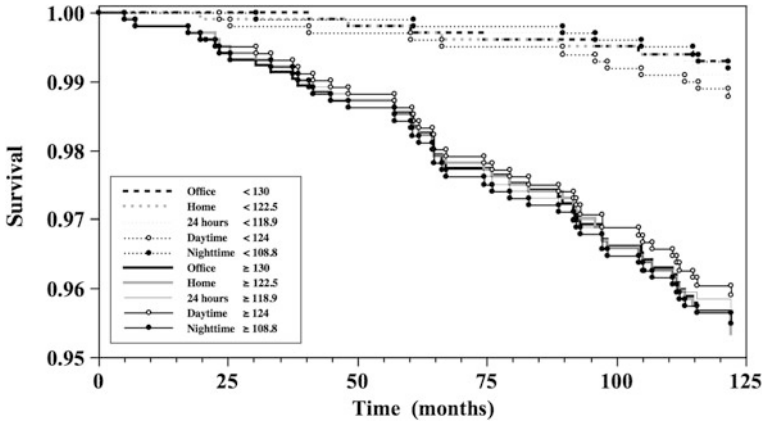

Fig. 9.1 Kaplan–Meier curves for survival free of CV disease in subjects with office, *home*, and ambulatory SBP values (above and below the median values shown; modified from [12], by permission). *CV* cardiovascular, *SBP* systolic blood pressure

When focusing on the risk of nonfatal CV events, it has to be mentioned that while in most studies home BP (HBP) has been shown to be a stronger predictor than OBP [15–17, 20–23, 25], in a population study HBP showed the same prognostic value as OBP [26]. On the other hand, when focusing on CV mortality (fatal CV events), the predicting ability of HBPM has been shown to be superior to that of OBPM in most studies [12, 14, 18, 19, 25–27], with one exception, where a similar predictive value was observed for both techniques [15] (see Fig. 9.1 and Table 9.2).

Cross-sectional studies have reported that target organ damage (i.e., left ventricular mass index, carotid intima-media thickness, microalbuminuria) is also more strongly correlated with HBP measurements than with OBP measurements in essential hypertension [28–33], as well as in patients with CKD on hemodialysis (HD) [34], in older subjects, in women with preeclampsia, and in hypertensive patients with diabetes [7].

In particular, in patients with CKD, HBPM was shown to be a better predictor of progression of CKD [as assessed using the estimated glomerular filtration rate (eGFR)] [35, 36], including its progression to end-stage renal disease (ESRD) [27], and of CV events and mortality [37] than OBPM. In particular, in ESRD, HBPM might result to be prognostically more informative than pre- and postdialysis OBP readings as it provides BP measurements that are more representative of the BP load over the interdialytic period. Indeed, several studies in ESRD have found HBPM to be prognostically superior than OBPM in predicting left ventricular hypertrophy [34], and all-cause and CV mortality [38, 39].

HBPM may offer clinically relevant information not only when focusing on average HBP levels, but also when considering HBP variability between days. Although most studies on the prognostic relevance of BP variability have focused

Table 9.2 Home blood pressure measurements and outcomes

Study	Population	Time of measurements	Average number of measurements	Outcome
[18, 19]	General population aged ≥40 years	Morning	21	Cardiovascular, noncardiovascular and all-cause mortality
[20]	General population aged ≥40 years	Morning	1–25	Total stroke morbidity
[21]	General population aged ≥40 years	Morning	25	Total stroke morbidity
[22]	General population aged ≥40 years	Morning	25	Total, hemorrhagic, and ischemic stroke morbidity
[23]	General population aged ≥40 years	Morning and evening	47	Total stroke morbidity
[24]	Community-dwelling, aged ≥65 years	Morning and evening	20	Cardiovascular, noncardiovascular, and all-cause mortality
[25]	Community-dwelling, aged ≥75 years	Morning and evening	20	Disability, cardiovascular and all-cause mortality; cardiovascular and stroke morbidity
[15]	Treated hypertensives, aged ≥60 years	Morning and evening	27	Cardiovascular and all-cause mortality; total cardiovascular morbidity
[12, 14]	General population aged 25–74 years	Morning and evening	2	Cardiovascular and all-cause mortality
[27]	Veterans with CKD	Morning, afternoon, and evening	Not available	Morbidity of end-stage renal disease; all-cause mortality
[17]	General population aged ≥60 years	Morning	3	Major cardiovascular events (cardiovascular death, myocardial infarction, and stroke)
[26]	General population aged ≥18 years	Morning and evening	12	Total cardiovascular morbidity and mortality

CKD chronic kidney disease
Modified from [7], by permission

on short-term BP changes assessed from 24-h ABPM, a recent retrospective analysis of observational studies and clinical trials has suggested that increased long-term BP variability [i.e., differences in OBP and in ambulatory blood pressure (ABP) values between weekly, monthly, or yearly visits] may also bear adverse implications for CV prognosis [40, 41]. However, it has also been suggested that increased long-term BP variability identified by HBPM may have prognostic significance in predicting the risk of CV events [42]. In the Ohasama study, increased day-by-day systolic HBP variability was indeed associated with increased risk of a composite of cardiac and stroke mortality [hazard ratio (HR) 1.27; $p = 0.002$]. When these conditions were separately considered, HBP variability remained a significant predictor of stroke mortality (HR 1.41; $p = 0.0009$), but not of cardiac mortality (HR 1.13; $p = 0.26$) [43].

As a general remark, it has to be acknowledged that the evidence available to support the prognostic value of HBPM is less than for ABPM, also because of the smaller number of outcome studies available thus far [7].

9.3 How to Best Exploit the Advantages of Home Blood Pressure Monitoring in Clinical Practice (Methodological Aspects)

9.3.1 Measurement Conditions and Procedures

Although automated and semiautomated HBPM devices based on the oscillometric technique are widely used by hypertensive patients, their application is not always accompanied by the required knowledge or sufficient training to ensure appropriate BP self-measurement at home. The resulting problems, which could be avoided with adequate training [44], often include the use of inaccurate devices, and errors in measurement methodology and in the interpretation of HBP values. Overall, conditions and procedures for proper HBPM performance are similar to those recommended for OBP measurements [3]. Specifically, the patient should be relaxed in the sitting position, with the back supported, without crossing the legs, in a quiet room and at least 5 min of rest should precede the measurement. The arm should be supported on a table and the cuff positioned at the heart level (when the cuff is below or above the heart level, BP will be overestimated or underestimated, respectively). At the time of the first visit, when prescribing HBPM, BP measurements should be comparatively performed for both arms. If the interarm BP difference exceeds 10 mmHg for systolic BP and/or 5 mmHg for diastolic BP and persists after repeated measurements, the arm with the higher BP should be selected for future BP measurements both in the office and at home [3]. Attention should be given to the selection of cuff size according to arm circumference, so that the bladder dimensions are adequate for accurate BP measurement.

9.3.2 Device Selection

Monitors that measure BP at the upper arm (brachial artery) have been shown to be the most accurate and reliable in measuring peripheral BP levels. Although some automatic devices for BP measurement at the wrist or at the finger level have been developed, it should be mentioned that they are subject to important limitations mainly related to peripheral vasoconstriction, alterations in BP waveform on going from central to more distal sites of recording, and the possibility of varying hydrostatic height difference between the peripheral cuff and the heart level, which may lead to significant inaccuracies in BP measurement. This is why the use of wrist cuff devices is currently discouraged. Finally, it should be mentioned that despite the multitude of devices available on the market for HBPM, only some of these have fulfilled independent validation criteria for use in clinical practice (updated lists of validated BP measuring devices are provided at dedicated websites such as www.dableducational.org, www.pressionearteriosa.net, or www.bhsoc.org). In summary, bearing in mind the available evidence, current guidelines for HBPM recommend the use of validated, automated, electronic, oscillometric, upper arm cuff devices, particularly those offering the possibility to store, transmit, or print measurements [7].

9.3.3 Frequency and Timing of Home Blood Pressure Monitoring

To achieve the maximum benefits from HBPM, the optimal HBPM schedule to be used for clinical decision-making should be able to offer a quantification of the prevailing level of HBP, aimed at yielding reproducible information on HBP values, with prognostic relevance.

Since the reliability of HBPM increases with the number of BP readings available for analysis, a minimum of 12 measurements and up to 25 measurements are needed to achieve clinically relevant information on HBP, and current guidelines recommend that HBP should be taken over 7 days, with at least two morning and two evening measurements [7]. For clinical decision-making, the average of all these values should be used with the exception of the first day, which should be discarded [7]. This 7-day schedule is recommended immediately before each visit to the physician's office, either at diagnosis or during follow-up. In recognition that long-term HBPM might allow a closer assessment of the stability of HBP control, improve patients' involvement and compliance with treatment, and maintain their BP measurement skills, it was suggested that 1–2 measurements per week might be useful also during the between-visit period [7].

9.3.4 Report and Teletransmission of Home Blood Pressure Monitoring Values

The interpretation of HBPM values in clinical practice is not always straightforward since data are usually reported in handwritten logbooks and sometimes are inaccurate and/or illegible. This makes it difficult to have a general idea of BP behavior over the recording period and/or to estimate BP changes in response to antihypertensive treatment, thus discouraging physicians from using HBPM data for clinical decision-making.

In an attempt to overcome these difficulties, HBP telemonitoring (HBPT) systems were developed that allow the upload of data obtained by patients at home to a remote sever (through a stationary or mobile phone or Internet connection) where HBPM values are stored and analyzed [45, 46]. Automatically generated reports of these data are easier to interpret by the physician, and are thus more useful when making therapeutic decisions, which may be communicated to the patient without the need for additional clinic visits. Several HBPT systems are available, some of which also allow sending reminders to patients indicating the time of BP measurement and/or medication intake. Available studies indicate that their use increases treatment compliance and improves BP control [47–49]. Preliminary reports also suggest a possible usefulness of HBPT for self-titration of antihypertensive medication by patients [50]. Although some financial aspects may limit the implementation of HBPT (i.e., costs of purchasing and maintaining the system, the need for trained personnel, and the need for telephone/Internet connections), they may be partly counterbalanced by the reduction in the costs of patient management compared with usual care.

9.4 How are Hypertension and Blood Pressure Control Defined Based on Office Blood Pressure and Home Blood Pressure Monitoring?

Hypertension has a strong, continuous relationship with CV risk. Traditionally, OBP measurements have been used to stratify CV risk and to define therapeutic targets. The classification of BP categories (i.e., optimal BP $<$ 120/80 mmHg; prehypertension 120–139/80–89 mmHg; and hypertension $\geq$140/90 mmHg) as well as the definition of BP targets to be achieved by treatment, have been based on epidemiological studies using OBP measurements [8, 51]. These values cannot be directly extrapolated to HBPM, because meta-analyses of several studies on unselected populations or hypertensive patients [52, 53], comparing HBP and OBP distribution curves, have demonstrated HBP values to be lower than corresponding OBP values.

Longitudinal studies in the general population [12, 14, 18, 20–24, 54, 55], and in hypertensive subjects [15, 27, 35], as well as clinical trials on the use of HBPM, have confirmed that the cut-off limit to define hypertension based on HBP should

be lower than that used for OBP [56, 57]. Although the relationship between BP values self-measured at home and the incidence of CV morbidity and mortality should be further clarified by prospective studies, there is agreement that hypertension is diagnosed when HBP is ≥135/85 mmHg (corresponding to an OBP of >140/90 mmHg). However, prospective data are still needed to formally recommend the proposed thresholds of <120/80 mmHg and <130/85 mmHg as the optimal and normal HBP, respectively.

A couple of studies suggested that HBP thresholds for hypertension in high-risk patients might be lower than 135/85 mmHg [21, 27]. Although the target HBP to be achieved with treatment should logically be below the threshold used to diagnose hypertension (i.e., <135/85 mmHg), these target HBP levels are currently unknown. This issue is being currently explored by the ongoing Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) study [58]. As proposed for OBP [2], lower treatment HBP targets might be advisable in high-risk patients (i.e., diabetes mellitus, history of stroke, coronary heart disease, or CKD). However, the question whether attaining lower BP levels is truly beneficial in these groups is still being debated [59] and direct evidence supporting these lower targets is not yet available. Although attaining therapeutic goals may be difficult in some patients, it should be remembered that even if BP is not fully controlled, each mmHg of reduction in HBP is important, as it contributes to the prevention of CV complications.

9.5 Clinical Applications of Home Blood Pressure Monitoring in the Diagnosis and Management of Hypertension

9.5.1 Identification of Masked Hypertension and White Coat Hypertension by Home Blood Pressure Monitoring

As mentioned previously, HBPM and ABPM provide out-of-office BP measurements, detecting BP changes in real-life conditions and preventing the nervous reaction associated with OBP [4]. The latter may contribute to the frequently observed disagreement between OBP and out-of-office BP measurements (performed either with ABPM or HBPM). Indeed, when considering the threshold values used to define hypertension using OBP (≥140/90 mmHg) and HBP or daytime ABP (≥135/85 mmHg), a given individual may fall into one of four BP categories: sustained normotension, sustained hypertension, white coat hypertension (WCH), or masked hypertension (MH; see Fig. 9.2).

The prognostic relevance of WCH, (i.e. an elevated OBP associated with normal ABP or HBP) is still being debated, although it seems to modestly increase CV risk [60]. On the contrary, the identification of MH (normal OBP and elevated ABP or HBP) [61, 62], is important against the background of the evidence showing MH to be associated with an elevated CV risk, close to that of patients with sustained hypertension (in whom both OBP and out-of-office BPs are

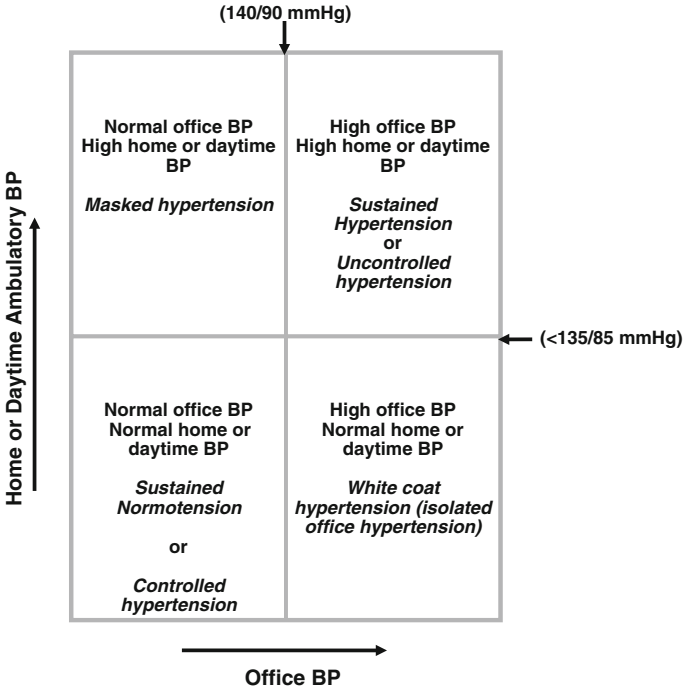

Fig. 9.2 Schematic relationship between office and home or daytime ambulatory BP. Classification of patients is based on the comparison of office and home or daytime ambulatory blood pressure (BP). Taken from [7], by permission

elevated) [14, 15, 63]. Although MH was first studied with ABPM [61], it has been demonstrated that HBPM is as reliable as ABPM in identifying this phenomenon as well as the target organ damage associated with MH [64]. Therefore, when the initial diagnosis in a subject with suspected hypertension is being made, HBPM may be useful in identifying *truly* hypertensive patients, likely to benefit from the implementation of antihypertensive therapy [56].

9.5.2 Assessment of Blood Pressure Control in Treated Hypertensives

In the light of the available evidence supporting the prognostic and clinical advantages offered by HBPM, current international and national guidelines recommend the use of HBPM as part of a routine diagnostic and therapeutic approach to hypertension, in particular in treated patients [2, 7, 8, 65–68]. By providing accurate and frequent BP measurements at regular time intervals over several days, weeks, or months, within a real-life setting, HBPM is able to accurately track changes in BP levels induced by antihypertensive treatment, thus

being a better indicator of BP control than OBP measurements alone [7]. HBPM might thus represent an excellent tool to assess and improve the achievement of BP control, in particular in patients with apparently resistant hypertension in whom BP cannot be easily controlled even with several types of antihypertensive medications.

In support of this concept, several studies exploring the benefits of HBPM for the long-term management of patients on antihypertensive therapy have shown that when properly implemented, HBPM may significantly increase the achievement of BP control when compared to conventional OBP [69, 70] while reducing the need for follow-up medical visits [71]. The benefits of HBPM in this regard may derive from several factors. First, the use of HBPM improves adherence to the prescribed treatment. Second, in subjects who receive antihypertensive treatment, OBP measurements alone may be inaccurate in assessing true BP control in everyday life. Indeed, a significant proportion of patients with adequately controlled HBP, are often classified as having refractory hypertension based on OBP (false resistant hypertension) [15, 72], while about half of individuals with elevated BP levels at home, may be, based on OBP, mistakenly classified as having adequate BP control (masked uncontrolled hypertension). In these cases, the result of HBPM may either be sufficient by itself to guide the decision on the need to modify antihypertensive treatment (e.g., in patients already known to present with WCH) or may indicate the need to perform ABPM, to ultimately confirm or discard the diagnosis of uncontrolled hypertension [73]. An accurate assessment of daily BP control is particularly important for the identification of masked uncontrolled hypertension, a condition associated with an adverse CV prognosis (similar to that of sustained uncontrolled hypertension) [15, 74]. It is also relevant in patients with uncontrolled clinic hypertension (or false resistant hypertension), as it prevents excessive BP-lowering treatment, which may reduce patient compliance due to the need to take more medication, to the occurrence of side effects, and of possible hypotensive episodes.

While emphasizing the above advantages of HBPM in assessing BP control by treatment, we have also to acknowledge that HBPM may not provide information on BP levels during nighttime sleep, which have shown to be of major clinical relevance because of their demonstrated prognostic value [12, 13, 75–78]. Moreover, HBPM is admittedly less effective than ABPM in assessing the time distribution of BP control by treatment. However, HBPM performed in the morning (before medication intake) and in the evening may nevertheless provide some information about the efficacy of therapeutic coverage over 24 h and may identify cases of morning hypertension attributable to the insufficient duration of action of prescribed antihypertensive medications.

A unique advantage of HBPM over both ABPM and OBP measurement is the possibility to easily perform BP measurements repeatedly and regularly over extended periods of time, which is crucial in optimizing BP control in treated patients. HBPM might result particularly effective in the case of hypertensive subjects with CKD, but especially in those with ESRD. In patients undergoing hemodialysis, BP control poses some unique challenges because of the marked reduction in intravascular volume immediately after hemodialysis and its

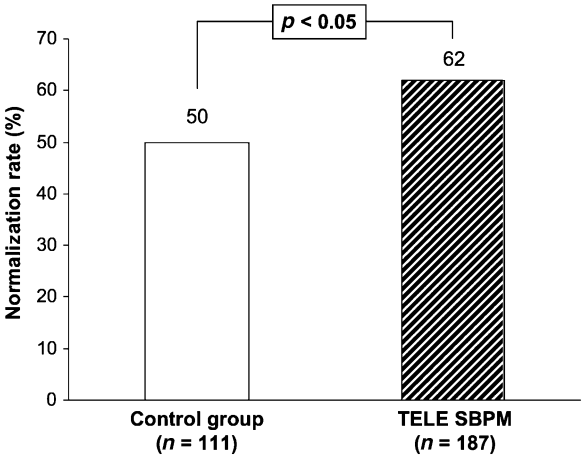

Fig. 9.3 Percentage of patients with daytime ambulatory blood pressure (BP) normalization (systolic BP <130 mmHg and diastolic BP <80 mmHg). In this study, hypertensive patients were randomized to be conventionally managed based on office BP measurement (*open bar*, $n = 111$) or to be managed based on teletransmission of home BP values (*dashed bar*: $n = 187$). Taken from [49], by permission. *SBPM* self-blood pressure measurement

progressive increases throughout the interdialytic period, which determine an extremely variable behaviour of BP [79]. In this context, HBPM might provide potential advantages, such as the possibility of sampling BP at various times throughout the interdialytic period, thus tracking daytime and day-to-day variations in BP, and providing BP measurements that are more representative of a subject's actual BP burden. The addition of telemonitoring of HBP has shown to further increase compliance to treatment and BP control [46, 49], and could result to be particularly advantageous in the ESRD setting (see Fig. 9.3).

These considerations emphasize the need of performing HBPM in all treated hypertensive patients, even if they have controlled OBP, to better define the actual BP normalization rate achieved by various drug regimens [7, 80].

9.5.3 Improving Adherence to Treatment and Achieving Blood Pressure Control

A poor adherence to therapy has been recognized as one of the most important causes of uncontrolled hypertension. By encouraging patients to become actively involved in their care, and by positively affecting their perceptions about the management of hypertension, HBPM offers the possibility to improve patient compliance and adherence to lifestyle changes and/or medical treatment [81]. Recent meta-analyses of randomized controlled trials have shown that compared with usual care based on OBP measurements, antihypertensive treatment guided by HBPM may significantly increase the rates of achievement of BP control [69],

probably as a consequence of better treatment compliance. As mentioned previously, it has also been shown that the addition of remote telemonitoring of HBP values may further increase BP control rates [49], especially in subjects with treatment-resistant hypertension due to poor compliance with multiple drug regimens [82]. Currently, HBPM is being increasingly implemented in clinical settings not only to guide antihypertensive therapy and to assess long-term BP control, but also as a means to improve patient compliance and adherence to antihypertensive treatment [83].

9.6 Conclusions

Consistent evidence supports the superior prognostic value of HBPM over conventional OBP measurements in predicting the initiation, establishment, and progression of subclinical organ damage as well as the development of fatal and nonfatal CV events and all-cause and CV mortality in hypertension. HBPM has also been demonstrated to offer significant clinical advantages over routine OBP measurements for the diagnostic and therapeutic approach to hypertension. It reduces the misclassification of hypertension by identifying WCH and MH. HBPM offers the possibility to perform accurate and frequent out-of-office BP measurements not only during a single day, but also over several days, weeks, or months in a real-life setting, thus allowing for a better assessment of BP response to antihypertensive treatment and guiding therapeutic decisions.

Unlike OBP, HBPM requires the active involvement of patients in managing their high BP levels, which enhances patient compliance and adherence to antihypertensive treatment, thus potentially increasing the rates of BP control. Based on its prognostic and clinical advantages over OBP measurements, the use of HBPM has been strongly supported by current guidelines for hypertension management as part of a routine diagnostic and therapeutic approach to hypertension, not as a substitute for, but as complementary to conventional OBP measurements, in particular in treated patients [2, 8].

Because HBPM combines improved accuracy with the advantages of low cost and easy implementation, most patients with known or suspected hypertension should have their BP assessed and managed also by means of HBP recordings. Care is required, however, to guarantee that HBP self-measurements are kept under close supervision by physicians, to prevent an excessive frequency of BP self-measurement due to anxiety, as well as incorrect self-management of drug treatment by patients. Despite the several advantages and potential applications offered by HBPM, evidence from population studies and randomized trials on hypertension is still needed to address several important issues in this field, such as the definition of HBP targets to be achieved with BP-lowering strategies or the optimal strategy for a meaningful application of both HBPM and ABPM in clinical practice.

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Obstructive Sleep Apnea

10

Jacek Wolf and Krzysztof Narkiewicz

10.1 Introduction

Cardiovascular control is markedly affected by normal sleep [1]. A blood pressure (BP) profile correlates directly to the amount of deep sleep and inversely with markers of sleep fragmentation [2]. Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders known. Recurring nightly apneic events are not only accompanied by severe impairment of the sleep pattern, but also provoke acute and chronic changes in cardiovascular performance. Most high-risk cardiovascular patients should be routinely screened and treated for concurrent OSA. This position has been reflected in both European and US recommendations for the management of arterial hypertension.

10.2 Sleep Apnea

Sleep disordered breathing (SDB) comprises different patterns of abnormal respiratory control during sleep, among which OSA appears to be the most prevalent [3]. Diagnosis of SDB is based on an overnight polysomnographic (PSG) recording, which is usually preceded by preliminary tests (e.g., questionnaires). Severity assessment of the majority of SDB forms is possible with PSG-derived indices. In spite of some limitations, the apnea–hypopnea index (AHI) has been widely accepted as a disease marker used in clinical practice, epidemiology, and

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research. OSA may affect every fourth man and every tenth woman in adulthood [4]; however, records show that the condition remains highly under recognized, especially in the cardiovascular population [5].

There are no pathognomonic symptoms of different forms of SDB. A patient may present the full-blown disease or the symptoms may hardly be apparent, with no clear correlation with the disease severity denoted by AHI. Symptoms may also vary substantially within one type of SDB, such as OSA. Management of different forms of sleep apnea comprises various modalities; however, noninvasive, continuous positive airway pressure (CPAP) administered at night appears to be the one most widely implemented. CPAP treatment not only effectively reduces excessive daytime sleepiness (EDS) and other OSA symptoms, thereby improving quality of life, but also decreases OSA-related morbidity and mortality. Unfortunately, adherence to CPAP therapy varies considerably across the OSA population [6].

10.3 Cardiovascular Aspects of Sleep Apnea

Repetitive apneic episodes during sleep elicit multiple deleterious stimuli which altogether negatively interfere with various control systems. Presently, sleep apnea is no longer recognized as a condition related to daytime somnolence only, but also as a disorder negatively affecting cardiovascular performance, morbidity, and mortality [7, 8]. Untreated OSA poses a great, and usually underestimated, financial burden on societies. Health-care expenditures related to OSA are mainly incorporated in the financing of a wide spectrum of cardiovascular diseases [9, 10]. Apart from obstructive apneas, other types of SDB (Cheyne–Stokes respiration, central sleep apnea, and alveolar hypoventilation syndromes) may further be implicated in heart and vascular pathologies; however, this problem requires additional, adequately designed and sufficiently powered studies.

10.3.1 Interrelationship between Obstructive Sleep Apnea and Hypertension

The link between recurring apneic episodes during sleep and abnormal BP control has been confirmed in multiple experimental and observational studies [11, 12]. Animal models have evidenced mimicked OSA as a potentially reversible cause of secondary hypertension [13]. Cross-sectional studies in humans have demonstrated that patients with untreated OSA are characterized by higher arterial BP and an increased rate of diagnosed hypertension [14, 15, 16]. The risk for incident hypertension appears to be independent of confounders and tightly relates to apnea severity denoted by AHI [17]. Reported studies suggest causality between OSA and hypertension only in the younger and middle-age populations, whereas no such relation is seen in the older population [18]. Conversely, patients with essential hypertension have a higher rate of undiagnosed sleep apnea [19]. This phenomenon is especially evident in the group of hypertensive patients who are

resistant to conventional BP-lowering pharmacological treatment assessed by both office and ambulatory BP [20, 21]. Up to 84–90 % of subjects receiving multiple antihypertensive drug therapy may suffer from concurrent OSA. In fact, recent analyses assessing the distribution of all potentially reversible causes of secondary hypertension have shown that previously undiagnosed OSA markedly outnumbers the sum of all other known conditions, including renovascular-, kidney-, or endocrine-related hypertension [22].

Evidence supporting the hypothesis of a causative association between OSA and secondary hypertension arose from multiple interventional studies pointed at sleep apnea elimination. Effective long-term CPAP treatment has been shown to improve BP control in hypertensive patients, particularly when BP is measured over 24 h [23, 24]. Whether or not the hypotensive effect ascribed to CPAP is dependent on either concomitant EDS [25, 26] or initial BP values, as well as ongoing antihypertensive treatment [27, 28], is not clear. Importantly, CPAP-related systolic and diastolic BP decrease is seen not only during sleep, but is also extended over the waking state; however, the overall hypotensive effect of CPAP is milder when directly compared to pharmacological treatment (e.g., a fourfold greater decrease in mean 24-h BP with valsartan vs. CPAP) [29]. Recently published meta-analyses on the impact of CPAP treatment on BP control confirmed significant, but modest reductions in both systolic and diastolic BP values in sleep apnea patients [30, 31].

Discrepancies related to the independent causality of OSA-induced hypertension emerged from three available longitudinal studies [32, 33, 34]. Prospective observation of normotensive subjects with unhandled sleep apnea showed that part of the relationship may be ascribed to confounders (mainly obesity); however, reported discrepancies may result from different methodological approaches.

10.3.2 Pathological Mechanisms Linking Obstructive Sleep Apnea to Hypertension

Autonomic nervous system activity, a key controller of the cardiovascular system, is tightly related to sleep stages [35]. Lines of evidence suggest that neural mechanisms not only mediate transient BP surges secondary to apneic episodes [36], but also play an important role in causing hypertension in normoxic wakefulness [37, 38, 39]. The exact mechanism explaining the *carryover effect* related to sustained sympathetic overdrive in wakefulness remains unclear. Part of this phenomenon may be explained by chemoreflex and baroreflex dysfunction in OSA patients [40, 41], which seems to be reversible following effective CPAP [42]. Increased sympathetic tone in OSA patients is paralleled by marked increases in BP variability, faster heart rate, and decreased heart rate (RR interval) variability which altogether appear to be closely linked to OSA severity [43].

The weight of evidence supports the hypothesis that the sympathetic nervous system plays a key role in abnormal BP control in OSA; however, various additional mechanisms linking OSA to cardiovascular disease have been explored. Although potentially reversible, endothelium-dependent vasodilation may add risk to the pathogenesis of hypertension in OSA, as has been shown in cross-sectional studies and experiments using CPAP [44, 45]. Several smaller studies have reported that unhandled sleep apnea may be associated with an increased concentrations of vasoactive hormones and/or their precursors, which both directly and indirectly regulate BP levels (endothelin-1, aldosterone, angiotensin II) [46, 47, 48]. However, data from interventional observations using CPAP produced conflicting results [49, 50]. Concentrations of inflammatory markers in OSA patients are higher when compared to matched subjects free of sleep breathing disorders. Intermittent hypoxia followed by reoxygenation naturally associated with apneic episodes may result in the generation of highly reactive oxygen-free radicals seen in OSA patients [51], and promote systemic inflammation. Elevated C-reactive protein [52, 53], adhesion molecules (e.g., intercellular adhesion molecule 1), interleukin-8, or monocyte chemotactic protein 1 [54] may accelerate atherosclerosis and add risk to adverse cardiovascular outcome. Lastly, there is also a growing body of evidence indicating that sleep disordered breathing may unfavorably influence metabolic regulation. Insulin sensitivity impairment has been reported in all OSA subjects independent from confounders (including central obesity, age, and sex) [55, 56]. Similar associations have also been reported for adipose-derived leptin metabolism, which may further favor weight gain. OSA is associated with higher leptin serum levels suggesting a decreased central response to its suppressant properties [57, 58]. In fact, frequent clustering of sleep apnea with other metabolic syndrome components has raised the question of whether or not OSA should be considered as a basic syndrome component [59, 60].

10.3.3 Obstructive Sleep Apnea-Related Target Organ Damage

Several complications primarily ascribed to hypertension alone, may in fact be partially related to untreated OSA. Numerous examples of reported associations between sleep apnea and adverse cardiovascular outcomes are reproducible in various study designs; however, randomized controlled trials (RCTs) are highly recommended.

Animal and human studies suggest that repetitive episodes of obstructive apneas impair left ventricular (LV) function and structure [61, 62, 63]. Part of these relationships may be explained by concurrent hypertension; nevertheless, shear mechanical stress associated with obstructive episodes (negative intrathoracic pressure swings) may aggravate that phenomenon [64]. In line with OSA-related LV dysfunction, significant relationships were found between sleep apnea and ischemic heart disease. Especially in younger populations, a more severe case

of sleep apnea denoted by the respiratory disturbance index may directly translate into a higher rate of incident coronary artery disease, as well as producing an adverse prognosis after myocardial infarction [65, 66, 67, 68]. Furthermore, unhandled sleep apnea has been frequently associated with the increased prevalence and reoccurrence of various cardiac arrhythmias [69, 70, 71]. Lastly, similar associations were found with reference to cerebrovascular disease showing that OSA patients are at increased risk of a first-time-ever stroke as well as a subsequent negative stroke outcome. The latter appears to be positively influenced by CPAP therapy [72, 73, 74]. Other common complications of long-standing hypertension, such as chronic kidney disease, and their possible interrelationship with OSA, require further testing.

10.3.4 Unanswered Questions

Several issues regarding the association between sleep apnea and incident cardiovascular disease warrant further investigation. Currently, there is no clear-cut answer to the question of why only a fraction of affected OSA patients suffer from cardiovascular disease, whereas others do not. Some of the discrepancies may be ascribed to genetic propensities [75], as well as the elapsed time of the disease, but the problem seems to be more complex.

Subjects with PSG-based OSA diagnosis presenting a similar phenotype may in fact suffer from pathophysiologically different disorders [76, 77]. The role of concomitant sleep apnea symptoms such as EDS, and its possible mediatory effect in terms of cardiovascular morbidity remains unclear [78]. Hypersomnolence across the group of OSA patients may itself predict acute cardiovascular response following apnea elimination [79, 80], which in fact may underscore the role of sleep architecture decomposition in abnormal cardiovascular control. Another problem concerns the mediatory effect of age in OSA patients. The reported associations between OSA and incident hypertension are evident in younger patients (aged <50–60 years) [81, 82], whereas such a relation is lost in older persons. Additionally, OSA may exert a protective effect on cardiovascular outcomes in older populations [83]. These unanswered issues pose the valid question of which patients should actively be screened and treated for concurrent OSA.

10.4 Hypertension Management in Obstructive Sleep Apnea Patients

10.4.1 Diagnosis of Hypertension

BP measurements in patients with concurrent OSA should be a matter of particular consideration, and accurate hypertension diagnosis should be carefully made. The actual prevalence of hypertension may be underestimated in OSA patients if the

diagnosis is based on office BP readings only [84]. The ambulatory blood pressure monitoring (ABPM)-based rate of incident hypertension in these patients may be approximately twofold higher when compared to office-based data. This phenomenon results mainly from a nondipping circadian BP pattern and the frequent development of nighttime hypertension in OSA [85, 86]. Experimental studies testing novel hypoxia-triggered BP monitoring systems showed that even standard ABPM monitoring devices may fail to record all apnea-induced BP surges, thus underestimating the diagnosis of hypertension [87]. Nevertheless, the high prevalence of nondippers in OSA patients diagnosed with standard ABPM underscores the important role of ambulatory BP for hypertension screening in this population. This may be of particular importance as nighttime hypertension better predicts cardiovascular adverse outcomes compared to daytime hypertension [88].

10.5 Hypertension Treatment

Given the fact that there are limited data available regarding pharmacological antihypertensive treatment in a group of OSA patients, no specific BP-lowering drug is recommended. Nonpharmacological and pharmacological management does not differ substantially from standard procedures in hypertensive patients, with the only exception being the necessity for apnea elimination. However, a commonly encountered nondipping BP profile and nighttime hypertension in OSA justify chronotherapy as a possible therapeutic supplement [89]. Additionally, taking into account the critical role of the sympathetic nervous system in the development of OSA-related hypertension, adrenergic antagonists may show superiority to other antihypertensive agents [90]. However, studies evaluating the BP-lowering effect of different drugs in sleep apnea as well as their interrelationship with OSA severity are anecdotal [91, 92, 93]. Recently published results of a study aimed at the evaluation of renal sympathetic denervation in OSA patients with resistant hypertension were very promising in terms of both BP control, glycemic metabolism, and OSA severity [94].

10.6 Conclusions

There is growing evidence of a causal and dose-dependent relationship between OSA and hypertension. Unmanaged OSA may also have been implicated in a higher rate of target organ damage primarily ascribed to hypertension alone. Long-term CPAP treatment attenuates neural and humoral abnormalities implicated in cardiovascular control, which translates into BP lowering. Whether or not treating sleep apnea independently reduces the risk of stroke, myocardial infarction, and cardiovascular deaths remain to be determined by RCTs.

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Hypertension, Obesity, and Metabolic Syndrome

11

Peter M. Nilsson

11.1 Introduction

Hypertension is a major risk factor for cardiovascular events and renal impairment [1], as evidenced by numerous observational studies, even if a recent genetic study revealed a close link mostly to cardiovascular disease but not to renal manifestations [2].

Close links between an increase in blood pressure (BP) and different measures of obesity are also well described in the literature; obesity can be calculated using the body mass index (BMI) or by means of the waist-to-hip circumference ratio used as a marker of abdominal obesity. This constitutes a serious public health problem as excess weight and obesity are increasing on a global scale. This increase is mirrored by a similar increase in the prevalence of type 2 diabetes, especially in countries and regions of the world with a more rapid transition in lifestyle and socio-economic conditions. Abdominal obesity is linked not only to elevated BP, but also to a typical dyslipidemia [high triglycerides, low high-density lipoprotein (HDL) cholesterol] and the impairment of glucose metabolism accompanied by hyperglycemia and hyperinsulinemia, often referred to as *metabolic syndrome*, with early historical observations having taken place more than 80 years ago [3]. Today, several definitions of metabolic syndrome exist, but the most recent one is the so-called *harmonized* definition dating from 2009 [4], which is based on earlier definitions (see Table 11.1).

What is less understood are the mechanisms and pathophysiological reactions linking the entities included in metabolic syndrome. It has been suggested that factors such as insulin resistance, chronic inflammation, and early life programming could all contribute to metabolic syndrome, especially in patients with

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Table 11.1 Criteria for the diagnosis of metabolic syndrome based on a *harmonized* definition from 2009 [3]

Measure	Categorical cut-points
Elevated waist circumference[a]	Population- and country-specific definitions
Elevated triglycerides (drug treatment for hypertriglyceridemia is an alternate definition)[b]	1.7 mmol/L
Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate definition)[b]	Less than 1.0 mmol/L in men Less than 1.3 mmol/L in women
Elevated blood pressure (antihypertensive drug treatment in a patient with elevated blood pressure is an alternate definition)	Systolic 130 mmHg and/or diastolic 85 mmHg
Elevated fasting glucose[c] (drug treatment of diabetes is an alternate definition)	Fasting plasma glucose 5.6 mmol/L

[a] The IDF cut-points should be used for non-Europeans, and either the IDF or AHA/NHLBI cut-points should be used for people of European origin until more data become available
[b] The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose omega-3 fatty acids treatment presumes high triglycerides
[c] Most patients with type 2 diabetes will have metabolic syndrome by the proposed criteria

established hypertension, as summarized in recent overviews from the European Society of Hypertension (ESH) [5, 6]. It should, however, not be forgotten that the concept of a metabolic syndrome has also been subject to critical debate ever since 2005, when the first critical arguments were published [7]. These critical arguments can be summarized (see Table 11.2), but do not diminish the important clinical message that these risk factors tend to cluster, and that when one of the risk factors is diagnosed it is wise also to look for the other accompanying risk factors. This could enhance the appropriate diagnostic work-up of, for example, the hypertensive patient to improve a correct risk classification for further therapeutic decisions on intervention strategies, as outlined in the ESH guidelines and risk charts from 2007 [8] and 2009 [9].

Lifestyle interventions should be the first goal to counteract the detrimental effects of obesity and metabolic syndrome, to be followed by appropriate drug therapies for the different cardiovascular risk factors that tend to cluster. The best choice of the appropriate drugs should be based on evidence and follow published guidelines, even if all recommendations could only be regarded as a preliminary guidance because the evidence base is constantly changing. Furthermore, different conditions in different countries and populations, according to the financial situation, standards of health care, and socio-economic conditions impact on the choice of appropriate therapies and structural solutions to improve public health in general and the health of patients with metabolic syndrome in particular.

Table 11.2 Critical arguments against using the diagnosis of metabolic syndrome

Cardiovascular risk prediction can be made based on the knowledge of the conventional risk factors that cluster into metabolic syndrome equally well as by using the syndrome itself
Important cardiovascular risk markers or risk factors are not included in metabolic syndrome, for example, markers of inflammation or smoking
There is no common genetic factor behind metabolic syndrome, which instead seems to be heterogeneous
Different definitions do not always target the same individuals and there is a substantial lack of overlap between definitions
Insulin resistance and hyperinsulinemia do not always characterize subjects with metabolic syndrome, even if these factors have been proposed to be core features of the syndrome
No specific drug exists to treat metabolic syndrome and all its components; drugs are only aimed at the control of individual risk factors

11.2 Epidemiology

Current trends of rising BMI and more prevalent obesity worldwide, as studied over a period of 30 years, can be described as being more or less uniform in various geographical areas and populations [10], however, they are more pronounced in some indigenous populations such as Pacific Islanders and inhabitants of countries close to the Persian Gulf. This might be caused by the rapid westernization that affects increased energy intake as well as reduced physical activity. One would expect that BP epidemiology would run in parallel, but this is not the case according to a similar survey of trends over a period of 30 years [11]. In fact, mean BP has tended to decrease in most Western countries, while it has been on the increase in other regions of the world, for example, in parts of Africa as well as in the Baltic States. This parallels similar downward shifts in mean cholesterol levels in many countries [12]. The explanation for these diverging trends are not fully understood as they cannot be completely explained by increasing use of drug treatment for hypertension or hyperlipidemia, nor can they likely be explained by changes in lifestyle. One possible explanation could instead be based on the influence of early life programming, as children born during the latter part of the 20th century have experienced better early life conditions when compared to children born during the previous decades. This could introduce an influence of birth cohort effects, as better conditions during fetal life or early infancy could well mean a decreased risk of cardiovascular risk factors, including hypertension, and future events. This is also mirrored by decreasing population-based and age-adjusted time trends for cardiovascular morbidity and mortality in most Western countries, especially for mortality due to coronary heart disease. This trend started in the USA in the late 1960s and in Sweden in the early 1980s. A similar development was recorded in the Baltic States in the mid-1990s, and more recently in Ukraine.

In spite of this positive development in relation to cardiovascular events, the alarming increase in the prevalence of type 2 diabetes could pose other health threats. For example, even if macrovascular complications are the most serious for morbidity and mortality, with improving trends in the USA and in Western Europe, hyperglycemia is also linked to microvascular complications. Among these, retinopathy, nephropathy, neuropathy, and peripheral vascular problems such as foot ulcers, cause human suffering and high costs for health care. In addition, the aging of the vasculature in poorly controlled diabetes is also mirrored by the aging of the brain and cognitive decline. It has repeatedly been shown that patients with both type 1 and type 2 diabetes risk impairment of central nervous function including cognitive decline, vascular dementia, and psychiatric problems such as depression [13]. Therefore, the control of hyperglycemia and other risk factors aims not only at preventing macrovascular, but also microvascular, complications in patients with established diabetes. However, many of these conditions, referred to as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or states of the metabolic syndrome already start in the early phases of prediabetes. In fact, hyperglycemia has been shown to predict a wide range of disease conditions and mortality from different causes, even in the nondiabetic range [14].

With regard to metabolic syndrome, prevalence data differ substantially based on the definition used, from around 15 % to more than 30 % in the adult population, and are also influenced by the distribution according to age and sex of the screened population [15]. One conceptual problem is that the different definitions of metabolic syndrome do not diagnose the same individuals, and that only a subfraction of the studied population is diagnosed by more than one of the definitions [16]. It has also been shown that insulin resistance and hyperinsulinemia, the corner stones of metabolic syndrome, are not uniformly found in all subjects with the syndrome, based on cross-sectional data from a large database of healthy Europeans within the European Group on Insulin Resistance project [17]. Furthermore, even if metabolic syndrome might well predict future morbid or fatal cardiovascular events [18, 19], it has been questioned whether the syndrome per se is able to offer a better prediction than the individual risk factors included in the syndrome [20]. This proves that the syndrome is at best heterogeneous and that different components of the syndrome can cluster in many different ways [21]. This is also reflected by the fact that no common genetic background factor has been found to explain the clustering of risk factors in metabolic syndrome [22]. These conceptual difficulties have led some researchers, mostly in diabetology, to question the usefulness of metabolic syndrome, while other researchers, mostly in cardiology and related disciplines, have defended the syndrome as a useful tool, especially for risk communication to patients and for supporting the clinical strategy of looking for other risk factors associated with the syndrome when one is found, for example, hypertension (see Table 11.3).

Table 11.3 Arguments in favor of using the diagnosis of metabolic syndrome

For clinical practice, it is a good practical rule to look for additional risk factors of the syndrome if one of these is diagnosed, for example, hypertension
During the clinical consultation with the patient, the metabolic syndrome concept can be used a teaching tool to support a better understanding and to motivate the patient to change to a better and healthier lifestyle
A better diagnosis of impaired glucose metabolism by the use of not only fasting plasma glucose but also oral tolerance testing in risk patients, as well as a search for target organ damage (TOD), can be motivated in risk patients exhibiting features of metabolic syndrome

Table 11.4 Mechanisms for the elevation of blood pressure associated with hyperinsulinemia

Sodium retention in renal tubuli
Increase in sympathetic nervous activity
Increased smooth muscle cell growth in the arterial media
Impaired endothelial function associated with insulin resistance
Disturbed intracellular electrolyte balance with reduced intracellular magnesium

11.3 Pathophysiology

It has been suggested that the explanation for increased BP associated with being overweight and obese is linked to factors such as underlying impaired insulin sensitivity (insulin resistance) and concomitant hyperinsulinemia, a state that could be sustained only as long as pancreatic beta-cell function is preserved. Hyperinsulinemia, for example, could act to elevate BP (see Table 11.4). The mechanisms involved would include sodium retention, increased sympathetic nervous activity, and enhanced growth of smooth muscle cells in the arterial wall, thereby promoting a narrowing of the arterial lumen and causing impaired vascular function [6, 23]. In addition, the influence of chronic inflammation, at the systemic, local, and perivascular level could contribute to impaired vascular function [24]. One consequence of these synergistic processes could be early endothelial dysfunction and increased arterial stiffness, these being early markers of the development of what has been called early vascular aging (EVA) [25–27] in subjects at increased vascular risk.

An underlying insulin resistance could also be a major factor contributing to impaired glucose uptake and gradually progressing hyperglycemia, which might impair overall metabolic control via a process called glucose toxicity [28]. Interestingly enough, this process can be counteracted by increased physical activity that engages the slow-twitch muscle fibers of the leg musculature, since

glucose uptake is increased via muscle activity in a noninsulin-dependent way. If insulin resistance, hyperinsulinemia, and glucose toxicity are allowed to progress, this will sooner or later lead to beta-cell exhaustion and the development of overt type 2 diabetes, which is most commonly diagnosed by a mean plasma glucose level of 7.0 mmol/L or above. In addition, oral glucose tolerance testing could also be used for diagnostic purposes when a repeated 2-h plasma glucose level of 11.0 mmol/L is a diagnostic criterion of diabetes. In addition, glycated hemoglobin can be used for screening purposes, as recommended by the American Diabetes Association, even if this procedure has not yet been widely applied [29].

Another aspect of obesity is that neuroendocrine dysregulation could impact on the preference for food intake, satiety, and the functioning of brain reward systems. Many obese subjects tend to have an imbalance between caloric (food) intake and energy expenditure. This is also influenced by genetic factors, such as the *fat mass and obesity associated* (*FTO*) gene, which interacts with the environment for increased risk of elevated BMI and obesity [30, 31]. Hormonal factors such as leptin, ghrelin, and the incretin system have all been explored for associations with eating behavior, satiety, and energy homeostasis. On the other hand, physical activity is also influenced by genetic factors regulating oxygen uptake, muscle fiber composition, and motivation (behavioral genetics). This means that the development of (abdominal) obesity, associated risk factors, and metabolic syndrome could best be understood on the basis of genetic–environmental interactions, while taking into account the socio-economic setting. For example, the federal state with the most pronounced obesity prevalence in the local population of the USA is Mississippi. This is also the federal state with the lowest socioeconomic status and a high proportion of ethnic minorities with an increased risk of obesity, hypertension, and cardiovascular events, especially stroke. Therefore, the biological clustering of risk factors that is called metabolic syndrome could not be fully understood without a broader view on the structural, cultural, and socioeconomic factors that determine lifestyle and health.

For over 20 years, researchers have tried to disentangle the contributions from early life development to adult cardiovascular risk. Based on epidemiological findings, it has been shown that babies born small for gestational age (SGA) following a period of intrauterine growth restriction (IUGR) are at increased risk of adult hypertension, type 2 diabetes, coronary heart disease, and other cardiovascular risk conditions [32, 33]. This risk is usually higher in boys than in girls and especially pronounced in SGA babies with a more rapid than usual catch-up growth in infancy, explained by the so-called mismatch hypothesis [34]. This means that early prevention directed toward pregnant women and babies born after IUGR pregnancies could contribute to better adult cardiovascular health. Some experts have advocated the view that regular screening programs for cardiovascular risk factors should be offered to children born SGA or pre-term. A smoke-free pregnancy with adequate health controls, a balanced nutrition, and increased physical and mental stimulation during childhood could be of great importance in improving public health, especially when linked to increased cardiovascular risk or diabetes.

As chronic inflammation has been highlighted as an important pathophysiological link for risk of obesity-associated medical conditions affecting metabolism and the cardiovascular system, much research has been devoted to better understand the origins of inflammation [35]. It has been suggested that the development of intra-abdominal fat deposits is a major source of proinflammatory cytokines affecting the hepatic production of inflammatory markers such as fibrinogen, high-sensitivity C-reactive protein (hsCRP), and acute phase reactants (proteins). Even chronic infection could contribute to chronic inflammation, examples being chronic bronchitis, cystitis, or periodontal disease with gingivitis. Even if there is serological evidence for the contribution of infectious agents to cardiovascular disease [36], randomized intervention studies based on antibiotic therapy versus placebo have generally not been successful [37].

11.4 Treatment

It seems a natural choice to improve lifestyle and support weight loss in the overweight or obese subject presenting with features of metabolic syndrome while they are still nondiabetic. Observational studies have shown that risk factors might decrease following weight loss, and a few studies have also shown the potential of preventing the development of type 2 diabetes when weight control and increased physical activity are combined in subjects with IGT [38, 39]. Surgical interventions leading to weight loss, e.g., bariatric surgery, have also shown encouraging effects in patients who can tolerate surgical interventions, and even a reduction of all-cause mortality in the Swedish Obese Subjects intervention study [40]. On the other hand, it is hard to both achieve and maintain a sustainable weight loss in overweight/obese patients, and weight fluctuations could be detrimental to metabolism and cardiovascular risk. Some observational, population-based studies showed an increased mortality risk associated with weight loss during follow-up in overweight/obese subjects, even after exclusion of all cancer causes and other comorbidities, while also adjusting for risk factors [41]. This finding remains enigmatic and could be caused by the influence of unmeasured factors despite any adjustments for risk factors. However, as weight-stable subjects are most commonly at the lowest risk, there is reason to recommend weight stabilization as a goal for many of these subjects. This will also prevent the annual weight increase that is typical of many middle-aged subjects.

In patients with established diabetes, there is more observational evidence to support weight loss [42], even if data from randomized intervention trials is still lacking. The final results of the Action for Health in Diabetes (Look AHEAD) trial in the USA, whose aims are to prevent all-cause mortality and cardiovascular nonfatal events, and which involves 5,000 overweight/obese patients with type 2 diabetes randomized to either intensive lifestyle modifications or to standard care [43], are expected in a few years' time.

If weight loss is not an easy strategy to apply, neither in theory nor in clinical practice, there are some other components of a healthy lifestyle that could be promoted based on the available evidence. These recommendations include

smoking cessation, increased physical activity, as well as a diet with components of the traditional Mediterranean diet to prevent cardiovascular disease [44], the major health burden in these patients.

There are no specific drugs available for obese patients diagnosed with metabolic syndrome. Instead, individual risk factors should be treated based on the available guidelines, for example, the control of hypertension, dyslipidemia, and hyperglycemia. Attempts have been made to use peroxisome proliferator-activated receptor gamma agonists (glitazones) in these patients. Such therapy can prevent, or rather postpone, the development of type 2 diabetes in IGT subjects, but cannot prevent cardiovascular disease manifestations in primary prevention. Only in secondary prevention, following coronary heart disease, one of the glitazones (pioglitazone) has shown some benefits in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (ProACTIVE) study, albeit for the secondary end point of that study [45]. Metformin is also useful for preventing or postponing the development of type 2 diabetes in subjects with IGT [39], but no data support the prevention of cardiovascular events in these patients based on metformin.

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, statin treatment was documented to be beneficial for subjects with or without metabolic syndrome, for example, for individuals who had normal levels of low-density lipoprotein (LDL) cholesterol but elevated levels of an inflammatory marker, hsCRP [46]. One interesting aspect of the pharmacological effects of statins is the elevation of glucose levels and an increased risk of new-onset type 2 diabetes in subjects treated with statins [47]. This marginal detrimental effect is more of a theoretical interest than of clinical relevance, as the benefits associated with statin treatment [48] seem to outweigh by far the adverse effect on glucose metabolism by these drugs, an effect that could eventually be linked to effects on the insulin secretion capacity of the pancreatic beta-cells when cholesterol levels are manipulated in vitro [49].

Fibrates have been advocated for treatment of the dyslipidemia characteristically found in patients with impaired glucose metabolism and metabolic syndrome. This kind of dyslipidemia consists of elevated levels of triglycerides, postprandial hypertriglyceridemia, decrease levels of HDL cholesterol, as well as an increase in small, dense and atherogenic LDL cholesterol particles (so-called pattern B). Unfortunately, fibrate therapy was not convincing in a placebo-controlled intervention study [the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial] in patients with type 2 diabetes [50]. Only in subgroups from other trials with patients showing more pronounced dyslipidemia and features of metabolic syndrome, a beneficial effect of fibrate therapy was shown. Other attempts at increasing HDL cholesterol levels by the use of nicotinic acid have not been successful, as shown by data from the AIM-High study [51]. On the other hand, new drugs that increase HDL cholesterol by inhabitation of a regulating enzyme (cholesteryl ester transfer protein) have shown a good safety profile [52]. Studies are ongoing with these new drugs (e.g., anacetrapib) to test them for their ability to achieve cardiovascular prevention.

Most of the commonly available antihypertensive drugs are useful in patients with metabolic syndrome or impaired glucose metabolism. Traditionally, agents that are metabolically neutral, such as calcium antagonists, have been recommended in these patients, or even more so drugs that block the renin–angiotensin system (RAS), as these drugs may improve insulin sensitivity and glucose metabolism [53]. The angiotensin-converting enzyme inhibitor ramipril prevented new-onset diabetes in the Heart Outcomes Prevention Evaluation (HOPE) trial in patients at risk for cardiovascular disease [54], but was not able to do the same in subjects with IGT in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial [55]. Differences in patient characteristics might contribute to the difference in outcomes between the studies. Several angiotensin-2 receptor blockers have been shown to prevent or postpone new-onset diabetes, for example, losartan in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial [56] and valsartan in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial [57]. However, these trials were not placebo-controlled, though they had an active comparison (atenolol used in the LIFE study and amlodipine in the VALUE study). Older classes of antihypertensive drugs such as beta-receptor blockers and thiazide diuretics have been accused of causing more new-onset diabetes than other classes of antihypertensive drugs. This could represent a real detrimental effect on insulin sensitivity and glucose metabolism. It is likely, however, that the effect is dosage-dependent and, for beta-receptor blocker drugs, that it is also related to drug selectivity and concomitant weight increase. New vasodilating beta-receptor blockers, such as the drug nebivolol, have a better metabolic profile and might even improve glucose metabolism [58].

In established type 2 diabetes, the hemodynamic preventive effect of lowering BP, even by the use of diuretics and beta-receptor blockers, often outweighs any metabolic side effects, as shown in the long-term follow-up of the Systolic Hypertension in the Elderly Program (SHEP) study in older US subjects with isolated systolic hypertension treated with chlorthalidone [59]. Often, the best choice for BP control in subjects with IFG/IGT or metabolic syndrome is to start therapy based on RAS-blocking agents and then to combine them with, for example, a calcium antagonist. Low-dosage of a thiazide diuretic could be used to enhance the effect of a RAS blocker, and a low-dose of traditional beta-receptor blockers or normal dose of modern vasodilating beta-receptor blockers could be used even in these patients, for example, if additional indications exist (angina pectoris, migraine, tachycardia). The intensity of BP control should be guided by the total estimated cardiovascular risk, when the presence or not of target organ damage (TOD) is of great importance. This means that screening should be started for at least the presence or absence of (micro)albuminuria. If resources allow it, screening for left ventricular hypertrophy (by echocardiography), arterial stiffness (by pulse wave velocity), or early atherosclerosis (by carotid intima-media thickness or measurement of the ankle-brachial index) should also take place.

Prior to screening, consultation with a clinician should take place, when not only signs and symptoms from the physical examination could suggest increased risk, but also taking the medical and family history of the patient could prove a

useful tool. Subjects from families with a positive family history of early-onset coronary heart disease or stroke (before age of 65 years) should be offered a more thorough medical examination including screening for TOD.

In established type 2 diabetes, patients with hypertension and microalbuminuria were recruited to the Steno type 2 (Steno-2) intervention trials where a multifactorial risk factor control strategy proved to be very beneficial for the prevention of cardiovascular events [60]. However, we lack similar data for cardiovascular prevention in patients with pre-diabetes (IFG/IGT) or metabolic syndrome. One Swedish study, however, showed that increased physical activity was associated with reduced cardiovascular risk in men with IGT [61]. Studies are ongoing to test the combination of two different drugs (a statin and an angiotensin-2 receptor blocker) for cardiovascular prevention in these patients. An example of such a study is the HOPE-3 trial based on treatment with rosuvastatin and candesartan versus placebo.

11.5 Conclusions

Being overweight or obese tends to increase BP levels and worsen metabolic risk factors, such as those collectively known as metabolic syndrome. Our current state of knowledge is a sound basis of evidence from which to recommend early intervention against the risk factors that cluster together in metabolic syndrome, with a higher degree of ambition in the presence of TOD or a positive family history of early-onset cardiovascular disease or type 2 diabetes. Many studies support the use of programs to increase physical activity in IGT patients to prevent or postpone type 2 diabetes, in combination with weight control programs. A reasonable goal for many overweight or obese patients is to aim for weight stabilization in midlife, as evidence is currently lacking for cardiovascular protection by the use of nonsurgical weight loss. It should also be remembered that in the old as well as in patients with established heart disease, weight loss is not recommended, as observed weight loss in these subjects has been associated with a worse prognosis.

Ultimately, a larger role for prevention in early life should be emphasized, including healthy pregnancies and healthy childhood based on optimal nutrition, energy balance, appropriate body growth, daily physical activity, and avoidance of tobacco products. Adult patients who are overweight/obese or present with signs of metabolic syndrome should be supported and motivated toward a healthy lifestyle based on realistic strategies and achievable goals that could be effectively incorporated into daily life. Interventions in obese Pima Indians showed that a strategy favoring empowerment, cultural identity, and self-respect proved to be more beneficial for glycemic control after 1 year when compared to a conventional strategy based on traditional lifestyle advice [62].

In the future, new strategies will need to be developed for a better understanding of the early phases of cardiovascular disease pathophysiology and metabolic impairment. The new concept of EVA [25–27] focuses attention on tissue biomarkers such as arterial stiffness, rather than circulating biomarkers, such as the ones included in metabolic syndrome. Future intervention studies should test if

early detection and intervention in risk subjects with EVA could prove to be a more or less beneficial strategy when compared to screening, detection, and treating subjects with the less stable condition that we call metabolic syndrome or impaired glucose metabolism (IFG/IGT), to prevent cardiovascular complications.

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Salt, Hypertension, and Cardiovascular Disease

12

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12.1 Introduction

The salt content of natural foods is in general modest [1] and, as a consequence, the diet of all mammals was very low in salt up to approximately 5,000 years ago, at which time human beings discovered that adding salt to foods would preserve them from natural corruption [2]. Nowadays, this practice is no longer needed thanks to the development of food preservation technologies. Notwithstanding, an impressive excess of dietary salt compared to human physiological needs is observed almost worldwide and is mainly sustained by the substantial addition of salt to foods during their industrial processing [3]. While this practice is still partly justified on technological grounds when it involves special foods such as some types of cheese (e.g., blue or parmesan cheese) and cured meats, in most other cases it is driven by an attempt to improve the otherwise poor organoleptic characteristics of food, led by the concern about the acceptance of less salty products by the consumer and last, but not least, by the commercial interest in maintaining a high salt intake to stimulate thirst, thus boosting the sales of soft drinks and mineral waters. Meanwhile, a growing bulk of scientific evidence has been collected in favor of the direct causal association between a high-salt intake, arterial hypertension, and cardiovascular disease (CVD) [4] (Table 12.1).

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Table 12.1 Types of studies featuring the relationship between dietary salt intake, blood pressure, and cardiovascular disorders

	Randomized controlled trials	Cohort studies	Ecological studies	Animal/ in vitro studies
Blood pressure	X		X	X
Subclinical cardiovascular damage	X	X		X
Cardiovascular events		X	X	

12.2 Salt Intake and Hypertension

The causal relationship between a high-salt intake and hypertension is supported by a wide array of experimental, epidemiological, and intervention-based studies; likewise, the possibility of significantly reducing blood pressure by reducing salt intake has been proven in both hypertensive patients and normotensive individuals [5].

The adverse effects of a high-salt intake occur over a lifetime starting with the early childhood. The International Study of Sodium, Potassium, and Blood Pressure (INTERSALT) showed that the well-recognized increase in blood pressure with age in different populations is proportional to their respective average salt consumption [6]. A Dutch randomized controlled trial, which investigated the effects of reduced salt intake in healthy newborns in the first 6 months of life, demonstrated a difference in systolic blood pressure of 2.1 mmHg with a 2.5-fold reduction in salt intake [7]. A significantly lower blood pressure was still observed in these children compared to controls when retested 15 years later [8]. A meta-analysis of controlled clinical trials conducted in children and adolescents showed that an average 42 % reduction of sodium intake was associated with a small, but statistically significant, reduction in blood pressure (1.2/1.3 mmHg) [9].

The causal relationship between salt intake and blood pressure is supported by the results of numerous intervention trials. A study in chimpanzees showed a remarkable rise in blood pressure in these animals when the salt content of their diet was increased over a period of several months [10]. The Dietary Patterns, Sodium Intake and Blood Pressure (DASH-Sodium) trial showed the occurrence of a dose-dependent blood pressure reduction with increasingly lower sodium intake in normotensive and grade 1 hypertensive study participants, in addition to greater fruit and vegetable consumption and reduced intake of saturated fat [11]. A meta-analysis of controlled trials on the effect of reduced salt intake on blood pressure in adults showed that in hypertensive patients a median reduction of 78 mmol of salt per day was associated with a blood pressure reduction of 5.0/2.7 mmHg, while in normotensive individuals a similar reduction produced a drop of 2.0/1.0 mmHg [12]. In a recent study,

sodium reduction was proved to be extremely effective in patients with *resistant* hypertension who were already on a full dose of diuretics [13].

Blood pressure sensitivity to the adverse effect of high salt intake may vary among individuals depending on age, genetic susceptibility [14], and neurohormonal factors, particularly sympathetic tone, renin–angiotensin–aldosterone system (RAAS) activity, and the degree of insulin and leptin resistance, all these factors being commonly altered in abdominally obese individuals and promoting a tendency to enhanced proximal tubular sodium and water reabsorption [15–17]. A similar phenomenon occurs in subjects with metabolic syndrome [18, 19]. Rocchini and colleagues showed that obese adolescents were more sensitive to a high-salt intake, inasmuch their blood pressure increased to a greater extent when switching from a low to a high dietary salt regimen compared with their lean counterparts [20]. However, when these obese subjects underwent partial correction of their weight by caloric restriction and physical exercise, their blood pressure salt sensitivity was significantly reduced [20]. The condition of obese individuals in this respect is worsened by their tendency to eat more salt than lean subjects, probably because of a generally higher calorie intake [21].

12.3 Salt Intake and Cardiovascular Disease

Several cohort studies evaluated the predictive role of habitual salt intake with respect to the morbidity and mortality for cardiovascular and cerebrovascular disease. The results of these studies are not unequivocal. In a sample of 11,629 men and women participating in the Scottish Heart Health Study, followed up for nearly 8 years, a higher salt intake, assessed using a food questionnaire, was associated with an increased risk of coronary events among women, with a positive, though not significant trend in men [22]. In contrast, in the Rotterdam Study, no association was found [23]. The results of different analyses conducted in the first National Health and Nutrition Examination Survey (NHANES I) were likewise discordant. In fact, whereas a significant association between salt intake and cardiovascular mortality was not detected in a first survey of 11,348 subjects aged 25–75 years on adjusting for energy intake [24], a subsequent analysis of the same data excluding those participants who had already suffered a cardiovascular event showed that people with excess body weight, in the presence of a higher salt intake, had a higher risk of death from coronary heart disease [25]. In an analysis of the participants of the second NHANES study (NHANES II), a sodium intake lower than 2,300 mg per day compared to a higher consumption was associated with higher mortality for total cardiovascular events, but not with coronary artery disease or stroke, when considered separately [26]. As a result of another study conducted in Finland between 1982 and 1995, it was reported that an increase of 100 mmol of urinary salt excretion was associated with a higher incidence of coronary heart disease, death from coronary heart disease, or a higher incidence of deaths from CVD [27].

The Trials of Hypertension Prevention phase I and II (TOHP I and II) were intervention trials aimed at evaluating the effect of nondrug therapy on blood pressure. In these trials, a group of participants underwent moderate sodium restriction which favorably affected blood pressure [28, 29]. In a phase II observation, after a period ranging from 10 to 15 years without any kind of active intervention, the incidence of cardiovascular events was significantly lower in the group that had initially reduced dietary salt intake than in the control group [30].

Many studies have evaluated the effect of salt intake on the incidence of cerebrovascular events. Among these, a study on about 8,000 participants of Japanese origin after 10 years of follow-up did not provide evidence of a relationship between salt intake and a risk of stroke [31]. Conversely, another study conducted in Taiwan with an average follow-up of 4 years showed that high salt intake at baseline was associated with an increased risk of stroke [32]. He and colleagues, in addition to demonstrating the interaction between excess weight and salt intake on total cardiovascular risk, confirmed the positive relationship between being overweight and morbidity and mortality from stroke in the same population [25]. Finally, in the Takayama Study, a prospective study conducted in Japan that excluded individuals with history of previous CVD with a follow-up of 7 years, participants in the higher tertile of habitual sodium consumption had a significantly higher mortality rate for stroke [33]. This relationship was stronger among participants with a relatively high body mass index.

A systematic review of available prospective studies has clearly demonstrated a direct and significant association between higher salt intake and the risk of stroke [34]. The meta-analysis in the review included 13 studies published between 1966 and 2008, with the participation of approximately 170,000 people and more than 11,000 vascular events. After a follow-up ranging between 3.5 and 19 years, a difference of 5 g of salt per day was associated with a highly significant difference of 23 % in the risk of stroke and a 17 % difference in the risk of total cardiovascular disease (CVD). This association refers to a difference in salt intake consistent with recommendations by the World Health Organization (WHO) and by major national and international guidelines.

12.4 Salt Intake and Atherosclerosis

Several studies suggest that excess salt intake may have an impact on the atherosclerotic process even independently of its effect on blood pressure (Fig. 12.1).

Salt-resistant rats pretreated with dehydrocorticosterone acetate (DOCA) and maintained on a high sodium intake developed cerebral infarction, without substantial changes in blood pressure, compared with a lower sodium control group [35]. In some experimental models it has been shown that a high-salt intake promotes the production of reactive oxygen species and oxidative stress [36]. An important role in the response to excess salt is probably played by the endothelium, which appears to function as a sensor of changes in salt intake. In a recent

experimental study on human endothelial cells in vitro, endothelial cell plasticity in response to increasing sodium concentrations was assessed by means of atomic force microscopy. The experiment showed that increasing extracellular sodium concentrations raised endothelial stiffness progressively in the presence of aldosterone, whereas endothelial stiffness did not vary when the hormone was absent. It was therefore suggested that, in the presence of relatively high concentrations of extracellular sodium, albeit within the physiological range, sodium is transported into the cells through the epithelial sodium channels, inducing a decrease in the production and release of nitric oxide, which in turn leads to greater arterial stiffness [37]. In keeping with these experimental findings, a clinical study in normotensive obese subjects showed that a reduction in salt intake over 2 weeks significantly improved endothelium-mediated arterial vasodilation in the presence of a very modest decrease in blood pressure [38]. On these same grounds, a very recent trial in normotensive volunteers comparing the acute effects of the ingestion of a salty versus a low-salt soup showed that the acute salt load (6 g) produced an average rise in plasma sodium concentration of 3 mmol/L and that each mmol increase in plasma sodium was associated with a systolic blood pressure rise of 1.9 mmHg [39].

Other pathophysiological and clinical studies provide evidence of adverse effects of excess salt intake on the cardiovascular system and the kidney that are independent and additive to the effects of the increase in blood pressure. Several observational studies have shown a positive relationship between salt intake and left ventricular mass independent of blood pressure [40–42]. One of these studies highlighted the significant interaction between salt intake and blood pressure as related to cardiac hypertrophy by showing that a given increase in pressure leads to a greater increase in left ventricular mass if it is associated with a higher salt intake [40]. A controlled intervention trial demonstrated that it is possible to achieve a reduction in left ventricular mass in hypertensive patients through salt intake reduction, at least in part independently of blood pressure [42].

Two different studies carried out in Chinese and Australian population samples consistently indicated that pulse wave velocity, a classic marker of arterial stiffness, as estimated by arterial tonometry, was significantly higher in subjects having a higher salt intake compared to controls, again, at least in part, independent of differences in blood pressure [43, 44]. Other studies reported favorable changes in brachial artery diameter [45], central aortic pressure [46], and arterial elasticity [46, 47] with lower, compared to higher, salt intake.

Population studies have provided evidence of the association between the habitual consumption of salt and the urinary albumin excretion [48, 49], and a recent study in hypertensive patients of African origin showed that a moderate reduction in salt intake significantly decreased urinary protein excretion [50].

It has been argued that reducing salt intake may lead to possibly dangerous increases in plasma renin, catecholamines, lipids, glucose, and insulin, as apparently confirmed by the results of a recent review of available controlled trials of salt intake restriction [51]. The results of this meta-analysis are unfortunately ambiguous and misleading inasmuch the majority of the trials included in the review evaluated the effects of quite a drastic, suddenly applied, and short-lasting salt intake reduction which, by inducing an abrupt fall in plasma volume, powerfully stimulates RAAS and sympathetic nervous system activity, as the authors' findings demonstrated. These results are as obvious on physiological grounds as irrelevant with regard to their impact on public health. In fact, the recommendations released by public health organizations and scientific societies speak in favor of a moderate and gradual reduction of salt intake that, as demonstrated by a previous meta-analysis including only trials of moderate reduction and longer duration, does not involve such untoward effects [52]. It is also important to consider that a diet high in salt is known to increase the expression of angiotensin II type 1 (AT1) receptors in the cardiovascular system, a finding that led to the hypothesis that excess salt consumption may induce vascular alterations and organ damage through the increased activity of the local RAAS in spite of concomitant decrease in circulating renin concentration and independently of changes in blood pressure [53, 54], in accordance with the previously mentioned results of different studies.

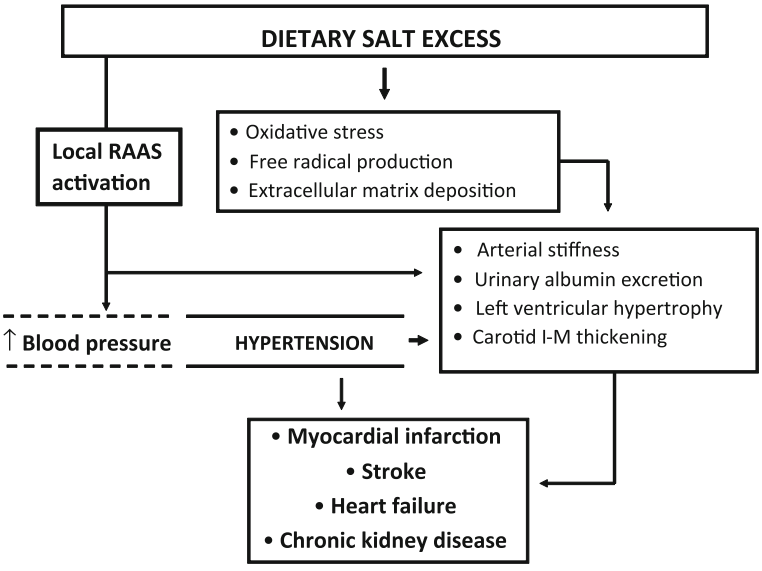

Fig. 12.1 Potential mechanisms involved in the relationship between excess salt intake and cardiovascular damage. *I-M* intima-media, *RAAS* renin–angiotensin–aldosterone system

12.5 Conclusions

The bulk of the evidence coming from a very large number of studies of different types calls for a direct responsibility of excess salt intake in the causation of cardiovascular and renal disease, not only through the established association between salt intake and blood pressure, but also through other less well-known direct effects of salt on the vascular system. Altogether, these effects explain the increased cardiovascular risk both in terms of morbidity and mortality shown by prospective studies [34] and in a recent controlled trial [55]. Since cardiovascular diseases are the first cause of death in people over 60 and the second one in subjects aged between 15 and 59 years [56], it is reasonable to expect a significant benefit on the risk of cardiovascular events by reducing the average salt intake at the population level, which in most countries worldwide is currently close to 10 g/day, twice as much the level recommended by the WHO. Reasonable evidence has been produced in favor of the feasibility of a strategy of salt intake reduction at the population level [57, 58] and of a highly favorable cost–benefit ratio of a similar policy [59, 60].

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The Optic Fundus and Retinal Circulation: New Technology for an Old Examination

13

Martin Ritt and Roland E. Schmieder

13.1 Introduction

As the cornea, lens, and vitreous humor lack blood vessels and are transparent, the retina offers the unique opportunity to examine the body's microvasculature in vivo safely, repeatedly, and noninvasively. Retinal arterioles undergo similar changes as cerebral, coronary, and peripheral arterioles in hypertension indicating that retinal arteriolar abnormalities mirror structural and functional microvascular changes elsewhere in end-organ tissues [1, 2]. As retinal and cerebral circulation share common anatomical, physiological, and embryological features, retinal circulation might be a model for cerebral microvasculature. This was supported by an autopsy study of patients with stroke, which showed a close correlation between retinal and cerebral arteriolar findings [3]. Therefore, it is not surprising that retinal microvascular abnormalities present an important prognostic value, in particular with respect to cardiovascular events and cardiovascular mortality [4].

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure lists retinopathy as one of several markers of target organ damage in hypertension [5]. In contrast, the current guidelines of the European Society of Hypertension and European Society of Cardiology 2007/2009 [6, 7] list retinopathy as target organ damage only for grades 3 and 4 of hypertensive retinopathy. This change in guidelines reflects the repeated criticism that arose over the last decade with respect to the usefulness of the traditional classification system of hypertensive retinopathy for current clinical

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practice [8–10]. As a result, much research effort has been focused on the development of new imaging techniques to analyze retinal arteriolar structure and function in subjects with hypertension more precisely.

13.2 Historical Context and Classification

Signs of hypertensive retinopathy were already described by Liebreich [11] in 1859 and then by Gunn [12] in 1892. The traditional classification of hypertensive retinopathy can be dated to a publication by Keith and colleagues in 1939 in which the authors classified hypertensive retinopathy into four grades of increasing severity [13]. In the last 20 years, retinal photographs were repeatedly used to assess the retinal microvasculature in patients with arterial hypertension. Further progress in imaging techniques [digital photography and scanning laser Doppler flowmetry (SLDF)] now allows the assessment of early structural [e.g., arteriole-to-venule ratio (AVR)] of retinal vessels, arteriolar length-to-diameter ratio, vessel density/rarefaction and tortuosity, the wall-to-lumen ratio of retinal arterioles and early functional parameters (e.g., vasoconstrictor and vasodilatory properties) of retinal microvasculature in arterial hypertension.

13.3 Assessment of Hypertensive Retinopathy

13.3.1 Hypertensive Retinopathy by Ophthalmoscopy

Direct ophthalmoscopy provides a magnified (x16) vision of the posterior pole of the retina. The procedure ought to be performed after the induction of pharmacological mydriasis and requires a certain degree of patient collaboration. It is an inexpensive method to assess retinal arteriolar structure. However, direct ophthalmoscopy has been shown to be subjective and unreliable [14–16], with significant interobserver (20–42 %) and intraobserver (10–33 %) variations in the assessment of different retinal lesions [16]. Moreover, it was found to be particularly unreliable in mild to moderate hypertension [15].

Test–retest analyses revealed poor reliability in the early stages of hypertensive retinopathy, whereas grade 3 and 4 retinopathy as classified by Keith and colleagues [13] is still a valid diagnostic criteria of severe retinal damage [4, 17–19]. In 2004, Wong and Mitchell proposed a new and simple classification system of retinal microvascular signs, detectable by ophthalmoscopy, based on the strength of the reported associations of various retinopathy markers [8]. They graded retinal vascular signs into mild [generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, and arteriolar wall opacity (silver wiring)], moderate [hemorrhage (blot-, dot-, or flame-shaped), microaneurysm, cotton-wool spot and hard exudates], and malignant (moderate retinopathy plus optic disc swelling) [8].

13.3.2 Hypertensive Retinopathy by Retinal Photography

The use of retinal photographs in combination with standardized protocols, blinded grading, and special software has improved the reliability of assessing retinal microvascular abnormalities and has led to a more precise and objective quantification of retinal microvascular signs [20]. Retinal photography can be carried using standard film or with digital equipment. Both traditional fundus cameras and *nonmydriatic* models are widely used.

13.3.2.1 Arteriole-to-Venule Ratio

Digital nonmydriatic cameras allow computer-assisted or fully automated detection of different retinopathy lesions, and the calculation of the AVR of retinal vessels. The calculation of the AVR is of particular interest since the measurement of arteriolar narrowing cannot be quantified by ophthalmoscopy. The calculation of the AVR is based on the assumption that high blood pressure is associated with narrower retinal arteriolar diameters [21–24], though it does not affect retinal venular diameters. However, recent data suggest that venular diameter is also affected by several conditions including diabetes, metabolic syndrome, smoking, and inflammation [25–29], and therefore influence the AVR independently from changes in the diameter of retinal arterioles. Nonetheless, the narrowing of arterioles is considered to represent the earliest alteration of the microvasculature, including the retinal microvasculature, in hypertensive subjects [30–32].

13.3.2.2 Topological Changes in Retinal Vascular Architecture

The parameters of the arteriolar and venular network may also be altered in patients with primary hypertension. Several parameters have been suggested to assess arteriolar narrowing (e.g., the length-to-diameter ratio) calculated as the ratio of the length of a vessel segment between two branching points to its average diameter), vascular rarefaction (e.g., the number of terminal branches), or vessel tortuosity (e.g., the ratio of the actual length of the vessel segment to the straight line distance between two connected branching points) [33, 34]. However, these parameters, although scientifically very interesting, are as yet to be introduced into clinical practice.

13.3.3 Hypertensive Retinopathy by Scanning Laser Doppler Flowmetry

SLDF with automatic full-field perfusion imaging analysis (AFFPIA) allows the measurement of retinal capillary perfusion as well as the calculation of the inner and outer diameters of retinal arterioles, thereby allowing the precise analysis of retinal vascular function and arteriolar remodeling in hypertension [35–37]. Of clinical interest, both vascular dysfunction—at least when assessed in the peripheral [38, 39] and coronary [40] circulation—and arterial remodeling—at least when assessed in

vitro in small subcutaneous arteries and arterioles [41–43]—have been found to be of prognostic significance with respect to cardiovascular events.

SLDF with AFFPIA is performed without the need for prior mydriasis. The method is safe, noninvasive, and has a short examination time of approximately 5 min. It is highly reliable [36, 44–46], but must be performed by a trained and certified observer.

13.3.4 Vascular Function of Retinal Vessels

Retinal vascular function can be assessed by examining the vasodilator capacity of retinal vessels, i.e., the increase in retinal capillary perfusion in response to flicker light exposure [37, 47–49], or more invasively, by examining the vasoconstrictor properties of retinal vessels by assessing the decrease in retinal capillary perfusion in response to the infusion of the nitric oxide synthase inhibitor NG-monomethyl-L-arginine (L-NMMA) [35, 37, 48, 49].

Recent studies have shown that the vasoconstrictor response of retinal vessels, assessed by the change in retinal capillary blood flow in response to the infusion of L-NMMA, is impaired in lean [35] and obese or overweight [37] subjects with primary hypertension. Blood pressure reduction induced pharmacologically by inhibitors of the renin–angiotensin system was found to improve the vasoconstrictor response of retinal vessels to L-NMMA infusion [35].

13.3.5 Remodeling of Retinal Arterioles

Remodeling of retinal arterioles is assessed by measuring the inner retinal arteriolar diameter in perfusion images and the outer retinal arteriolar diameter in reflection images, with subsequent calculation of the wall-to-lumen ratio [36, 37, 50, 51], wall cross-sectional area [37, 50, 51], and other parameters of retinal arteriolar remodeling according to previously described formulas [50, 51] (see Fig. 13.1).

The wall-to-lumen ratio of retinal arterioles was found to be greater in hypertensive compared to normotensive patients and systolic and diastolic blood pressure levels were found to be related to the wall-to-lumen ratio of retinal arterioles [37]. Treated hypertensive patients with well-controlled hypertension revealed lower wall-to-lumen ratio of retinal arterioles than patients with uncontrolled hypertension [36]. Moreover, in hypertensive patients, the wall-to-lumen ratio of retinal arterioles was negatively related to the vasodilatory response of retinal vessels to flicker light exposure, indicating that hypertensive patients with a greater wall-to-lumen ratio might reveal impaired vasodilatory properties of their retinal vessels [48].

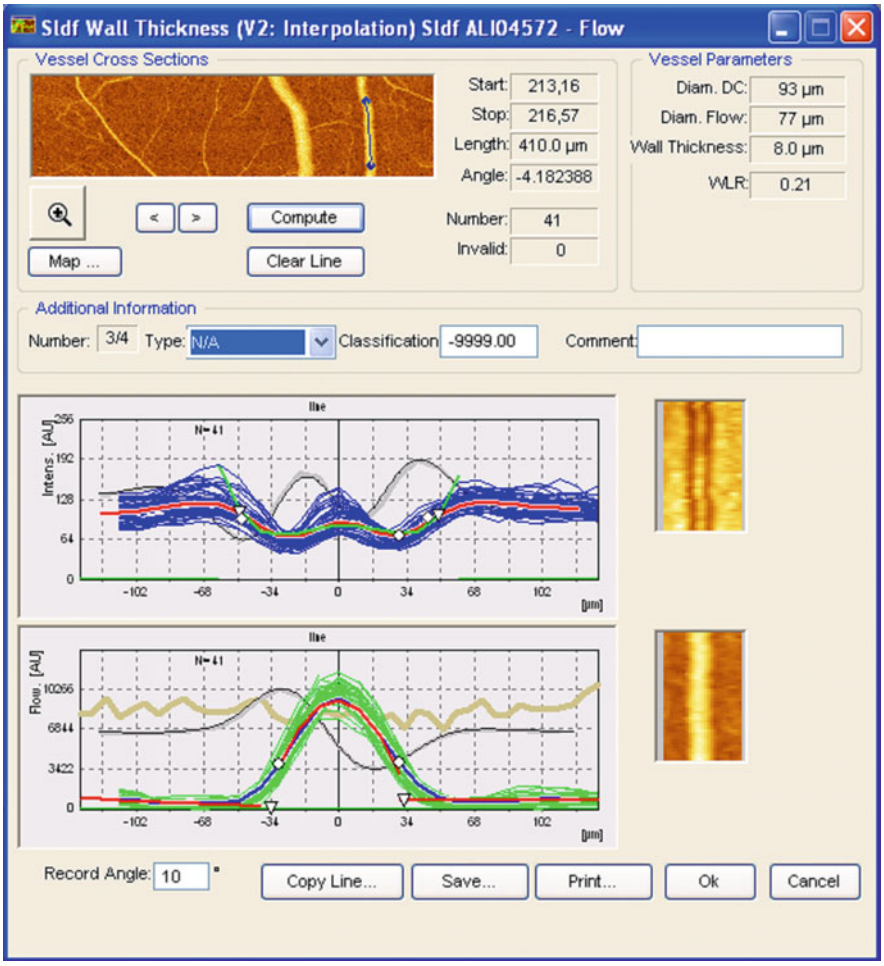

Fig. 13.1 Screenshot for the assessment of remodeling of retinal arterioles using scanning laser Doppler flowmetry with automatic full-field perfusion imaging analysis. The outer diameter is measured in reflexion images, whereby differences between the light intensity of reflected light between two points lying side by side, due to the acute angle at the outer vessel wall border, allow the detection of the outer diameter of the arteriole. The inner diameter is measured in perfusion images, whereby the bloodstream, due to high velocity in the center of the arteriolar lumen, and decreasing blood velocity toward to periphery of the arteriolar lumen allow the calculation of a parabolic velocity curve and thereby the measurement of the inner diameter of the arteriolar vessel. Subsequently, the wall-to-lumen ratio, wall cross-sectional area, and wall thickness can be calculated based on the measurements of the inner and outer diameter of the arteriole [37]

13.4 Retinal Microvascular Abnormalities and Hypertensive Organ Damage

13.4.1 Cerebrovascular Disease

The Atherosclerosis Risk in Communities (ARIC) study [17], the Cardiovascular Health Study [18], the Beaver Dam Eye Study [4], and the Shibata Study [19] revealed an increased risk of stroke in patients with hypertensive retinopathy, analysed by retinal photographs, than in patients without signs of hypertensive retinopathy. However, these population-based studies also indicate that earlier signs of hypertensive retinopathy (e.g., generalized and focal narrowing of arterioles and arteriovenous nicking) were weaker and less consistent when associated with stroke [17] and death from stroke [4]. The ARIC study demonstrated that hypertensive retinopathy adds additional predictive value for incident stroke in patients with cerebral white matter lesions [52]. Retinal microvascular alterations were also associated with magnetic resonance imaging-defined subclinical cerebral infarction [53], cerebral white matter lesions [52], cognitive impairment [54, 55], dementia [55], and cerebral atrophy [56]. The wall-to-lumen ratio [36] and wall cross-sectional area [57] of retinal arterioles have been found to be greater in hypertensive subjects with a history of a cerebrovascular event compared with uncomplicated hypertensive and normotensive subjects.

13.4.2 Cardiac Disease

Retinal microvascular abnormalities have been found to be associated with ischemic changes on electrocardiography [58], left ventricular hypertrophy [59], coronary heart disease [60–63], congestive heart failure [64], and lower hyperemic myocardial blood flow and perfusion reserve in subjects without coronary artery calcification [65].

13.4.3 Renal Disease

In the ARIC study, subjects with retinopathy were more likely to develop renal dysfunction than individuals without [66]. This was confirmed by the Cardiovascular Health Study [67]. In a cross-sectional study, we found a close relationship between the wall-to-lumen ratio of retinal arterioles and urinary albumin excretion, and an estimated creatinine clearance >60 mL/min in 37 male subjects who were either normotensive or revealed primary hypertension [68].

13.5 Arterial Stiffness, Carotid Intima-Media Thickness, and Carotid Plaques

In the ARIC study, carotid arterial stiffness, estimated from high-resolution ultrasonic echo tracking of the left common carotid artery and defined as the adjusted arterial diameter change, was related to generalized retinal arteriolar narrowing, as assessed by examining the AVR of retinal vessels in subjects aged 45–64 [69]. In the Multi-Ethnic Study of Atherosclerosis, reduced aortic distensibility, as an indicator for aortic stiffness, was associated with reduced arteriolar caliber in participants free of cardiovascular disease [70]. In a small study in patients with primary hypertension, retinopathy was associated with carotid intima-media thickness and carotid plaque score [71].

All these trials clearly indicate a coincidental occurrence of microvascular retinal abnormalities and cardiovascular morbidity and hypertensive target organ damage, respectively. However, although some of these studies adjusted for other classic cardiovascular risk factors to a greater or lesser extent, none of them adequately evaluated whether the assessment of microvascular retinal changes is of additive value on top of the assessment of established parameters of target organ damage [6] (e.g., urinary albumin excretion, left ventricular hypertrophy, carotid artery intima-media thickness, and pulse wave velocity). This lack of inclusion of other measures of target organ damage limits the value of evaluating retinopathy in hypertension (unless in hypertensive emergency). Nonetheless, with the advancement of imaging technologies, changes in retinal microvascular circulation may be detected noninvasively at an early stage and more accurately than other subclinical target organ damage.

13.6 Retinal Microvascular Alterations and Mortality

Several studies performed in the middle of the 20th century or thereafter, which relied on ophthalmoscopy (with all its limitations), revealed that hypertensive patients with moderate to severe retinal microvascular abnormalities had an increased risk of mortality [13, 58, 72–78]. However, it can be problematic to generalize from these earlier studies, carried out in patients with uncontrolled and untreated hypertension to current patients with cardioprotective treatment, who present with less severe signs of hypertensive retinopathy.

In a nested case–control analysis of the Beaver Dam Eye Study, an increased risk of ischemic heart disease death was associated with a suboptimal relationship of retinal arteriolar diameter at bifurcation, even after adjusting for age, sex, past history of cardiovascular disease, and other known cardiovascular risk factors [79]. In another nested case–control analysis of the Beaver Dam Eye Study, a weak association between generalized retinal arteriolar narrowing, defined by the AVR of retinal vessels, and cardiovascular mortality was found for subjects aged 43–74 but not for subjects aged 75 years or older [4], whereas an analysis of the entire

Beaver Dam cohort did not reveal an association between the AVR of retinal vessels or its components (arteriolar and venular diameter) and all-cause or vascular disease-related mortality [80]. However, adjustment for other parameters of hypertensive target organ damage was not performed in the aforementioned studies.

Unfortunately, studies analyzing the impact of retinal vascular function (i.e., the change of retinal capillary blood flow in response to flicker light exposure or to an infusion of L-NMMA) and/or precise analyses of retinal arteriolar remodeling (i.e., the calculation of the wall-to-lumen ratio and wall cross-sectional area of retinal arterioles) on cardiovascular mortality have not been conducted as these methodical approaches have only recently been introduced [35, 36].

13.7 Conclusions

There is an abundance of evidence that advanced retinopathy [grade 3 and 4 hypertensive retinopathy or moderate to severe (malignant) retinopathy] implies an increased risk of cardiovascular complications and mortality in hypertensive subjects. However, the evidence is weaker and inconsistent for the earlier signs of hypertensive retinopathy. Earlier signs of hypertensive retinopathy are very common among hypertensive subjects and appear to be among the earliest signs of vascular alterations in hypertension. Unfortunately, the detection of early retinopathy in hypertension is currently associated with several limitations.

First, direct ophthalmoscopy is subjective and unreliable in patients with grade 1 and 2 hypertensive retinopathy. Second, grade 1 and 2 hypertensive retinopathy cannot be distinguished by most physicians, even when retinal photographs are analyzed. Third, the approach of calculating the AVR of retinal vessels, as a parameter of generalized retinal arteriolar narrowing, from digitized photographs has insufficient explanatory power since AVR is not only dependent on the arteriolar diameter but also on the venular diameter. However, a novel approach, SLDF with AFFPIA, might be useful in better characterizing early retinal microvascular alterations, since this method allows the detection of retinal vascular function and the detailed analysis of retinal arteriolar remodeling. Future studies with large cohorts that also adjust for other markers of target organ damage and cardiovascular risk factors are needed to assess the impact of retinal vascular function and arteriolar remodeling on clinical cardiovascular disease as well as mortality.

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Part III

Arterial Stiffness as an Early Marker of Organ Damage

14

Stephane Laurent and Pierre Boutouyrie

14.1 Introduction

Cardiovascular (CV) disease manifestations still pose a substantial threat to public health. In asymptomatic hypertensive subjects, the guidelines of the European Society of Hypertension for the management of hypertension [1] recommend to screen for classical CV risk factors and to control with lifestyle advice or drug therapy to best prevent CV disease. However, the role played by aging is prominent compared to the classical CV risk factors. As the risk of CV disease still represents a challenge in spite of prevention and all treatment efforts, there is a need for new pathophysiological models to better understand cardiovascular risk and its treatment, based on new concepts [2–4]. The present chapter successively addresses the concept of *imaging* biomarker, applies it to arterial stiffness, describes the methodology of its measurement, provides some pathophysiological links between arterial stiffness and organ damage, and raises the issue of whether arterial stiffness is a surrogate end point.

14.2 *Circulating* Biomarkers Versus *Imaging* Biomarkers

Although classical risk scores, such as the Framingham risk score (FRS) [5] and the European Systematic Coronary Risk Evaluation [6], detect patients at high risk of CV events, they are largely influenced by aging, leading to the under management of CV risk in other risk groups, particularly those at intermediate risk.

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A very large number of newer biomarkers have been proposed in the literature [7] to increase risk prediction beyond classical risk scores. According to the Biomarkers Definition Working Group of the National Institutes of Health (NIH) [8], a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention." Thus, biomarkers could be either *circulating* ones, i.e., requiring blood sampling and specific dosage, or *imaging* ones, i.e., requiring measurement with either ultrasound—such as the left ventricular mass index or the carotid intima-media thickness—or any imaging technology, such as aortic stiffness [7].

The use of sophisticated circulating biomarkers has been suggested for increasing the individual prediction of CV risk beyond the established CV risk factors, such as age, systolic blood pressure, antihypertensive treatment, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering treatment, diabetes, smoking status, and body mass index. Results were contrasted. For instance, in the Framingham cohort, using high-sensitivity C-reactive protein (hsCRP), plasma renin, brain natriuretic peptide, homocysteine, and urinary albumin/creatinine ratio, did not improve the prediction of outcome [9]. However, in a community-based cohort of old men, a combination of circulating biomarkers reflecting myocardial cell damage, left ventricular dysfunction, renal failure, and inflammation (such as troponin I, N-terminal probrain natriuretic peptide, cystatin C, and CRP, respectively) improved risk assessment beyond the established CV risk factors, and increased the C statistics [10]. The C statistics quantifies the area under the receiver operating characteristic [i.e., sensitivity vs. (1-specificity) curve]. This is a useful means for quantifying discrimination, i.e., to distinguish those who will get the disease from those who will not.

As an alternative to using *circulating* biomarkers in hypertensive patients, the estimation of CV risk can investigate target organ damage, such as left ventricular hypertrophy, carotid wall thickening, or aortic stiffening [1]. Thus, target organ damage could play the role of an *imaging* biomarker [7, 11] and may help to identify patients at high risk of developing CV disease. This strategy has a strong background since target organ damage, which integrates the long-lasting cumulative effects of all identified and unidentified CV risk factors, can be detected before clinical events occur, at an early stage when intervention may reverse damage [1, 11]. By contrast, *circulating* biomarkers may fail to adequately predict the risk of CV events, due to their instantaneous fluctuations, as many individual *snapshots* of the complex deleterious situation [11]. Among the available *imaging* biomarkers, arterial stiffness in general and aortic stiffness in particular can be considered as a measure of the cumulative influence of CV risk factors with aging of the arterial tree, having limited acute variability (mainly depending on blood pressure) and enough inertia to reflect the integrated damage of the arterial wall [11, 12]. Recent studies showed the potentiating effect of the *large* and *small artery cross talk* [13] on heart, brain, retina, and kidney damage, as detailed later in the chapter.

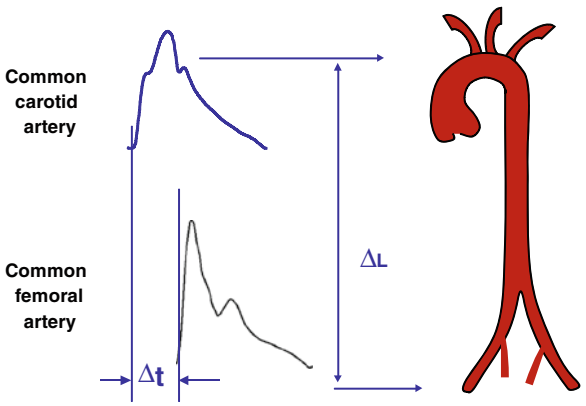

Fig. 14.1 Carotid-femoral pulse wave velocity (PWV) is usually measured using the foot-to-foot velocity method, as the ratio of the distance (L) between the measurement sites (common carotid and common femoral arteries) and the transit time (Δt) between the feet of the carotid and femoral pressure waveforms, according to the Bramwell-Hill equation (from Ref. [12])

14.3 Methods of Measurement

An expert consensus document reviewed the methodological agreement for measuring arterial stiffness [12]. In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional and local arterial stiffness can be measured directly, and noninvasively, at various sites along the arterial tree. The measurement of pulse wave velocity (PWV) is generally accepted as the simplest, noninvasive, robust, and reproducible method with which to determine arterial stiffness [12].

Carotid-femoral PWV is a direct measurement of aortic stiffness and it corresponds to the widely accepted propagative model of the arterial system. Measured along the aortic and aortoiliac pathway, it is the most clinically relevant, since the aorta and its first branches are what the left ventricle *sees*, and are thus responsible for most of the pathophysiological effects of arterial stiffness. Carotid-femoral PWV is usually measured using the foot-to-foot velocity method, as the ratio of the distance between the measurements sites (common carotid and common femoral arteries) and the transit time between the feet of the carotid and femoral pressure waveforms (Fig. 14.1) [12].

14.4 Arterial Stiffness, Organ Damage, and Cardiovascular Events

A generally accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in the late systole, increasing central pulse pressure (PP), and thus systolic blood pressure (SBP). The damaging effect of local PP has been well demonstrated on large arteries [14] and to a lesser extent on small arteries. Elevated PP can stimulate hypertrophy, remodeling (increased media-to-lumen ratio), or microcirculatory rarefaction, leading to increased

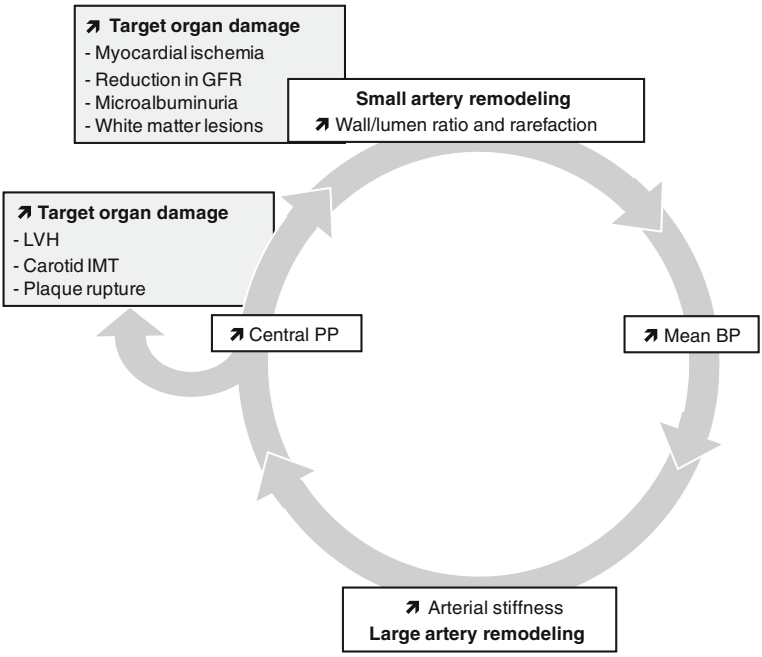

Fig. 14.2 Large/small artery cross talk: a vicious *circle* of aggravation between micro- and macrocirculation in hypertensives (from Ref. [13]) *BP* blood pressure, *GFR* glomerular filtration rate, *IMT* intima-media thickness, *LVH* left ventricular hypertrophy, *PP* pulse pressure

resistance to mean flow. Recent studies showed a close relationship between microvascular damage in the heart, brain, retina, and kidney and either PP or arterial stiffness. Indeed, significant relationships have been demonstrated between brachial pulse pressure and either glomerular filtration rate (GFR) [15, 16], microalbuminuria [16], or white matter lesions [17]; between arterial stiffness and either GFR [18, 19], urinary albumin [19], retinal arteriolar narrowing [20, 21], white matter lesions [17] or cognitive function [22]; and between carotid stiffness and GFR [18, 19]. Although not all of these relationships are independent of confounding factors [17], there is a large amount of evidence for linking the pulsatility of blood pressure to target organ damage.

Cross talk between the small and large artery [13] can be exemplified by the following sequence (Fig. 14.2): (1) increased wall-to-lumen ratio and rarefaction of small arteries [23, 24] are major factors for an increase in mean blood pressure; (2) the higher mean blood pressure in turn increases large artery stiffness, through the loading of stiff components of the arterial wall at high blood pressure levels; (3) increased large artery stiffness is a major determinant of the increased PP, which in turn damages the small arteries [25] in the heart, brain, retina, and kidney [26], as seen earlier, and favors the development of left ventricular hypertrophy, carotid intima-media thickening, and plaque rupture. These various types of target

organ damage have been shown to be related to CV events. Thus, the cross talk between the small and large artery exaggerates arterial damage, following a vicious circle.

The damage of target organs in response to aortic stiffening, and the subsequent elevated central SBP and PP, can explain the occurrence of CV events, particularly myocardial infarction. For instance, an elevated SBP increases the load on the left ventricle, increasing myocardial oxygen demand [27]. In addition, arterial stiffness is associated with increased sympathetic nerve activity [28] and left ventricular hypertrophy. The increase in central PP and the decrease in diastolic blood pressure may directly cause subendocardial ischemia [27].

Arterial stiffening can increase the risk of stroke through several mechanisms, including an increase in central PP, by influencing arterial remodeling both at the site of the extracranial and intracranial arteries, increasing carotid wall thickness and the development of stenosis and plaques, the likelihood of plaque rupture, and the prevalence and severity of cerebral white matter lesions, as seen earlier. Finally, coronary heart disease (CHD) and heart failure, which are favored by high PP and arterial stiffness, are also risk factors for a stroke.

14.5 Arterial Stiffness as a Surrogate End Point

This section details how arterial stiffness has proven its usefulness as an imaging biomarker and what should be demonstrated before stating that arterial stiffness is a true surrogate end point, i.e., whether the reduction in arterial stiffness translates into a reduction in CV events. Surrogate end points are a subset of biomarkers. According to the Biomarkers Definition Working Group of the NIH [8], a surrogate end point is "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence [8]."

Several review articles [7, 29] have recently analyzed the various methods for estimating the clinical utility of a biomarker. Particularly, a statement from the American Heart Association recommended that several steps should be completed when evaluating a novel risk marker, and ultimately concluding that the novel risk marker could be used as a surrogate end point of CV events [29]. Six phases of increasing stringency are described here and in Table 14.1:

1. Phase 1 (Proof of concept): Do novel marker levels differ between subjects with and without outcome [29]? This is clearly the case for arterial stiffness, since a large number of pathophysiological conditions are associated with it, as reported in several reviews [12, 30]. In addition to aging, they included several physiological conditions, genetic background, classical CV risk factors, and established CV disease. Importantly, arterial stiffness is also increased in several diseases of non-cardiovascular origin, although complicated by CV events, such as end-stage renal disease (ESRD), moderate chronic kidney disease, and disease characterized by chronic low-grade inflammation, such as rheumatoid

Table 14.1 Phases to be completed before aortic stiffness can be considered as a surrogate end point of CV events (see Ref. [29]). References (original studies, meta-analyses, and reviews) related to each phase are indicated in brackets

Phase	Aortic stiffness
1. Proof of concept	Yes [11–13, 30]
2. Prospective validation	Yes [32–38]
3. Incremental value	Yes [34–36]
4. Clinical utility	Yes [35–38]
5. Clinical outcomes	Weak indirect evidence [39]
6. Cost-effectiveness	No

arthritis, systemic lupus erythematosus, acquired immune deficiency syndrome, and inflammatory bowel disease [31].

2. Phase 2 (Prospective validation). Does the novel marker predict development of future outcomes in a prospective cohort or nested-case cohort study [29]? Yes, aortic stiffness has predictive value for all-cause and CV mortality, and total CV events. This was initially reported in the late 1990s–early 2000s [32]. Currently, as many as 19 studies consistently showed the predictive value of aortic stiffness for fatal and nonfatal CV events in various populations having different levels of CV risk: general population, hypertensive patients, older subjects, type 2 diabetic patients, and patients with end-stage renal disease. Seventeen longitudinal studies consisting of 15,877 subjects in total with a mean follow-up of 7.7 years were included in a recent meta-analysis [33], which showed, for one standard deviation increase in PWV, a risk ratio of 1.47 (1.31–1.64) for total mortality, 1.47 (1.29–1.66) for CV mortality, and 1.42 (1.29–1.58) for all-cause mortality.
3. Phase 3 (Incremental value): Does the novel marker add predictive information to established, standard risk markers [29]? Yes, the predictive value of aortic stiffness for CV events has been demonstrated after adjustment for classical CV risk factors, including brachial PP. According to this definition, all studies described previously showed the predictive value of aortic stiffness for CV events independently of classical CV risk factors. The additive value of PWV above and beyond traditional risk factors was quantified by three separate studies [34–36]. The first was performed in 1,045 hypertensive patients, with a longitudinal follow-up of 5.9 years for CHD events [34]. The increase in CHD with tertiles of PWV was steeper for patients belonging to the first and second tertiles of the FRS. In the group of low-to-medium risk patients, the C statistics showed that FRS and PWV had similar predictive value [area under the curve (AUC) $= 0.65 \pm 0.07$ and 0.63 ± 0.08, respectively], and when combined, the predictive value increased since the AUC significantly rose to 0.76 ± 0.09, indicating that PWV improved the prediction of CV events beyond FRS. This improved ability of aortic stiffness to predict CV mortality was confirmed by

Mattace-Raso and colleagues [35] in older subjects from the general population, and by Sehestedt and colleagues [36] in middle-aged subjects from the general population. The various mechanisms by which an increase in aortic stiffness generates higher risk of cardiac and cerebrovascular events have been described above.

4. Phase 4 (Clinical utility): Does the novel risk marker change predicted risk sufficiently to change recommended therapy [29]? In other words, does the addition of a PWV result in a substantial proportion of individuals being reclassified across a predefined treatment threshold? The answer is yes, since several studies showed that a substantial amount of patients at intermediate risk could be reclassified into a higher or a lower CV risk, when arterial stiffness was measured [35–37]. For instance, in the Framingham study, 15.7 % of patients at intermediate risk could be reclassified into a higher (14.3 %) or lower (1.4 %) risk [37]. In a recent unpublished meta-analysis, 19 and 22 % of intermediate risk individuals were reclassified into higher or lower quartiles of risk for CHD and stroke outcomes respectively [38].
5. Phase 5 (Clinical outcomes): Does the use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial [29]? An important issue here is whether the reduction in arterial stiffness translates into a reduction in CV events. There is only very little indirect evidence. To our knowledge, only one study reported CV outcomes in patients having repeated measurements of PWV along several years [39]: 150 patients (aged 52 ± 16 years) with ESRD were monitored for 51 ± 38 months for blood pressure and PWV. Fifty-nine deaths occurred, including 40 cardiovascular and 19 non-cardiovascular events. Cox analyses demonstrated that the lack of PWV decrease in response to blood pressure reduction was a strong independent predictor of all-cause [relative risk (RR) 2.59 (1.51–4.43)] and cardiovascular mortality [RR 2.35 (1.23–4.41)]. However, this study suffered several limitations: it was not a randomized clinical trial, rather a post hoc retrospective analysis; baseline PWV was different in the two groups and there was no mention that statistical analysis was adjusted to it; finally, it included patients at very high risk and results cannot be extrapolated to other (milder) clinical situations, as discussed thereafter. It remains to be shown in a population of hypertensive patients at lower CV risk that a therapeutic strategy aiming at normalizing arterial stiffness proves to be more effective in preventing CV events than usual care. Such a study requires a large number of patients, benefiting from a long-term follow-up.
6. Phase 6 (Cost-effectiveness): Does use of the novel risk marker improve clinical outcomes sufficiently to justify the additional costs [29]? The cost-effectiveness issue describes the balance between the additional cost associated with the measurement of aortic stiffness and the subtracted cost due to fewer CV complications when patients are managed according to aortic stiffness measurement. Cost-effectiveness is a complex public health issue, particularly regarding the quantification of avoided or delayed clinical complication and improved quality of life. This issue is far from being solved, even forwell-established tests in other medical specialties (for instance, mammography in breast cancer).

14.6 Conclusions

These data highlight the importance of aortic stiffness for providing direct evidence of target organ damage and determining the overall CV risk of asymptomatic hypertensive subjects. Aortic stiffening is also able to predict CV outcomes, beyond classical CV risk factors. Aortic stiffness proved to complete a number of criteria for being considered as a true surrogate end point for CV events, although not all. There is a need for studies comparing aortic stiffness-guided therapeutic strategies with classical guidelines-guided strategies for preventing CV events.

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Central Aortic Pressure: The Next Frontier in Blood Pressure Measurement?

15

Bryan Williams and Peter S. Lacy

15.1 Introduction

Blood pressure (BP) has been conventionally measured over the brachial artery by sphygmomanometry for more than a century. Measured in this way, systolic BP (SBP), diastolic BP, and pulse pressures (PP) have all been shown to be predictors of cardiovascular risk [1–5]. More recently, automated blood pressure measurement devices have increased in popularity but are still designed to measure brachial blood pressure (BrBP). A key question is: how representative of aortic pressure is BrBP? This question is considered important because it is reasonable to assume that the pressure in the large conduit arteries, the so-called *central aortic pressure* (CAP), is more representative of the hemodynamic stress on major organs such as the heart, brain, and kidney. Furthermore, BrBP and CAP are not the same. Indeed, cardiologists undertaking cardiac catheterization will have long recognized that the directly measured pressure at the aortic root is invariably lower than that simultaneously measured over the brachial artery [6–8]. This aortic root-brachial artery pressure difference is most noticeable for SBP and PP. In contrast, mean arterial pressure (MAP) remains relatively constant across the larger conduit arteries of the circulation [9]. The increase in SBP and PP from the aortic root to the brachial artery results from pressure wave amplification as it moves from the aortic root to the periphery of the circulation [10], an amplification ratio of 1.2–1.5 for pulse pressure being typical [11].

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If the magnitude of pressure amplification remained constant in an individual patient or between patients, then BrBP measurement would always be a good surrogate for CAP and there would be no point in endeavoring to measure the latter. However, the degree of pressure amplification is highly variable and is influenced by a number of factors, including: age (usually as a surrogate for arterial stiffness), BP, heart rate, and drug therapies. Consequently, there is a rationale for considering the noninvasive measurement of CAP; i.e., that it is based on the fact that BrBP is often not a perfect surrogate for true arterial pressure.

This chapter will discuss the principles and methods for the noninvasive measurement of CAP, the pathophysiological basis for the differences between CAP and BrBP, the normal ranges for CAP, and the impact of drug therapies on CAP. The chapter concludes with a look into future developments in this field and the clinical utility of CAP measurement.

15.2 Noninvasive Measurement of Central Aortic Pressure

Current methods for the noninvasive measurement of CAP are dependent on the capture of an arterial waveform which is then calibrated to conventionally measured BrBP, usually via oscillometric methods. There are two methods currently being used to capture the arterial waveform: (1) applanation tonometry over the radial or carotid arteries, or more recently (2) oscillometric methods, using a standard brachial BP cuff, which are used to capture the brachial artery waveform at or near diastolic pressure.

15.2.1 Applanation Tonometry-Derived Arterial Waveforms

The tonometer is applied to the skin overlying the radial or carotid arteries. Carotid tonometry is a less practical option for routine clinical use and therefore recent attention has focused on radial artery tonometry. The latter originally used a pencil-like handheld tonometer to acquire the radial artery waveform (e.g., SphygmoCor, AtCor Medical Pty Ltd, West Ryde, Sydney, Australia). This works well in the hands of trained users, however, more recent innovations have endeavored to simplify and stabilize the application of the tonometer by incorporating it into the wrist strap of a watch-like device (e.g., BPro, Healthstats, Singapore), or a wrist grip which closes over the wrist to align the tonometer with the radial artery Omron HEM 9000AI (Omron Healthcare, Kyoto, Japan) (Fig. 15.1). All of these methods produce a high-fidelity recording of the radial artery pulse wave [12–14]. This is then calibrated to conventionally measured BrBP to yield a radial artery pressure waveform. From this, a variety of methods have been used to mathematically derive the CAP and central hemodynamic indices.

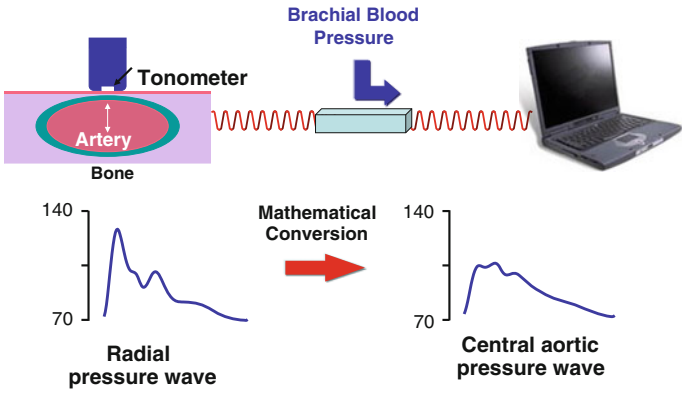

Fig. 15.1 Schematic diagram showing the process for acquiring the radial artery waveform via applanation tonometry and its calibration to brachial blood pressure (BP). The central aortic pressure is then derived from the resulting radial artery pressure waveform

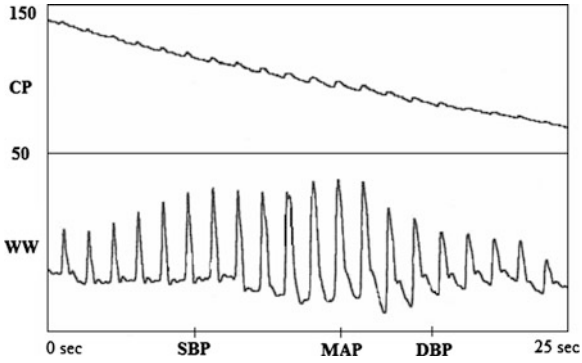

Fig. 15.2 Oscillometric waveforms from automated wrist-cuff BP measurement showing that the shape of the wrist waveforms (WW) resembles a typical radial artery waveform at or near the level of diastolic BP [16]. *BP* blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *SBP* systolic blood pressure

15.2.2 Oscillometric-Derived Brachial Artery Waveforms

A more recent development has been the use of oscillometric-derived waveforms captured at the time of inflation or deflation of a conventional brachial artery BP cuff. The standard method for automated BrBP measurement detects pressure oscillations via a pressure sensor within the cuff. It has been noted that at, or just below, diastolic pressure, the oscillometric arterial waveforms resemble those acquired by conventional tonometry [15] (Fig. 15.2). Thus, by adjusting the inflation or deflation cycle of the cuff, it is possible to acquire a sequence of brachial artery waveforms from which central pressure could be derived using the

processes described later in the chapter. This property has been used to develop conventional cuff-based devices to derive central aortic pressure.

15.2.3 Derivation of Central Aortic Pressure from Arterial Waveforms

The arterial waveforms acquired by tonometry or oscillometry require calibration, usually acquired from noninvasive BrBP measurement. For the radial tonometry devices, the BrBP is measured using a conventional cuff-based device and this data is then used directly to calibrate the radial waveform acquired by tonometry and assumes minimal amplification between brachial and radial arteries. Radial waveform capture is usually undertaken just following measurement of BrBP, with the patient seated and rested. For carotid tonometry, carotid waveforms are calibrated to mean and diastolic pressure based on the principle that mean and diastolic pressure remain relatively constant across the larger conduit arteries of the circulation. In the case of the cuff-based oscillometric method, the BrBP is acquired at the same time as the brachial arterial waveform is acquired, as they both use the same information from the oscillometric pressure waveforms. Both methods generate a radial or brachial arterial pressure waveform from which the CAP is then derived. Three main approaches for the derivation of the CAP from the peripheral artery pressure waveforms have been described: (1) the use of a generalized transfer function; (2) the derivation of the inflection point on the downstroke of the systolic pressure wave, the so-called SBP2; and (3) the use of a simple n-point moving average.

15.2.4 Generalized Transfer Function

A number of generalized transfer functions (GTFs) have been developed to transform the peripheral artery pressure waveform into a representative CAP waveform [17–20]. The GTFs describe the relationship between peripheral and central waveforms in the frequency domain. This information is then applied to a captured radial artery pressure wave to predict and plot the corresponding CAP wave, the peak of which represents the central aortic systolic pressure (CASP), the foot of which represents the central aortic diastolic pressure (CADP). As well as CASP, the CAP waveform has also been used to predict the peak of the outgoing pressure wave (P1) using derivative plots to demark the key inflection point. The difference between P1 and CASP represents the augmented pressure which tends to be accentuated by aging and aortic stiffening. Furthermore, the percentage of the central aortic pulse pressure (CAPP), which is accounted for by the augmented pressure, has been termed the augmentation index (AIx). The GTF method has also be used to transform the oscillometric brachial artery pressure waveforms to derive the CAP and related hemodynamic parameters [21].

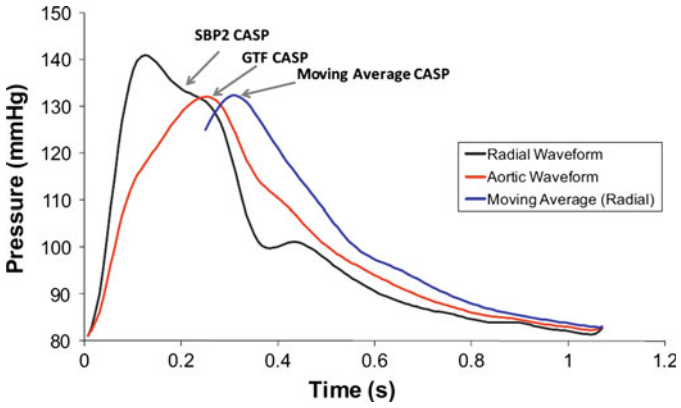

Fig. 15.3 Comparison of different methods for deriving CASP from the radial artery pressure waveform [14]. *CASP* central aortic systolic pressure, *GTF* generalized transfer function

15.2.5 Derivation of Central Aortic Systolic Pressure from the Radial Systolic Pressure Wave Inflection Point (SBP2)

The downstroke of the peripheral artery systolic pressure waveform contains an inflection point which has been termed SBP2. This has been shown to correspond to CASP, the physiological basis for which is unclear [22–24]. Thus, identification of SBP2 has been used to derive CASP. As MAP is already known and is assumed to be representative of mean pressure in the aortic root, after derivation of CASP, the CADP can then be calculated. A potential problem with this method is that SBP2 is not always easy to identify, especially in older people with stiffer arteries, who tend to have more rounded arterial waveforms in which the SBP2 inflection point is hidden, and in younger people where the inflection point frequently merges with the dichrotic notch.

15.2.6 Derivation of Central Aortic Systolic Pressure Using an N-Point Moving Average

The n-point moving average (NPMA) is a mathematical low-pass filter that is used to smooth data in a variety of applications, including economic data trends and image smoothing in sophisticated imaging techniques. CASP is defined predominantly by low-frequency harmonics, and the application of an NPMA to a peripheral artery pressure waveform has the potential to smooth high-frequency harmonics to reveal the underlying peak of the CAP waveform or CASP. The key to this technique is the stringency of the filter and we have shown that an NPMA set at one-quarter of the sampling frequency of a radial artery tonometer yields an

accurate measurement of CASP [14]. Figure 15.3 shows the correspondence of the three different methods for deriving CASP (GTF, SBP2, and NPMA) from a radial artery pressure waveform.

15.2.7 Validation of Methods for the Measurement Central Aortic Pressure

There has been much debate, and in some cases scepticism, about the validity of noninvasive CAP measurements derived from pulse wave analysis. The reality is that each of the aforementioned methods of processing the peripheral artery pulse wave provides remarkably accurate measurements of CASP. As the MAP is known (i.e., assumed from brachial mean pressure), the CADP can be derived. The gold standard for validation compares noninvasive derivation of CAP with the simultaneous direct measurement of aortic root pressure at the time of cardiac catheterization, usually using a Millar solid-state pressure transducer [25–28]. Other validation studies have compared newer devices and technologies with previously validated and well-established technologies for the noninvasive measurement of aortic pressure [14, 29–32].

Concern about the use of mathematical algorithms to derive central pressure is all the more remarkable when one reflects on the fact that the automated measurement of BrBP via commonly used oscillometric devices also uses mathematical algorithms to derive brachial systolic and diastolic pressure! In fact, the greatest source of error in the noninvasive measurement of CAP is the automated measurement of BrBP used to calibrate the peripheral arterial waveform [33–35]. While the initial scepticism about the validity of non-invasive central pressure measurement was understandable, the time has come for the debate to move on, from whether noninvasive CAP measurement can be done, to the more important question as to why it should be done, which is discussed in more detail in the following sections.

15.2.8 Deriving Parameters Beyond Central Aortic Pressure Using Pulse Wave Analysis

The use of the GTF has allowed the generation of a CAP wave from which a variety of indices have been derived, including an augmentation index (see previous section), pulse pressure amplification (PPA, from central to brachial artery), and subendocardial viability index, to name but a few (Fig. 15.4). These parameters have generated a large number of publications but they are poorly validated, do not predict cardiovascular outcomes beyond conventional risk factors, and have little clinical utility. They have served as a huge distraction from the two key measurements, i.e., CAP and pulse wave velocity (PWV), which should be the primary focus.

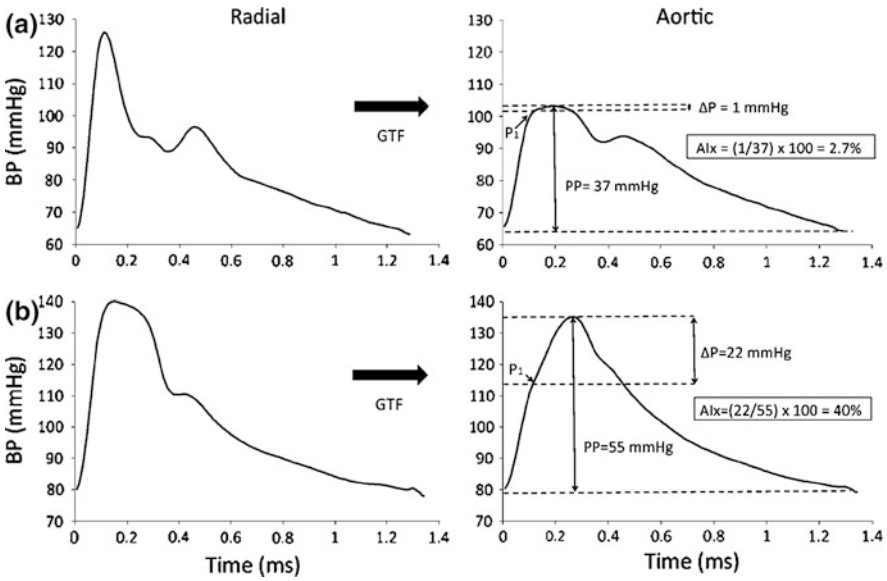

Fig. 15.4 Schematic showing the key features of the radial artery pressure waveforms (*left* panels) and the resulting central aortic pressure waveform (derived using a GTF) (*right* panels) from which various central hemodynamic parameters have been derived. Panel A shows a younger man (age 24, brachial BP 126/65 mmHg) and Panel (B) an older man (age 72, brachial BP 140/80 mmHg). *AIx* the augmentation index, *BP* blood pressure, *DP* the portion of the aortic pressure wave attributed to the influence of wave reflections returning during systole, GTF generalized transfer function, P1 the height of the outgoing pressure wave, *PP* pulse pressure [36]

15.2.9 Factors Influencing the Relationship Between Brachial and Central Aortic Pressure

BrBP is higher than CAP, principally due to the amplification of systolic and pulse pressures (Fig. 15.5). This is expressed as the ratio of brachial to central pulse pressure, i.e., PPA, which in a healthy individual is approximately 1.5 and ranges from a maximum of around 1.7 in youth to a minimum of 1.2 in old age. If the magnitude of PPA and thus the relationship between central and brachial pressure were fixed, then there would be no point in measuring CAP because BrBP would always be a good surrogate for central pressure. As noted previously, the relationship is not fixed, because PPA is highly variable according to a number of factors. Factors leading to reduced PPA and thus a reduced difference between central and brachial pressure include: (1) advancing age; (2) reduced heart rate; (3) aortic stiffening, which in large part accounts for the impact of age; (4) reduced body height, which is probably a surrogate for reduced aortic length/volume; (5) female gender, which is in part, but not wholly, explained by the impact of a reduced average body height versus male gender; and (6) increased blood pressure [11]. The presence of any of these factors, and frequently a combination of them, means that CAP is on average higher for any given level of BrBP.

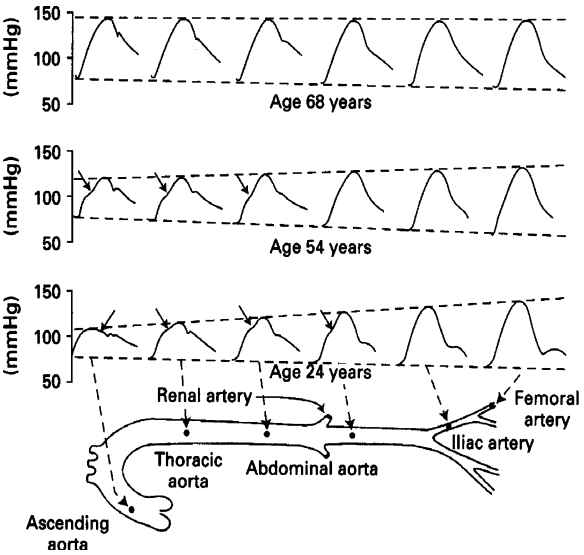

Fig. 15.5 Pulse wave amplification as it moves from the aortic root to the distal circulation. Note that the magnitude of amplification is influenced by age [9]

Conversely, increased PPA is a feature of a higher heart rate, youth, male gender, and tall stature, which results in a lower CAP for any given value of BrBP. Finally, the relationship between central and brachial pressures can be influenced by drug therapies that in particular influence heart rate and vasodilation [37–39].

The effect of age (see Fig. 15.5) and heart rate (Fig. 15.6) on PPA is particularly striking. Scrutiny of the radial artery waveform illustrates profound changes in waveform shape that correspond to changes in the augmented CASP ([40]; see Fig. 15.4). Likewise, heart rate has a profound effect, with reducing heart rate leading to a diminishing PPA [39].

15.2.10 Controversies Surrounding the Origins of Central Pressure Augmentation

As discussed previously, there is no doubt that there is evidence of augmentation of CASP and central pressure pulse (CPP) relative to corresponding brachial pressures. A popular explanation for variation in the augmentation of the CPP is founded on the concept of pressure wave reflection [41, 42], specifically the timing of wave reflection from distal reflection sites, especially the aortic bifurcation relative to the incident pressure wave. It is argued that in health, with less stiff arteries and thus a low PWV, most of the wave reflection returns in diastole, augmenting diastolic filling of coronary vessels. Conversely, with aging and stiffening of the larger conduit arteries, PWV is increased and thus the reflected wave occurs earlier. This results in much of the reflected wave arriving in late systole leading to the augmentation of CASP and CPP, thereby increasing left ventricular work, with a corresponding reduction in diastolic filling pressures.

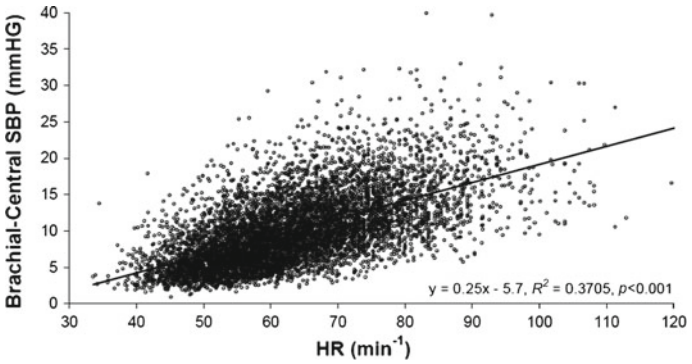

Fig. 15.6 Data from the CAFE trial showing the relationship between heart rate and the difference between CASP and BrSP [39]. BrSP brachial systolic pressure, CAFE Conduit Artery Function Evaluation (trial), *CASP* central aortic systolic pressure, *HR* hazard ratio

Others have dismissed the aortic wave reflection hypothesis and pressure amplification as an artifact of using the radial artery waveform calibrated to brachial pressure, arguing that the main pressure amplification is between the radial artery and the brachial artery and not the brachial artery and the central aorta. Proponents of this hypothesis have pointed to a critical role for ventricular–vascular coupling and in particular the impedance of the aortic root in determining the shape of the aortic pressure wave, and the resulting aortic pressure and flow characteristics [43]. Finally, others have suggested that CAP is a less important index of circulatory stresses than another parameter they have termed *reservoir pressure*, based on modeling the aortic reservoir, its volume changes in systole and diastole, and the pressure needed to fill the reservoir, which is related to the compliance of the aorta [44]. Discussion of the relative merits of each of these hypotheses is beyond the scope of this chapter. Nevertheless, the debate is important to further our understanding of the aortic pressure pulse and flow wave propagation and their role in disease pathophysiology. In the meantime, there is now much less dispute about the fact that CAP can be accurately measured noninvasively. The key debate now relates to the *added value* of doing so.

15.2.11 Relationship between Central Aortic Pressure and Aortic Stiffness

While it is clear that, as a general rule, the stiffer the arteries the higher the CASP and CAPP for any given level of BrBP, this rule does not appear to hold true at the extremes of aortic stiffness. A good example of this is in people with diabetes, where PWV, a surrogate for arterial stiffness, rises more steeply than in the

general population from midlife. However, this is not associated with a corresponding, inexorable rise in wave reflections CASP and CPP relative to BrBP [45, 46]. These observations point to a more complex relationship between CAP and PWV in which the absence of augmentation of CASP with the stiffest arteries must point to deeper propagation of the pressure pulse into the more distal circulation. It has been argued that this most likely relates to changes in distal aortic impedance due to progressive dilatation of the distal aorta with aging and a higher energy pressure pulse [47]. Similar findings are likely in patients with advanced renal disease and calcified aortas in whom CAP is unlikely to track as expected with the extreme increases in PWV. Further dissociations between CAP and PWV have also been noted in antihypertensive therapy trials which have produced differential effects on CASP and CPP [37, 48–50] but no difference in PWV. From the previous discussion, it is clear that although increases in aortic stiffness are likely to produce a disproportionate rise in CASP and CPP relative to BrBP, this is not always the case. Thus, although related, PWV is not a surrogate for CAP and vice versa

15.2.12 Potential Clinical Applications of Central Aortic Pressure Measurement

To date, CAP measurement has been used as a research tool. A key question is whether such a measurement will ever have clinical applicability. In this regard, a key requirement will be to show the incremental value of CAP measurement versus conventional BrBP measurement in the clinical setting. There are three areas where CAP measurement could prove to be clinically useful: (1) to improve diagnostic stratification of hypertension status, especially in younger people; (2) as a better predictor of clinical outcomes in people with hypertension; and (3) to improve treatment by providing a more accurate assessment of the effect of drug therapy on BP.

15.2.13 Improving Diagnostic Stratification of Hypertension Status

As noted previously, BrBP is higher than CAP, especially for systolic pressure. The difference between the two, i.e., brachial SBP (BrSBP) minus CASP, is highly variable. Typically, this difference is 10–15 mmHg but can extend to differences of as much as 30 mmHg [11]. This difference tends to be greater in younger people, especially men, and at higher levels of pressure. This means that some younger people in particular could be classified as hypertensive based on their clinic BrBP, but actually have a completely normal CAP. Conversely, some younger people with a *normal* clinic/office BrBP could have disproportionately elevated CAP, a phenomenon that could be termed *masked central hypertension*.

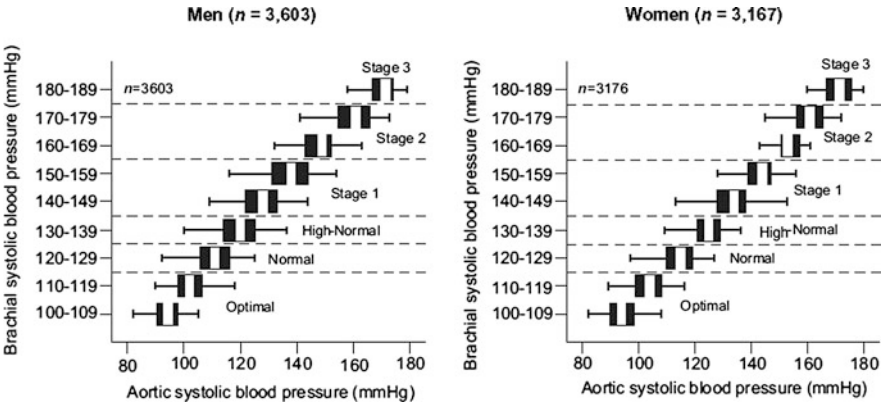

Fig. 15.7 Data from the ACCT study showing the relationship between blood pressure (BP) stratification according to brachial BP measurement and the corresponding central aortic pressure values in men and women [51]. *ACCT* Anglo-Cardiff Collaborative Trial

This is illustrated in Fig. 15.7, where it is clear that use of CAP measurements could lead to a shift in classification of hypertensive status when compared to BrBP measurements in a substantial number of patients [51]. Further studies are necessary to determine if the use of CAP measurement is a better predictor of target organ damage than conventional BrBP measurement in younger people and thus, a better way of establishing an accurate diagnosis of hypertension.

15.2.14 Central Aortic Pressure as a Better Predictor of Clinical Outcomes in People with Hypertension

Intuitively, it would seem logical that estimating the pressure in the central circulation is likely to be more predictive of target organ damage and clinical outcomes when compared to pressure measured in the peripheral circulation. This is especially so when one considers the potential variability in the relationship between central and brachial pressures. To date, there are no studies with adequate power to definitively address this important question, although patient-level meta-analyses of data from multiple clinical studies is ongoing to address this important question. In studies in which CAP and BrBP have both been measured, CASP or CPP have usually been shown to be more strongly related to target organ damage [36, 52–55] and clinical outcomes [36, 37, 52, 55, 56]. This data is of interest and supports the *central pressure hypothesis* but can only be considered *hypothesis generating*. Demonstrating that CAP is a better predictor of clinical outcomes versus conventional BrBP measurement in sizeable and properly powered clinical outcome studies is required to drive a step change in clinical practice.

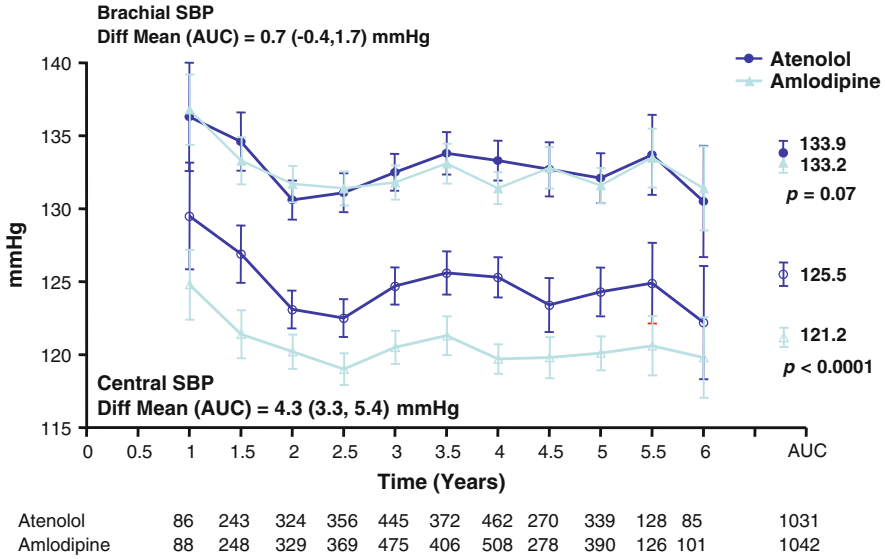

Fig. 15.8 Data from the CAFE study showing the differential effects of two different blood pressure (BP)-lowering treatment strategies (amlodipine ± perindopril vs. atenolol ± bendroflumethiazide) on BrBP versus CASP. Despite similar lowering of BrBP, the amlodipine-based regimen was significantly more effective at reducing CASP and CAPP (latter not shown) [37]. *AUC* area under the curve, BrBP brachial blood pressure, *CAFE* Conduit Artery Function Evaluation (trial), *CASP* central aortic systolic pressure, *SBP* systolic blood pressure

15.2.15 Improving Treatment by Providing a More Accurate Assessment of the Effect of Drug Therapy on Blood Pressure

This final area of potential deployment of more routine CAP measurement is in the assessment of the central hemodynamic effects of BP-lowering interventions. This is to some extent contingent on the aforementioned need to demonstrate the superiority of CAP as a predictor of clinical outcomes. It is, however, clear that even when the effects of different treatments appear similar with regard to BrBP lowering, there may be substantial differential effects of different classes of drug therapy on CAP. This is most noticeable for beta-blockers (atenolol being the best studied), which appear significantly less effective than other drug classes at lowering CASP and CAPP for any given change in BrSBP and brachial PP (BrPP) (Fig. 15.8). Of interest and perhaps related to this deficit in CAP reduction, beta-blockers are also the least effective of the commonly used BP-lowering drugs at preventing stroke [57]. Furthermore, in the Conduit Artery Function Evaluation (CAFE) study, this lack of effectiveness of beta-blockers at reducing CASP and CPP appeared in large part to be due to their heart rate-lowering effect, which reduces PPA [39] (see earlier in the chapter and Fig. 15.6). This finding also questions whether therapeutic heart rate lowering with other drug types could also

reduce PPA, so that for any given BrBP, CAP is higher. In contrast, nitrates appear to have potent but short-lived effects to reduce CASP and CAPP relative to BrBP [58, 59]. If such properties could be harnessed by such treatments, or others like them, this could provide a means of testing the *central pressure hypothesis* with regard to clinical outcomes. Whatever develops from a therapeutic perspective, the ability to noninvasively measure CAP and hemodynamics has provided a novel insight into hitherto unrecognized mechanisms of drug action, which could provide the template for future drug design for treating hypertension.

15.3 What is a Normal Central Aortic Pressure?

Mean CAP is similar to its brachial counterpart. CADP is slightly higher than brachial DP. The important difference between CAP and BrBP is in the pulsatile component of pressure, i.e., systolic and pulse pressure which are substantially lower centrally when compared to BrBP. The optimal way to define the normal range for CAP would be to relate it to levels of cardiovascular risk and to define the CAP yielding the similar levels of risk relative to the corresponding BrBP. As discussed previously, such data is not yet available. An alternative strategy is to define the CAP equivalent to a conventionally defined normal BrBP. Using this approach, population studies (see Fig. 15.7 as an example) suggest that an optimal CASP is <110 mmHg and closer to 100 mmHg, i.e., equivalent to a BrSP of <120 mmHg. Likewise, a CASP of <120 mmHg would be equivalent to a BrSP of <140 mmHg. This may change with future studies, but it seems likely that the CASP threshold for currently defined stage 1 hypertension is approximately ≥120 mmHg.

15.4 Future Developments in the Measurement of Central Aortic Pressure—24-h Ambulatory Central Aortic Pressure

The technological developments in this field have been dramatic in pace and scale. The most recent development in the field of CAP measurement has been the report of the first successful measurement of 24-h ambulatory CAP: (1) We recently reported the measurement of 24-h ambulatory CAP within a randomized controlled trial of over 300 patients undergoing evaluation for antihypertensive therapy, using the BPro watch-based wrist tonometry device [60]; (2) a second study reported an observational study of approximately 200 people using the cuff-based oscillometric device [61]. These studies, reported at the European Society of Hypertension meeting held in London in April 2012, demonstrated similar alterations in the circadian pattern for 24-h ambulatory CAP versus conventional 24-h brachial ambulatory BP monitoring. Specifically, there was a reduced dip in nocturnal CASP and CAPP when compared to the corresponding BrBP values for the nocturnal BP dip, pointing to reduced nighttime PPA. Further work will be

necessary to understand the mechanisms underpinning these effects and the relevance of nocturnal CAP to clinical outcomes. This is an important advance and adds a new dimension to future studies of CAP.

15.5 Conclusions

The study of CAP is moving rapidly from niched laboratory science to mainstream clinical evaluation. There seems little doubt that the noninvasive assessment of CAP is robust with regard to the validation of the measurements, the main limitation being the accuracy of the conventional BrBP measurements used to calibrate the arterial waveforms. There has been an explosion of enabling technologies and wider interest in this field of clinical research as the technology has simplified toward the ease of conventional BP measurement.

Controversy remains about the mechanisms underpinning the evolution of CAP with age and drug therapy and further work is needed to understand such mechanisms. The debate, while initially stimulating, has become bedevilled by polarized views; now is the time for more light, less noise, and fresh ideas. It is also the time for definitive studies evaluating the clinical relevance and utility of CAP measurement for mainstream clinical practice.

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Assessment of Total Cardiovascular Risk in Hypertension: The Role of Subclinical Organ Damage

16

Renata Cífková

16.1 Introduction

Historically, hypertension guidelines have focused on blood pressure values as the only or main variable for determining therapeutic interventions. Although this approach was retained in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [1], the 2003 European Society of Hypertension–European Society of Cardiology (ESH–ESC) guidelines [2] emphasized that the management of hypertension should be related to the quantification of total cardiovascular (CV) risk. The rationale for this approach is based on the fact that only a small proportion of the hypertensive population has an elevation of blood pressure alone, while the great majority exhibits additional CV risk factors [3–7], with a relationship between the severity of blood pressure elevation and that of alterations in glucose and lipid metabolism [8]. When blood pressure and metabolic risk factors are present concomitantly, they potentiate one another's risk [3, 9, 10]. Thresholds and goals for antihypertensive treatment, as well as treatment strategies for concomitant risk factors, may differ based on total CV risk [2]. Therefore, the estimation of total CV risk is essential for guiding patient management.

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16.2 Assessment of Total Cardiovascular Risk

A number of complex, computerized methods have been developed for estimating total CV risk, i.e., the likelihood of developing a CV event, usually within the next 10 years. Many risk stratifications use systems based on the Framingham study [11], estimating the 10-year risk for both fatal and nonfatal coronary heart disease (CHD) by systolic blood pressure (SBP) and the presence of other risk factors. The easy and rapid calculation of the Framingham risk score using published tables [12] can assist the physician and patient in demonstrating the benefits of treatment.

The Framingham risk stratification has been shown to be reasonably applicable to some European populations [13], though requiring recalibration in other populations [14, 15] due to geographical differences in the incidence of coronary and stroke events.

More recently, a European model became available based on the large database provided by the Systemic Coronary Risk Evaluation (SCORE) project [16]. SCORE charts are available for high-risk and low-risk countries in Europe, estimating the risk of dying from CV (not just coronary) disease over 10 years and allowing calibration of the charts for individual countries provided that national mortality statistics and estimates of the prevalence of major CV risk factors are available. The SCORE model has also been used in the HeartScore tool, the official European Society of Cardiology management tool for the implementation of CV disease prevention in clinical practice (www.escardio.org).

The main disadvantage associated with an intervention threshold based on relatively short-term absolute risk is that younger adults (particularly women), while having more than one risk factor, are unlikely to reach treatment thresholds despite being at high risk relative to their peers. By contrast, most older men (e.g., over 70 years) often reach treatment thresholds while being at very little increased risk relative to their peers. This situation results in most resources being concentrated on the oldest subjects whose potential life span, despite intervention, is relatively limited, while younger subjects at high relative risk remain untreated despite, in the absence of intervention, a predicted significant shortening of their otherwise much longer potential life span [17, 18].

On the basis of these considerations, the 2007 ESH–ESC guidelines [19] suggest total CV risk be stratified as shown in Table 16.1. The terms *low*, *moderate*, *high*, and *very high added risk* are used to indicate, approximately, an absolute 10-year risk of CHD of <15, 15–20, 20–30, and >30 %, respectively, according to the Framingham criteria [11], or an approximate absolute risk of fatal CV disease (both CHD and stroke) of <4, 4–5, 5–8, and >8 % according to the SCORE chart [16]. The term *added* is used to emphasize that, in all categories, relative risk is greater than average risk (i.e., the reference category, see Table 16.1). Although the use of categorical classification provides data that are in principle less precise than those obtained from equations based on continuous variables, this approach has the merit of simplicity.

Table 16.1 Stratification of risk to quantify prognosis

	Blood pressure (mmHg)				
Other risk factors, OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP $\geq$ 180 or DBP $\geq$ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS or OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disese	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

CV cardiovascular; *DBP* diastolic blood pressure; *MS* metabolic syndrome; *OD* subclinical organ damage; *SBP* systolic blood pressure
Adopted from [19]

Table 16.2 indicates the most common clinical variables to be used for risk stratification as shown by Table 16.1. They include risk factors, subclinical organ damage, diabetes mellitus, and established CV or renal disease.

Table 16.3 summarizes the definition of high/very high-risk subjects. Multiple risk factors, diabetes, or organ damage always place a patient with hypertension, and even with high-normal blood pressure, in the high-risk category.

16.3 Searching for Subclinical Organ Damage

Due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease and as a determinant of overall CV risk, signs of organ involvement in hypertensive individuals should be sought for carefully using the appropriate techniques.

16.3.1 Heart

Electrocardiography (ECG) is used as part of routine assessment of hypertensive individuals to detect left ventricular hypertrophy (LVH), a pattern of *strain*, ischemia, and arrhythmias. Its sensitivity in detecting LVH is low; nonetheless, hypertrophy detected by the Sokolow–Lyon index or by Cornell voltage-QRS

Table 16.2 Factors influencing prognosis

Risk factors	Subclinical organ damage	Diabetes mellitus	Established CV or renal disease
• Systolic and diastolic BP •Pulse pressure (in the elderly) •Age (M > 55 years; W > 65 years) •Smoking •Dyslipidemia - TC > 5.0 mmol/l (190 mg/dl) or; - LDL-C > 3.0 mmol/l (115 mg/dl) or; - HDL-C: M <1.0 mmol/l (40 mg/dl), W < 1.2 mmol/l (46 mg/dl) - TG > 1.7 mmol/l (150 mg/dl) •Fasting plasma glucose 5.6–6.9 mmol/l (102–125 mg/dl) •Abnormal glucose tolerance test •Abdominal obesity (waist circumference M > 102 cm, W > 88 cm) •Family history of premature CV disease (at age < 55 years M, < 65 years W) Note: Metabolic syndrome is defined as the cluster of 3 out of 5 risk factors among abdominal obesity, altered plasma glucose, BP >130/85 mmHg, low HDL-C, and high TG (defined as above)	•Left ventricular hypertrophy (electrocardiogram: Sokolow–Lyon > 38 mm; Cornell > 2,440 mm×ms; echocardiogram: LVMI M ≥ 125, W ≥ 110 g/m^2) •Ultrasound evidence of arterial wall thickening (carotid IMT > 0.9 mm) or plaque •Carotid-femoral pulse wave velocity > 12 m/s •Ankle-brachial index < 0.9 •Slight increase in serum creatinine M: 115–133 μmol/l (M 1.3–1.5 mg/dl) W: 107–124 μmol/l (W 1.2–1.4 mg/dl) •Low estimated GFR* (< 60 ml/min/1.73 m^2) or creatinine clearance** (< 60 ml/min) •Microalbuminuria 30–300 mg/24 h or albumin-creatinine ratio: M ≥ 22, W ≥ 31 mg/g creatinine	•Fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) on repeated measurements •Postprandial plasma glucose > 11.0 mmol/l (198 mg/dl)	•Cerebrovascular disease: Ischemic stroke; Cerebral hemorrhage; Transient ischemic attack •Heart disease: Myocardial infarction; Angina; Coronary revascularization; Heart failure •Renal disease: Diabetic nephropathy; Renal impairment (serum creatinine M > 133 μmol/l or > 1.5 mg/dl; W > 124 μmol/l or > 1.4 mg/dl); proteinuria (> 300 mg/24 h) •Peripheral artery disease •Advanced retinopathy: Hemorrhages or exudates; Papilledema

*MDRD formula; **Cockcroft-Gault formula

CV cardiovascular; *GFR* glomerular filtration rate; *HDL-C* high-density lipoprotein cholesterol; *IMT* intima-media thickness; *LDL-C* low-density lipoprotein cholesterol; *LVMI* left ventricular mass index; *M* men; *TC* total cholesterol; *TG* triglycerides; *W* women

Adopted from [19]

Table 16.3 High/very high-risk subjects

• Systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg
•Systolic BP > 160 mmHg with low diastolic BP (< 70 mmHg)
•Diabetes mellitus
•Metabolic syndrome
•≥ 3 CV risk factors
•One or more of the following subclinical organ damage:
– Electrocardiographic (particularly with strain) or echocardiographic (particularly concentric) left ventricular hypertrophy
– Ultrasound evidence of carotid artery wall thickening or plaque
– Increased arterial stiffness
– Moderate increase in serum creatinine
– Reduced estimated glomerular filtration rate or creatinine clearance
– Microalbuminuria or proteinuria
•Established CV or renal disease

BP blood pressure; *CV* cardiovascular
Adopted from Ref. [19]

duration is an independent predictor of CV events [20]. In a prospective survey including 7,495 American adults, a new indicator of LVH, the Novacode estimate of left ventricular mass index (LVMI; based on both voltage and strain pattern criteria) was reported to be significantly related to a 10-year CV mortality [21]. A further analysis from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed that hypertensive patients with ECG LVH or left bundle branch block are at increased risk of CV mortality and hospitalization due to heart failure [22]. A prospective study by Verdecchia and colleagues [23] documented that R wave voltage in the augmented vector left (aVL) is closely associated with left ventricular mass (LVM) and is predictive of CV events when hypertension is not accompanied by ECG LVH.

Echocardiography is more sensitive than ECG in diagnosing LVH [24] and predicting CV risk [25]; it may also be more helpful in risk stratification [26]. There are also some technical limitations such as interobserver variability and low-quality imaging in obese individuals and in patients with obstructive lung disease. Although the relationship between LVMI and CV risk is continuous, thresholds of 125 g/m^2 for men and 110 g/m^2 for women are widely used for conservative estimates of LVH. Concentric hypertrophy (wall-to-radius ratio ≥0.42 with an increased LVM), eccentric hypertrophy (increased LVM and wall-to-radius ratio <0.42), and concentric remodeling (wall-to-radius ratio ≥0.42 with normal LVM) all predict an increased incidence of CV disease, but concentric hypertrophy has consistently been shown to be associated with the highest risk [27, 28].

In addition, echocardiography is a tool for assessing left ventricular systolic and diastolic function; ejection fraction and midwall fractional shortening have been proposed as possible additional predictors of CV events. Alterations of diastolic function are frequent in hypertensives and particularly in older subjects [29]. Diastolic dysfunction is associated with an increased risk of atrial fibrillation [30], heart failure [31], and increased total mortality [32]. Finally, echocardiography

provides information on the size of the left atrium; left atrial enlargement is associated with a higher risk of atrial fibrillation, CV disease, and death [33–35].

16.3.2 Blood Vessels

Ultrasound examination of the carotid arteries, with measurement of intima-media thickness (IMT) or the presence of plaques, has been shown to predict stroke and myocardial infarction (MI) [36, 37]. The relationship between carotid IMT and CV events is a continuous one but, for the common carotid arteries, an IMT >0.9 mm can be taken as a conservative estimate of existing abnormalities. Ultrasound scans limited to the common carotid arteries (an infrequent site of atherosclerosis) are likely to measure vascular hypertrophy only, whereas assessment of atherosclerosis also requires scanning of the bifurcations and/or internal carotids where plaques are more frequent [38–40]. Further analysis from the European Lacidipine Study on Atherosclerosis (ELSA) [41] showed that baseline carotid IMT (both at carotid bifurcations and at the level of the common carotid artery) predicts CV events independent of blood pressure (clinic and ambulatory). This suggests that both atherosclerosis (reflected by the IMT at bifurcations) and vascular hypertrophy (reflected by the common carotid IMT) exert an adverse prognostic effect in addition to that of high blood pressure.

The presence of a plaque can be identified by IMT >1.3 or 1.5 mm, or by a focal increase in thickness of 0.5 mm or 50 % in the surrounding IMT value [38–40]. There is evidence that, in untreated hypertensive individuals without target organ damage as detected by routinely performed tests, these alterations are common and thus carotid ultrasound examination may often detect vascular damage and make risk stratification more precise [26]. An adverse prognostic significance of carotid plaques (hazard ratio = 2.3) has also been reported in a sample of Copenhagen county residents free of overt CV disease, followed for about 13 years [42].

A low ankle-brachial index (ABI) signals peripheral arterial disease and, in general, advanced atherosclerosis [40], whereas carotid IMT measurements are able to detect earlier changes. A reduced ABI (<0.9) relates to further development of angina, MI, congestive heart failure, the need for coronary bypass surgery, stroke, carotid and peripheral vascular surgery [43–47] and, in patients with multivessel coronary disease, it confers additional risk [48].

A large body of evidence has been accumulated on large artery stiffening and the wave reflection phenomenon, identified as the most important pathophysiological determinants of isolated systolic hypertension and pulse pressure increases [49]. Measurement of carotid-femoral pulse wave velocity (PWV) provides a comprehensive noninvasive assessment of arterial stiffness that is simple and accurate enough [50]. This measure was shown to have an independent predictive value for all-cause mortality and CV morbidity, coronary events, and strokes in patients with uncomplicated essential hypertension [51–54]. More recently, in the Copenhagen

county population, an increased PWV (>12 m/s) was associated with a 50 % increase in the risk of a CV event [42].

Indirect indices of aortic stiffness and wave reflection such as the central blood pressure and augmentation index were confirmed as independent predictors of CV events in two studies [55, 56]. In one of these studies, only central SBP consistently and independently predicted CV mortality after adjustment for various CV risk factors including LVM and carotid IMT [56]. In the Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), central pulse pressure was significantly associated with a post hoc-defined composite outcome of fatal CV events/procedures and the development of renal impairment [57].

16.3.3 Kidney

The diagnosis of induced renal damage is based on the finding of reduced renal function and/or the detection of elevated urinary albumin excretion [58]. Renal insufficiency is currently classified based on the estimated glomerular filtration rate (eGFR), calculated by the abbreviated modification of diet in renal disease formula, which requires age, gender, race, and serum creatinine [59]. Values of eGFR <60 mL/min/1.73 m^2 indicate stage 3 chronic kidney disease (CKD), while values <30 and 15 ml/min/1.73 m^2 indicate stages 4 and 5 CKD, respectively [60]. The Cockcroft–Gault formula estimates creatinine clearance and is based on age, gender, body weight, and serum creatinine [61]. This formula is valid in the range >60 mL/min, but it overestimates creatinine clearance in stage 3–5 CKD [60]. Both formulae help to detect mild deterioration of renal function when serum creatinine values are still within the normal range [60]. A reduction in GFR and an increase in CV risk are also reflected by increased serum cystatin C [62].

Hyperuricemia is frequently seen in untreated hypertensives (particularly in preeclampsia) and has also been shown to correlate with reduced renal blood flow and with the presence of nephrosclerosis [63].

While elevated serum creatinine or low eGFR (or creatinine clearance) indicate reduced glomerular filtration, an increase in urinary albumin or protein excretion reflects the derangement in the glomerular filtration barrier. Microalbuminuria has been shown to predict the development of overt diabetic nephropathy in both type 1 and 2 diabetics [64], while the presence of overt proteinuria generally indicates the existence of established renal parenchymal damage [65]. Microalbuminuria, even below the current threshold values, has been shown to predict CV events in both diabetic and nondiabetic hypertensive patients [66, 67]. There is a continuous relationship between CV and non-CV mortality and urinary protein excretion [68, 69]. Microalbuminuria can be measured from spot urine samples (24-h or night urine samples are discouraged due to the inaccuracy of urine collection) by indexing the urinary albumin concentration to the urinary creatinine concentration [60]. Serum creatinine, eGFR, and urinalysis, including testing for

microalbuminuria, are considered routine laboratory tests to be performed in all hypertensive patients.

16.3.4 Retinal vessels

Today, most hypertensive patients present early in the progress of their disease, and hemorrhages and exudates (grade 3) and papilledema (grade 4) are observed very rarely. On the other hand, grade 1 (focal or general arteriolar narrowing) and 2 (arteriovenous nipping) retinal changes are reported much more frequently than other subclinical organ damage with documented clinical significance (LVH, carotid plaques, and microalbuminuria), but the prognostic significance of these mild retinal changes has been questioned [70–72]. These changes appear to be largely nonspecific, except for young patients in whom a deviation from an entirely normal retina should raise concern. Grades 3 and 4 are always associated with an increased risk of CV events [73, 74]. More selective methods for the objective assessment of the ocular fundus have been developed, e.g., digitalized retinal photographs, which showed that retinal arteriolar and venular narrowing may precede the development of hypertension [75, 76].

16.3.5 Brain

Several studies have shown that small silent brain infarcts, microbleeds, and white matter lesions detected by magnetic resonance imaging (MRI) are quite frequent in the general population [77, 78], their prevalence increases with age and the level of hypertension. They are all associated with an increased risk of stroke, cognitive decline, and dementia [78–80]. Availability and cost considerations do not allow the widespread use of MRI in the evaluation of very old patients, but silent brain infarcts should be sought in all hypertensive subjects with neural disturbance and, particularly, memory loss. Tests evaluating cognitive function should be used in the clinical assessment of older hypertensive subjects.

16.4 Prognostic Value of Treatment-Induced and Multiorgan Subclinical Organ Damage

The 2007 ESH–ESC guidelines [19] emphasized that the treatment-induced changes of organ damage affect the incidence of CV events and thus recommended that organ damage be measured also during treatment [81] because of the evidence that regression of LVH and reduction of proteinuria indicate treatment-induced CV protection [81, 82].

Whenever possible, search for subclinical organ damage should be made simultaneously in various organs because multiorgan subclinical organ damage is associated with a worse prognosis [83].

More recently, a population-based study from Denmark has shown that subclinical organ damage predicted CV death independently of SCORE. Combining SCORE and subclinical organ damage may improve risk prediction, particularly in subjects with moderate CV risk, by implementing urinary albumin excretion and PWV [84].

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The Microcirculation and Hypertension

17

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17.1 Introduction

The hemodynamic characteristic of essential and most forms of secondary hypertension consists of elevated blood pressure (BP) and peripheral vascular resistance. BP comprises two components: a pulsatile (pulse pressure) and a steady [mean arterial pressure (MAP)] component. Pulse pressure is predominantly influenced by the elastic properties of the larger conduit arteries, whereas MAP is determined by the resistance to flow in smaller arteries and arterioles, ranging in diameter from 10 to 300 μm. The small arteries and arterioles are a continuous segment of the vascular system associated with a gradual drop in pressure. Instead of referring to specific components as resistance vessels, the entire arterial microcirculation vessels of between 10 and 300 μm should be regarded as a site of resistance, and thus MAP, control. The exact location of the pressure drop may differ in relation to tissue. In cardiac tissue, for example, the pressure drop occurs distally in the arterial tree, whereas in the mesentery it is located more proximally. The role of the microcirculation is increasingly being recognized in the pathophysiology of cardiovascular disease [1, 2]. The microcirculation is a major site of damage in most target organs of cardiovascular disease, such as the heart, brain, and kidney. Both functional and structural alterations in the small arteries, arterioles, and capillaries are the basis of target organ damage (Table 17.1).

Detailed mechanistic studies in both human and animal models of cardiovascular disease have revealed the nature of microcirculatory dysfunction. Large-scale epidemiological studies in the last two decades have identified the associations between deranged microvascular perfusion and structure, target organ

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Table 17.1 Microvascular involvement in target organ damage in cardiovascular disease

Target organ	Morbid events	Mortality
Eye	Retinopathy	
Brain	Ischemia, Dementia	CVA
Kidney	Albuminuria, Glomerulopathy	ESRD
Heart	Ischemia	Heart failure
Periphery	Arteriosclerosis, Ischemia	

CVA cerebrovascular accident; *ESRD* end-stage renal disease

Table 17.2 Major methods to assess the microcirculation

Intravital microscopy
Capillaroscopy
Retinal imaging
Isolated small arteries
Contrast angiography
Magnetic resonance imaging
Positron emission tomography
Laser Doppler flowmetry

damage, and subsequent cardiovascular disease [3]. Major technological developments now allow the study of the microcirculation both in mechanistic and epidemiological studies. The purpose of this brief review is to provide a critical appraisal of these developments and their particular impact on hypertension research.

17.2 Methods to Assess the Microcirculation

Table 17.2 provides an overview of the major methods used to assess the microcirculation. In Table 17.3, the tissues that can be studied using these methods are summarized, whereas Table 17.4 indicates the major parameters that are used to assess the microcirculation. Intravital microscopy has been used by many groups in experimental models to study microcirculatory (dys)function. It has been the primary technology underlying our present knowledge of microcirculatory function in health and disease. Originally, this technique was used in relatively transparent tissues like the bat wing, hamster cheek pouch, or rat mesentery. Later developments using trans- and epi-illumination have allowed wider access to the microcirculation of other tissues, such as skeletal muscle, the brain, and the heart.

Table 17.3 Accessible tissues for microcirculation studies

	Intravital microscopy (animals)	Capillaroscopy	OPS/SDF imaging	(Laser scanning) ophthalmoscopy
Transillumination	Mesentery	–	–	–
	Skeletal muscle			
Epi-illumination	Brain	Skin	Skin	Retina
	Lung	Nailfold	Nailfold	
	Liver		Sublingual mucosa	
	Skeletal muscle		Brain	
			Intestine	

OPS orthogonal polarization spectroscopy, *SDF* sidestream dark field imaging

Table 17.4 Parameters used to assess the microcirculation

Small vessel density
Capillary density
Microvascular diameter
Microvascular wall-to-lumen ratio
Arteriolar tortuosity
Arteriolar branching angles
Microvascular flow
Microvascular glycocalyx size

The recent introduction of molecular imaging probes now allows detailed analyses of molecular mechanisms in microcirculatory control [4].

The major advantage of intravital microscopy is that it allows direct and precise observation of the microcirculation and its dynamics in vivo. However, access to tissues usually requires surgery and anesthesia, thus limiting its application in human studies. New techniques for video microscopic examinations have been introduced in the past two decades that do not require surgery and anesthesia. These techniques are based on the use of orthogonal polarization spectral (OPS) or sidestream dark-field (SDF) imaging [5–8]. Both devices use the principle that green light illuminates the depth of a tissue and that scattered green light is absorbed by the hemoglobin of the red blood cells contained in superficial vessels [6]. These techniques have been applied in humans for the study of various tissues, but mostly the cutaneous and sublingual microcirculation. Video recordings by handheld cameras now allow microcirculatory observations to be made even in

epidemiological studies. The parameters used to assess the microcirculation using OPS and SDF imaging include: total vascular density; arteriolar, venular, and capillary density; and microvascular flow and microvascular diameters. Broekhuizen and colleagues [9] have even used SDF imaging recently to study the behavior of the endothelial glycocalyx in humans. Endothelial glycocalyx perturbation contributes to increased vascular permeability and has been shown to be involved in the vascular complications of type 2 diabetes and perhaps other cardiovascular diseases [9].

17.3 Capillaroscopy

Until recently, nailfold capillaroscopy, using rather bulky microscopes, was the standard technique to study the microcirculation in hypertensive patients. Capillaroscopy consists of the direct in vivo observation of skin capillaries using a microscope with an epi-illumination system [10]. Nailfold capillaries are parallel to the surface of the skin, which facilitates their observation. Fluorescent tracers such as Na-fluorescein and indocyanine green have been used to improve image contrast and to study the dynamics of the microcirculation in addition to studying transcapillary diffusion. Abnormal patterns have been observed in diseases affecting the digital skin microvasculature, such as systemic sclerosis, but also in diseases like diabetes and hypertension [10, 11]. Skin capillary density has been consistently found to be 10–20 % lower in patients with untreated hypertension, when compared to normotensive controls [12–15]. This defect might be an early feature of hypertensive disease, as it was reported in borderline hypertensive subjects [16] and even in the normotensive offspring of hypertensive parents [17]. He and colleagues [18] recently showed that modest dietary salt reduction can restore capillary density in patients with mild hypertension.

17.4 Retinal Imaging

A major advantage in large-scale epidemiological studies on the pathophysiology of hypertension has been the introduction of retinal imaging methods [3, 19, 20]. Hypertensive retinopathy was first described in the nineteenth century and has been used since in the diagnosis of the severity of hypertension-induced target organ damage. However, the classical assessment of retinopathy was descriptive and gave no quantitative and mechanistic data on microcirculatory dysfunction. In the last two decades, several groups have advanced the technology of retinal microcirculatory image analysis with the use of nonmydriatic video cameras [20–22]. In particular, the advances introduced by Knudtson and colleagues [23] have allowed retinal microcirculatory analysis to become part of both mechanistic and epidemiological studies. A further, major technical advance was the introduction of scanning laser Doppler flowmetry, which allows perfusion imaging analysis

[24]. This technique also allows the determination of the wall thickness and wall-to-lumen ratio of individual retinal arterioles [25].

Retinal microcirculation undergoes a series of pathophysiological changes during and after the development of hypertension. In the initial, vasoconstrictive stage, there is vasospasm and an increase in retinal arteriolar tone [20]. Persistently elevated BP leads to intimal thickening, hyperplasia of the media wall, and hyaline degeneration in the subsequent sclerotic stage. This stage corresponds to more severe areas of arteriolar narrowing and changes in the arteriolar and venular junctions (arteriovenous nicking/nipping) [20]. In an even later stage, there is disruption of the blood–retina barrier with microaneurysms, hemorrhages, necrosis of the smooth muscle and endothelial cells, and retinal ischemia.

17.5 Retinal Microcirculation and Cardiovascular Disease

Retinal microcirculatory imaging techniques have substantial reproducibility [26, 27] and can be used repeatedly in the same individuals for follow-up. Such longitudinal studies have shown that signs of hypertensive retinopathy can be observed already in relatively young individuals without a history of hypertension [20]. These data suggest that retinal arteriolar narrowing may precede the development of hypertension [28]. Retinal microcirculatory analysis has been used for the risk stratification of hypertensive patients since it shows a strong association with the risk to develop stroke [29], coronary heart disease [30, 31], and renal complications [32]. An autopsy study of patients with stroke showed a close correlation between retinal and cerebral arteriolar changes [33]. At an even more advanced level, retinal microcirculation imaging allows the analysis of arteriolar and venular branching patterns and retinal vascular fractal dimensions [34]. We have previously suggested that abnormal growth and branching of the vascular tree may represent an early genetic or fetal programming-related characteristic of hypertensive-prone individuals [35].

Retinal arteriolar narrowing is associated with increased aortic [36] and carotid artery [37] stiffness, whereas data from the Hoorn Study [38] did not show an independent association of retinal microvascular abnormalities with indices of large artery endothelial dysfunction and intima-media thickness. Thus, the value of retinal microvascular disease for risk stratification of future cardiovascular events needs to be further investigated [39].

17.6 Advanced Imaging Technologies

The (video)microscopy techniques discussed previously allow both structural and functional studies of the microcirculation. Over the past two decades, there has been a growing interest in advanced perfusion imaging technologies, such as laser Doppler flowmetry, positron emission tomography (PET), magnetic resonance imaging (MRI), and angiography. Laser Doppler flowmetry is based on the

backscattering of a beam of laser light. The light undergoes changes in wavelength when it hits moving cells. The magnitude and frequency distribution of these changes in wavelength are related to the number and velocity of red blood cells [10]. Laser Doppler flowmetry assesses the blood flow of superficial tissue (i.e., skin) over a small volume and is accurate at detecting and quantifying relative changes in skin blood flow in response to a given stimulus [10]. Due to spatial variability, the reproducibility of this technique is relatively poor. The more recently developed two-dimensional laser Doppler perfusion imaging, in which a region of skin is progressively scanned, reduces spatial variability. However, it does not provide an exact linear measure of flow [10]. This makes laser Doppler mostly suited to assess microvascular reactivity instead of absolute measurement of the structure or flow of microvasculature.

PET has been used for more than 35 years as a powerful tool to study cardiac physiology [40]. Apart from studies on metabolism, it allows the assessment of myocardial perfusion in combination with molecular studies. Coronary microvascular function was conventionally assessed by studying flow changes detected by thermodilution or intracoronary Doppler flow wires [40]. The invasive nature of these technologies limits their applicability. PET has become an alternative technique to study microvascular function, although still only used in highly specialized centers. For a detailed review on PET and coronary microvascular function, readers are referred to two recent review papers [40, 41].

MRI has undergone major advances in the past years and is now used to study the structure of arteries in various organs, such as the brain and the heart. However, its resolution is still not high enough to assess the microcirculation. The same is true for angiography on the basis of computed tomography or dyes. Again, most advances are being made in the area of myocardial microvascular studies. The recent progress in MRI and angiography has been reviewed recently [42].

17.7 Isolated Small Arteries

All of the previously discussed methods used to study the microcirculation share an in vivo approach. Isolated small arteries have been used in the past 20 years successfully to study other aspects of microcirculatory behavior in health and disease. Small arteries have been obtained either from surgical procedures or from specific subcutaneous gluteal biopsies [43–45]. A clear advantage of the in vitro approach has been the possibility for detailed structural analyses of the small arteries both in diseased conditions and during pharmacological treatment of patients. With respect to structural alterations, small arteries remodel in hypertension with two types of remodeling. Inward eutrophic remodeling is usually found in primary forms of hypertension in humans and rats, whereas inward hypertrophic remodeling has been described in secondary hypertension and hypertension associated with diabetes [43–45]. The mechanisms of these forms of remodeling are still poorly understood, but seem to involve growth of both cellular

and matrix components of the vessel wall. Low-grade inflammation of the arterial wall, and perhaps perivascular fat, also plays a role in arterial remodeling.

Park and colleagues have proposed that small-artery remodeling may be an early manifestation of target organ damage in hypertension [46]. Small-artery structure has important prognostic significance for later cardiovascular events in both hypertensive and normotensive individuals [44, 47]. Although there are limitations to the in vivo relevance of these isolated artery studies, they provide an excellent approach to the study of the molecular and cellular mechanisms of microvascular changes in hypertension and cardiovascular disease.

17.8 Microcirculatory Dysfunction: Cause or Consequence of Hypertension?

Microcirculatory dysfunction seems to be both a cause and consequence of elevated BP [2] (Fig. 17.1). Arteriolar and capillary rarefaction and small-artery remodeling are the early hallmarks of hypertension and have been shown to occur already before or early in the onset of primary hypertension in human or animal models [2, 45]. On the other hand, the microcirculation is a primary target of the organ damage caused by an elevated BP. Microvascular damage is now held responsible for much of the pathology related to cardiac, brain, and renal dysfunction in hypertension [48]. The microcirculation is part of a vicious cycle that initiates, maintains, and amplifies high BP if it is not treated adequately [49].

The most rigorous way to investigate the behavior of this vicious cycle is to follow the dynamics of the microcirculation throughout life in a population at risk of developing hypertension. Ideally, such a population should be followed up from birth. In animal models like the spontaneously hypertensive rat, such studies have been performed [50], but the most challenging study is, of course, a human one. A beginning of such studies has been made on the basis of retinal imaging and OPS video capillaroscopy. In 6–8-year-old children, those with the higher quartiles of BP had significantly narrower retinal arterioles [51]. Recent studies showed that low-birth-weight children, who are at risk of developing hypertension later in life, have a narrower retinal arteriolar caliber at the ages of 6 and 12 years [52, 53]. Earlier studies had already associated low birth weight with capillary rarefaction in both prepubertal children and in adults [54–57]. Surprisingly, low-birth-weight infants do not have capillary rarefaction at birth [58]. In low-birth-weight infants, capillary density may be even higher because of the relative systemic hypoxia that these infants experienced in utero [56]. Basal capillary density decreases progressively after the first week of life because of a process of pruning. It may be speculated that low-birth-weight infants undergo a process of capillary hyperpruning because of a relative hyperoxia of the extrauterine environment, together with supplemental oxygen in the postnatal period of preterm infants. Alternatively, a *catch-up* process, with abundant availability of nutrients, may cause capillary hyperpruning [59]. Follow-up studies on the neonatal cohort described by D'Souza and colleagues [58] have to be awaited to decide on this hypothesis.

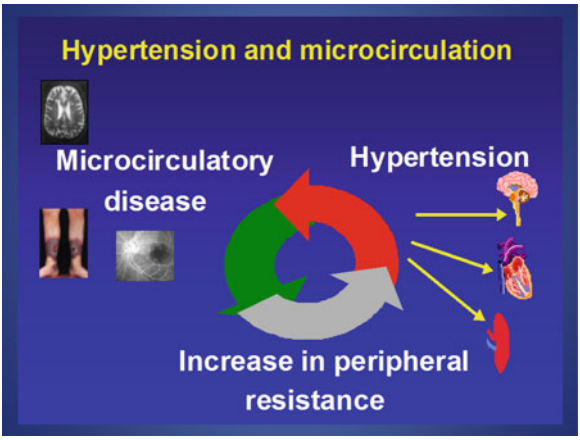

Fig. 17.1 The microcirculation is part of a vicious cycle and is both the cause and consequence of hypertension

17.9 Genetic Determinants of Microcirculatory Phenotypes

The genetic components of hypertensive disease have been the focus of recent, intense research efforts. Apart from several rare forms of monogenic causes, hypertension seems associated with subtle changes in a range of genes. Recent genome-wide association studies indicate that perhaps more than 30 genes can contribute—each to a small degree—to average BP values in a population [60, 61]. Since BP is a highly variable phenotype in an individual, it can be speculated that more robust underlying phenotypes, such as microvascular structure, give better correlations. With respect to the microcirculation, recent studies have focused on the genetic influence on the structure of the retinal microcirculation. There is a strong heritability for retinal arteriolar and venular caliber [62]. Genome-wide association studies have revealed several loci that were significantly associated with retinal arteriolar and venular caliber [62–64]. However, there was no overlap in the specific loci found in the three published genome-wide association studies. This may suggest a lack of power or may indicate regional differences, since the studies were based on populations from different parts of the world. Another approach in genetic studies is the candidate gene approach. Using this approach we recently found that the diameters of the retinal arterioles are associated with the +1675 G/A polymorphism in the *angiotensin II receptor, type 2* (*AGTR2*) gene [65].

17.10 Conclusions

The microcirculation is both a major site of vascular resistance control and of target organ damage in hypertensive disease. Evidence from animal, clinical, and epidemiological studies has confirmed its essential role in the pathogenesis of hypertension. Major advances in technology now allow the noninvasive study of

various aspects of the microcirculation in clinical and even population-based research. Such studies have revealed the major phenotypic microcirculatory changes in hypertension, such as arteriolar narrowing, capillary rarefaction, and altered branching patterns. Future research should focus on the mechanisms underlying these changes in microcirculatory phenotype as well as on how these are influenced by drug treatment.

This chapter is based upon a brief review we published earlier in *Hypertension* [66].

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Smoking, Nicotine and Blood Pressure

18

Dagmara Hering and Krzysztof Narkiewicz

18.1 The Epidemiology of Smoking

Smoking is a major global health issue accounting for more than 5 million deaths per year worldwide [1]. Although globally tobacco is the most single preventable cause of premature death, it kills approximately 12 % of men and 6 % of women annually. Moreover, the number of deaths is projected to rise even further, particularly in high-income countries, unless urgent action is taken [2].

Among the various risk factors for morbidity and mortality, smoking has been ranked second only to high blood pressure in terms of the global burden of cardiovascular disease [1]. The prevalence of current tobacco use has been higher among men than women, with the current estimation being around 33 % of the adult population. Along these lines, almost 1 billion men are current smokers worldwide, ranging from 35 in high-income countries to 50 % in developing countries. While female smoking rates accounts for 250 million worldwide, reaching 22 in high-income countries and 9 % in low- and middle-income countries [3], tobacco use is becoming more prevalent among women [4–6].

In contrast to active smoking, many concerns have been raised over the detrimental effects of passive smoking. Recent estimation of the global burden of disease attributable to passive smoking based on data from 192 countries clearly indicates that 40 of children, 33 of nonsmoker males, and 35 % of nonsmoker females were exposed to passive smoking in 2004 [7]. The total number of deaths currently attributable to passive smoking in the 25 countries of the European

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Union accounts for over 79,000 of the adult population, including more than 32,000 deaths from ischemic heart disease and over 28,000 deaths from stroke [3]. More than 600 deaths annually in the United Kingdom are associated with passive smoking at work, while smoking at home accounts for further 10,700 deaths [8].

As smoking increases the overall risk of major cardiovascular disease at any given level of blood pressure [9], arterial hypertension alone remains the leading and growing clinical problem responsible for 7.5 million deaths per year [1]. There is mounting evidence to suggest that high blood pressure is associated with poor cardiovascular outcome by increasing the risk of coronary heart disease, heart failure, stroke, and chronic kidney disease. Importantly, 45 of ischemic heart disease deaths and 51 % of stroke deaths are directly attributable to systolic blood pressure [1].

Clearly, smoking and high blood pressure are two major problems threatening global public health. Although tobacco use and hypertension often coexist, the relationship between smoking and the risk of developing hypertension is multifactorial. Here, we summarize the potential mechanisms linking smoking and high blood pressure to cardiovascular morbidity and mortality.

18.2 Smoking and Cardiovascular Disease

Undoubtedly, smoking is a major powerful contributor to the global burden of cardiovascular morbidity and mortality [10]. The risk of acute cardiac and vascular events, including myocardial infarction (MI), stroke, heart failure, cardiac arrhythmia, and sudden cardiac death dramatically increases in habitual smokers [9, 11, 12]. Data from large case–control study involving 52 countries (the INTERHEART study) clearly demonstrated the graded relationship between the number of cigarettes smoked and the risk of acute MI, showing that even smoking 1–5 cigarettes daily raises the risk by 40 % [13]. Moreover, the risk of stroke also rapidly increases with the number of cigarettes smoked per day [14, 15].

Furthermore, smoking is a potent risk for developing symptomatic peripheral arterial disease [16], in particular for current and former smokers [17]. Active smoking is a risk factor for type 2 diabetes [18] and amplifies the cardiovascular risk in this patient cohort, however, there is no evidence that the relative risk of tobacco use is greater in diabetic patients than in nondiabetics [19].

The adverse effect of even brief passive smoking on the cardiovascular system appears to be larger than that of chronic active smoking. Exposure to passive smoking has been shown to increase the risk for coronary and tobacco-related diseases [20–22]. Importantly, the mechanisms underlying the link between passive smoking and an increased risk of heart disease represent a multiple interaction that includes platelet activation, endothelial dysfunction, vascular inflammation, infection, increased oxidative stress, decreased energy metabolism, sympathetic activation, impaired autonomic function, reduction in heart rate variability, insulin

resistance, and increased arterial stiffness [20, 21]. All of the pathophysiological factors play a causal role in smoking-related cardiovascular complications.

18.3 Smoking and Blood Pressure

The relationship between smoking and high blood pressure is complex. Smoking exerts direct and immediate hemodynamic alterations in cardiovascular regulation that include increases in heart rate, systolic and diastolic blood pressure, and myocardial contractility [23, 24]. These deleterious effects in response to smoking occur within 1–2 min of the act of smoking and result in increased myocardial oxygen consumption. Blood pressure measurements may be unnoticed as the pressor and tachycardic effects of smoking are evident for 30 min after the last smoke [25]. Similar cardiovascular responses are induced when nicotine replacement therapy is administered [26]. However, despite the acute pressor and vasoconstrictor effects of smoking, results from epidemiological studies have failed to confirm the role of smoking in the development of hypertension, indicating lower blood pressure levels among smokers [27] and higher blood pressure levels after smoking cessation [28]. While smoking status is associated with increased risk of hypertension in older men [29], in normotensive women the risk of developing hypertension occurs in those who smoke over 15 cigarettes per day [30]. Studies based on office blood pressure measurements taken in the sitting position have shown that blood pressure levels among smokers were the same or lower than those in nonsmokers [31]. This controversy may result in office measurements in subjects who refrain from smoking. Standardized office blood pressure is lower than the blood pressure in subjects who are currently exposed to smoking. Indeed, studies using 24-h daytime blood pressure recordings confirmed that smokers present with higher blood pressure values than nonsmokers, even with similar office blood pressure [32, 33]. The increase in ambulatory daytime blood pressure profile is evident in young and older hypertensive subjects. Thus, smoking is associated with persistent rise in diurnal blood pressure and blood pressure variability that occurs during smoking rather than during nonsmoking [24].

18.4 Smoking and Cardiorenal Risk

Undoubtedly, the mortality from cardiovascular disease in end-stage renal disease is 20–40 % higher than in general populations [34]. Among the lifestyle choices, smoking dramatically increases all-cause mortality and cardiovascular morbidity in this population [35]. Smoking is considered as one of the important, remediable renal risk factors even in high-risk patients without primary renal disease, and in both diabetic and nondiabetic patients [36]. Cigarette smoking increases albuminuria and creatinine concentrations, leading to abnormal renal function and the progressive deterioration of kidney function over time [37]. In a large prospective

observational study of 23,523 individuals, 31 % of the attributable risk of chronic kidney disease was associated with cigarette smoking [38]. Death rates are particularly high in active smokers due to the increased incidence of new-onset congestive heart failure and peripheral vascular disease in patients starting hemodialysis [39], and peripheral-related vascular events in hemodialysis patients [40]. Given that patients who smoke are at high risk for renal and cardiac disease, all efforts should be focused on aggressive counseling on smoking cessation so as to lower the total morbidity and mortality.

18.5 The Mechanisms Underlying Smoking-Related Cardiovascular Disease

Smoking exerts direct and indirect effects on the cardiovascular system. The mechanisms by which smoking is likely to contribute to increased morbidity and mortality are multifactorial and interact with one another (Fig. 18.1). First, smoking decreases arterial distensibility [41], impairs endothelial function [42], accelerates atherosclerosis, and reduces arterial baroreflex sensitivity [43]. Second, the activation of the sympathetic nervous system as evidenced by the parallel increase in plasma catecholamines and blood pressure [25] is a key modulator involved in adverse consequences related to smoking. However, pressor and tachycardic responses to smoking produce a marked reduction in efferent muscle sympathetic nerve activity suggesting an attenuation of the sympathetic nervous system during smoking [25, 44].

Blood pressure increase in response to smoking acting via the arterial stretch baroreceptors elicits sympathetic inhibition in peripheral sympathetic activity to muscle blood vessels. When the pressor effect during cigarette smoking is masked by concomitant infusion of sodium nitroprusside, a dramatic increase in efferent sympathetic outflow occurs (Fig. 18.2) [45]. Thus, the reflex mediated via arterial baroreceptors in response to the pressor effects of smoking may have a protective effect by blunting the sympathetic excitatory effect of cigarette smoke.

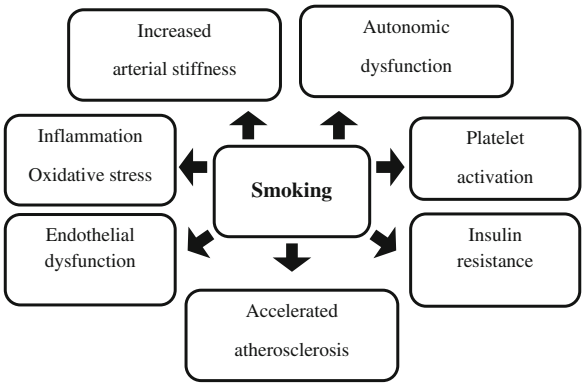

Fig. 18.1 Potential mechanisms linking smoking to cardiovascular disease

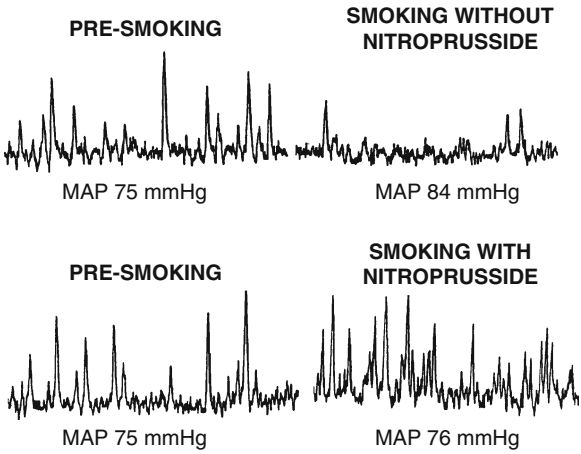

Fig. 18.2 Recordings of muscle sympathetic nerve activity (MSNA) before smoking and during smoking without an infusion of nitroprusside (*top*) and during smoking with an infusion of nitroprusside (*bottom*) in a normal subject. Smoking without nitroprusside was associated with a marked increase in mean arterial pressure (MAP) and with a decrease in MSNA (*top*). When the smoking-induced elevation in blood pressure was attenuated with nitroprusside, MSNA increased dramatically (*bottom*). Modified with permission from [45]

Clearly, smoking increases plasma catecholamines, and sympathetic neural traffic to the muscle blood vessels and to the heart, indicating activation of the sympathetic nervous system at central and peripheral levels.

Another potential mechanism through which smoking leads to poor cardiovascular outcome is structural and functional vascular remodeling. Acute smoking adversely affects endothelial function [42] and increases inflammatory biomarkers that further promote atherosclerotic disease linking to arterial hypertension [46, 47]. Acute smoking initiates alterations in the mechanic properties of the arterial wall in habitual smokers [41] and healthy nonsmokers [48], leading to systemic arterial stiffening [49]. Importantly, smoking is an independent risk factor for developing end-organ damage. It has been demonstrated that smokers have greater aortic systolic blood pressure and arterial stiffness compared with nonsmokers, resulting in a greater left ventricular growth response in current or exsmokers [50]. Smoking-enhanced alteration in arterial wall properties plays a causative role in the development and progression of systemic hypertension [49].

Importantly, the association between passive smoking and cardiovascular disease includes several pathophysiological pathways that are similar to active smoking. [20, 21].

18.6 Age-Dependent Response to Smoking

Regardless of age, smoking increases the risk for cardiovascular disease. The risk is more evident in middle-aged subjects. In young, healthy habitual smokers, smoking a cigarette leads to a blood pressure increase and to sympathoinhibition, indicating the reflex responses mediated via arterial baroreceptors [25, 44]. However, despite the pressor effects of smoking in middle-aged subjects, sympathetic vasoconstrictor activity is not suppressed [51]. The differential sympathetic cardiovascular responses in habitual young and middle-aged smokers result in age-dependent attenuation of baroreflex sensitivity.

18.7 Gender Differences in the Response to Smoking

The risk for cardiovascular morbidity and mortality increases with the number of cigarettes smoked per day. The risk is evident in both sexes, however, it is greater in women who smoke [9, 52]. Female smokers are at greater risk of developing coronary heart disease than their male counterparts [6]. Cigarette smoking exerts greater deleterious effects on the hemodynamics of females than it does for males. In contrast to men, women have greater pressor, tachycardic, and sympathetic responses to smoking [53]. The detrimental effect associated with the increased risk of smoking in women appears to be limited to cardiovascular disease, since smoking-related risk of cancer is not influenced by gender [54].

18.8 Chronic Effects of Smoking

The prognostic significance of smoking for the development of hypertension has been demonstrated in an 11-year follow-up of a population-based cohort study of middle-aged normotensive men [47]. Cigarette smoking was linked to blood pressure increase independently of inflammation, abdominal obesity, and lifestyle factors. As sympathetic activation plays an important role in the short- and long-term modulation of arterial compliance, this conceivably contributes to the well-established association between arterial stiffening and cardiovascular risk [55]. Consequently, both acute and chronic cigarette smoking exert adverse hemodynamic effects on vascular remodeling by decreasing arterial distensibility, and by increasing aortic systolic blood pressure and carotid intima-media thickening [41, 56, 57]. Smoking a cigarette independently linked to chronic sympathetic activation in untreated hypertension [58], indicating that the effects of smoking on arterial wall properties in habitual smokers may be mediated by the chronic sympathetic drive. Chronic sympathoexcitation in response to smoking contributes to further impairment of arterial wall geometry and reduction of arterial baroreflex sensitivity, leading to sustained blood pressure increase and hypertension-related end-organ damage.

18.9 Smoking and Antihypertensive Efficacy

Pressor and tachycardic responses to smoking may attenuate the potential efficacy of antihypertensive medications, mainly beta-blockers, alpha-blockers, and diuretics. Smoking transiently reduces the diuretic effect of furosemide [59]. The beneficial blood pressure lowering effect of beta-blockers appears to be diminished in chronic smokers due to the downregulation of beta-adrenoreceptors [60]. Thus, angiotensin-converting enzyme inhibitors are likely to be superior to beta-adrenoreceptors [61]. However, the efficacy of nebivolol was not influenced by smoking in newly treated essential hypertension [62]. Studies evaluating the effectiveness of angiotensin receptor blockers are lacking. Treatment with losartan was more effective than atenolol for the reduction of cardiovascular outcome in nonsmoking hypertensive subjects, whereas not in previous or current smokers as suggested in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study [63].

18.10 Smoking Cessation as an Integral Therapeutic Strategy

Evidence from several cohort studies clearly indicates that quitting smoking is the most effective intervention with the potential to reduce tobacco-related morbidity and mortality. Besides, practical guideline for smoking cessation should be instituted for all patients, regardless of drug treatment, for the prevention of cardiovascular events [64]. Evidence based on the Framingham study reported rapid reduction in coronary heart disease after smoking cessation [9]. Hypertensive patients who smoked one pack daily decreased their risk by 35–40 % by not smoking. Smoking cessation following MI is associated with significant reduction in mortality [65]. Several potential benefits have also been attributed following smoking cessation, including alterations in target organ damage, as evidenced by a reduction in albuminuria in type 1 diabetes [66] and in vascular stiffening [67]. It is unclear whether blood pressure is affected by smoking cessation, however, cessation has been shown to have a beneficial effect on vascular remodeling. The occurrence of peripheral arterial disease is reduced after abstaining from smoking [17]. Interestingly, the subsequent weight gain associated with smoking cessation does not lower blood pressure. Furthermore, the progressive increase in both blood pressure and incidence of hypertension were noted after quitting smoking [28, 68]. Despite an increase in body weight following smoking cessation, there is a sustained improvement in endothelial function [69]. Interestingly, smoking cessation substantially increased the expected gain in life expectancy [70]. Therefore, all smokers should be counseled about smoking cessation, which importantly prevents the development of arterial hypertension and cardiovascular disease.

18.11 Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) appears to be a powerful way to enable smokers to cut down on their smoking and improve the likelihood of quitting. Although nicotine acutely increases blood pressure, heart rate, myocardial oxygen consumption, and sympathetic activation [26], the dose of nicotine and associated deleterious cardiovascular effects delivered during tobacco use substantially exceed the amount being administered using NRT [71]. First-line medications to improve the quitting rates prior to attempting smoking cessation use include: bupropion SR, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline. While nicotine in a regular cigarette induces rapid hemodynamic and neural effects, the slow release of nicotine administered with a transdermal patch or nicotine gum may help minimize craving. Clearly, current available data indicate that NRT is not associated with any increase in the risk of acute MI, stroke, or sudden death [72]. Indeed, the recent largest study of more than 33,000 patients over 18 years of age treated with NRT has shown that there is no increased risk for acute cardiovascular events and mortality for a period of 8 weeks following the first prescription for NRT. In contrast, the increased incidence of MI and stroke occurred 8 weeks prior to the first NRT recommendation. Moreover, the use of nicotine replacement as a routine therapy for the management of smoking cessation is a safe and effective intervention even in patients with underlying cardiovascular disease, who substantially benefit from tobacco treatment. Smoking cessation is particularly crucial in cardiovascular patients and NRT is undoubtedly safer than continuing to smoke.

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Biomarkers in Hypertension

19

Rhian M. Touyz and Dylan Burger

19.1 Introduction

Hypertension is a major risk factor for cardiovascular morbidity and mortality. Unlike most chronic conditions, diagnosis is relatively simple, involving the measurement of blood pressure. However, by the time hypertension is diagnosed, cardiovascular risk is already increased, due in part to target organ damage. Accordingly, early detection and intervention are critically important in preventing long-term complications. In this regard, plasma biomarkers, reflective of the early processes contributing to the development of hypertension, are of particular interest as their presence may precede and predict the onset of overt hypertension. Additionally, biomarkers may provide an insight into disease pathogenesis.

The Biomarkers Definitions Working Group has defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]." In the context of hypertension, a biomarker may be more specifically defined as any characteristic that may be measured as an indicator of the presence of hypertension or susceptibility to its development. The measurement/detection of such characteristics may thereby aid in the early detection of the disease and may also provide insights into the biological/biochemical processes underlying the development of hypertension.

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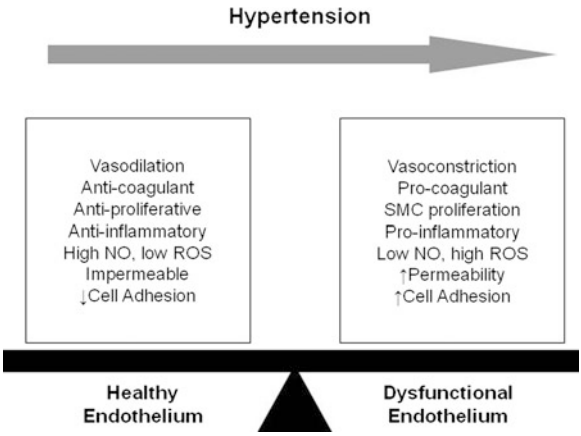

Fig. 19.1 Shift from a healthy to a dysfunctional endothelium during hypertension. This is associated with the production of factors that reflect endothelial injury, coagulation, vascular contractility, inflammation, and arterial remodeling. NO (nitric oxide), ROS (reactive oxygen species), SMC (smooth muscle cell)

Among the many pathophysiological factors associated with hypertension is endothelial dysfunction. Endothelial dysfunction is a shift from a healthy endothelium that serves to mediate vasorelaxation and inhibit coagulation and inflammation, to a procoagulative, proinflammatory endothelium with an impaired ability to facilitate vasorelaxation [2, 3]. Endothelial dysfunction may be considered both a cause and a consequence of hypertension in that its presence has a major impact on vascular function and is critically involved in the adaptive response to vascular stress caused by elevated blood pressure [4]. In human hypertension, endothelial dysfunction is observed in both conduit and peripheral vessels and is present at the earliest stages of disease [5, 6]. In fact, it may even precede the development of hypertension.

One of the most important mechanisms leading to endothelial dysfunction is the reduced bioavailability of nitric oxide (NO), due to decreased expression/activity of endothelial nitric oxide synthase (eNOS) [7]. Reduction in NO bioavailability can also result from an excessive NO degradation through the interactions with superoxide which generates peroxynitrite. Oxidative stress is considered a major cause of endothelial dysfunction and eNOS is the master gene regulator of endothelial cells that orchestrate cell phenotype, function, apoptosis, and survival. Given the tight interplay between endothelial dysfunction and hypertension, most surrogates of endothelial damage are also biomarkers of hypertension (Fig. 19.1). These biomarkers are most commonly related to specific aspects of endothelial function such as NO bioavailability, the presence of reactive oxygen species (ROS), and indices of coagulation and inflammation. The present chapter provides an overview of some of these endothelium-associated factors and discusses their potential as biomarkers in hypertension. Many other biomarkers, independent of endothelial function, have also been suggested as useful predictors of hypertension and cardiovascular disease, including inflammatory mediators, adipocytokines,

albuminuria, growth factors, neurohormones, and soluble extracellular matrix proteins, among others. These will not be discussed here and the reader is referred to other excellent reviews [8–10].

19.1.1 Nitrate and Nitrite

Endothelial-derived NO is a key determinant of vasodilation and vascular health. NO inhibits coagulation, inflammation, and oxidative stress [11, 12]. It is a short-lived free radical that rapidly reacts with other molecules. As such, levels of oxidative degradation products, such as nitrite (NO_2^-), and nitrate (NO_3^-) are commonly used as surrogate measures [13, 14]. Reductions in NO_2 and NO_3^- levels have been reported in hypertensive patients [15, 16]. However, diet and inflammatory status are major determinants of NO_2^- and NO_3^- [17–20]. Thus, plasma levels of NO degradation products may not accurately reflect endothelial NO production. Nevertheless, a reduction in NO bioavailability is considered to be a hallmark of both endothelial dysfunction and hypertension.

19.1.2 Asymmetric Dimethylarginine

Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of NO production [21]. Its levels are increased in human hypertension and correlate with NO production [22–26]. Additionally, ADMA may have prognostic value as increases in plasma levels have been shown to predict adverse cardiac events [27]. Importantly, antihypertensive treatment is associated with reductions in plasma ADMA [28].

19.1.3 Uric Acid

Uric acid can reduce NO levels through both direct inactivation and by inhibiting the transport of arginine, which is essential to NO synthesis [29, 30]. Levels of uric acid are increased in individuals with hypertension [31, 32]. Interestingly, rats with mild hyperuricemia develop hypertension within several weeks [33], suggesting a potential pathogenic role for uric acid.

19.1.4 Indices of Reactive Oxygen Species

ROS are a class of highly reactive molecules and free radicals derived from molecular oxygen [34]. ROS, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$) are formed as intermediates in redox reactions commonly occurring in biological systems that can exert significant

effects on the vasculature. In particular, O_2^- may react with NO to form peroxynitrite ($ONOO^-$), itself a ROS, thereby reducing NO bioavailability and contributing to impaired vasorelaxation [35]. Accordingly, measures of oxidative stress may also be considered biomarkers of hypertension. The most commonly used measures of oxidative stress are measures of lipid peroxidation (F_2^--isoprostanes and thiobarbituric acid-reactive substances) [36, 37]. Measures of oxidative stress are consistently increased in experimental and human hypertension (reviewed in [38, 39]).

19.1.5 Indices of Prostacyclin Bioavailability

Similar to NO, prostacyclin is produced by endothelial cells and is also a key determinant of vasorelaxation/vascular resistance and is an inhibitor of coagulation [40]. Much like NO, prostacyclin is also a short-lived factor and, accordingly, its metabolite 6-keto-prostaglandin F1α (PGF1α) is used as a surrogate of prostacyclin bioavailability. Levels of 6-keto-PGF1α are known to correlate with endothelial function [41]. Additionally, levels of 6-keto-PGF1α are decreased in human hypertension [42]. However, in some experimental models, levels of 6-keto-PGF1α may be increased [43].

19.1.6 Inflammatory Mediators

Both hypertension and endothelial dysfunction are also frequently accompanied by the presence of persistent, low-grade inflammation [44]. Because of this, inflammatory markers and mediators have been extensively examined for their utility as biomarkers of hypertension. Additionally, experimental evidence suggests an inflammatory/immune component to the pathogenesis of hypertension [45].

Cellular adhesion molecules play a critical role in regulating the attraction and anchoring of inflammatory cells. Soluble forms of cell adhesion molecules including vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule1 (ICAM) may be found in plasma samples, are increased in hypertensive subjects, and their levels correlate with blood pressure [46, 47]. Similarly, increased expression of ICAM, VCAM, and platelet endothelial cell adhesion molecule (PECAM) has been reported in preclinical models of hypertension [48, 49].

Inflammatory cytokines are also increased in hypertension and may correlate with disease severity. Accordingly, C-reactive protein, a protein found in plasma, which rises in response to inflammation, is increased in both hypertension and prehypertension, and is an independent predictor of abnormal endothelial function and cardiovascular risk [50–54]. Tumor necrosis factor (TNF-α) is a primary inflammatory cytokine secreted mainly by monocytes and macrophages but also by vascular cell populations (endothelial cells, vascular smooth muscle cells) [55]. Several studies have reported increases in plasma TNF-α levels in both

prehypertensive and hypertensive patients [54, 56]. Importantly, lowering of blood pressure with candesartan has been shown to reduce plasma TNF-α levels, suggesting a tight relationship between blood pressure and TNF-α levels [57]. In addition interleukin-1, a proinflammatory cytokine involved in early inflammatory processes, interleukin-6 (IL-6), a proinflammatory cytokine produced by macrophages, endothelial cells, and vascular smooth muscle cells are increased in hypertensive subjects [54, 58, 59]. Normalization of blood pressure is also associated with a parallel reduction in IL-6 levels [60].

19.1.7 Markers of Coagulation

A prothrombotic state is a hallmark of endothelial dysfunction [61]. As such, measures of coagulation have been examined as potential biomarkers of endothelial health and hypertension. In this regard, plasminogen activator inhibitor 1 (PAI-1), an inhibitor of fibrinolysis produced by the endothelium, is increased in hypertension [9, 62, 63]. Similarly, P-selectin, a marker of platelet activation is increased in hypertensive individuals and is reduced by antihypertensive treatment [64]. Additionally, increases in PAI-1 and P-selectin are increased in disease and correlate with endothelial dysfunction, suggesting a potential role in the pathogenesis of hypertension [65]. Finally, von Willebrand factor, a glycoprotein which is secreted by endothelial cells and plays a role in blood coagulation, is increased in hypertension and correlates with measures of endothelial function [64, 66–68].

19.1.8 Microparticles

Microparticles are small (0.1–1.0 μm) fragments of cellular membrane shed from the surface of stressed or damaged cells [69]. Microparticles are believed to be formed by all cell types and contain surface proteins and cytoplasmic material derived from their cells of origin. There is strong evidence to suggest that elevations in plasma endothelial-, platelet-, and leukocyte-derived microparticles are indicative of endothelial dysfunction [69–72]. Additionally, levels of both platelet and endothelial microparticles correlate with functional assessments of endothelial function such as flow-mediated vasodilation and erectile dysfunction [73, 74]. Emerging evidence suggests that both endothelial and platelet microparticles are increased in hypertensive individuals, and that levels of endothelial microparticles correlate with systolic and diastolic blood pressures [75].

19.1.9 MicroRNAs

MicroRNAs (miRNAs) are small, endogenously expressed, noncoding RNAs that regulate gene expression, mainly at the post-transcriptional level. Several hundred miRNA genes have been identified in human, mouse, and rat genomes (see

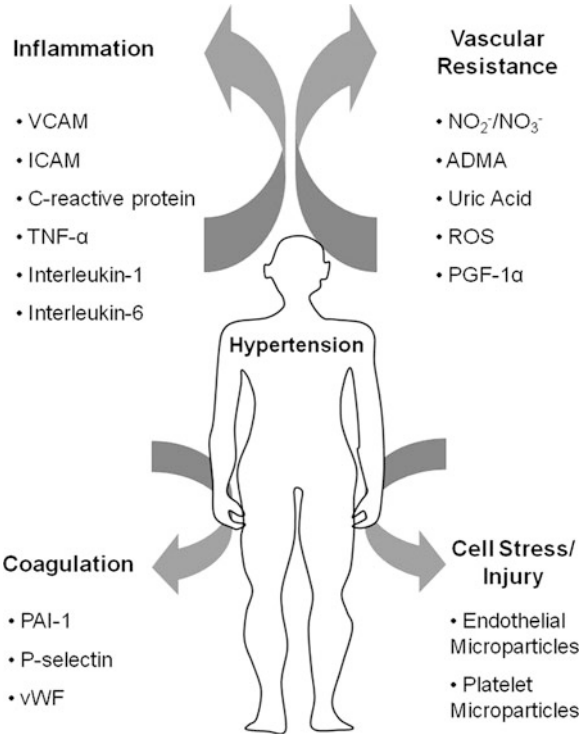

Fig. 19.2 Some biomarkers of hypertension and the underlying (patho)physiological processes that they reflect. *ADMA* (asymmetric dimethylarginine), ICAM (intercellular adhesion molecule1), NO_2^- (nitrite), NO_3^- (nitrate), PAI-1 (plasminogen activator inhibitor 1), ROS (reactive oxygen species), TNF-α (tumor necrosis factor), VCAM (vascular cell adhesion protein), vWF (Von Willebrand factor), 6-keto PGF-1α (6-keto prostaglandin F1 alpha)

miRBase: the microRNA database; http://microrna.sanger.ac.uk). This occurs through the degradation or translational inhibition of target mRNAs. A single miRNA can modulate the expression of multiple downstream target genes [76]. Many miRNAs are expressed in the vasculature, and their expression is impaired in diseased vessels; miRNAs in turn influence processes associated with vascular remodeling and inflammation in hypertension. MiRNAs of significance in hypertension include: mir-155 and mir-122 [77, 78]. Recent evidence indicates that microparticles are major transport vehicles for miRNA in the circulation [79]. Accordingly, miRNAs may serve as novel biomarkers and/or therapeutic targets for vascular damage in hypertension. However, this still needs to be validated in clinical studies.

19.2 Conclusions

Biomarkers of hypertension allow for the noninvasive identification of inflammation, endothelial dysfunction, vascular injury, and alterations in vasoactive peptide levels (Fig. 19.2) and may be of significant clinical utility as they could provide a *fingerprint* of molecular and cellular processes contributing to the development and severity of hypertension. When combined with the accurate

measurement of blood pressure, biomarkers of hypertension offer an insight into disease pathogenesis and may allow for the early diagnosis and stratified treatment of disease. Basal and serial measurement of plasma biomarkers may also provide insights into treatment efficacy. Ultimately, a comprehensive strategy using a multimarker approach together with blood pressure measurement to assess and diagnose hypertension will provide the best foundation for the early detection and identification of the underlying causes of hypertension, and the guidance of therapeutic approaches. Although potentially useful in better stratifying patients at risk, biomarkers still need to be carefully validated in large population studies in a prospective manner.

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Part IV

Antihypertensive Therapy Benefits: Pleiotropic Versus Blood Pressure-Dependent Mechanisms

20

Sverre E. Kjeldsen and Gordon T. McInnes

20.1 Morbidity and Mortality Trials Comparing Active Treatment with Placebo

The accumulated evidence from numerous trials in many thousands of individuals with high blood pressure indicates that, compared with placebo or control therapy, antihypertensive drug treatment reduces the risk of stroke, coronary heart disease, and progression of renal impairment [1–6]. The benefits are seen in systolic and diastolic hypertension, in mild-to-moderate hypertension, and in all age groups, and they appear to be constant in proportion across the blood pressure range. People at all levels of risk benefit; therefore, the bigger the absolute risk, the greater the absolute benefit.

A comprehensive meta-analysis of the results of 147 randomized trials involving 464,000 people in the context of epidemiological data from 958,000 people [4] indicated that the proportional reduction in cardiovascular disease events is the same or similar regardless of pretreatment blood pressure and the presence or absence of cardiovascular disease. These conclusions were supported by a Blood Pressure Treatment Trialists' Collaboration meta-analysis of trials in 201,566 individuals, all presenting with hypertension [3]. It is unlikely that the effectiveness of blood pressure lowering depends substantially on the starting

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blood pressure. This suggests that additional blood pressure reduction will result in further benefit.

Recent trials have challenged the concept that cardiovascular benefits are determined primarily by blood pressure lowering and that the lower the blood pressure, the better the outcome [7–12]. However, some of these trials were underpowered [8, 11, 12] and all had complex design issues which made interpretation difficult [13].

Despite these observations, rigorous blood pressure control is still recommended [14]. Monotherapy is inadequate to achieve target blood pressure in most treated individuals [15]. Reliance on monotherapy is associated with increased cardiovascular complications [16–18]. The early introduction of combination therapy was proposed [14] and the utility of this approach has been tested in the Aliskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Treatment Strategy for Hypertension (ACCELERATE) trial [19]. Compared with initial monotherapy with the constituent drugs, initiation of combination therapy with aliskiren and amlodipine resulted in not only superior early, but also late blood pressure control, after a period of free addition of other drugs. This supports the concept that failure to achieve early blood pressure control impairs later control—the never catch up phenomenon. There was no downside to initiation with the combination therapy, which was better tolerated than the conventional approach of starting with monotherapy. The early introduction of combination drug therapy should result in the earlier and more prompt achievement of targets and thus in improved outcomes. These preliminary conclusions require confirmation in further well-designed studies.

20.2 Morbidity and Mortality Trials Comparing Treatments Initiated by Different Drug Classes

Identifying the outcome differences between antihypertensive drug classes has been the focus of attention over the last two decades. Numerous comparative trials have been conducted at enormous cost, but even the largest and most expensive of these [17, 20] has failed to provide conclusive results. The challenge of finding clear evidence of benefit beyond that provided by blood pressure reduction has proved elusive. However, three recent trials are worthy of mention.

The Anglo-Scandinavian Cardiac Outcomes Trials (ASCOT) [20] compared two treatment strategies—contemporary (amlodipine ± perindopril) and conventional (atenolol ± a very low dose of bendroflumethiazide) in hypertensive subjects with high cardiovascular risk. Although failing to achieve statistical significance for the primary cardiac outcome, the results favored contemporary therapy for all prespecified secondary end points, including mortality (reason for stopping early). As in most trials, there was a difference between the treatment regimens in blood pressure control, particularly early in the follow-up. In an accompanying analysis [21], it was concluded that blood pressure and other

measured factors accounted for about 50 % of the observed difference in coronary heart disease events and that blood pressure alone was responsible for 40 % of the difference in stroke events. The residual differences suggest possible pleomorphism or inadequate statistical adjustment. Several subgroup analyses [22, 23] have been taken to favor the former explanation, but the latter explanation is equally as likely. A commentary published with the main paper [24] pointed out that the observed 2.7 mmHg systolic gradient was sufficient to explain the cardiovascular benefits of amlodipine ± perindopril. Furthermore, one subgroup analysis of the ASCOT data [25] suggested a positive interaction between amlodipine and atorvastatin sufficient to explain virtually all of the observed benefit of contemporary therapy.

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial [9] compared the fixed combination therapy of benazepril with amlodipine or hydrochlorothiazide in hypertensive patients at high risk—mainly older systolic hypertension subjects, many with type 2 diabetes. The results suggest that a thiazide diuretic may provide less cardiovascular protection than that provided by a calcium channel blocker when combined with a renin–angiotensin system (RAS) blocker. In this trial, blood pressure differences were more modest (1/1 mmHg), but this favored the calcium channel blocker and might explain around half of the 20 % benefit attributed to amlodipine-based therapy and render the outcome difference statistically (and clinically) insignificant. An ambulatory blood pressure monitoring substudy [26] showed no significant on-treatment blood pressure difference between the groups. However, this substudy was conducted 2 years after randomization and therefore the data (on survivors) may not be relevant to the overall analysis.

There has been much speculation about the possible differences between angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) with respect to cardiovascular outcomes [27]. This speculation is based on incomplete, indirect comparisons, which are likely to be inaccurate. The issue was finally addressed in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial [10], involving a direct comparison of telmisartan and ramipril in high-risk individuals, most of whom had a history of treated hypertension. There was no significant difference between those allocated to ARB or ACE inhibitor for stroke or myocardial infarction. The combination of telmisartan and ramipril resulted in slightly more blood pressure reduction but no greater reduction in cardiovascular or renal events, and was associated with more side effects [10, 28]. Thus, ACE inhibitors and ARBs appear to be equivalent in protecting against cardiovascular events, but the combination provides no added benefit.

In the absence of clear-cut differences between drugs in individual trials, investigators have resorted to meta-analyses. In the most comprehensive of these, Law and colleagues [4] concluded that, with the exception of the extraprotective effect of beta-blockers shortly after myocardial infarction and a minor additional effect of calcium channel blockers in preventing stroke, all classes of blood pressure-lowering drugs have similar effects in reducing coronary heart disease

and stroke, for a given reduction in blood pressure. A major pleiotropic effect was excluded.

Other studies have suggested possible differences between drug classes. A network meta-analysis of studies in hypertension and people at high cardiovascular risk (n = 223,313) [29] found that, in the prevention of heart failure, diuretics were superior to ACE inhibitors and ARBs. All were more effective than calcium channel blockers. Individual diuretics may differ in utility. Chlorthalidone appears to be more effective than hydrochlorothiazide in blood pressure lowering and in reducing cardiovascular outcomes [30, 31]. Thiazide-like diuretics (such as chlorthalidone) have now superseded thiazide diuretics (such as hydrochlorothiazide) in the UK guidelines for the management of hypertension [32].

Beta-blockers have also been downgraded in UK guidance [32] and their role as first-choice agents has been questioned by others [33]. The implied reduced cardiovascular protection may be related to the reduced effect on blood pressure in predominantly older study populations [14]. The meta-analysis usually cited as showing a reduced beneficial effect from beta-blockers [33] was incomplete and selective, ignored heterogeneity for estimates of relative risk, and failed to adequately take into account reduced blood pressure lowering [27]. The largest meta-analysis [4] found beta-blockers to be marginally less effective in stroke prevention and no different for other outcomes compared with other agents. Long-term observations suggest no differences in outcomes between beta-blockers and other agents [34, 35]. Although blood pressure lowering may be less than with other agents in older subjects, overall, the blood pressure-lowering effect is no different from others [36]. Thus, beta-blockers may have an advantage in blood pressure lowering in younger subjects.

Recent meta-analyses [4, 37] suggest that calcium channel blockers may have advantages over other agents in preventing stroke, perhaps mediated by better blood pressure control. This appears to be offset by a reduced effect in preventing heart failure [4, 38]. There is no doubt that blood pressure reduction secondary to calcium channel blockade reduces incident heart failure [20]. Whether calcium channel blockers have a lesser effect than other drugs for the same level of blood pressure control is uncertain.

Meta-analyses [4, 38] suggest that, compared with calcium channel blockers and diuretics, ACE inhibitors may have a slightly reduced effect in stroke prevention, but findings are inconclusive. ACE inhibitors and ARBs have similar blood pressure-dependent effects for risk of stroke, coronary heart disease, and heart failure [27]. Observational data [39] suggest within-class differences between ARBs for cardiovascular disease events. Candesartan appears to be superior to losartan, perhaps because of longer-lasting blood pressure lowering with the former drug.

It has been suggested that drug class effects on long-term (visit-to-visit) blood pressure variability may account for the differences in the effects of antihypertensive drugs on stroke, independent of changes in mean blood pressure [22]. Data from the ASCOT study [20] has been used to support this hypothesis which

ignores the previously discussed usual blood pressure differences [24], which can fully explain the findings without resort to further speculation. More work is needed.

The main benefit from antihypertensive treatment is blood pressure reduction. Any benefit beyond blood pressure reduction is unclear. There has never been a reliable trial where significantly worse blood pressure control has been associated with significantly better outcome. To some extent the issue is irrelevant since most people with high blood pressure need multiple drugs.

20.3 Trials on Intermediate End Points

20.3.1 Left Ventricular Size and Function

For similar blood pressure reduction, newer agents (ACE inhibitors, calcium antagonists, and ARBs) may be more effective than conventional drugs [40]. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study is particularly relevant, since the greater regression of electrocardiographically or echocardiographically determined left ventricular hypertrophy with losartan compared with atenolol was accompanied by a reduced incidence of cardiovascular events [41]. In a further LIFE substudy [42], N-terminal proatrial natriuretic peptide and N-terminal probrain natriuretic peptide (NT-proBNP) were reduced in parallel with blood pressure in losartan-treated patients whereas these variables increased with decreased heart rate in atenolol-treated patients. In heart failure, aliskiren plus ARB was superior to ARB alone in reducing plasma NT-proBNP [43]. An ASCOT substudy [44] indicated better diastolic function in patients randomized to amlodipine ± perindopril independent of blood pressure reduction and other factors known to influence diastolic function. These findings suggest that newer drugs, particularly RAS blockers, improve left ventricular function as well as reducing left ventricular mass.

20.3.2 Arterial Wall and Atherosclerosis

Several randomized trials have compared the long-term (2–4 years) effects of different antihypertensive regimens on carotid artery intima-media thickness. The most convincing evidence is with calcium antagonists, including results from a long-term trial in more than 2,000 patients [45]. For a similar reduction in blood pressure, carotid artery wall thickening and plaque formation was slowed down further with these drugs than with conventional therapies [45–47]. Similar evidence, although less consistent, is also available for ACE inhibitors [48] and ARBs [49]. Compared with other agents, beta-blockers are less effective in reducing aortic stiffness [50] and small-artery wall/lumen ratio [51].

20.3.3 Renal Function

The most abundant evidence concerns renal function in diabetic patients [52]. More intensive blood pressure lowering consistently reduces urinary protein, both overt proteinuria and microalbuminuria. Progression of renal dysfunction can be delayed by introducing an ARB [53, 54] in diabetic patients with advanced nephropathy. The ARB irbesartan was superior to the calcium antagonist amlodipine in delaying the development of renal failure [54], and losartan was more efficacious in reducing the progression to new overt proteinuria compared with the beta-blocker atenolol [55].

The benefit of ARBs may be apparent even in those with microalbuminuria [56]. In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial, olmesartan medoxomil prevented the onset of microalbuminuria but did not preserve renal function [57]. Blood pressure was reduced by 3/2 mmHg in the ARB group and this may explain much of the benefit. Other studies suggest that the benefit of ARB may be dose-dependent and independent of blood pressure [58].

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron—MR Controlled Evaluation (ADVANCE) trial [7], when perindopril and indapamide were added to conventional therapy, new microalbuminuria was attenuated. This may illustrate an equivalent benefit of an ACE inhibitor, but blood pressure reduction of 6/2 mmHg over placebo was probably crucial. In the ACCOMPLISH trial [59], where most patients had type 2 diabetes, the administration of benazepril + amlodipine was more renoprotective than benazepril + hydrochlorothiazide. The conclusion that there is an advantage in using a calcium channel blocker over a diuretic in renal protection has been criticized [60] and may be more apparent than real. The renoprotective effects of ARBs and ACE inhibitors are likely to be mediated through a reduction in blood pressure and albuminuria. The more these are reduced in the early months of treatment, the greater the reduction in renal events in later years [61].

In both type 1 and type 2 diabetes with normoalbuminuria and normotension, the early blockade of the RAS with either ARB or ACE inhibitor did not prevent the progression of albuminuria [62] or nephropathy. Trials of low-risk (renal and cardiovascular) patients with normoalbuminuria have failed to identify the clear benefits of ARBs in the progression of nephropathy [62–65].

A meta-analysis of 11 randomized trials comparing antihypertensive regimens, including ACE inhibition, in patients with nondiabetic renal disease [66] indicates a significantly slower progression in patients achieving a blood pressure of 139/85 rather than 144/87 mmHg. It is not clear, however, whether the benefit could be ascribed to ACE inhibition or to the lower blood pressure achieved. In the African-American Study of Kidney Disease and Hypertension (AASK) [67, 68], ACE inhibitors were shown to be somewhat more effective than beta-blockers or calcium antagonists in slowing the decline in glomerular filtration rate.

In proteinuric renal disease, a high-dose ARB (candesartan, 28 mg) further reduced albuminuria independent of blood pressure reduction [69]. However, the evidence that particular drug classes are renoprotective is not strong. In the Telmisartan Randomised Assessment Study in ACE intolerant Subjects with Cardiovascular Disease (TRANSCEND) [70], telmisartan reduced albuminuria but not progression to renal disease. The beneficial effect of calcium channel blockade on the progression to chronic kidney disease seen in the ACCOMPLISH trial [59] was not confirmed in other studies, despite blood pressure reduction [71]. A meta-analysis of 127 studies in nondiabetic nephropathy [72] showed that blockers of the RAS slowed progression of kidney disease in advanced proteinuric nephropathy, but were similar to other antihypertensive drugs in patients with no or slightly raised urinary protein. This analysis concluded that there was no special benefit of RAS blockade or calcium channel blockade for renal disease.

Many studies and meta-analyses have suggested further reduction in albuminuria when ACE inhibitors and ARBs are combined [73], although results of all studies are not consistent [74]. Similar results have been seen with an ARB/direct renin inhibitor combination [75]. The one study that suggested that enhanced reduction in proteinuria with ACE inhibitor plus ARB translated into renal protection [76] was questioned [77] and the paper retracted [78]. In the ONTARGET trial [28], an ACE inhibitor plus ARB was associated with a reduced increase in proteinuria than that with either alone, but no reduction in cardiovascular events and increased renal events. Even in high vascular risk patients with low glomerular filtration rate or albuminuria, a post hoc analysis of the ONTARGET/TRANSCEND trials [65] does not support dual therapy.

20.3.4 New-Onset Diabetes

Thiazide diuretics and beta-blockers facilitate the development of new-onset diabetes [14, 20, 79], an effect seen predominantly in those with pretreatment-impaired glucose tolerance [14, 80]. The prognostic significance may have been exaggerated since the high cardiovascular risk in those with already impaired glucose tolerance is ignored, and remains uncertain. Some studies show no associated increased cardiovascular risk [81, 82], while others suggest that the risk is increased [83].

Although a network meta-analysis [79] and individual studies [80] suggest that ARBs might significantly reduce new-onset diabetes, this was not confirmed in three major trials with telmisartan [10–12], suggesting that peroxisome proliferator-activated receptor gamma (PPAR-gamma) activity has no important antidiabetic role. Overall, ARBs and ACE inhibitors appear to have marginal benefits, calcium channel blockers appear neutral, while diuretics and beta-blockers increase the risk of new-onset diabetes [79].

20.4 Trials on Hypertension and Concomitant Diseases

20.4.1 Diabetes Mellitus

The level of blood pressure achieved during treatment influences greatly the micro- and macrovascular outcomes in diabetic patients. In patients with diabetic nephropathy, the rate of progression of renal disease is in a continuous relationship with blood pressure down to levels of 130 systolic and 70 mmHg diastolic. Rigorous control of blood pressure protects patients with type 2 diabetes against cardiovascular events. The primary goal of antihypertensive treatment in diabetics should be to lower blood pressure below 130/80 mmHg whenever possible, the best blood pressure being the lowest one that is also well tolerated.

The pharmacological treatment of blood pressure in diabetes mellitus to normalize blood pressure is associated with a primary preventive influence against diabetic nephropathy. However, targeting systolic blood pressure to <120 compared with <140 mmHg did not reduce cardiovascular end points in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [84]. Likewise, in a subgroup analysis of the International Verapamil SR Trandolapril Study (INVEST) [85] trial, tight control of systolic blood pressure in patients with diabetes and coronary heart disease was not associated with improved cardiovascular outcomes. A meta-analysis of studies in diabetes, including these recent trials [86], indicates that protection against stroke increases with the magnitude of blood pressure reduction. Although the effect on myocardial infarction was not significant, there is no evidence that tight blood pressure control worsens outcomes, including myocardial infarction. Also, there is lack of firm evidence favoring one specific drug class over another for stroke or myocardial infarction, for benefit or harm.

No major trial has been performed to assess the effect of pharmacological blood pressure lowering on cardiovascular morbidity and mortality in hypertensive patients with type 1 diabetes. Tight blood pressure control protects against microvascular complications including nephropathy and retinopathy [87, 88]. Recent evidence suggests a possible protective effect of the RAS blockade [64, 89], although findings are far from conclusive. In albuminuric patients with type 1 diabetes, protection against renal function deterioration is obtained with ACE inhibition [90]. It remains unknown whether this is related to blood pressure reduction or whether ARBs are equally effective in this indication.

In type 2 diabetes evidence of the superiority or inferiority of different drug classes is still vague and contradictory. A large meta-analysis shows substantial equivalence of various antihypertensive drug classes in preventing cardiovascular outcomes in type 2 diabetes [91]. Additional cardiovascular and renal benefits have been claimed for ACE inhibitor + diuretic [7] and for ACE inhibitor + calcium channel blocker [9], although the increased risk of heart failure associated with calcium channel blockers is more marked in diabetes [38]. After a 20-year follow-up, there was a 23 % reduction in all-cause mortality favoring atenolol-based compared with captopril-based therapy [35]. ACE inhibitors + diuretics had

no effect on eye complications in the ADVANCE trial [7], but there was a trend for benefit against retinopathy with candesartan in the second Diabetic Retinopathy Candesartan Trial (DIRECT 2) [92]. Although olmesartan medoxomil reduced the incidence of microalbuminuria in the ROADMAP trial [57], this was associated with an increased risk of cardiovascular death, fatal myocardial infarction, and sudden cardiac death. This study was underpowered for cardiovascular outcomes, but the findings are worrying because of similar results in the Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) [93], a trial of olmesartan medoxomil in onset nephropathy. If renal end points are also considered, the benefits of angiotensin II receptor antagonists become more evident; the Irbesartan Diabetic Nephropathy Trial (IDNT) [54] showed a reduction in renal dysfunction and failure by the use of irbesartan rather than amlodipine, and the LIFE trial [41] indicated that losartan reduced the incidence of new proteinuria compared with atenolol. In view of the consensus that blood pressure in type 2 diabetic patients must be lowered, whenever possible, to <130/80 mmHg, it appears reasonable to recommend that all effective and well-tolerated antihypertensive agents can be used, generally in multiple drug combinations. Available evidence suggests that renoprotection may be improved by the inclusion of an ARB and that, in patients with high normal blood pressure, who may sometimes achieve the blood pressure goal with monotherapy, the preferred first drug should be an ARB. As discussed earlier, there is little good evidence to support combination therapy with an ACE inhibitor and ARB in the management of diabetic nephropathy.

20.4.2 Hypertensive Patients with Deranged Renal Function

To preserve renal function, the first requirement is rigorous control of blood pressure. To prevent or delay the development of nephrosclerosis, blockade of the RAS has been reported to be more important than attaining very low blood pressure (68). It seems prudent to start antihypertensive therapy in patients (diabetic or nondiabetic) with reduced renal function, especially if accompanied by proteinuria, with an ACE inhibitor or an angiotensin receptor antagonist, and then to add other antihypertensive agents to further lower blood pressure. Most of the evidence comes from studies in people with concomitant diabetes, and the issues in relation to optimal drug selection have been discussed earlier. In particular, the added value of combined ACE inhibitor and ARB therapy to preserve renal function is not supported by good quality data. The renoprotective effect of the RAS blockade is less convincing in nondiabetic nephropathy [72]. Thiazide-like diuretics continue to have an important role in cardiovascular and renal protection in chronic kidney disease [94]. Treatment with beta-blockers improved all-cause mortality in patients with chronic kidney disease and chronic systolic heart failure [95]. There is insufficient evidence to conclude whether people with chronic kidney disease, but without heart failure, benefit from the beta-blockade.

20.4.3 High Risk in General

The results from the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial illustrated the importance of prompt and effective control of blood pressure in hypertensive individuals with high cardiovascular risk [18]. To achieve the required statistical power, recent trials have targeted such individuals even if blood pressure was already controlled at randomization. Essentially, these studies attempted to study populations similar to that in the Heart Outcomes Prevention Evaluation (HOPE) trial [96], in which patients with evidence of cardiovascular disease (60 % with treated hypertension and 50 % with type 2 diabetes) exhibited considerable cardiovascular and renal benefit from modest blood pressure reduction with ramipril.

Several such trials [10–12, 97–100] have evaluated the role of ARB therapy. Results were inconsistent and undermined either by an open design with soft end points and/or blood pressure differences which might explain the findings. The most important deficiency of these trials was that they were underpowered, partly because of the very low event rate. Since the publication of HOPE [96], the use of cardioprotective pharmacotherapy has increased greatly with consequent influences on morbidity and mortality. For instance, in the TRANSCEND trial [11], the event rate on placebo was the same as that on active treatment in the HOPE trial [96]. In such circumstances, the result is futility.

There is now clear evidence for the benefit of blood pressure reduction in people with high blood pressure aged up to and over 80 years [8]. In the very old, cardiovascular events were reduced within 12 months [101], supporting the clinical utility of treatment. It is important to note that participants in the Hypertension in the Very Elderly Trial (HYVET) had a starting systolic blood pressure of at least 160 mmHg and that target blood pressure was not rigorous [8]. Furthermore, frail older subjects were excluded. Thus, the evidence supports careful blood pressure reduction of significant hypertension with patient selection based on biological rather than chronological age.

A recent analysis [102] indicates no age-related differences in outcomes between different classes of antihypertensive drugs. Absolute benefits are greater in older people. Calcium channel blockers and diuretics are generally more effective than RAS blockers and beta-blockers in reducing blood pressure in older people [103]. This may explain the borderline benefit seen with valsartan in the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) trial [104], although this study of isolated systolic hypertension in older subjects was underpowered. Likewise, the reduced effect of beta-blockers compared with other drugs in stroke prevention may relate to reduced blood pressure lowering in predominantly old study populations (see earlier in this chapter). Once again, blood pressure lowering is dominant.

20.5 Secondary Cardiovascular Prevention

20.5.1 Concomitant Coronary Heart Disease and Congestive Heart Failure

Only a few trials have tested the effects of blood pressure lowering in patients with coronary heart disease or congestive heart failure. A meta-analysis [4] indicated that blood pressure lowering proportionally reduces stroke and coronary heart disease events in patients with pre-existing coronary heart disease and heart failure. However, some recent evidence [85] suggests that the tight control of systolic blood pressure in patients with diabetes and coronary disease is not associated with improved cardiovascular outcomes compared with the usual controls.

Beta-blockers and RAS blockers are well established in the treatment regimens for preventing cardiovascular events and prolonging life in patients with coronary heart disease and heart failure [4, 95, 96], but how much of the benefit is due to concomitant blood pressure lowering and how much is due to specific drug action has never been clarified. The role of calcium antagonists in the prevention of coronary events has been vindicated by the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which showed a long-acting dihydropyridine to be equally effective as the other antihypertensive compounds [17]. Calcium antagonists are possibly less effective in the prevention of congestive heart failure and should be avoided in patients with heart failure.

20.5.2 Concomitant Cerebrovascular Disease

Lowering blood pressure in patients with previous cerebrovascular disease events protected them against subsequent vascular events even when initial blood pressure was in the normal range [105], if treatment was initiated beyond the acute phase (2 weeks) of stroke; the average time to randomization was 1 year. In the Morbidity and Mortality After Stroke—Eprosartan Compared With Nitrendipine For Secondary Prevention (MOSES) [106] trial, the time from the qualifying event to randomization was about the same. Eprosartan reduced total cerebrovascular events compared with nitrendipine despite very similar blood pressure control. However, the results were driven by reduced transient ischemic attacks in patients with multiple events. There were no differences in time to first event, disability, and cognitive function or mortality. Whether ARBs offer advantages in secondary protection after stroke remains unclear and whether elevated blood pressure should be lowered during the acute phase is still disputed.

An observational study [107] suggested that patients treated with an ARB for hypertension prior to stroke had reduced stroke severity and better outcome. Although a cerebral protective effect of ARB was proposed, the study was small and retrospective with uncertainty about the influence of blood pressure control and confounders. Trials [12, 108] have not supported the cerebral protection

feature of ARB, when given early after stroke. Indeed, there was a hint of a harmful effect [108]. Although further trials are under way, the enthusiasm for the early reduction of blood pressure after stroke has waned.

20.6 Protection as a Function of Gender and Ethnicity

The proportional reduction in blood pressure and in cardiovascular risk from blood pressure reduction in randomized clinical trials appears to be similar in women and in men [109]; there were no gender-related differences between different antihypertensive regimens. Information on ethnicity is limited as trials have mostly included white subjects; however, both the ALLHAT [17] and LIFE [110] trials suggested that African-Americans may achieve lesser cardiovascular risk reduction with drugs which block the RAS. Younger/white individuals and older/black individuals can be characterized as high and low renin hypertension, corresponding to better response to treatment with RAS and beta-blockers or calcium channel blockers and diuretics, respectively [103]. However, no difference in blood pressure response to amlodipine was noted in ethnic groups in the ASCOT trial [111]. In black Americans, high doses of valsartan resulted in a greater blood pressure response than in white Americans [112] and both benefited equally from the benazepril + amlodipine combination as white subjects in the ACCOMPLISH trial [113].

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Blood Pressure Targets with Antihypertensive Treatment

21

Giuseppe Mancia

21.1 Introduction

A large number of trials have shown that antihypertensive treatment is associated with a reduction in hypertension-related cardiovascular complications such as stroke, coronary heart disease, heart failure, and renal insufficiency [1]. They have also shown that these beneficial effects can be obtained regardless of the drug or drug combinations used [2, 3] and that a close relationship exists between the magnitude of blood pressure reduction induced by treatment and the cardiovascular protective effect [4]. There is therefore no question that blood pressure must be reduced in individuals with blood pressure elevation, a recommendation made by all international guidelines [1, 5, 6].

How much blood pressure should be reduced by and which should be the target blood pressure values to reach with treatment is much less clear. Epidemiological studies have shown that cardiovascular and renal outcomes continue to decrease to low blood pressure values (approximately 110 mmHg for systolic and 70 mmHg for diastolic) [7]. However, the conclusion that the lower the blood pressure the greater is the cardiovascular and renal protection cannot *tout court* be applied to antihypertensive treatment because patients with a blood pressure elevation may have structural and functional cardiovascular alterations that reduce the ability of vital organs to autoregulate and preserve their perfusion when blood pressure is lowered [8]. Target blood pressure values must therefore be established in intervention trials, which regretfully have not obtained univocal results.

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This chapter reviews the available evidence on the blood pressure targets to be reached with treatment in hypertensive patients. Emphasis will be given to those blood pressure values recommended by the existing guidelines, i.e., <140/90 mmHg in the general hypertensive population and <130/80 mmHg in the high cardiovascular risk one [1].

21.2 Target Blood Pressure Lower Than 140/90 mmHg

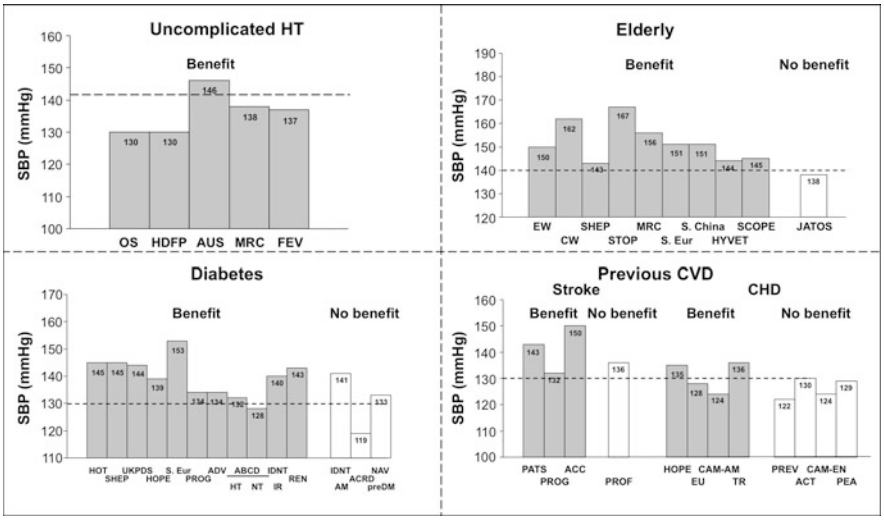

Fig. 21.1 Effects of systolic blood pressure (SBP) to values <140 mmHg in patients randomized to more active antihypertensive drug treatment in trials on uncomplicated hypertensive patients (HT, *top left panel*), older patients (*top right panel*), patients with diabetes (*left bottom panel*), and patients with previous cardiovascular disease (CVD) (*right bottom panel*). In each panel the abbreviations identify the trials considered for the analysis (Figure drawn from data from [10]). *CHD* coronary heart disease

21.2.1 Randomized Trials in Grade 1 Uncomplicated Hypertension

As shown in Fig. 21.1 (upper left panel), in five randomized trials on uncomplicated grade 1 hypertensive patients a variety of antihypertensive treatments were compared to a placebo or an otherwise control group [9]. In all trials, treated patients showed a reduced incidence of cardiovascular events with an on-treatment average blood pressure that was less than 140/90 mmHg, while being above 140 mmHg in the comparison group. Thus, evidence exists that in uncomplicated hypertension systolic blood pressure should be reduced to less than 140 mmHg.

This has a caveat, however; in all the trials mentioned the definition of uncomplicated grade 1 hypertension was based on diastolic blood pressure, and in some of the trials baseline average systolic blood pressure was close to or even

above 160 mmHg [9]. Furthermore, a noticeable fraction of patients were (1) recruited while they were already under antihypertensive treatment and (2) showed evidence of organ damage and a projected 10-year cardiovascular risk above 20 % [9]. Thus, rather than belonging to the grade 1 uncomplicated risk category, several patients had a more severe blood pressure elevation and a high cardiovascular risk. This makes a trial focused on truly low risk, mild-to-moderate hypertension, i.e., the most frequent hypertensive condition, desirable [10].

21.2.2 Randomized Trials in Old Hypertensive Subjects

Figure 21.1 (upper right panel) shows that in a large number of randomized trials on old hypertensive patients, blood pressure reduction was associated with cardiovascular protection [9]. In no such trials, however, the treated group showed an average systolic blood pressure less than 140 mmHg. This value was achieved in one additional trial in which, however, no difference in cardiovascular morbid and fatal events was seen between the treated and the control group. It can thus be concluded that, although blood pressure must also be reduced in old hypertensive patients, it is still unproven that the reduction should take systolic values below 140 mmHg, as recommended by the existing guidelines . This is thus another area where ad hoc randomized trials would be desirable [10]. It would also be desirable to obtain more information on the blood pressure target to be reached in hypertensive patients aged 80 years or older. In the only randomized trial involving hypertensive octogenarians, treatment reduced systolic blood pressure below a preset goal of 150 mmHg (actual on-treatment value: 144 mmHg) with a significant reduction in the risk of stroke, heart failure, and all-cause death compared to patients in the placebo group in whom systolic blood pressure remained around 160 mmHg [11].

21.2.3 Post Hoc Analysis of Randomized Trials

Data from randomized trials have often been analyzed post hoc to compare cardiovascular outcomes in patients in whom treatment had or had not reduced systolic and diastolic blood pressure to less than 140 and 90 mmHg, respectively. The results have usually shown that achieving this blood pressure target is accompanied by cardiovascular protection. To mention some examples, in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial [12], the hypertensive group in which the on-treatment systolic blood pressure was less than 140 mmHg showed a major reduction of cardiac events, cardiovascular mortality, stroke, and heart failure compared to the group that remained above this value, regardless of whether treatment was based on an angiotensin receptor antagonist or a calcium channel blocker. In the International Verapamil SR Trandolapril Study (INVEST) [13], the incidence and risk of cardiovascular events, stroke, and

myocardial infarction decreased progressively as the number of visits in which blood pressure was reduced to less than 140/90 mmHg increased from <25 to ≥75 % of all visits. In the Felodipine Event Reduction (FEVER) trial [14], patients with an on-treatment systolic blood pressure just below 140 mmHg (approximately 139 mmHg) showed an incidence of cardiovascular events that was 44 % less than those with an on-treatment systolic blood pressure of 144 mmHg. This strengthens the conclusion that reducing blood pressure below 140/90 mmHg has a protective effect. It suggests that this may be so also in old hypertensive patients because in all trial populations individuals of advanced age were largely represented or even predominant over middle-aged ones.

21.3 Target Blood Pressure Lower Than 130/80 mmHg

21.3.1 Randomized Trials in Patients with Diabetes or a History of Cardiovascular Events

As shown in Fig. 21.1 (bottom left panel), in a large number of randomized trials on type 2 diabetic patients, reducing systolic blood pressure to less than 140 mmHg was accompanied by a reduced incidence of cardiovascular morbid or fatal events. However, except for one small trial in which the primary end point was the treatment-induced change in creatinine clearance, the systolic blood pressure of the treated group always remained above 130 mmHg [9]. Thus, there is no support from randomized trials for the recommendation to lower systolic blood pressure to less than 130 mmHg in diabetes. This remains the case after the results of two more recent trials, i.e., the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials. In the NAVIGATOR trial [15], patients with impaired fasting glucose (and thus at a higher risk of developing diabetes [16]) were randomized to a treated and control group, neither of which, however, achieved a systolic blood pressure lower than 130 mmHg. In the ACCORD trial [17], the diabetic hypertensive patients in whom systolic blood pressure was reduced by treatment to less than 120 mmHg did not show a reduced risk of cardiovascular events compared to the group in which the on-treatment blood pressure value remained above 130 mmHg.

The results obtained in the randomized trials on patients with a high cardiovascular risk because of cerebrovascular or coronary disease are shown in Fig. 21.1 (right bottom panel). In three out of four trials on patients with a history of cerebrovascular events, the group under antihypertensive treatment exhibited a cardiovascular benefit, with a systolic blood pressure that remained always above 130 mmHg. In the larger number of trials on patients with a history of coronary disease, the treated group frequently showed a systolic blood pressure lower than 130 mmHg. This was not associated with consistent beneficial effects, however, because compared to the control group a reduced risk of cardiovascular events was

seen in two trials, whereas no risk reduction was seen in three others [9]. Thus, not only in diabetes but also in other conditions characterized by a high cardiovascular risk there is no randomized trial evidence in favor of aggressive blood pressure reduction. Indeed, because in the ACCORD trial the more aggressively treated patients showed a three times greater incidence of serious side effects compared to the less aggressively treated ones [17], the evidence rather suggests that this strategy may be associated not just with no advantage but with a disadvantage.

21.3.2 Post Hoc Analysis of Randomized Trials and the J-Curve Phenomenon

This conclusion is supported by data obtained via post hoc analysis of randomized trials on high cardiovascular risk patients. In the diabetic patients of the INVEST trial [18], a reduction in systolic blood pressure to between 130 and 139 mmHg was associated with a clear-cut reduction in the incidence of cardiovascular events compared with patients who remained above 140 mmHg. However, the reduction was not greater in patients who achieved an on-treatment systolic blood pressure below 130 mmHg. Likewise, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) involving diabetic or nondiabetic patients with a frequent history of cardiovascular disease, a reduction of cardiovascular risk was seen when systolic blood pressure was reduced from a baseline value greater than 140 mmHg to between 140 and 130 mmHg. Again, however, no additional benefit was seen in those in whom an on-treatment blood pressure below 130 mmHg was achieved [19, 20]. Indeed, in both trials, patients whose on-treatment systolic blood pressure was less than 130 mmHg showed a tendency for morbid or fatal cardiovascular events to progressively increase, i.e., a J-curve phenomenon.

The possibility that an excessive blood pressure reduction leads to a J-curve phenomenon deserves further consideration. In the ACCORD trial [17], patients whose systolic blood pressure was reduced to less than 120 mmHg showed a small but significant reduction in the incidence of stroke compared to the group remaining at an on-treatment systolic blood pressure of 133 mmHg. Furthermore, in the ONTARGET, INVEST, and VALUE patients [18, 19, 21], lowering systolic blood pressure to less than 130 mmHg was associated with a reduction in the incidence of stroke and renal events (end-stage renal disease, new microalbuminuria and macroalbuminuria) with no reduction, and indeed even an increase, in the incidence and risk of myocardial infarction and heart failure (Fig. 21.2). Vital organs may thus react differently to an aggressive blood pressure drop, a cerebrovascular or renal protection perhaps coexisting with no benefit or even harm to the heart. This may be due to a better ability of the brain and kidney to autoregulate their blood flow and thus preserve perfusion at low blood pressure values. It may also originate, however, from the characteristics of the recruited patients, i.e., from the fact that in all the previously mentioned trials the high cardiovascular risk

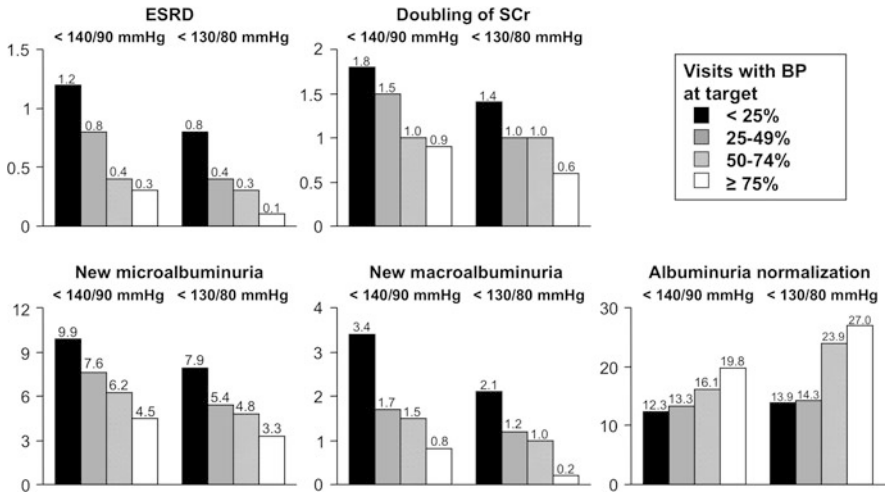

Fig. 21.2 Incidence of renal events according to the percentages of visits in which blood pressure (BP) was reduced to <140/90 or <130/80 mmHg in patients with baseline systolic blood pressure ≥140 and ≥130 mmHg, respectively. ESRD indicates end-stage renal disease (Figure drawn from data from [21]). *SCr* serum creatinine

was mainly due to a previous coronary event, which could have selectively impaired coronary autoregulation. The possibility of a better ability of the brain to preserve its perfusion is supported by a post hoc analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which showed that in patients with a history of stroke or transient ischemic attacks, a treatment-induced reduction of systolic blood pressure to less than 120 mmHg was associated with a parallel reduction of hemorrhagic, and to a lesser extent, ischemic stroke [22]. It is, however, refuted by another post hoc analysis of the PROFESS trial in which patients with a history of stroke showed an increased stroke recurrence if their systolic blood pressure was reduced to less than 130 or 120 mmHg [23] (Fig. 21.3). This suggests that when cerebral damage exists, the brain behaves like the heart, i.e., it shows a J-curve phenomenon when blood pressure is excessively lowered.

If future evidence confirms that a systolic blood pressure reduction below 130 mmHg protects the brain but not the heart, physicians will face the difficult task of deciding whether to prioritize cardiac or cerebral protection by the adoption of a conservative or aggressive blood pressure-lowering strategy, respectively. An overall aggressive blood pressure-lowering strategy might turn out to represent the most common choice in Asia because in that continent hypertension-related cardiovascular complications mainly consist of stroke. This could be the case also in patients with a previous cerebrovascular event because in this condition the chance of stroke recurrence greatly exceeds that of a cardiac event [24]. A more conservative strategy may on the other hand be the choice in patients with a history of

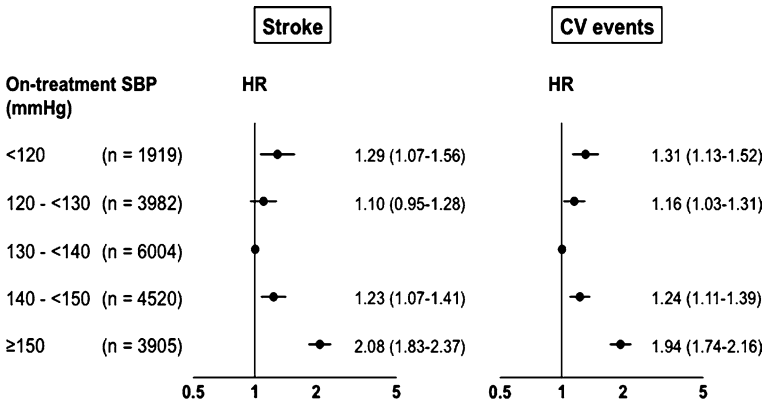

Fig. 21.3 Adjusted risk of stroke (*left panel*) and cardiovascular (CV) events in patients with recurrent stroke according to achieved systolic blood pressure (SBP) values in the PROFESS trial (figure drawn from data from [21]). *HR* hazard ratio

myocardial infarction in whom a second cardiac event is much more likely than a cerebrovascular event [24].

21.3.2.1 Limitations of the Post Hoc Approach

The results obtained by post hoc analysis of the trials need to be interpreted with caution. As regards the J-curve phenomenon, for example, the groups in which an increased incidence of events is seen are usually small, which means that a chance finding cannot be excluded [25]. Furthermore, because nonrandomized groups are compared, between-group differences other than the achieved blood pressure may be responsible for the results. It is possible, that the increased incidence of cardiovascular events in groups with a low target blood pressure is due to an initially high cardiovascular risk that favors a greater event incidence, irrespective of the achieved blood pressure. This is in line with the observation of a J curve not only in actively treated patients but also in patients from the placebo group [26]. It is also in agreement with recent evidence from the patients of the ONTARGET trial in whom systolic blood pressure was reduced by treatment to <130 mmHg; the subgroups with and without events did not differ in the achieved blood pressure values (Fig. 21.4), but rather for the increased number and severity of risk factors in those in whom an event did occur [27]. Ultimately, whether there are blood pressure values that antihypertensive treatment should not pursue because of their association with an increased risk of cardiovascular events can only be resolved with trials that randomize patients to different blood pressure targets. No fewer than three randomized groups will be required, because this is the minimum number needed to see whether the association between blood pressure and events is not a linear one.

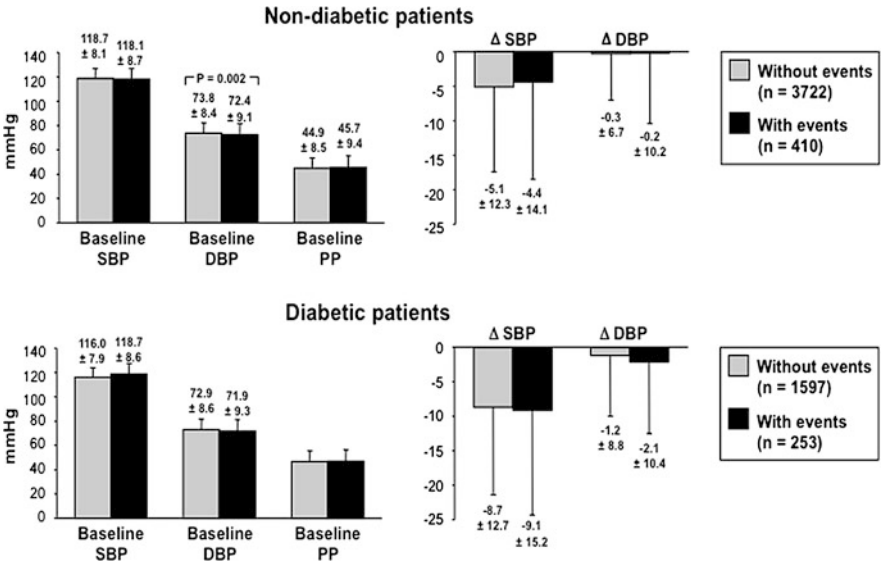

Fig. 21.4 Lack of difference in baseline blood pressure, treatment-induced blood pressure reductions in non-diabetic and diabetic patients who experienced or not experienced in the follow-up period cardiovascular events in the ONTARGET trial (figure drawn from data from [28])

21.4 Target Ambulatory and Home Blood Pressure

Ambulatory and home blood pressure have been systematically measured in trials addressing the effect of treatment on intermediate end points, such as regression of left ventricular hypertrophy [28] or progression of carotid artery atherosclerosis [29]. Conversely, their use in randomized, event-based trials has been limited to small subgroups, which means that no information is available on the ambulatory and home blood pressure targets that provide the maximum cardiovascular benefit and that should thus be reached with treatment. Currently, on-treatment target ambulatory and home blood pressure values are inferred from their correspondence to the higher office blood pressure values, as observed in observational studies on hypertensive patients or population cohorts [30, 31]. Direct information on target out-of-office blood pressure values to be achieved with treatment represents a most important future goal.

21.5 Conclusions

Given the inconsistency and limitations of current evidence on blood pressure targets to be reached with antihypertensive treatment, a more conservative position than that taken by a number of current guidelines seems wise. This is what the European Society of Hypertension has done in a document published in 2009 [10]. The advice is that "On the basis of current data, it may be prudent to recommend lowering systolic blood pressure and diastolic blood pressure to values within the range 130–139 and 80–85 mmHg, respectively, and possibly close to lower values in this range, in all hypertensive patients. More critical evidence from specific randomized trials is desirable, however [10]".

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The Role of the Polypill in Hypertension

22

Andrew Mente, Prem Pais, Denis Xavier, Koon Teo and Salim Yusuf

22.1 Introduction

Cardiovascular diseases (CVD) continue to occur in epidemic proportions globally. Any epidemic requires multiple strategies and the mobilization of a large number of individuals to contain and reverse it, so that the burden on mortality and morbidity can be substantially reduced. At present, hypertension is the most common modifiable cause of disease globally and accounts for about 8 % of all global deaths. Hypertension occurs in about 40 % of the adult population in most countries and in nearly 60 % of all individuals who are destined to have a cardiovascular event. Incremental increases in blood pressure (BP) confer an increasing and graded risk. Randomized controlled trials (RCTs) have demonstrated that greater degrees of BP lowering in those with hypertension will lead to greater risk reductions in stroke and coronary heart disease (CHD).

The challenge with hypertension control is fourfold: (1) diagnosis through screening because it is *silent* in most individuals; (2) initiation of treatment in the majority of individuals; (3) rapid achievement of optimal BP lowering; (4) and enhancing long-term treatment adherence. There are extensive guidelines for controlling hypertension in most countries in the world and inexpensive, generic BP-lowering drugs such as diuretics and beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers are widely available.

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Despite this, there is a huge treatment gap and the majority of individuals with hypertension in most countries are not detected, poorly treated, and not controlled. In general, only half of those with hypertension in the population are detected, but once detected about 60–70 % of individuals are treated. However, in the majority BP control is poor with only about 10–20 % of those with hypertension achieving adequate control [unpublished data from the Prospective Urban Rural Epidemiology (PURE) study]. Therefore the two major *gaps* in the management of hypertension are a lack of a systematic approach to screening of the adult population and the use of simple, low-cost, and effective BP-lowering therapies.

The control of high BP is rarely achieved using single BP-lowering drugs. Therefore, in most individuals (especially those with multiple concomitant risk factors such as diabetes or obesity or those with established CVD), it requires the use of two or more effective antihypertensive medications. The benefits of a two-drug combination in improving hypertension control and enhancing long-term adherence is well established, but even with two drugs in combination, the degree of BP lowering is inadequate in most individuals with hypertension. Further, in most countries there are few low-cost combinations of two BP-lowering medications and a three-drug combination has only recently become available. Further, most individuals with hypertension would benefit from a lipid-lowering agent such as a statin, either because they have abnormal lipids, concomitant diabetes, or a high global risk for future CVDs (e.g., a high risk score using the Framingham or other risk scoring methods), or because they have established CVD. Therefore, a combination of two or three BP-lowering agents along with a statin (with aspirin in those with CVD), may be a very useful strategy to lower the risk of CVD by a large degree in most individuals with hypertension.

If a single pill or capsule can replace the use of four or five separate pills, there are substantial advantages (Table 22.1). First, it will make initiation of treatment easy for the practitioner (one instead of four or five prescriptions). Second, it will reduce BP quickly (with fewer visits) and to a greater extent. Third, it could enhance subject adherence to the drugs and achieve an effective BP lowering regimen. Fourth, by reducing the costs of packaging, distributing, and dispensing drugs, the costs to the patient and to the system could be substantially reduced. Finally, it would simultaneously reduce lipids. Consequently, this could lead to a substantially greater risk reduction in CVD events, which could turn out to be greater than 65 %.

However, the potential of the polypill can only be realized and demonstrated through systematic research and ultimately large RCTs. In this chapter, we first discuss the results of studies on the formulation of a polypill and the initial pharmacokinetic (PK) and pharmacodynamic (PD) studies, then proceed to look at the effects of such a polypill on risk factor reduction in a large phase 2 study of different formulations in those with hypertension. These are followed by dose escalation studies and finally by an overview of a large ongoing RCT targeted at assessing efficacy (to reduce CVD) and effectiveness as a community-level intervention for hypertension control.

Table 22.1 Potential advantages of a polypill in hypertension

Advantage	Comment
Improved delivery of care	By avoiding complex algorithms to identify individuals for therapy, increasing the ease of prescribing, and avoiding multiple steps for dose titration of each drug, more at-risk individuals could be treated and blood pressure would be reduced more quickly and substantially. A study of high-risk patients with ischemic heart disease (IHD) or diabetes mellitus showed that use of a *cardioprotective bundle*, a simplified regimen involving fixed doses of a generic statin and ACE inhibitor/ARB, delivered with minimal physician visits, reduced hospitalizations for IHD or stroke within 1 year. Moreover, fixed-dose combination drugs are already widely used in hypertension and in other conditions such as AIDS and tuberculosis
Improved adherence	Individuals would need to take only one instead of several pills per day for CVD prevention, which may enhance adherence
Reduced cost	Costs of a polypill using generic components (estimated at approximately US$1 per day in developed countries and <10 cents/day in developing countries) are likely to be much lower than the total costs of individual drugs
Polypill as a platform for efficient strategies to widespread CVD prevention	Current CVD prevention approaches (detailed selection of individuals who require therapy, prescribing one drug at a time, frequent dose titration, monitoring of tests, and physician visits) cannot be scalable to tackle a global epidemic. Use of trained nonphysician health-care workers to deliver the polypill plus lifestyle advice in those with hypertension or CVD could lead to a substantial increase in the proportion of high-risk individuals receiving appropriate risk factor control. Physician referral for side effects, complications, or dose escalation is complementary

22.2 Components of the Polypill for the Control of Hypertension

In 2002, Yusuf [1] proposed a four-drug combination of aspirin, beta-blocker, statin, and ACE inhibitor to reduce CV events as secondary prevention in those with established clinical disease, and estimated that such a combination would reduce CVD by 75 %. Wald and Law [2] proposed a polypill for use in both primary and secondary prevention containing low-dose aspirin (50–125 mg/d),

folic acid 0.8 mg/d, a potent statin (e.g., atorvastatin 10 mg or simvastatin 40–80 mg), and three BP-lowering drugs at half the standard dose [among thiazide diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers]. They claimed that the polypill would reduce CVD by 80 %. Some of their assumptions have been refuted by recent evidence, but the basic principles remain sound. Folic acid has not prevented CVD in large randomized trials [3]. Statins and BP-lowering drugs, on the other hand, are proven in both primary and secondary prevention. This has lead our group to conduct a series of studies to initially formulate a polypill (as a capsule—the Polycap), then test its PK and PD properties in preliminary trials followed by two large phase 2 trials to assess the impact of the Polycap on tolerability and on BP and lipid reduction. We are about to embark on two large individual randomized trials of the Polycap in primary prevention, the first involving 8,000 individuals in Africa, Canada, China, India, the Philippines, and South America, and the second a large community-based hypertension programme where the Polycap is a central part of the strategy for community-wide BP control in 80 communities in Colombia and Malaysia.

22.3 Bioavailability of the Polycap

Formulating a stable five-drug preparation is challenging. In conjunction with Cadila Pharmaceuticals (Ahmedabad, India), we have developed a capsule that contained five key drugs, evaluated the bioavailability of each ingredient of the Polycap, and determined any drug–drug interactions relative to single-component reference preparations [4]. In a five-arm, randomized, crossover trial with a 2-week washout period in 195 healthy volunteers, the bioavailability of the ingredients of the Polycap (T; test) when formulated as a single capsule was compared with that of identical capsules with each of its ingredients administered separately (R; reference). The test Polycap contained five drugs (enteric-coated aspirin 100 mg, ramipril 5 mg, simvastatin 20 mg, atenolol 50 mg, and hydrochlorothiazide 12.5 mg). The reference market preparations of its individual components were Altace [ramipril] 5 mg capsules, Tenormin [atenolol] 50 mg tablets, Microzide [hydrochlorothiazide] 12.5 mg capsules, Zocor [simvastatin] 20 mg tablets, and enteric-coated low-dose Baby Aspirin [aspirin] 81 mg tablets. Plasma concentrations of each drug and, where applicable, its active metabolite were measured using validated liquid chromatography/tandem mass spectrometry and ultra performance liquid chromatography. Mean pharmacokinetic parameters and their standard deviations were computed for each analyte. No drug–drug interaction was found and there was no difference in the comparative bioavailability for each ingredient when given individually or in the Polycap. This preparation was tested in two large phase 2 trials—the first and second The Indian Polycap Study (TIPS).

22.4 Trials on the Effects of the Polypill on Risk Factor Levels and Projected Theoretical Risk Reductions in Cardiovascular Events

22.4.1 The Indian Polycap Study—Trial 1

The original TIPS-1 trial [5] randomized 2,053 individuals (733 with hypertension or BP $\geq$ 140/90 mmHg) aged 45–80 years without CVD and with at least one risk factor to the Polycap, consisting of thiazide (12.5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg), or to six other groups (aspirin alone, simvastatin alone, hydrochlorothiazide alone, three combinations of two BP-lowering drugs, three BP-lowering drugs alone, three BP-lowering drugs plus aspirin) administered for 12 weeks. In participants with hypertension, mean BP was 147/90 mmHg, 27.3 % had diabetes, and baseline low-density lipoprotein (LDL) cholesterol was 2.78 mmol/L. All study participants received lifestyle advice. Compared with the groups not receiving BP-lowering drugs, the Polycap reduced systolic and diastolic BP by 8.25 and 5.85 mmHg, respectively, which was similar to the groups with three individual BP-lowering drugs, with or without aspirin (Fig. 22.1). LDL cholesterol-lowering in the Polycap group was

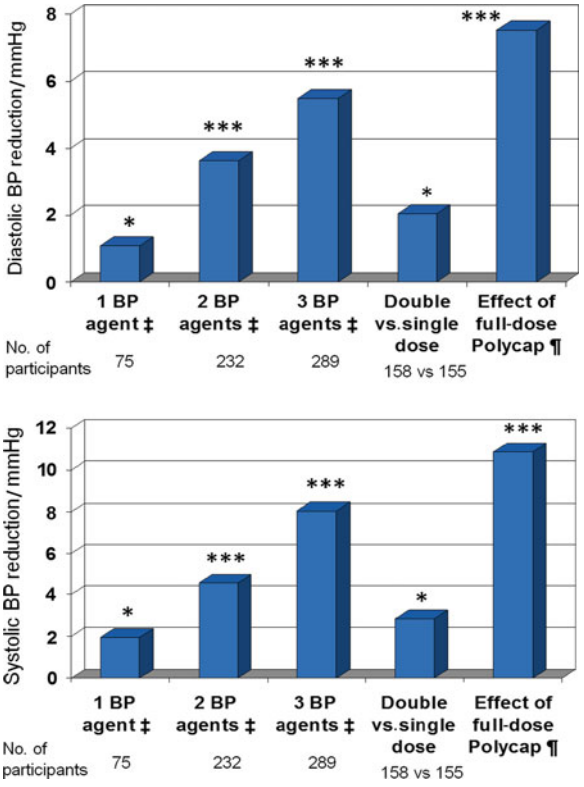

Fig. 22.1 Effect of one, two, and three drugs used at low doses and in combination in TIPS-1 and double-dose Polycap in TIPS-2 on systolic and diastolic BP in participants with hypertension. *BP* blood pressure. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Hypertension at baseline defined as systolic BP > 140 mmHg. ‡ BP reduction relative to ASA/Simvastatin ($n = 139$). The effect of full-dose Polycap is derived by adding the additional effects of two doses of the Polycap from TIPS-2 to the effects of the Polycap + three drug combinations in TIPS-1

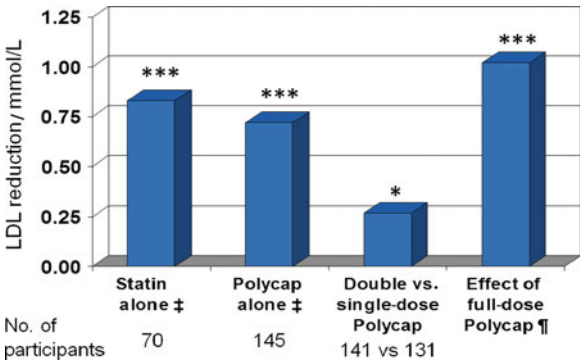

Fig. 22.2 Effect of simvastatin or Polycap in the TIPS-1 study and double-dose Polycap in the TIPS-2 study on LDL cholesterol in participants with hypertension. *BP* blood pressure, *LDL* low-density lipoprotein. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Hypertension at baseline defined as systolic BP > 140 mmHg. ‡LDL cholesterol reduction relative to nonstatin ($n = 489$). The effect of full-dose Polycap is derived by adding the additional effects of two doses of Polycap from TIPS-2 to the effects of Polycap or simvastatin in TIPS-1

0.72 mmol/L, which was slightly less than with simvastatin alone (0.83 mmol/L), both being greater than the groups without simvastatin (Fig. 22.2).

22.4.2 The Indian Polycap Study—Trial 2

Although the Polycap used in TIPS-1 is a suitable candidate for the evaluation of its impact on clinical outcomes in large trials, only *half doses* of the individual components were used, and it is important to evaluate whether a *full-strength* Polycap can be developed. If tolerability and a significantly greater impact on risk factors of a full-strength Polycap can be established, then such a formulation may lead to substantially greater benefit. Accordingly, in the recently completed TIPS-2 trial, the investigators compared the impact on BP and lipids of two doses of low-strength Polycap to one dose of low-strength Polycap in a double-blind RCT. As with TIPS-1, the single dose of low-strength Polycap consisted of thiazide (12.5 mg/day), atenolol (50 mg/day), ramipril (5 mg/day), simvastatin (20 mg/day), and aspirin (100 mg/day). The trial included 518 patients with stable cardiovascular disease or elevated risk factors from 27 centers in India. Of these participants, 313 had baseline hypertension or BP ≥ 140/90 mmHg. Participants were randomized to a single capsule of low-strength Polycap plus placebo or two capsules of low-strength Polycap. At entry into the trial, nonstudy statins, low-dose ACE (ACEI), thiazides, and beta-blockers were stopped. All subjects entered a 4-week run-in period and then were allocated to receive the study medications for 8 weeks, with an additional follow-up 4-weeks later after stopping the medication (wash out period to assess the sustainability of effects and ensure that there was no evidence of *clinical rebound*). Participants on the two doses of low-strength

Polycap also received potassium supplementation (30 mEq). In participants with hypertension, compared to patients receiving the single-dose Polycap, the double-dose Polycap reduced systolic BP by a further 2.84 mmHg and diastolic BP by a further 2.03 mmHg which represents an additional 25 % drop in BP with the double dose compared to the single dose from the randomization visit at baseline (Fig. 22.1). Moreover, compared to patients receiving the single-dose Polycap, the double-dose Polycap reduced LDL by a further 0.27 mmol/L which represents an incremental reduction in LDL with the higher dose of the Polycap by about one quarter (Fig. 22.2).

The TIPS-1 and -2 trials also shed light on whether calcium channel blocker (CCB) background therapy in hypertensive patients influences the BP-lowering effect of the Polycap since 33 % of participants were on a CCB as background therapy. These data suggest that the Polycap can be safely added to a CCB when further control of BP is needed and may potentially lead to the development in the future of a combination of four antihypertensive drugs for those with very high BP (e.g., those with a systolic BP > 160 mmHg) in whom a 20 mmHg or larger reduction in systolic BP is desirable.

22.4.3 Effect on Blood Pressure Control and the Framingham Risk Scores

The results from TIPS-1 show a positive linear relationship between the number of BP drugs taken and achievement of BP control (p for trend < 0.0001) (Fig. 22.3). Compared to hypertension patients taking no BP drugs, patients assigned to Polycap are nearly twice as likely to attain BP control (80.7 vs. 47.9 %, $p < 0.0001$). Moreover, use of low doses of one component drug controls BP only in 58.1 %, two drugs at low doses control BP in 68.5 %, and low doses of three drugs control BP in 71.3 %. This suggests that the use of three drugs simultaneously as in the Polycap will control BP in most patients rapidly.

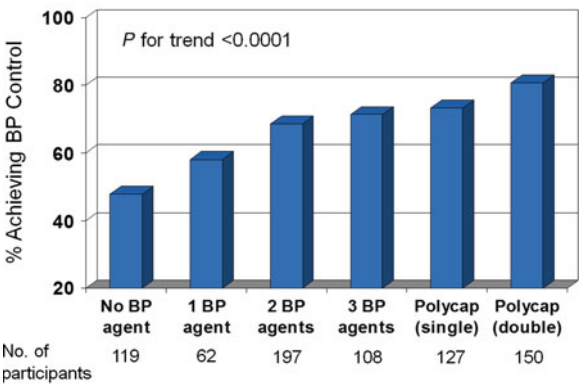

Fig. 22.3 Efficacy of the Polycap in achieving blood pressure control in participants with hypertension in TIPS-1 and TIPS-2. Hypertension at baseline defined as systolic BP > 140 mmHg. *BP* blood pressure

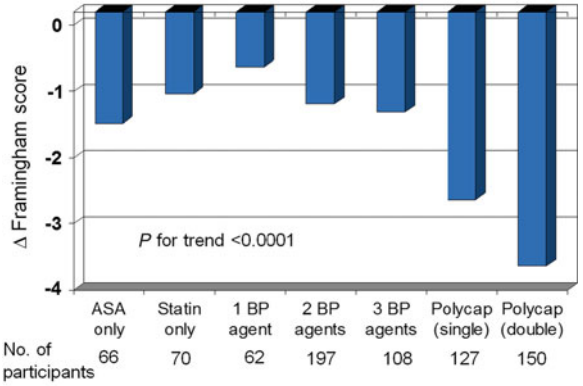

Fig. 22.4 Efficacy of the Polycap in reducing Framingham risk score in participants with hypertension† in TIPS-1 and TIPS-2. Hypertension at baseline defined as systolic BP > 140 mmHg. *ASA* acetylsalicylic acid (aspirin), *BP* blood pressure

Since hypertension often clusters with unfavorable lipid levels, the Polycap has the potential to produce large reductions in CV risk by substantially lowering both BP and LDL cholesterol. As shown in Fig. 22.4, allocation to a higher number of BP drugs produces a larger reduction in Framingham score (p for trend < 0.0001). The single-dose Polycap yields a 2.84 point reduction and the double-dose Polycap a 3.84 point reduction in Framingham score compared to a 0.83 point reduction with one antihypertensive at low doses ($p < 0.001$). This translates into a 47.3 % reduction in CVD risk with the single-dose Polycap and a 64.0 % reduction in CVD risk with the double-dose (Fig. 22.5).

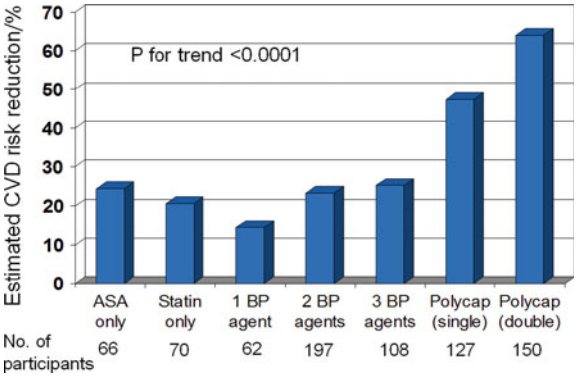

Fig. 22.5 Efficacy of the Polycap on estimated CVD relative risk reduction in participants with hypertension in TIPS-1 and TIPS-2. Estimates derived from the Framingham score corresponding to 10-year CVD relative risk reduction (National Cholesterol Education Program). Hypertension at baseline defined as systolic BP > 140 mmHg. *ASA* acetylsalicylic acid, *BP* blood pressure, *CVD* cardiovascular disease

22.4.4 Tolerability of the Polycap

The tolerability of the Polycap was evaluated in the TIPS-1 and -2 trials. In TIPS-1 [5], while there were low rates of discontinuation for side effects (about 3 %), the rates of discontinuation for nonspecific symptoms or for social reasons was high (18 %) (Fig. 22.6). This may be partly because this study did not use a run-in period prior to randomization, because apparently healthy individuals were not keen to take the pills, and because of the need for frequent visits and blood tests (six visits in 12 weeks). This has implications for the design of larger and longer trials (need for a run-in, inclusion of individuals at moderate or high risk, systematic approach to lifestyle advice, and so on, so that participants feel that their involvement in the trial is worthwhile; need to avoid frequent visits; and the need to invest resources in enhancing long-term adherence). Importantly, as TIPS-2 showed, tolerability of the Polypill was similar in the single- and double-dose Polycap groups. In particular, there was no increase in the overall rates of drug discontinuation for side effects with the higher dose (other than for dyspepsia, which is related to the higher dose of acetylsalicylic acid (ASA) in the group receiving two doses of the low-strength Polycap), so that the number of individuals stopping the double-dose Polycap was similar to individuals taking the single dose (6.9 vs. 7.8 %, single-strength vs. double-strength Polycap). Compared to the original TIPS, there were lower rates of discontinuation for nonspecific symptoms or for social reasons (7.3 %), likely due to the use of a run-in period prior to randomization. Also, since the participants in TIPS 2 had pre-existing CVD, their compliance to the secondary prevention medication may have been better.

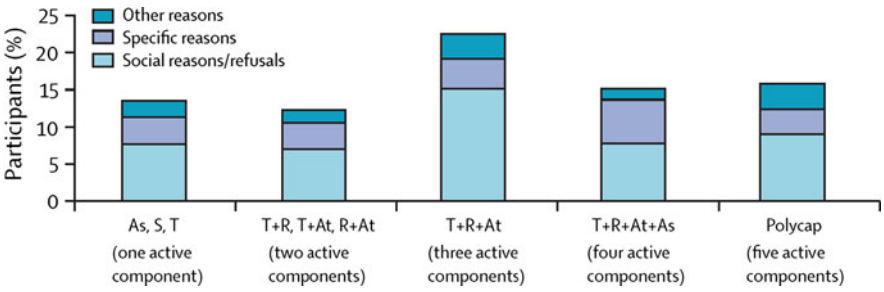

Fig. 22.6 Rates of discontinuation of study drug by categories of reasons. Some patients indicated more than one reason for the discontinuation of study drugs. In this figure, we use a hierarchical and mutually exclusive approach in which drug-specific reasons are given first priority, other reasons the next priority, and social reasons the last priority. With increasing number of active components in the Polycap, there was no pattern of a progressively increasing rate of discontinuation. Although we noted an apparent higher rate of discontinuation of study drug with three active components, it was accounted for by social reasons, and rates of discontinuation were lower with four and five active components. Rates of discontinuation with four and five active components were similar to those for one or two active components. *As* aspirin, *At* atenolol, *R* ramipril, *S* simvastatin, *T* thiazide. (From [4])

22.5 Completed and Ongoing Studies of the Polypill Concept

22.5.1 Projected Theoretical Risk Reductions in Coronary Heart Disease and Stroke

Statins and BP-lowering drugs are proven in both primary and secondary prevention. If reductions of both lipids and BP could be achieved in large proportions of people at risk, large reductions in CVD may be possible globally. Law and Wald [6, 7] estimate that a low-dose high-strength statin is safe and lowers LDL cholesterol by at least 1.8 mmol/L (from a high pre-treatment level of 4.8 mmol/L) and that a combination of three antihypertensive agents at half standard doses safely reduces BP by about 20/11 mmHg (from pre-treatment levels of 154/97 mmHg), with similarly proportionate reductions at all pre-treatment levels [6, 7]. Each of these therapies would be expected to *theoretically* reduce the risk of CV events by over 30 % within a few years [2, 6, 7], with their combined effects potentially reducing CVD by over 70 % within 5 years. Even if the *observed* effects of combined therapy were lower (40–50 %), its widespread use could radically alter primary prevention of CVD and avoid millions of premature CV events worldwide. These estimates are supported by the recent Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), in selected high-risk hypertensive patients, where combined BP (comparing two approaches to BP lowering but with similar targets) and cholesterol lowering reduced the risk of CVD by about 45 % in 3–5 years [8].

In the TIPS-1 trial [5], on the basis of the magnitude of risk factor lowering observed and using calculations similar to those used by Law and Wald [6, 7], it was estimated that the Polycap could reduce ischemic heart disease by 62 % and stroke by 42 % in a population at moderate risk but free of CVD. From TIPS-2, it is expected that the larger reductions in risk factors with the full-dose of the Polycap will translate into a 50–60 % relative risk reduction in major CVD. These projected benefits are lower than the expected benefits estimated by Law and Wald [6, 7]. However, this difference may be due to the markedly higher pre-treatment BP levels in that study compared to the TIPS trial (154/97 in the meta-analysis by Law and Wald vs. 134/85 mmHg in TIPS 1 and 2).

Taken together, on the basis of the available data on the individual component drugs, and the TIPS-1 and -2 trials, the Polypill could potentially be widely used in secondary prevention and in selected high-risk individuals without CVD (e.g., those with severe hypertension or diabetes mellitus with additional risk factors). In such individuals, a 50–60 % proportional reduction in risk can be anticipated from long-term therapy.

22.5.2 Trials of the Polypill or Polypill Concept on Clinical Outcomes

The next important step in the evolution of the Polypill concept is to conduct large trials focusing on individuals without prior CVD (primary prevention) but at moderate or high risk. The ongoing third Heart Outcomes Prevention Evaluation

(HOPE-3) trial is evaluating the concept of combined BP and cholesterol lowering in individuals without vascular disease and with average BP and cholesterol levels [9]. The trial is being conducted in 256 centers in 22 countries in Africa, Asia, Australia, Europe, and North and South America. It enrolled 12,500 individuals at moderate risk (men aged >55 years and women aged >65 years with one risk factor or women aged >60 years with two risk factors, with an expected annual placebo event rate of 0.9–1 %) randomized to rosuvastatin 10 mg/d alone, a fixed-dose combination of candesartan 16 mg/hydrochlorothiazide 12.5 mg/d alone, both or neither (2 × 2 factorial design) for 5 years. All participants receive structured lifestyle advice. The main outcomes include major CVD events and changes in cognitive and renal function. The study has high power to detect relative risk reduction of 25–30 % for each of the cholesterol- and BP-lowering arms and of 35–40 % relative risk reduction for the combination of BP-lowering + lipid-lowering versus double placebo. Results are expected in 2014 or 2015 (Table 22.2).

The TIPS-3 trial which commenced recruitment in August 2012 will evaluate a double-strength Polycap (as tolerability was similar to single-strength Polycap in the TIPS-2 trial), a low-dose aspirin, and vitamin D supplementation in a primary prevention setting to reduce CVD outcomes over 5 years in over 6,000 individuals without CVD and with an estimated risk of major CVD of 1 % per year in India and China [5]. Participants will be randomized to double-blind study therapy consisting of daily Polycap [thiazide (25 mg), atenolol (100 mg), ramipril (10 mg), simvastatin (40 mg)] vs. placebo (to reduce CVD), daily aspirin (75 mg) vs. placebo (to reduce CVD and ASA), and monthly Vitamin D (60,000 IU) or placebo (to reduce fractures and perhaps cancers and CVD) using a 2 × 2 × 2 factorial design. The factorial design will help to assess the effects of the three distinct treatments within one efficient design. No interaction is anticipated among these three therapies.

Both of HOPE-3 and TIPS-3 will include health economic analyses and will conduct passive follow-up for an additional 5 years beyond the active trial phase as additional benefits beyond the actual duration of treatment may emerge during long term follow-up.

22.6 The Role of the Polypill as the Cornerstone of an Innovative Strategy for Hypertension Detection, Treatment, and Control in Two Middle-Income Countries: Hypertension Outcomes Prevention and Evaluation (HOPE-4)

Despite clear evidence of the benefits of BP reduction using low-cost and safe drugs for two decades [10], currently most countries do not have a systematic approach to screening and identifying individuals with hypertension or CVD. This is left to busy clinicians, who in primary care may have less than a few minutes for each patient and hence too little time to record BP at most contacts. In addition, in

Table 22.2 The Polypill trials

Trial/sample size/principal investigator(s)	Population	Polypill composition/sponsor/ (Trial registration)	Outcomes	Current status
Trials evaluating the effects of a polypill on risk factor levels				
Indian polycap study (TIPS)/ $n = 2{,}053$/Yusuf S, Pais P [5]	Men and women aged 40–80 years without CVD and with at least one cardiovascular risk factor in India	Aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg (Polycap)/St John's Research Institute, Bangalore, Population Health Research Institute, Hamilton, Canada, Cadila Pharmaceuticals Ltd. (NCT00443794)	Feasibility; effect on risk factor levels; safety and tolerability	Completed
Indian polycap-K trial (TIPS-2)/ $n = 500$/Yusuf S., Pais P.	Men and women aged ≥40 years with stable chronic CVD in India	Single-dose Polycap versus double-dose Polycap with or without potassium citrate 30 mEq (2×2 factorial design)/St John's Research Institute, Population Health Research Institute, Cadila Pharmaceuticals Ltd (CTRI/2010/091/000054)	Effect on risk factor levels; safety and tolerability	Completed and submitted for publication in April 2012
Poly-Iran: phase II study of heart polypill safety and efficacy in primary prevention of cardiovascular disease50 / $n = 475$/Malekzadeh F., Marshall T., Pourshams A.	Men and women aged 50–80 years without indications or contraindications for aspirin, BP-lowering drugs, and statins in Iran	Aspirin 81 mg, hydrochlorothiazide 12.5 mg, enalapril 2.5 mg, atorvastatin 20 mg/Tehran University of Medical Sciences and University of Birmingham, UK (NCT00603590)	Effect on risk factor levels; safety and tolerability	At 12 months, the polypill was associated with significant reductions in BP (4.5/1.6 mmHg) and LDL (0.46 mmol/L); the study drug was well tolerated
Improving adherence using combination therapy (IMPACT) trial51 //$n = 200$/Soliman E.Z., Mendis S., Dissanayake W.P.	Age ≥40 years without CVD and with estimated 10-year total CVD risk score >20 % in Sri Lanka	Aspirin 75 mg, simvastatin 10 mg, lisinopril 10 mg, hydrochlorothiazide 10 mg (Red Heart Pill 2b)/Wake Forest University, Dr Reddy's Laboratories Ltd (NCT00567307)	Effect on estimated 10-year total CVD risk score	Polypill and standard practice resulted in marked reductions in systolic BP and total cholesterol, but the differences between the groups were not significant. No safety concerns were reported. High rate of patient acceptability (94 %)

(continued)

Table 22.2 (continued)

Trial/sample size/ principal investigator(s)	Population	Polypill composition/sponsor/ (Trial registration)	Outcomes	Current status
Program to improve life and longevity (PILL Pilot)/$n = 378$/ Rodgers A., Patel A., Berwanger O.	Moderate–high-risk primary prevention in Australia, Brazil, India, New Zealand, The Netherlands, UK, US	Aspirin 75 mg, lisinopril 5–10 mg, hydrochlorothiazide 12.5 mg, simvastatin 10, 20, and 40 mg (Red Heart Pill)/Health Research Council of New Zealand, Dr Reddy's Laboratories Ltd (ACTRN12607000099426)	Adherence; feasibility; effect on risk factor levels; safety and tolerability	Over 12 weeks, the polypill reduced systolic blood pressure by 9.9 mmHg (95 % CI: 7.7–12.1) and LDL by 0.8 mmol/L (95 % CI 0.6–0.9). The discontinuation rates in the polypill compared to placebo were 23 % vs. 18 % (RR 1.33, 95 % CI 0.89–2.00, $p = 0.2$); Excess of side effects known to the component medicines (58 % vs. 42 %, $p = 0.001$), mostly apparent within a few weeks, and usually did not warrant cessation of trial treatment
Kanyini guidelines adherence with the polypill study (Kanyini-GAP)/ $n = 1000$/Patel A.	Established CVD or high-risk primary prevention (5-year risk ≥15 %) among indigenous and nonindigenous people in Australia	Aspirin 75 mg, atenolol 50 mg, simvastatin 40 mg, lisinopril 10 mg (Red Heart Pill 1) or aspirin 75 mg, hydrochlorothiazide 12.5 mg, simvastatin 40 mg, lisinopril 10 mg (Red Heart Pill 2)/National Health and Medical Research Council of Australia, Dr Reddy's Laboratories Ltd (ACTRN12608000583347)	Adherence; effect on risk factor levels; safety and tolerability; quality of life	Started April 2008; planned 18-month follow-up
Use of a multidrug pill in reducing cardiovascular events (UMPIRE)/$n = 2000$/ Thom S.A., Rodgers A.	Established CVD or high-risk primary prevention (5-year CVD risk of ≥15 %) in India, The Netherlands, UK	Aspirin 75 mg, atenolol 50 mg, simvastatin 40 mg, lisinopril 10 mg (Red Heart Pill 1) or aspirin 75 mg, hydrochlorothiazide 12.5 mg, simvastatin 40 mg, lisinopril 10 mg (Red Heart Pill 2)/Imperial College London, Dr Reddy's Laboratories Ltd (NCT01057537)	Adherence; effect on risk factor levels; safety and tolerability; CVD events (secondary outcome)	Expected to start recruitment in June 2010 with 24-mo follow-up

(continued)

Table 22.2 (continued)

Trial/sample size/ principal investigator(s)	Population	Polypill composition/sponsor/ (Trial registration)	Outcomes	Current status
Trial in secondary prevention/details not available/Fuster V.	Survivors of myocardial infarction in Spain and in Latin American countries	Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5, 5, 10 mg/Ferrer Internacional Ltd and CNIC (Centro nacional de Investigationes Cardiovasculares)	Feasibility; effect on risk factor levels; safety and tolerability	Expected to start in 2010
PILL collaborative group/$n = 378$/ Rodgers A.	Men and women aged ≥18 years with raised CV risk (5-year Framingham risk ≥7.5 %) in seven countries (Australia, Brazil, India, New Zealand, The Netherlands, United Kingdom, United States)	Aspirin 75 mg, simvastatin 20 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg (Red Heart Pill)/The Clinical Trials Research Unit, University of Auckland, New Zealand, (ACTRN 12607000099426)	Effect on risk factor levels; safety and tolerability	Completed and published
Trials evaluating effects of a polypill on cardiovascular events				
Indian polycap trial 3 (TIPS-3)/$n = 5{,}000$/ Yusuf S., Pais P., Xavier D., Liu L.	Primary prevention with estimated yearly CVD event rate of 1 % using the INTERHEART risk score in China and India	Polycap; dose to be chosen after completion of the TIPS-K trial/Wellcome Trust, UK, Cadila Pharmaceuticals Ltd	Major CVD events; neurocognitive function	Expected to start in May 2012
Trials evaluating the polypill concept				
Heart outcomes prevention evaluation (HOPE-3)/ $n = 12{,}500$/Yusuf S., Lonn E.	Primary prevention in men aged ≥55 years and women aged ≥65 years with at least one cardiovascular risk factor and women aged ≥60 years with at least two risk factors and with average BP and cholesterol levels in 22 countries	Rosuvastatin 10 mg, candesartan 16 mg/ hydrochlorothiazide 12.5 mg (2 × 2 factorial design)/Canadian Institutes of Health Research, AstraZeneca (NCT00468923)	Major CVD events; neurocognitive function; renal function	Expected to complete recruitment by fall 2010; planned duration of follow-up of 5 years

most countries, there are complex algorithms to start drug treatment that are cumbersome and use individual drugs to lower BP, which is only moderately effective and which, if started in a stepwise fashion, delays BP control so that only 15–20 % of those treated are controlled. Lastly, most physicians cannot pay more attention to concomitant risk factors and make no systematic efforts to enhance adherence to treatment or to educate patients about risk factors. Consequently there is a failure to manage hypertension effectively and efficiently (both at the clinical and community levels) in most countries.

Accordingly, we have designed the HOPE-4 program to develop and evaluate an evidence-based, cost-effective, contextually appropriate model programme for a national strategy for hypertension detection, treatment, and control for two middle-income countries—Colombia in Latin America and Malaysia in Southeast Asia, in which the Polycap will be a central component of the hypertension control strategy.

Improving the detection, treatment, and control of hypertension would use a hybrid of a structured clinical/community program with a multilevel, multifaceted intervention that targets the health system, individual practitioners, and those with hypertension. Importantly, the study will involve developing simplified algorithms and task shifting to trained nonphysician health workers to whom most routine hypertension-related tasks will be shifted. Second, it aims to ensure access to appropriate combination therapies (which substantially reduce BP and, when appropriate, the associated risk factors). Lastly, with these foundations in place, the HOPE-4 investigators will evaluate a streamlined approach to hypertension detection, treatment, and control (using the Polycap) in a cluster RCT in 90 communities in Columbia and Malaysia.

When used together with lifestyle interventions (of which smoking cessation is the most important) the effect on reducing CVD by simultaneously affecting the three dominant risk factors would likely be profound (>75 % relative risk reduction in theory) [2, 11]. Therefore, making provision for affordable generic polypills of multiple BP-lowering agents with or without a statin costing below US$5–10/month in these countries would markedly simplify the management of hypertension, in a way that synergizes with the task-shifting process. Further, the use of a polypill will simplify prevention as a similar approach can be used for hypertension, secondary prevention of CVD, and in diabetes [12].

The primary outcome will be the mean difference in change in systolic BP among individuals with hypertension at baseline between the intervention and control communities at 24 months. In addition, given that the ultimate goal is to reduce CVD risk, and this requires modifying multiple associated risk factors, by using both drugs and lifestyle changes the most important secondary outcome will be the mean differences in INTERHEART risk score, as an index of change in CVD risk.

22.7 Conclusions

Combination pharmacotherapy is more effective in achieving a target blood pressure among subjects with risk factors for CVD. The tolerability of the Polycap has already been demonstrated. Targeting multiple risk factors is essential to reduce the burden CVD. The polypill concept aims to reduce multiple risk factors through the administration of a single drug that combines various effective medications at lower doses.

The Polycap has three BP-lowering agents and has been shown to be superior to the combination of these antihypertensives with and without aspirin. In the general population, subjects with mild to moderate risk factors seem to have a higher incidence of cardiovascular events. Effective control of these risk factors through an easy-to-administer Polycap can significantly reduce the incidence of these events. The Polycap can form a key part of an overall strategy to enhance community-wide hypertension treatment and control in multiple regions of the world.

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J-Curve Phenomenon: Does It Exist?

23

Sripal Bangalore and Franz H. Messerli

23.1 Introduction

Increased blood pressure (BP) is the most common modifiable risk factor for cardiovascular disease, accounting for an estimated 17 million deaths worldwide each year. This number is projected to increase to 23 million or 24 % of total deaths worldwide by 2030 [1]. Clinical trials have shown that reduction in BP is associated with up to 40–45 % reduction in the incidence of stroke, 20–25 % reduction in the risk of myocardial infarction and up to 50 % reduction in the risk of heart failure [2, 3]. Though the prognostic importance of blood pressure [4–9] is now well established, the school of thought, over the past 100 years, has largely switched from the initial *essential* hypertension *leaving it alone* principle to the current aggressive control, *the lower the better* principle. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that "the relationship between blood pressure and risk of cardiovascular events is *continuous*, consistent, and independent of other risk factors [10]."

Though this linear theory and *the lower the better* hypothesis has been challenged for three decades with reports of a J curve relationship showing higher event rates at both high and low BP [11–18], it has been brought into the limelight recently with the publication of the Action to Control Cardiovascular

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Risk in Diabetes Blood Pressure (ACCORD BP) trial. ACCORD BP is one of the few large randomized trials designed to evaluate a BP-lowering strategy (intensive vs. standard), rather than two different treatments. At the end of 4.7 years of follow-up, targeting a systolic pressure of <120 mmHg, when compared with <140 mmHg in patients with diabetes, did not reduce the rate of fatal and nonfatal major cardiovascular events except for stroke [19]. The observation of a J curve in observational studies has led to hotly debated issues and has proved controversial. The JNC 7 thus states "there is no definitive evidence of an increase in risk of aggressive treatment (a J-curve) unless DBP is lowered to <55 or 60 mmHg by treatment [10]." This chapter discusses the findings of recent studies and critically reviews the effect of excessive BP lowering on adverse cardiovascular events.

23.2 The J-Curve Phenomenon

The J-curve phenomenon, wherein the risk of cardiovascular events follows a bimodal distribution with an increase in risk at both high and very low BP, was reported first in the literature approximately three decades ago, when Stewart demonstrated a fivefold increase in the risk of myocardial infarction (MI) in patients who had achieved a diastolic BP below 90 mmHg compared to those with a diastolic BP in the range 100–109 mmHg [20]. Subsequently, other investigators reported similar findings and extended these observations to systolic BP as well [21, 18, 17]. Should there be a J-curve relationship between BP and cardiovascular events? The simple answer is a resounding *yes*, as it is obvious that mortality will be high and reaching 100 % if the BP is zero or extremely high. The bigger question however is whether there is a J-curve within a physiological BP range.

23.3 Plausible Mechanisms for the J-Curve Phenomenon

Five potential *pathophysiological* mechanisms have been proposed to explain the existence of a J-curve. First, the J curve may be an epiphenomenon of a more severe and debilitating underlying chronic condition (including cancer). Thus, the low BP may be a mere marker of this illness thereby increasing mortality at low BP (reverse causality) [22]. Second, low BP may be an epiphenomenon of impaired cardiac systolic function (i.e., in heart failure or post-MI), hence the increase in mortality [12, 23]. Third, the J-curve may represent an epiphenomenon of increased arterial stiffness, i.e., a low diastolic pressure might be simply a marker for high pulse pressure and hence the increase in mortality [24]. Fourth, low diastolic BP may compromise coronary perfusion. Since coronary perfusion occurs predominantly in diastole, diastolic hypotension could lead to coronary hypoperfusion in patients with a compromised coronary flow reserve, such as those with coronary artery disease. In an analysis of the International Verapamil SR-Trandolapril Study

(INVEST) [11], a J-shaped relationship between BP, especially diastolic, and the risk of cardiovascular events was observed in a group of patients with hypertension and coronary heart disease (CHD). In that study, a significant interaction effect of revascularization was noted, suggesting that patients who had revascularization before enrollment tolerated lower diastolic BP relatively better than those who did not have revascularization [11]. However, this does not completely explain the J-curve relationship seen with systolic BP. Finally, Greenberg and colleagues [25] hypothesized that the J-curve phenomenon may be due to statistical confounding that artifactually elevates mortality risk at low risk factor levels (e.g., low systolic or diastolic BP) in survival analyses of longitudinal data.

23.4 J-Curve Phenomenon in Patients with Coronary Heart Disease

As described previously, a low BP, especially diastolic, can compromise coronary artery perfusion in patients with fixed coronary obstruction, such as those with CHD. During systole, the intramuscular arteries and arterioles of the coronary circulation are compressed, preventing myocardial perfusion (and the majority of coronary perfusion occurs in diastole). In diastole, myocardial perfusion therefore depends on the pressure gradient between the aorta and the myocardial bed. In the presence of significant low diastolic aortic pressure, and in the setting of a fixed coronary stenosis (such as in those with CHD), myocardial perfusion may be reduced resulting in ischemia and adverse consequences.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial that enrolled patients with recent acute coronary syndrome (in the 10 days before enrollment), a J-shaped relationship was found with both systolic and diastolic BP (Fig. 23.1) for adverse cardiovascular outcomes (death due to any cause, myocardial infarction, documented unstable angina requiring hospitalization, revascularization with either percutaneous coronary intervention or coronary artery bypass graft performed >30 days after randomization, and stroke) [26]. The lowest incidence (nadir) of adverse cardiovascular outcomes was found at 135/85 mmHg, with an increase in adverse outcomes associated with both lower and higher BP. When compared with the reference group (BP > 130–140 mmHg), the risk of adverse cardiovascular outcomes increased 4.9-fold in the group with systolic BP $\leq$ 100 mmHg and by 1.2-fold in the group with a systolic BP > 160 mmHg (Fig. 23.1). Similarly, the risk of adverse outcomes increased 3.7-fold in the group with a diastolic BP $\leq$ 60 mmHg and 2.1-fold in the group with a diastolic BP >100 mmHg, when compared with the referent diastolic BP group of >80–90 mmHg.

Similar relationship with either systolic or diastolic BP and all-cause mortality, cardiovascular mortality, and nonfatal MI was also observed [26]. Moreover, in the Treating to New Targets (TNT) trial, a double-blind, parallel study of >10,000 patients with CHD followed over 5 years, a J-curve relationship for systolic BP as

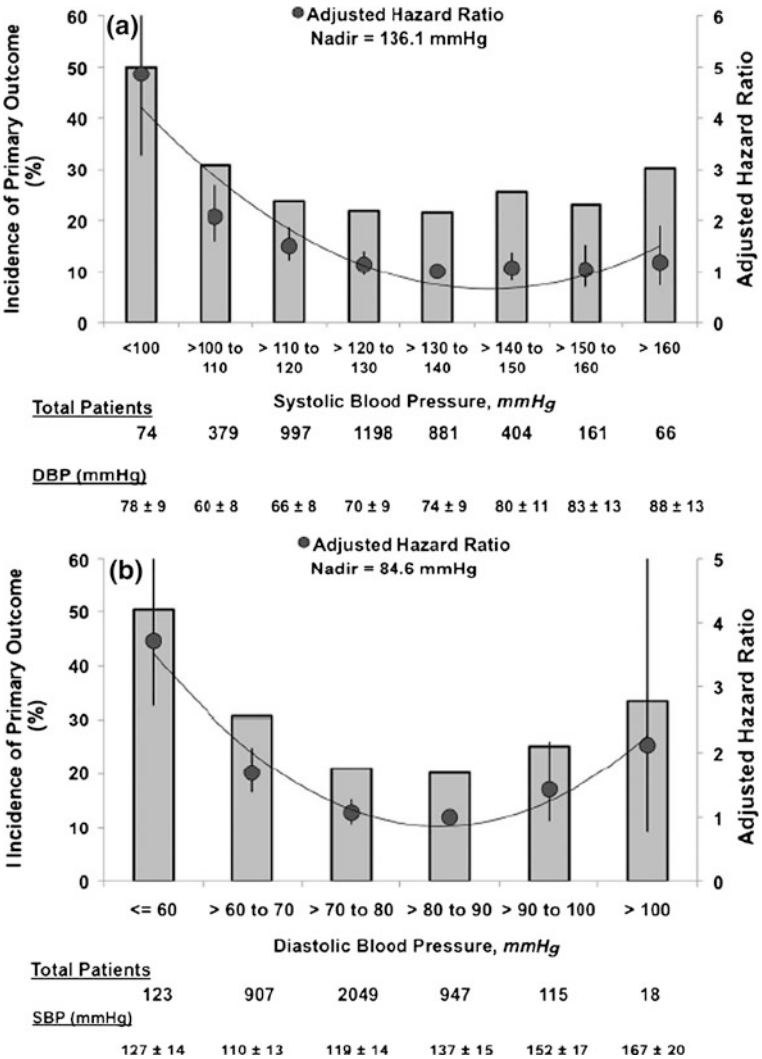

Fig. 23.1 Relationship between (**a**) systolic and (**b**) diastolic BP and the risk of adverse cardiovascular outcomes in the PROVE IT TIMI 22 trial. (Reproduced with permission from [26]). *PROVE IT TIMI* pravastatin or atorvastatin evaluation and infection therapy–thrombolysis in myocardial infarction

well as for diastolic BP (Fig. 23.2) was observed for adverse cardiovascular outcomes (death from CHD, nonprocedure-related MI, resuscitated cardiac arrest, and stroke) and for most of the secondary outcomes of all-cause mortality, cardiovascular mortality, nonfatal MI, or angina [27]. The nadir of BP where the event rate was at its lowest was 146.3/81 mmHg. In both of the above studies, although a J-curve relationship was observed, the curve was relatively shallow for systolic BP

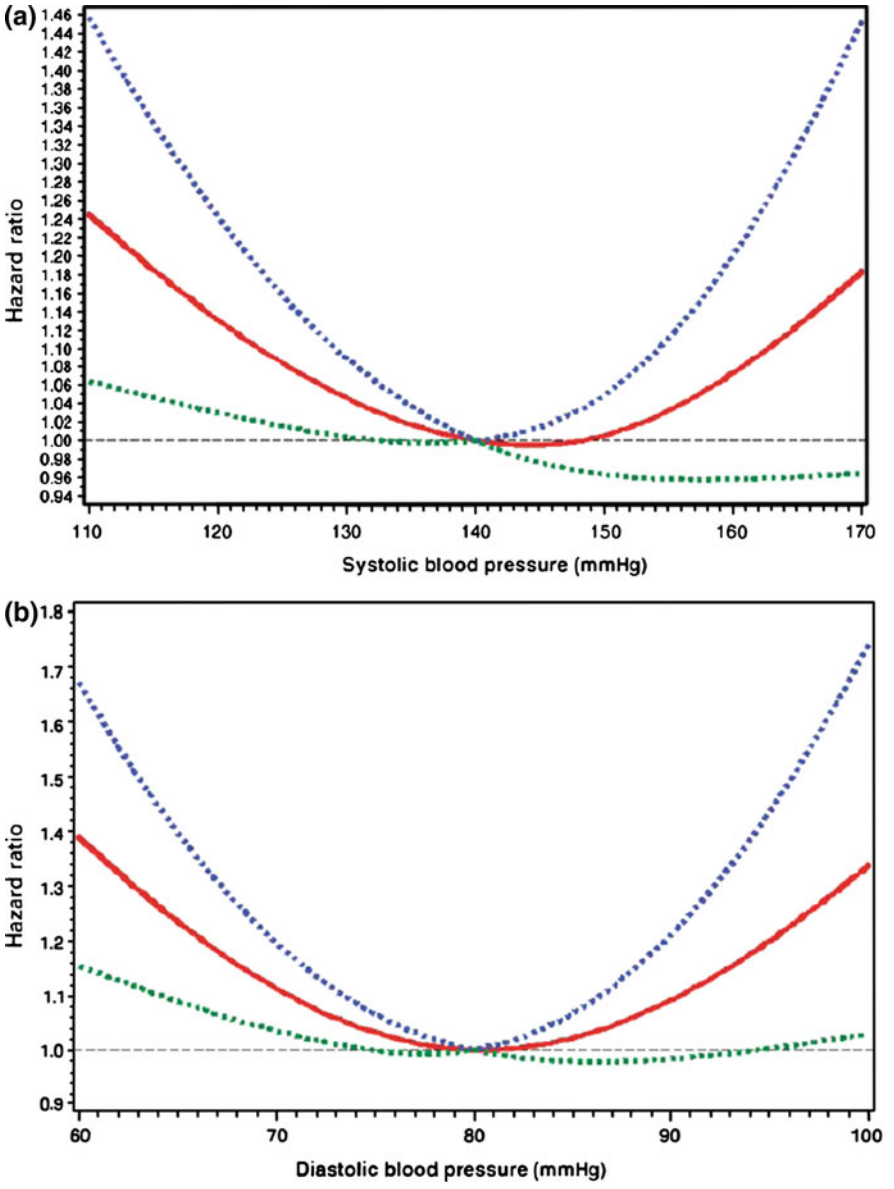

Fig. 23.2 Relationship between (**a**) systolic and (**b**) diastolic BP and the risk of adverse cardiovascular outcomes in the TNT trial. The dashed lines represent the 95 % confidence interval around the estimates (reproduced with permission from [26]). *TNT* treating to new targets (trial)

between 110 and 140, and for diastolic BP between 70 and 90 mmHg. However, the event rate increased exponentially above and below these thresholds.

The J-curve phenomenon has been consistently shown in few other studies in patients with CHD [the INVEST study [11], and the CHD cohorts of the study by Cuickshank and colleagues [16], the Framingham Heart Study [28], and the Systolic Hypertension in Europe (Syst-Eur) trial [29] (Table 23.1).

In the large Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), involving patients ($n = 25{,}588$) who were older than 55 years and with coronary, peripheral, and cerebrovascular disease or diabetes with end-organ damage, a J-curve relationship was seen with both systolic and diastolic BP. Patients with baseline systolic BP > 130–140 mmHg witnessed a greater reduction in stroke with a reduction in BP but not in cardiovascular mortality, MI, or heart failure. However, patients with a baseline systolic BP < 130 mmHg had an increased risk of adverse cardiovascular outcomes and a J-curve was observed starting at a systolic BP < 130 mmHg. Furthermore, at any given systolic BP, the mortality risk was highest with the lowest in-trial diastolic BP (mean diastolic BP = 67 mmHg) [30].

23.5 J-Curve Phenomenon in Patients without Coronary Heart Disease

Data from observational studies involving more than 1 million individuals without pre-existing vascular disease indicate that death from both ischemic heart disease and stroke increases progressively and *linearly* with BP [31]. Consequently, the notion that *lower is better* [32] has been popular and a BP of <120/80 mmHg has been considered as *optimal* or *normal* [10]. The JNC has consistently lowered the definition and threshold for *normal BP* from JNC 1 through to JNC 7 over the last three decades (Fig. 23.3). Major national and international guidelines recommend a more aggressive BP goal of <130/80 mmHg in patients with type 2 diabetes or those with chronic renal dysfunction [10, 33–35]. However, this linear theory and the evidence for the beneficial effect of aggressive BP lowering have also been challenged for nearly three decades (Table 23.1) [36–39]. The vast majority of the studies are in hypertensive patients without CHD, where the literature is controversial regarding the existence of a J-curve (Table 23.1).

In high-risk cohorts, such as those with diabetes, there is no evidence to suggest that *lower is better*. In the ACCORD BP trial, a strategy of intensive therapy targeting a systolic BP of <120 mmHg, as compared with a standard value of <140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. Intensive therapy is not without its downsides. In the ACCORD BP trial, though a J-curve phenomenon (lower BP associated with higher event rates) was not observed, the risk of serious adverse events was 2.6 times higher in the intensive group compared to the standard therapy group, with a 17-fold increase in hypotension and a tenfold increase in

Table 23.1 Major studies evaluating the J-curve phenomenon

Study (References)	Cohort	*N*	CHD (%)	Total mortality	CV mortality	Myocardial infarction	Stroke	Nadir, mmHg	Comment
[50]	Hypertension	169	NR	NR/NR	NR/PRO	NR/PRO	NR/CON	NR/100–109	Relationship with SBP not assessed. Only few categories of DBP. Adjusted risk not reported
ANBP [51]	Hypertension, RCT	3,931	0	NR/NR	NR/PRO	NR/PRO	NR/PRO	NR/85–89	Only few categories of DBP. Adjusted risk not reported
IPPPSH [52]	Hypertension, RCT	6,357	0	NR/NR	NR/CON	NR/CON	NR/CON	NR/NR	CAD patients excluded
[53]	Hypertension	954	NR	PRO/PRO	PRO/PRO	NR/NR	NR/NR	NR/NR	Only three baseline BP categories, low, medium, high assessed. No adjustment for baseline confounders
[16]	Hypertension, No CHD cohort	597	0	NR/NR	CON/CON	NR/NR	NR/NR	NR/NR	Only few categories of DBP. Adjusted risk not reported
[16]	Hypertension, CHD cohort	342	100	NR/NR	CON/PRO	NR/NR	NR/NR	NR/85–90	Only few categories of DBP. Adjusted risk not reported
[28]	Hypertension	5,209	4.1	NR/NR	PRO/PRO*	NR/NR	NR/NR	NR/NR	*J-curve only in patients with prior MI. Very few patients with known CAD
[54]	Hypertension, RCT	18,790	16.4	NR/NR	PRO/PRO	PRO/CON	PRO/CON	138.8/86.5	Analysis not adjusted for baseline confounders within BP strata
[55]	Hypertension	6,287	13.4	NR/NR	NR/NR	NR/NR	PRO/PRO	140/80	J-curve only for patients on antihypertensive agents. Baseline BP used
[56]	Meta-analysis of individual patient data from seven hypertension RCTs ([57]; EWPHE [37]; HDFP [38]; MRC1, 2 [36]; SHEP; STOP)	40,233	3.3	PRO/PRO	PRO*/PRO	NR/NR	NR/NR	156/84	*J-curve in untreated patients only

(continued)

Table 23.1 (continued)

Study(References)			Cohort	*N*	CHD (%)	Total		mortality
CV mortality	Myocardial infarction	Stroke	Nadir, mmHg		Comment	[39]		Hypertension
1,332	5.6	NR/NR	PRO/PRO*	NR/NR	NR/NR	NR/NR	*J-curve for 24-h	ambulatory BP. Range of BP was small (<112 to >134 mmHg)
[58]	Hypertension, RCT	1,715	NR	PRO/PRO	PRO/CON	CON/PRO	CON/CON	120/85	Very few patients in the lower BP strata
[11]	Hypertension and CHD, RCT	22,576	100	PRO/PRO	PRO/PRO	PRO/PRO	CON/CON	116/83	None
[29]	Hypertension, RCT	4,583	14.5	NR/NR	NR/PRO*	NR/NR	NR/PRO**	NA/75	*J-curve only in patients with CAD **J-curve only in placebo arm. Relationship with systolic BP not reported. Only small proportion of patients with CAD

ANBP Australian National Blood Pressure Study, *BP* blood pressure, CAD coronary artery disease, CHD coronary heart disease, *CON* Does not favor the J-curve hypothesis, *CV* cardiovascular, *DBP* diastolic blood pressure, *EWPHE* European Working Party on High blood pressure in the Elderly, *HDFP* Hypertension Detection and Follow-up Program, *IPPPSH* International Prospective Primary Prevention Study in Hypertension, MI myocardial infarction, MRC Medical Research Council trial of treatment of hypertension, *NR* not reported, *PRO* Favors the J-curve hypothesis, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SHEP* Systolic Hypertension in the Elderly Program, *STOP* Stroke Prevention Trial in Sickle Cell Anemia

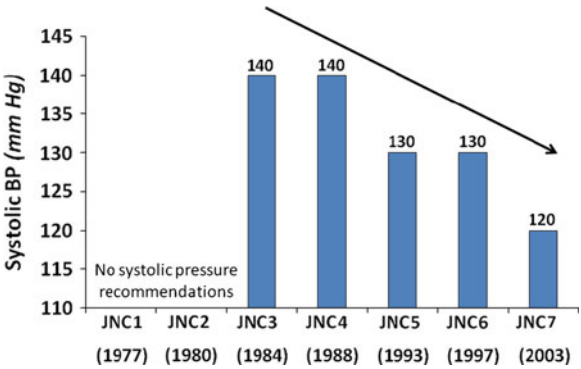

Fig. 23.3 Trends in the definition of *normal* systolic BP from JNC 1 through to JNC 7

hyperkalemia. In addition, a recently published analysis from our group further confirms the findings from the ACCORD BP trial. In an analysis from 13 randomized trials enrolling 37,736 subjects with diabetes, the optimal systolic BP target was 130–135 mmHg [40]. A further lower BP was not associated with any benefit for any macro- (except stroke) or microvascular events, with significant increase in the risk of serious adverse events [40].

Similarly, in a subgroup analysis from the INVEST trial in participants with concomitant diabetes mellitus and CHD, there was an increase in all-cause mortality with a tight BP control group as compared to the usual control group [41]. Finally, in the Appropriate Blood Pressure Control in Diabetes normotensive cohort (ABCD-NT) [42] trial, participants achieving the target systolic BP values of <130 mmHg with active treatment failed to gain a benefit in the primary outcome (renal dysfunction) or any other cardiovascular outcome (except stroke). In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial consisting of more than 4,000 patients, the number of composite deaths from cardiovascular causes was significantly higher with olmesartan than with placebo [43]. A further analysis showed that the highest cardiovascular mortality occurred in patients with the lowest systolic BP (<121 mmHg) and in those who had the greatest systolic BP reduction (>17 mmHg). Whether or not we have reached the lowest BP or the lowest cardiovascular risk in these patients is not clear, as was lucidly discussed by Zanchetti [44].

Even in the chronic kidney disease (CKD) cohort, a J-curve relationship between all-cause mortality and low diastolic BP (<70 mmHg) was observed [45]. Investigators found a linear association between elevated systolic BP and the development of end-stage renal disease (ESRD). However, a low diastolic BP (<70 mmHg) was found to be a marker of higher mortality in patients with advanced CKD (estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2). Higher systolic BP had a significant effect on the development of ESRD whereas low diastolic BP had an effect on overall mortality [45]. In nondiabetic hypertensive participants with proteinuria and nephropathy already on baseline angiotensin-converting enzyme inhibitor therapy, aggressive BP control (goal

BP < 130/80 mmHg) with dihydropyridine calcium-channel blocker therapy did not delay the rate of GFR decline, nor the development of ESRD, cardiovascular events, and death [45]. Whether delay in the progression of ESRD can be attributed to tighter BP control or effective inhibition of the renin–angiotensin system still needs to be evaluated.

23.6 Target Organ Heterogeneity

In patients with CHD, though the existence of a J-curve has been shown in several studies, this relationship has been observed mainly for cardiovascular outcomes and less so for cerebrovascular ones, suggesting target organ heterogeneity. In the TNT trial, though a J-curve relationship was observed between systolic BP and most outcomes, it was not so for stroke, where *lower was better* until the tested range of 110–120 mmHg systolic BP [27]. Similarly, in the ACCORD BP trial, an intensive BP strategy (to <120 mmHg) resulted in a 41 % reduction in the risk of *any* stroke [hazard ratio (HR) = 0.59; 95 % confidence interval (CI) 0.39–0.89; $p = 0.01$] when compared with the standard BP strategy (140 mmHg) [19]. Other analyses have shown similar results with a sustained benefit for stroke with lower BP [40, 42]. Epidemiological studies have shown that the greatest effect of BP lowering is to reduce the risk of stroke and comparatively less so for coronary events. It is therefore not surprising that this sustained benefit for stroke goes down to a systolic BP of 120 mmHg. However, in normotensive patients with recent noncardioembolic ischemic stroke enrolled in the Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) trial, a similar J-curve relationship was observed between systolic BP and the risk of recurrent stroke [46]. Patients with a systolic BP below 120 mmHg had a 31 % higher stroke risk than those in the high-normal range (130 to <140). Mancia and colleagues [47], by thoroughly reviewing the available evidence, suggested that there was a differential behavior of the brain and heart with regard to tight BP control by treatment. The authors suggested that tight BP control may be recommended whenever patients are at higher risk of stroke rather than heart attack, as it is the case in subjects with a history of cerebrovascular events.

23.7 Conclusions

Numerous studies over the past few years have documented an inverse relationship between BP and CHD (i.e., a J-shaped curve), especially in patients with known CHD. Similarly, this relationship is being increasingly shown in other patient populations including the elderly, diabetics, and those with chronic kidney disease. When a J-curve relationship was observed in most of these studies, however, the J-curve was shallow for a systolic BP range of 110–140 mmHg and a diastolic BP of 70–90 mmHg, below and above which the risk of cardiovascular outcomes

increased exponentially. Although this J-curve relationship has been extensively debated, the possibility of confounders cannot be completely ruled out and the association could be explained by one of five pathophysiological mechanisms, including statistical aberration. This can only be addressed in a randomized trial powered to test this association. Unfortunately, the arguments surrounding the J-curve phenomenon have often become unnecessarily controversial [48, 49]. Regardless of whether a J-curve exists within the physiological range of BP, there is no evidence to date to suggest that aggressive BP control lower than 130–140 mmHg is beneficial for cardiovascular outcomes but is associated with an increase in the risk of serious adverse effects including hypotension. Ongoing trials, such as the Systolic Blood Pressure Intervention Trial (SPRINT) and THRESHOLD trials, will assess if a BP target of 120 mmHg is beneficial in any subgroups.

In the interim, these considerations should not deter practicing physicians from pursuing a more aggressive control in treating hypertension, to achieve a BP target of <140/90 mmHg, since only approximately one-third to half of such patients are at such a target. It would be prudent, though, for health-care providers to set targets judiciously when selecting patient populations, while considering the underlying pathophysiology and individual patient risk of cerebrovascular and CHD. As health-care providers, we still need to practice medicine keeping *Primum non nocere* or *First, do no harm* in mind.

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Residual Risk in Treated Hypertension

24

Alberto Zanchetti

24.1 Introduction

The finding in observational studies that systolic (SBP) and diastolic (DBP) blood pressure values are continuously (semi-logarithmically) related to cardiovascular outcomes (coronary outcomes and stroke) [1], and that serum total or low-density lipoprotein cholesterol (LDL-C) levels are also continuously related to coronary outcomes [2] has revived the expectation that reductions of BP or serum cholesterol levels may return cardiovascular risk to normal values at least for a given age. Indeed, drug-induced reductions of elevated BP and/or serum cholesterol have been repeatedly shown to be capable of significantly reducing all types of cardiovascular outcomes [3, 4]. Likewise, antiplatelet agents have also been shown to decrease cardiovascular outcomes in both secondary and primary types of prevention [5], whereas successful prevention of macrovascular disease in diabetes patients by aggressively lowering blood glucose is still open to debate [6, 7].

The question whether correction of risk factors can reduce cardiovascular outcome incidence to the same lowest level in patients with a previous history of cardiovascular disease (CVD) as in individuals free of CVD has never been systematically explored. In principle, it is reasonable to expect that the lowest risk level achieved by aggressive reduction of cardiovascular risk factors (i.e., the residual risk despite treatment) is higher in initially high-risk patients than in individuals in whom treatment has been initiated before irreversible, or scarcely reversible, cardiovascular damage has occurred. This chapter summarizes the available evidence in hypertensive patients.

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24.2 Evidence from Trials Enrolling Hypertensive Patients at Different Levels of Risk

24.2.1 Hypertension Detection and Follow-Up Program Trial

In this trial, both the patients with and those without baseline organ damage had lower all-cause mortality when randomized to stepped care rather than to usual care (i.e., more intense and more frequent antihypertensive drug treatment), but the 5-year mortality achieved by stepped care remained at least three times higher in patients with organ damage (Fig. 24.1a) [8]. The same was observed for stroke: though reduced by more active treatment (stepped care) in both groups, it remained four times more frequent in patients with organ damage (Fig. 24.1b) [9].

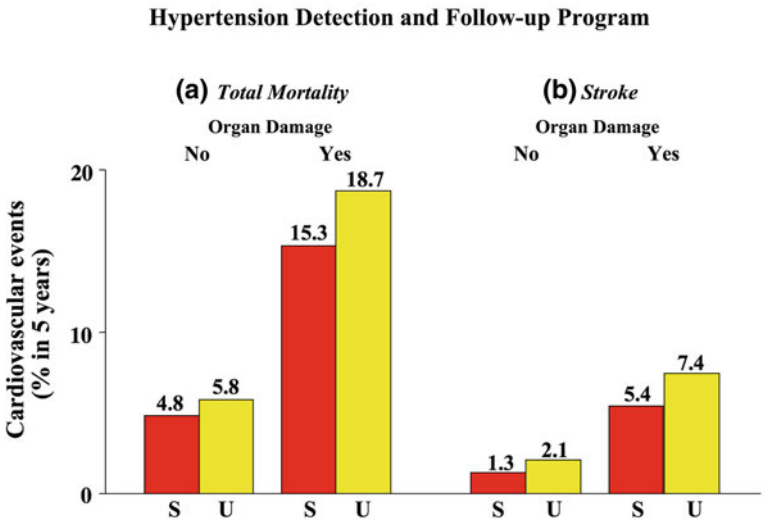


Fig. 24.1 Outcome incidence in patients of the Hypertension Detection and Follow-up Program [8, 9] with (*yes*) and without (*no*) organ damage. **a** Total mortality, **b** Stroke. *S* stepped care group, *U* usual care group (from [18], by courtesy of the *Journal of Hypertension*)

24.2.2 Hypertension Optimal Treatment Study

In this very large study (almost 19,000 hypertensive patients), patients with either lower or higher baseline cardiovascular risk, despite similar BP reductions, had quite different incidences of major cardiovascular events, myocardial infarctions, strokes, and all-cause and cardiovascular deaths—all these incidences being more than two

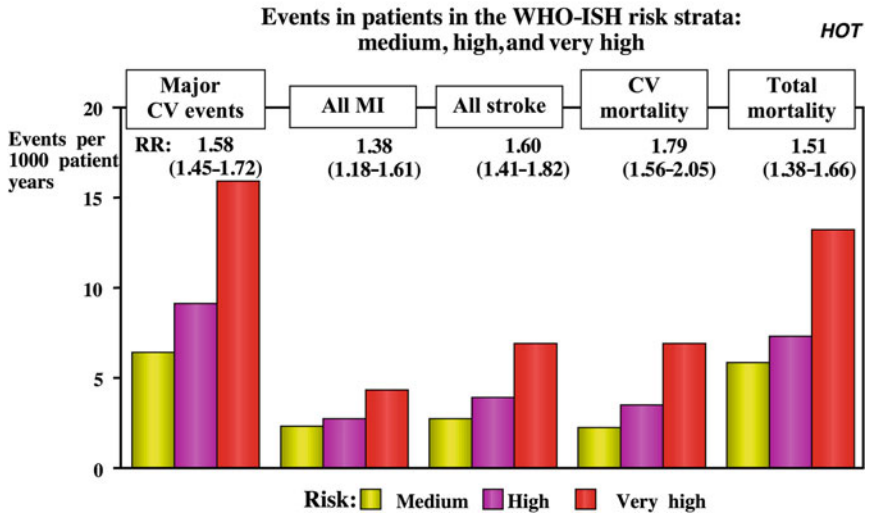


Fig. 24.2 Events incidence in patients of the HOT study classified as at medium, high, and very high risk according to the WHO/ISH guidelines. The types of events are listed in the upper part of the figure. Relative risks (RRs) indicate the trends to increase from one risk category to the following one (from [10], by courtesy of the *Journal of Hypertension*). *CV* cardiovascular, *HOT* Hypertension Optimal Treatment (trial), *ISH* International Society of Hypertension, *MI* myocardial infarction, *WHO* World Health Organization

times greater in hypertensive patients at very high than at medium baseline cardiovascular risk (Fig. 24.2) [10]. This was not only due to the uncontrolled effect of concomitant risk factors, since in the HOT study half of the patients were also randomized to low-dose aspirin and since incident cardiovascular events among hypertensive patients receiving aspirin in addition to intense antihypertensive therapy remained about two times greater in those at higher rather than at lower baseline cardiovascular risk (11.6 vs. 6.4 per 1,000 patient-years) [11].

24.2.3 International Verapamil: Trandolapril Study

A sub-analysis of this large trial, which included only hypertensive patients with coronary heart disease [12], has shown that those coronary patients who had suffered an event, i.e., were enrolled with a history of myocardial infarction, had 13.7–14.4 % incidences of primary end points in the two treatment arms of the trial, whereas patients with a history of coronary disease other than myocardial infarction had much lower incidences of 7.5–7.6 % of primary end points [13].

24.2.4 Felodipine Event Reduction Study

In this large trial including 9,711 Chinese hypertensive patients, about half of the patients had a previous history of CVD or diabetes whereas the other half comprised uncomplicated hypertensives [14]. The complicated hypertensives had, as expected, a much higher incidence of strokes and major cardiovascular outcomes during follow-up [15]. Furthermore, although the benefits of administering felodipine rather than placebo were observed in both complicated and uncomplicated participants, among the more intensively (felodipine) treated patients, those with baseline complications had stroke incidences (13.4 %) 1.6 times greater than patients without baseline complications (Fig. 24.3) [16].

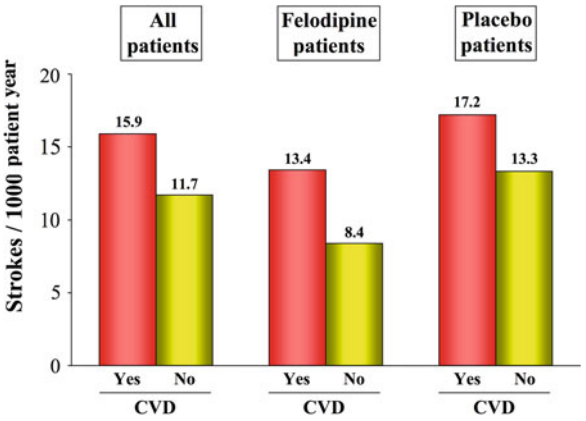


Fig. 24.3 Incidence of stroke in patients of the FEVER trial with and without baseline cardiovascular disease (CVD) or diabetes. *Left columns*: all patients together independent of randomized treatment; *middle columns*: patients randomized to felodipine; *right columns*; patients randomized to placebo. Based on data from [16] *FEVER* Felodipine Event Reduction (trial)

24.2.5 Meta-analysis of Antihypertensive Treatment Trials

In the very large meta-analysis of trials of antihypertensive treatment conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration and comparing diabetic and nondiabetic patients [17], the relative benefits of active antihypertensive treatment (vs. placebo) were very similar. On the whole, treated diabetics remained at a considerably higher risk of major cardiovascular events and cardiovascular death than treated nondiabetics (17.3 vs. 10.7 % and 7.6 vs. 4.05 %, respectively) (Fig. 24.4).

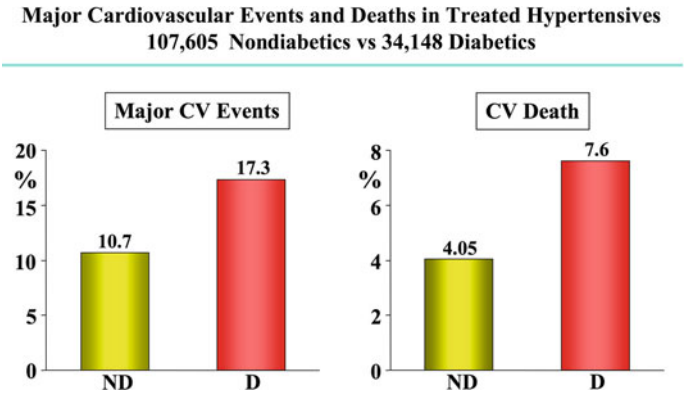


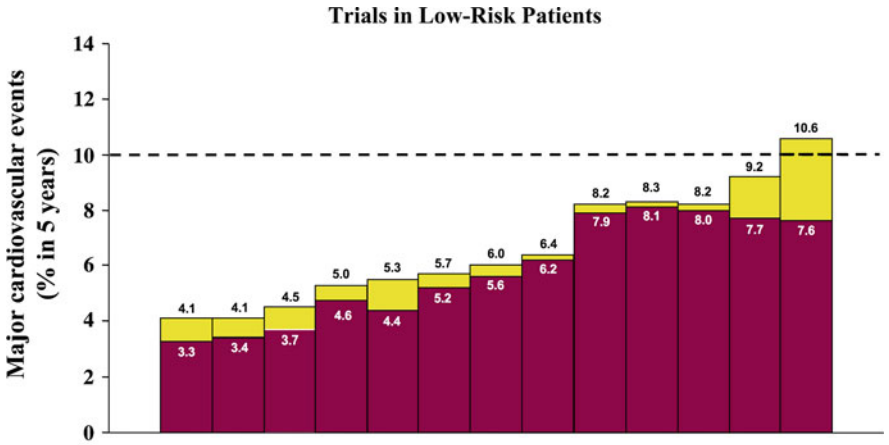
Fig. 24.4 Major cardiovascular events and deaths in treated hypertensive subjects: comparison of diabetics and nondiabetics. Original drawing from data in [17]

24.3 Systematic Analysis of Trials

In 2009, we carried out a systematic comparison of the incidence of cardiovascular events occurring in trials with antihypertensive agents in patients at different baseline levels of cardiovascular risk. We reviewed outcome data in all major trials after classifying them in four categories: (1) trials specifically enrolling low-risk patients or not requiring cardiovascular events as one of the inclusion criteria; (2) trials specifically enrolling older hypertensive patients; (3) trials only enrolling diabetic patients or trials allowing separate analyses of diabetic subgroups; and (4) trials specifically enrolling patients with previous cardiovascular events or diseases [18].

In this chapter we concentrate on the first and last categories: low-risk and high-risk patients at baseline, respectively. As shown in Fig. 24.5, an incidence of major cardiovascular events below the conventional cut-off of high risk (10 % in 5 years or 20 % in 10 years) was consistently observed in trials not enrolling or not regularly enrolling high-risk patients [14, 19–30]. In trials comparing active treatment with placebo or less active treatment, the incidence of cardiovascular events was further and often significantly reduced in the active treatment arm, but even in the comparative arm with higher outcome incidence this systematically remained below the high-risk cut-off, the only exception being the FEVER trial [14] in which the presence of about 50 % of patients with baseline cardiovascular disease or diabetes (see earlier) brought the overall risk of the less actively treated group just above the high risk cut-off (10.6 % in 5 years).

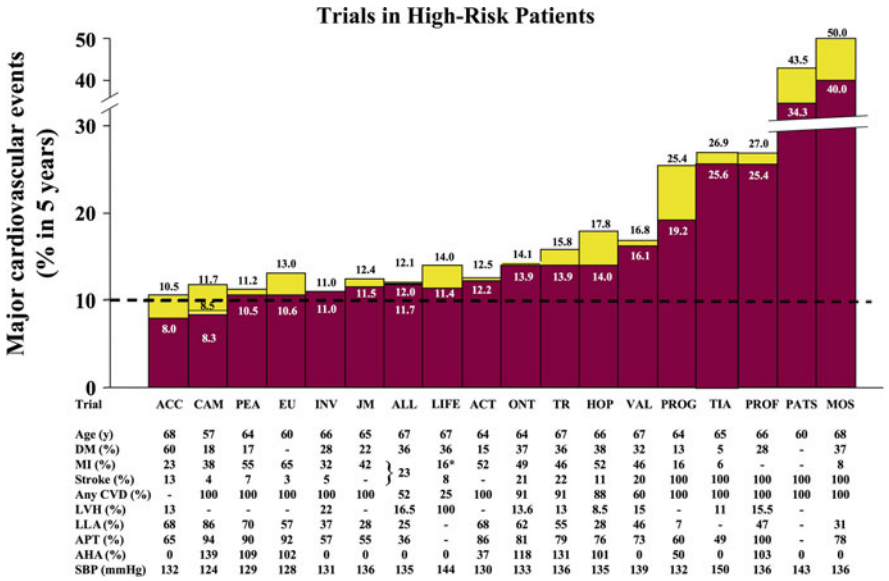
The overall low incidence of cardiovascular outcomes occurred in these trials despite the fact that concomitant therapies with lipid-lowering and antiplatelet agents were practically negligible, the only exception being the HOT [22] and ASCOT [30] studies, which also explored the effects of an antiplatelet agent and a statin, respectively, in a factorial design. Incidences below 6 % in 5 years, i.e., in



Trial	AUS	MRC M	ELSA	HOT	OSLO	CAP	IPP	HAP	CONV	NORD	INS	ACS	FEV
Age (y)	50	51	56	61	45	52	52	52	65	60	66	63	62
DM (%)	0	0	7	8	0	5.2	-	-	20	7	21	27	12.5
MI (%)	0.4	1.5	1	1.5	0	0.9	0	2	8	21	6	0	2
Stroke (%)	0	0.7	1	12	0	1.6	0	-	7	2.6	0	11	15
Any CVD (%)	0	0	13	8.6	0	4	0	27	17	6	~12	~20	42
LVH (%)	-	-	-	-	-	-	-	-	12	-	11	22	11
LLA (%)	-	-	-	-	0	-	-	-	-	-	-	50	1
APT (%)	-	-	-	50	0	-	-	-	-	-	-	9	18
AHA (%)	0	0	0	0	0	0	0	0	0	0	0	0	0
SBP (mmHg)	146	138	142	140	130	148	144	140	137	152	138	134	137

Fig. 24.5 Incidence of major cardiovascular events in trials on low-risk hypertensive patients. For each trial the brown portion of the column indicates the incidence in the trial arm with lower event incidence, the yellow portion incidence in the trial arm with higher event incidence. The dashed horizontal line indicates the conventional threshold of high risk. Trial abbreviations are shown at the bottom of the columns. *AUS* Australian trial on mild hypertension [19], *MRC-M* MRC trial on mild hypertension [20], *ELSA* European Lacidipine Study on Atherosclerosis [21], HOT Hypertension Optimal Treatment trial [22], OSLO Oslo study [23], *CAP* Captopril Prevention Project [24], *IPP* International Prospective Primary Prevention Study in Hypertension [25], *HAP* Heart Attack Primary Prevention in Hypertension trial [26], *CONV* Controlled Onset Verapamil Investigation of Cardiovascular End points trial [27], *NORD*, Nordic Diltiazem Study [28], *INS* International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment [29], *ASCOT* Anglo-Scandinavian Cardiac Outcomes Trial [30], *FEV* Felodipine Event Reduction study [14]. The *bottom rows* indicate the baseline characteristics of the patients: age (in years), prevalence (%) of diabetes mellitus (DM), previous myocardial infarction (MI), cerebrovascular disease (stroke), any type of cardiovascular disease (any CVD), left ventricular hypertrophy (LVH), and concurrent therapies continued from baseline throughout the trial: lipid-lowering agents (LLA), antiplatelet agents (APT), antihypertensive agents (AHA). *Dashes* indicate that information was unreported. The *last row* reports the systolic blood pressure (SBP) achieved in each trial (arm with the lower outcome incidence) (From [18] by courtesy of the *Journal of Hypertension*)

the low-risk range, only occurred in trials with a very low prevalence of diabetes mellitus and previous cardiovascular disease. Figure 24.5 also shows that the SBP values achieved in the treatment group with the lower outcomes does not appear to correlate closely with the achieved level of risk, which was probably more strictly correlated with baseline characteristics.



Trial	ACC	CAM	PEA	EU	INV	JM	ALL	LIFE	ACT	ONT	TR	HOP	VAL	PROG	TIA	PROF	PATS	MOS
Age (y)	68	57	64	60	66	65	67	67	64	64	67	66	67	64	65	66	60	68
DM (%)	60	18	17	-	28	22	36	36	15	37	36	38	32	13	5	28	-	37
MI (%)	23	38	55	65	32	42	} 23	16*	52	49	46	52	46	16	6	-	-	8
Stroke (%)	13	4	7	3	5	-		8	-	21	22	11	20	100	100	100	100	100
Any CVD (%)	-	100	100	100	100	100	52	25	100	91	91	88	60	100	100	100	100	100
LVH (%)	13	-	-	-	22	-	16.5	100	-	13.6	13	8.5	15	-	11	15.5	-	
LLA (%)	68	86	70	57	37	28	25	-	68	62	55	28	46	7	-	47	-	31
APT (%)	65	94	90	92	57	55	36	-	86	81	79	76	73	60	49	100	-	78
AHA (%)	0	139	109	102	0	0	0	0	37	118	131	101	0	50	0	103	0	0
SBP (mmHg)	132	124	129	128	131	136	135	144	130	133	136	135	139	132	150	136	143	136

Fig. 24.6 Incidence of major cardiovascular events in trials on high cardiovascular risk patients. *Trial abbreviations* are indicated at the bottom of the columns, as follows: *ACC* Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial [31], *CAM* Comparison of Amlodipine versus Enalapril to Limit Occurrence of Thrombosis [32], *PEA* Prevention of Events with Angiotensin Converting Enzyme Inhibition [33], *EU* European trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease [34], *INV* International Verapamil SR–Trandolapril study [12], *JM* Japan Multicenter Investigation for Cardiovascular Diseases-B [35], *ALL* Antihypertensive and Lpid-Lowering Treatment to Prevent Heart Attack [36], *LIFE* Losartan Intervention For Endpoint Reduction in Hypertension study [37], *ACT* A Coronary Disease Trial Investigating Outcome with Nifedipine GITS [38], *ONT* Ongoing Telmisartan Alone or in Combination with Ramipril Global Endpoint Trial [39], *TR* Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease [40], *HOP* Heart Outcomes Prevention Evaluation [41], *VAL* Valsartan Antihypertensive Long-Term Use Evaluation [42], *PROG* Perindopril Protection Against Recurrent Stroke Study [43], *TIA* Dutch Transient Ischemic Attack Study [44], *PROF* Prevention Regimen For Effectively Avoiding Second Stroke [45], *PATS* Post-stroke Antihypertensive Treatment Study [46], *MOS* Morbidity and Mortality after Stroke Eprosartan Compared with Nitrendipine for Secondary Prevention of Stroke [47] (from [18] by courtesy of the *Journal of Hypertension*). *APT* antiplatelet agent, *CVD* cardiovascular disease, *AHA* antihypertensive agent, *DM* diabetes mellitus, *LVH* left ventricular hypertrophy, *LLA* lipid-lowering agent, *MI* myocardial infarction, *SBP* systolic blood pressure

Figure 24.6 shows that intensive antihypertensive treatment often associated with treatment of concomitant risk factors was unable to reduce cardiovascular outcome incidence below the high risk cut-off in most trials that deliberately enrolled high cardiovascular risk patients [12, 31–47]. In these trials, cardiovascular diseases were present at baseline for a minimum of 50 % and a maximum of 100 % of patients, with the exception of the LIFE trial in which previous

cardiovascular disease was present in 25 % of patients only, but all patients had left ventricular hypertrophy. Antiplatelet drugs were given to 36–100 % of patients in all these trials (no information available for the LIFE [37] and Post-Stroke Antihypertensive Treatment Study (PATS) trials [46]), and lipid-lowering agents to 25–68 % (with the exception of three trials on patients with cerebrovascular disease [43, 46, 47]).

In many of these studies, pre-existing antihypertensive therapies were continued throughout the trial with the addition of the drugs to be tested, so that antihypertensive drug usage was quite high, and in 15 of the 18 trials considered the average SBP achieved in the more actively treated arm was well below 140 mmHg. Despite the aggressive treatment of elevated BP and the frequent concomitant treatment of other risk factors in 16 of the 18 trials, cardiovascular outcome incidence remained above the high risk cut-off of 10 % in 5 years (and in patients with previous cerebrovascular disease well above that cut-off). The only two exceptions were the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) [31] and the Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) [32] trials, in which cardiovascular outcome incidence was below 10 % in 5 years in one arm. However, the overall prevalence of cardiovascular disease was not given in ACCOMPLISH, while in CAMELOT angina largely predominated among baseline cardiovascular disease. Furthermore, in both trials, the incidence of revascularization procedures was very high, twice and three times as large, respectively, as the cardiovascular events (myocardial infarction, stroke, and cardiovascular death) considered as major outcomes. Also in trials such as Heart Outcomes Prevention Evaluation (HOPE) [41], Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [39], and Telmisartan Randomised Assessment Study in Angiotensin Converting Enzyme Inhibitor Intolerant Subjects with Cardiovascular Disease (TRANSCEND) [40], inclusion of revascularization procedures among end points would have brought their incidence to very high levels (about 30 % in 5 years) [18].

In conclusion, the systematic review of the trials summarized here [18] clearly indicates that a high incidence of cardiovascular events persists despite intense lowering of BP and concurrent therapeutic correction of other risk factors, such as serum cholesterol and platelet aggregation, when therapeutic intervention is made once organ damage is advanced and, especially, when overt disease is present. This does not deny the known benefit of interventions even in secondary prevention, as shown by many trials and their meta-analyses [3–5], but it points out that pre-existing high risk sets a ceiling effect to the benefits of treatment because of a residual risk that is not amenable or scarcely amenable to be reduced by treatment.

24.4 When Should Antihypertensive Treatment Be Initiated?

Figure 24.7 represents the continuum of CVD as an arch, the thickness of which progressively increases while the risk of CVD events continuously increases [48]. Indeed, cardiovascular disease begins when a risk factor such as BP is present, but the risk of cardiovascular events in the subsequent 10 years is still low. Risk factors, however, are progressively leading to subclinical (or asymptomatic) organ damage (e.g., microalbuminuria, left ventricular hypertrophy, carotid plaques, and so on), with a consistent increase in risk. If left untreated, asymptomatic organ damage may progress to become symptomatic (e.g., angina, overt proteinuria, claudication, and so on), and ultimately to cardiovascular events (stroke, myocardial infarction, heart failure), and death may occur. Intervention trials indicate that antihypertensive therapy is capable of reducing outcomes by approximately 25–30 % independent of the risk level at which treatment is started [4]. This means that when CVD is more advanced along its continuum and the initial risk is higher, the residual level of risk will also be higher, even after all possible treatment benefits have been achieved, because some vascular damage, such as that caused by a myocardial infarction or a stroke, may be irreversible. This also explains

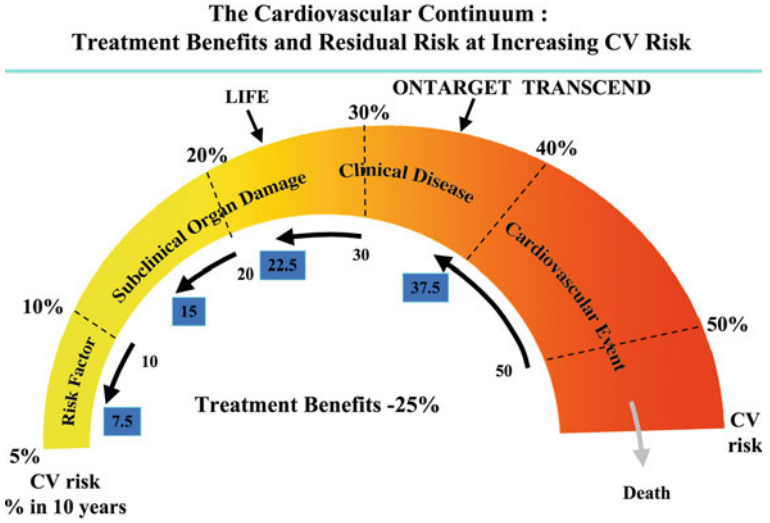


Fig. 24.7 The continuum of cardiovascular (CV) disease and the effects of antihypertensive treatment initiated at different levels of risk. LIFE and ONTARGET/TRANSCEND indicate the approximate level of risk along the continuum at which treatment was initiated in the LIFE study [37] and in the ONTARGET [39] and TRANSCEND [40] studies. Other explanations in the text (modified from [48] by courtesy of *Nature Reviews Cardiology*). *LIFE* Losartan Intervention For Endpoint Reduction in Hypertension, *ONTARGET* Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, TRANSCEND Telmisartan Randomised Assessment Study in Angiotensin Converting Enzyme Inhibitor Intolerant Subjects with Cardiovascular Disease

some discrepancies between the presence and absence of clinical benefits of organ damage regression in different trials of antihypertensive treatment. In the LIFE trial, in which all patients had left ventricular hypertrophy at baseline, but only a minority of them had a previous myocardial infarction (16 %) or stroke (8 %), treatment-induced regressions of left ventricular hypertrophy [49] or urinary albumin excretion [50] were found to be associated with a reduced incidence of cardiovascular outcomes, whereas in the ONTARGET and TRANSCEND trials (about 70 % of previous myocardial infarctions and strokes at baseline) regression of these two types of organ damage was not accompanied by lower outcome incidence [51, 52]. Figure 24.7 suggests that organ damage represents the main cause of the added risk, whereas it may be less important in those patients where high risk is mostly represented by the consequences of a previous event.

24.5 Conclusions

The existence of a consistent *residual* risk in high-risk patients scarcely amenable to treatment benefits underlines the limitations of late interventions and suggests that the recommendations by many private or public health-care providers [including the 2011 National Institute for Health and Clinical Excellence (NICE) guidelines in the United Kingdom] to limit interventions to patients with a total cardiovascular risk above 20 % in 10 years (or 10 % in 5 years) may be unwise. The alternative recommendation is *the earlier the better*, but then the challenge facing the experts is establishing when early is not too late but also not excessively early.

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Poor BP Control in the Hypertensive Population: Which Factors are Involved?

25

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High blood pressure is the leading cause of global mortality and burden of disease [1]. A compelling body of evidence from randomized controlled trials has shown that BP lowering treatment reduces the risk of cardiovascular and renal morbidity and mortality in hypertensive patients. Moreover, the magnitude of the mean BP change throughout the treatment period is significantly related to the incidence of cardiovascular events regardless of the class of antihypertensive drugs employed. [2, 3]. Although guidelines for hypertension control are available and updated according to the best available evidence to facilitate better diagnosis and management of hypertension, [4, 5], recent observational surveys continue to show persistently low rates of BP control. A Canadian national survey conducted in 2007–2009 showed that about 65 % of hypertensives in the general population of hypertensive patients achieved the goal of BP control (defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg for the general population)[6]; the control rate was about 50 % in the United States (2007–2008) [7], 28 in England (2006) [8], and only 6 % in China (2002) [9]. The control rate among the treated patients was also far from optimal in the above countries, at 82, 69, 52 and 25 %, respectively (Table 25.1). The control rate was even poorer among hypertensive patients who were older or obese; had diabetes or chronic renal disease; or lived in low or low-middle income countries or in rural areas. Li et al. [9–11] in spite of a significant improvement in treatment and control rates observed in many countries [6, 8, 9, 12], the vast majority of hypertensive patients live in countries with low control rates.

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Table 25.1 Unaware and untreated hypertensive subjects in the general population of hypertensive patients identified in national surveys [6–9]

National surveys	Percentage of controlled hypertensives	Percentage of unaware subjects	Percentage of uncontrolled subjects		Percentage of untreated in uncontrolled
			Treated	Untreated	
Canada (2007–2009)	65	17	14	21	59
USA (2007–2008)	50	19	19	31	62
England (2006)	28	34	26	46	64
China (2002)	6	70	19	75	80

This overall poor control of BP in the world can be attributed to three major reasons. First and most importantly, a very large proportion of the patients are not identified or not treated, especially in low or low-middle income countries. Secondly, many treated patients are not adequately or not persistently managed by their physicians, or the patients do not comply with the prescribed treatment. Finally, a smaller but substantial proportion of hypertensive patients are difficult to control due to resistant hypertension including drug induced hypertension and secondary hypertension.

25.1 Patients Unidentified or Untreated

Among the hypertensive patients whose BP is not controlled to goal, more than half remain untreated in both high- and low-middle income countries (Table 25.1). The situation is more severe in less developed areas [10]. For example, the extremely low BP control rate in China can be explained by the very high proportion of unaware (70) and untreated (75 %) hypertensive patients. This unappreciated situation was largely due to inadequate health policy and poor primary health care services for the detection and continual management of chronic diseases such as hypertension. Patients usually do not seek professional help unless they are aware of their condition and understand the consequences of uncontrolled hypertension. Proactive screening and registration of hypertension in primary care settings would help to identify most patients at an early stage and continual management would help to improve the overall control rate and prevent cardiovascular and chronic renal events.

25.2 Poor Management

The poor control rate among treated hypertensive patients could be largely due to inadequate or non-persistent management provided by health care professionals or attributed to poor compliance by patients to the treatment prescribed. In the general population, the control rate was only about 25 % among treated hypertensive patients [9]. When treated by specialists in tertiary hospitals, the control rate for patients with various complications was about 30 % [13], while for patients treated in an interventional study with close monitoring a control rate of 72 % was achieved [14]. Evidently, better management with individualized prescription and regular monitoring can largely improve the BP control rate.

Regarding drug therapy, more and more studies have shown that combination therapy with low-doses of two or more different drugs is more effective than mono-therapy in controlling BP [13–19]. Meanwhile, fixed doses of two or more drugs in a single pill taken once daily promotes better compliance due to better tolerability and simplicity in daily use, which are especially important for elderly patients and those with co-morbidities [20, 21].

Compliance to prescribed medication and lifestyle modification are important factors for better BP control. Knowledge and motivation influence a patient's decision to comply with treatment. It is not uncommon that patients discontinue antihypertensive treatment when symptoms disappear or side effects appear, without consulting their doctors. Innovative means of intervention have been developed, such as: counseling services provided by physicians or nurses, [22, 23] physician-pharmacist collaborative interventions, [24] and telemonitoring and self-management [25] to help improve compliance to treatment and achieve better BP control.

Health policy can also impact compliance to persistent treatment and can therefore affect the BP control rate, especially in under privileged patients who cannot afford long term treatment in those countries without universal health care coverage.

25.3 Resistant Hypertension

A smaller but substantial proportion of poor controlled hypertensive patients have resistant hypertension, defined as failure to achieve goal BP when patients adhere to full doses of an appropriate regimen of 3 or more antihypertensive drugs, whether or not including a diuretic [5, 26–28]. Although resistant hypertension is commonly seen by both primary care clinicians and specialists, a definitive prevalence is not available. According to the estimate using data from the NHANES 2003–2008 in the United States, the prevalence of resistant hypertension was about 9 % among US adult hypertensives or 13 % among treated hypertensives [29]. Data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attach Trials (ALLHAT) suggests that the prevalence of resistant

hypertension is about 20–30 % among the general hypertensive population [26, 28, 30]. Studies from the United States indicate that resistant hypertension is more likely to be older, non-Hispanic black and obese, and more likely to have reduced renal function, arterial stiffness, isolated hypertension, left ventricular hypertrophy, history of coronary heart disease, heart failure, stroke, or diabetes mellitus. [26–29, 31–33]. The above characteristics of resistant hypertension are similar to those of patients at highest risk of cardiovascular events, in whom control of BP would be particularly beneficial.

Apart from the demographic characteristics, a number of lifestyle or biological factors as well as drugs can contribute to failure to achieve BP goals despite effective treatment (Table 25.2) [26, 33, 34]. Excess dietary salt intake is a common factor of resistant hypertension. High salt intake leads to volume overload in susceptible patients, especially in elderly or overweight patients. High sodium intake can contribute to resistant hypertension by increasing BP and by blunting the BP-lowering effect of several classes of antihypertensive drugs.

Increased body weight is also associated with more severe hypertension. Obesity contributes to BP elevation through various mechanisms, such as insulin resistance, impaired sodium excretion, increased sympathetic nervous system activity, activation of the rennin-angiotensin-aldosterone system, presence of obstructive sleep apnoea, and relative reductions in active drug levels.

The presence of diabetes or chronic kidney disease also makes hypertension control difficult. Chronic kidney disease is the most frequent cause of resistant hypertension. Kidney disease can be both a cause and a consequence of hypertension. The impaired ability to excrete sodium loads with kidney function deterioration interferes with BP control, establishing a vicious cycle of hypertension and chronic kidney disease.

Another cause of resistant hypertension is intake of pharmacologic agents that increase BP. Drugs that commonly raise blood pressure include NSAID, oestroprogestinics, carbenoxolone, liquorice/glycyrrhizinic acid, steroids, immunosuppressive agents, erythropoietin, cocaine and amphetamines, alcohol, caffeine, clozapine, modafinil, sympathomimetic amines, angiogenesis/kinase inhibitors, antidepressants, HDL-raising agents, anti-HIV drugs [34].

Secondary causes of resistant hypertension include several diseases. Some are fairly common in tertiary hospitals, such as obstructive sleep apnea, renal parenchymal disease, primary aldosteronism or renal artery stenosis. It was estimated that about 10 % of resistant hypertension was due to primary aldosteronism [26].

Resistant hypertension needs to be differentiated from “pseudoresistance”, which is mainly due to inadequate management of hypertension (Table 25.3). Diagnoses and adjusting treatment for resistant hypertension usually need to be facilitated by specialists. Patients with suspected resistant hypertension should be referred to specialists for further examination.

In summary, the major factor responsible for overall poor control of BP is that a majority of hypertensive patients remain unidentified or untreated, especially in low or low-middle income countries. Another factor related to poor BP control is inadequate management of patients by their doctors and poor compliance by

Table 25.2 Common causes of resistant hypertension [26, 33, 34]

Patient characteristics
Older age
Obesity
Diabetes
Chronic kidney disease
Lifestyle-related factors
High salt intake
Excess alcohol intake
Drug-induced
Non-steroidal anti-inflammatory drugs (including cyclooxygenase-2 inhibitors)
Oral contraceptives and hormone replacement therapy
11β-hydroxysteroid dehydrogenase type 2 inhibitors, carbenoxolone, glycyrrhizinic acid, Licorice (included in some chewing tobacco or herbal medicines)
Steroids
Calcineurin inhibitors
Cyclosporine, tacrolimus, erythropoietin
Sympathomimetics (decongestants, anorectics)
Cocaine, amphetamines, other illicit drugs
Nasal decongestants
Alcohol
Caffeine
Antiangiogenesis and kinase inhibitors
Bevacizumib, receptor tyrosine kinase inhibitor, antidepressants
Monoamine oxidase inhibitor, tricyclics, selective serotonin inhibitors
Reuptake inhibitors (selective serotonin reuptake inhibitors), high-density lipoprotein cholesterol-raising agents, torcetrapib
Herbal supplements (e.g., ginseng, ma huang)
Secondary causes of hypertension
Obstructive sleep apnea
Renal parenchymal disease
Primary aldosteronism
Renal artery stenosis
Pheochromocytoma
Cushing disease
Thyroid disease
Aortic coarctation

Table 25.3 Causes of pseudoresistant hypertension [26, 33]

Incorrect blood pressure measurement
White-coat effect
Related to antihypertensive medication
Inadequate doses
Inappropriate combinations
Physician inertia (failure to change or increase dose regimens when not at target)
Poor patient compliance
Side effects of medication
Complicated dosing schedules
Memory or psychiatric problems
Poor relationship between doctor and patient
Inadequate patient education
Costs of medication

patients to prescribed treatment. However, the most common and challenging factor in clinical settings is resistant hypertension. To improve overall BP control, efficient primary health care services for screening and continual management of hypertensive patients; nationwide education programs for the prevention and control of hypertension, and specialist training programs should be promoted.

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Ramadan Fasting in Health and Disease

26

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26.1 Introduction

Fasting is defined as partial or complete abstinence from food and drink, and may be associated with restriction of calorie intake, certain food items, mainly macronutrients, or both [1]. Fasting can be practiced continuously over a prescribed period or on alternate days. Alternate day fasting consists of succeeding periods of abstinence (*fast* period) and nutrition (*feast* period) over a 24 h cycle [1]. During the *fast* period, food and fluid intake is discontinued completely, while during the *feast* period, those who fast resume food and fluid intake ad libitum [1]. Fasting may be partaken for health reasons or for religious or spiritual purposes. Although it may elicit favorable effects on several health-related outcomes, fasting may also impact negatively on the health of the individual.

The aim of this chapter is twofold: (1) a review of the studied effects of Ramadan fasting, a form of alternate day fasting, on the biochemical, hemodynamic, and cardiorenal parameters in healthy individuals and in those suffering

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from one or more of the high cardiovascular risk conditions such as hypertension, diabetes mellitus, and or chronic kidney disease; and (2) to offer therapeutic recommendations for safe fasting under various conditions.

26.2 Ramadan Fasting

26.2.1 Definition

Ramadan fasting, a fundamental requirement of the Islamic religion, is a form of annual alternate day fasting that is characterized by periods of *fasting* and *feasting*, generally separated by a 12 h interval [2, 3]. During the *fast* period, which generally lasts about 12 h, the individual must refrain from eating, drinking, smoking, sexual intercourse, and medicating from sunrise (Suhoor) to sunset (Iftar). On breaking the fast, the individual consumes a large meal at sunset and one lighter meal before dawn [2, 3]. An additional meal may be consumed before sleeping. Ramadan differs from total fasting as refeeding is essential once or twice within 24 h and as there is no restriction in the nature and extent of the food consumed between sunset and dawn [2].

While the abstinence period during Ramadan may be about 12 h, several factors modify the length of the daytime fast. Since the Islamic Calendar (Hijra) is a lunar calendar, the first day of Ramadan, which advances by 11 days each year in relation to the Gregorian calendar, falls in different days of the seasonal year over a 33 year cycle [1, 2]. This can result in Ramadan fasting being undertaken in markedly different environmental conditions between years in the same country. In addition, the time of sunrise and sunset varies between 12 h at the equator and about 22 h at 64° of latitude in summertime, thus altering substantially the daily fasting event [3]. In Polar regions, fasting may be as long as 22 h [3]. However, Muslims living in such regions are allowed to adopt the fast period of either Mecca or Medina or the nearest temperate location [3].

Not only is the eating pattern greatly altered during the month of Ramadan, the type of diet consumed during the night is also significantly different from that consumed during the rest of the year. Food items are richer in fat, carbohydrates, sugar, and proteins [2–4]. The consumption of vegetables and fruits appears to be reduced.

26.2.2 Effects of Ramadan Fasting on Health Parameters and Outcomes

The physiological changes induced by Ramadan fasting have not been well evaluated. The changing seasonal and dietary variables have raised health concerns in the fasting individual. The health impacts have been attributed to the abstinence from food, dehydration, or a combination of both [3].

Fasting during the month of Ramadan is characterized by repeated cycles of fasting and refeeding which extend over a 24 h period [2, 3]. This pattern is associated with significant disruption in normal regular activities and sleep habits. Several confounding factors may influence health-related biomarkers and outcomes such as variability in fasting, smoking status, alterations in drug chronotherapy, type of diet, and cultural habits [3]. While the average fast period during Ramadan is 12 h, it can be much longer in Polar Regions during the summertime [3]. Smoking and caffeinated beverages are forbidden during the daylight hours. Similarly, administration of oral and/or intravenous medications is also prohibited during the abstinence period [5].

The change in the number and timing of meals and the reduction in daily food intake into two instead of the usual four or five portions have been shown to influence the metabolic environment [3].

26.2.3 Fluid Balance in Non-Fasting Normal Conditions

Under normal physiological conditions, the healthy nonfasting individual maintains water balance in the face of two opposing processes, namely water gain and water loss. The body gains water through oral intake, preformed water from ingested food, and the oxidation of nutrients (water of oxidation). Water is lost through urine, feces, and evaporation through respiratory and transcutaneous pathways, and through sweat if body transpiration is elevated [3, 6]. Fluid intake tends to be associated with eating and when intake is restricted, fluid consumption is also voluntarily reduced [3, 7].

Under stressful conditions, water balance is preserved by thirst and urinary concentration mechanisms. Urinary concentration, which is regulated by the secretion of antidiuretic hormone (ADH), minimizes water loss through urine while thirst favors water intake. Both mechanisms are controlled by alterations in serum osmolality and body fluid volumes [3].

26.2.4 Fluid Balance in Ramadan Fasting

Fasting during the daylight hours of Ramadan is associated with alterations in eating and sleeping patterns and reduced physical activity which in turn induce changes in several physiological functions.

Several studies have indicated that healthy individuals who refrain from food and drink during the daylight hours of the month of Ramadan dehydrate [3]. The water deficit is, however, corrected at least partly by the resumption of eating and drinking at the break of fasting during the night hours from sunset to sunrise [3].

Water and food deprivation during daylight hours is associated with changes in some indices of renal function. Urine output falls while urine becomes maximally concentrated. In a study on 16 Sudanese healthy males aged 20–22 years,

urine output was significantly lower than in the prefasting and post-Ramadan fasting periods and continued to fall as fasting proceeded [8]. In contrast, urine osmolality tended to increase throughout the month of intermittent fasting and became markedly elevated at the end of Ramadan, indicating an additional stress of water deprivation [8]. In another study in 20 Malaysian Ramadan fasters aged 20–45 years, the afternoon urine collection (12:00–16:00) was constantly lower than the prefasting levels throughout the month of Ramadan but recovered rapidly to control levels 1 week after fasting cessation [9]. However, overnight urine output (16:00–08:00 of the following day) remained unchanged and compensated for the slightly reduced 24 h fasting urine output [9]. On the other hand, urine osmolality in the morning (08:00–12:00) and afternoon (12:00–16:00) samples, which corresponded to the abstinence period, was very high [9]. These findings indicate effective water conservation both by maximal urinary concentration and reduced urine output.

The solute content of the urine in healthy adult fasters was characterized by reduced sodium, and to a lesser extent potassium excretion and increased urea excretion rates [9]. The urea excretion which paralleled urine osmolality appears to be a major contributor to high urine osmolality in fasting [9]. There was no detectable protein or hemoglobin in the urine. Serum creatinine and urea levels during the month of intermittent fasting showed no increase from pre- or post-fasting levels [9].

These observations indicate that the intermittent fasting during Ramadan has no adverse effects on renal function, that the human body can adopt adequately to water deprivation, and that the concentration capacity of the kidney remains unimpaired during the daylight fasting hours of Ramadan. Further, the relatively constant dilute osmolality of the urine during the overnight periods demonstrates that the subjects were adequately rehydrated during the night hours [10].

26.2.5 Energy Balance

Generally, meal frequency is reduced from 3–5 to two daily meals during the month of Ramadan fasting [11]. However, there is no consensus as to energy or kilocalorie intake or as to the anthropometric measurements. Energy intake and body mass have been reported to be increased in Saudi Muslims and to be reduced in Muslims in several other countries or communities such as India, Malaysia, and Sudan [12, 13]. Nevertheless, some studies have reported no change in either parameter in Ramadan fasting subjects from the Arab Emirates and Tunisia [14]. The discrepant findings in energy balance have been attributed to differences in food choice and habits, and socio-economic status resulting from a diversity of cultures and customs in different Muslim countries around the world [3].

The changes in body mass are usually relatively small. Further, body weight changes appear to be greater during the first 2 weeks of the fasting event [3]. Several factors have been postulated to explain the Ramadan fasting-induced body mass loss: (1) a hypoenergetic diet: reduction to two daily meals in 16 young adult male fasting

subjects was associated with a decrease in energy balance and in loss of body mass, although fasting subjects were allowed to eat as much as they wished at each meal [15]; (2) a mild–moderate degree of dehydration secondary to reduced salt intake [3].

26.3 Hematological, Biochemical, and Metabolic Effects of Ramadan Fasting

26.3.1 Hematological Parameters

Several studies evaluated the effects of Ramadan fasting on selected hematological parameters. These studies reported reductions in red cell packed cell volume (hematocrit) and hemoglobin concentrations, and worsening anemia [16]. Total red and white cell and platelet counts remained unchanged 16]. Serum iron, ferritin, and iron-binding capacity may fall or remain unchanged during Ramadan fasting, returning to pre-Ramadan levels at the end of the fast [1].

An interesting study on 100 healthy males that compared fasting subjects to nonfasting subjects during the month of Ramadan documented a reduction in the hematocrit only in the fasting subjects, suggesting that fasting may have a deleterious effects on red cell production [17].

Ramadan fasting has been shown to have an additional deleterious hematological effect: a decreased response of platelets to different aggregating agents [adenosine diphosphate (ADP), collagen, and adrenaline) associated with the prolongation of bleeding and coagulation times [18]. However, in a study on patients with cardiovascular disease, fasting did not appear to influence the dose or the effect of warfarin anticoagulation [19].

26.3.2 Biochemical Profile

In healthy subjects, Ramadan fasting is associated with changes in some metabolic parameters. Blood glucose levels generally remain unchanged although reductions have been reported, but with no hypoglycemic symptoms [20]. However, some studies reported increased blood glucose levels toward the end of Ramadan, though glycated hemoglobin levels remained normal [21].

Regarding the lipid profile, results are heterogeneous and often contradictory. Total serum cholesterol, triglycerides, low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) may increase, decrease, or remain unchanged [1, 22–24]. Glutamate oxaloacetate transaminase and glutamate pyruvate transaminase activities may increase slightly, but return to normal values after fasting cessation. However, no changes have been reported in other liver function tests [25]. Blood urea nitrogen, serum creatinine, and serum electrolytes remain unchanged. However, serum uric acid levels increase; this has been attributed to reduced renal urate excretion [26]. Reductions in interleukin-6, C-reactive protein, and homocysteine have been reported [27].

26.3.3 Chronic Kidney Disease

Concerns about the safety of a month-long daylight abstention from food and drink during Ramadan have been raised in patients with various types of chronic kidney disease (CKD). Several factors have been postulated to have a negative impact on the health and well-being of this potentially vulnerable group of patients. Such factors include reduced medication or drug regimen compliance, fluid restriction during daylight hours, and a possible state of chronic hypohydration.

26.3.3.1 Predialysis Chronic Kidney Disease

Only a limited number of clinical studies have evaluated the safety of Ramadan fasting on predialysis CKD patients.

In a prospective study, the effect of Ramadan fasting on renal functional indices was evaluated in 12 predialysis CKD patients with a clearance below 60 ml/min and six healthy controls. The glomerular filtration rate (GFR) was measured by Technetium-99 m diethylenetriaminepentaacetic acid (DTPA) renography and tubular function by urinary excretion of beta-N-acetyl-D-glucosaminidase (NAG) as a marker of tubular damage. Compared to the pre-Ramadan period, Ramadan fasting was associated, in predialysis CKD patients, with a significant increase in serum potassium (K^+), a significant percentage increase in NAG, but insignificant change in serum creatinine. The renal tubular changes were more significant in diabetic CKD patients [28]. According to the authors, these findings suggest that, in patients with renal impairment, Ramadan fasting may have adverse effects on renal function, in particular in patients with poorly controlled diabetes mellitus. The rise in serum K^+ has been attributed to the traditional Ramadan meal, a rich source of K^+, consisting of large amounts of dates, apricot juice, and coffee [28].

A prospective observational study evaluated the effect of Ramadan fasting in 36 patients with moderate to severe renal insufficiency during and 2 weeks after the fasting event. There was a significant deterioration of both biochemical profile and renal function which persisted for 2 weeks after the end of Ramadan. Calculated creatinine clearance dropped from a prefasting level of 17.2 ± 3.5 to 13.2 ± 2.2 and 13.7 ± 3.2 mL/min to the end of Ramadan and 2 weeks postfasting, respectively. In nine patients, there was also a progressive fluid accumulation, weight gain, lower limb edema, and poor control of BP, requiring frequent adjustment of management [29]. These findings suggest that, in patients with moderate to severe renal impairment, Ramadan fasting may be associated with further deterioration in renal function which may become irreversible and cause adverse serious health manifestations.

In contrast, Ramadan fasting had no adverse effects on renal function in healthy controls [26].

26.3.3.2 Chronic Hemodialysis

Only one single study of 40 patients receiving hemodialysis therapy for more than 6 months examined the effect of fasting during Ramadan. Patients fasted on nondialysis days. An interdialytic weight gain and a significant rise in serum K^+

levels occur, but with no change in BP. However, no hospitalization for pulmonary edema or for the adverse effects hyperkalemia was required [30].

26.3.3.3 Renal Transplant Recipients

Concerns have been raised about the safety of Ramadan fasting in renal transplant recipients. These individuals are thought to be at increased risk of adverse reactions. Dehydration, accumulation of metabolites, and reduced compliance with immunosuppressant medications may cause deleterious effects on renal function and undermine the immune system.

Several studies evaluated the influence of a month-long daylight deprivation of food and drink on renal function in renal transplant recipients with stable normal or stable impaired renal allograft function [31]. A group of 43 renal transplant patients with stable renal function demonstrated excellent urinary concentrating capacity after a day long fast [32]. Similarly, in a large study that included 145 renal transplant recipients, 71 of whom fasted for the whole month, renal allograft function remained unchanged in both fasting and nonfasting subjects. Likewise, in a study from Saudi Arabia that involved renal transplant patients, 17 with normal and six with impaired but stable renal allograft function, respectively, were examined 1 week before, weekly during, and 1 week after Ramadan. The biochemical profile, and the serum and urinary renal indices showed no significant change [33]. Ramadan fasting was also evaluated in a group of 68 renal transplant recipients (35 of whom fasted and 33 nonfasting controls) over 3 years. The mean GFR, after the third year, did not differ significantly from baseline values in both fasting and nonfasting groups [34]. Further, no rejection episodes or deterioration of renal function were reported [34].

The authors of these various studies suggest that Ramadan fasting appears to be safe and not associated with adverse reactions in renal transplant recipients with stable normal or stable impaired renal allograft function. However, due to the possible deteriorating effect of chronic hypohydration on renal function in animals with impaired renal function, it might be advisable to avoid Ramadan fasting in renal transplant recipients with impaired allograft function.

26.3.3.4 Urolithiasis and Renal Colics

The occurrence of urolithiasis and renal colics during the month of Ramadan was compared to the nonfasting months of the year. In western Saudi Arabia, a region with a high prevalence of urolithiasis, the rate of renal colics was related to the climatic environmental conditions rather than to the fasting event. Similar observations were reported from Iran [35]. The admission rates to two hospitals for renal colics were higher during the warm seasons than during the cold months, but were unrelated to the fasting festivities [36]. These data indicate that the daylight fasting process by itself does not appear to predispose to stone formation.

26.4 Blood Pressure and Hypertension During Ramadan Fasting

Several factors have been postulated to alter the 24 h circadian cycle and control of BP during Ramadan fasting. These include: (1) repeated fasting–refeeding cycles; (2) altered sleep and feeding patterns; (3) reduced compliance and changing chronotherapeutic timing of antihypertensive medications; and (4) Ramadan drinks (licorice).

Studies on the effect of fasting in experimental animals have reported conflicting observations. Some studies have shown that repeated cycles of fasting–refeeding may cause or exacerbate hypertension [37]. In another study in hypertensive rats, fasting for 48 h was associated with a significant drop in BP, possibly related to reduced metabolic function [38]. In 1993, the effects of 12, 36, and 72 h of fasting was assessed in 29 healthy normotensive subjects, whose systolic blood pressure (SBP) increased during the 12–36 h fast, and returned to near prefasting values at 72 h [39].

Several studies in hypertensive subjects assessed the influence of a month-long daytime food and drink deprivation on BP control and indices of circadian 24 h cycle [40]. In 99 hypertensive patients, the BP profile was studied using ambulatory BP monitoring (ABPM) before and during Ramadan [41]. No statistical difference was observed between fasting and nonfasting periods in 24 h BP level, SBP, and diastolic BP (DBP) in diurnal or nocturnal intervals [41]. However, during the month of Ramadan, the peak of awakening BP and nocturnal trough were delayed by 2 and 1 h, respectively [41]. Similarly, in 17 treated hypertensive subjects, ABPM was performed twice, before and during the last week of Ramadan. All patients continued to take their medications administered to them once daily [42]. No differences were reported in average 24 h BP, as well as in average awake and average sleep BP between the two recording periods. These results were confirmed in a study of treated subjects with grade 2 and 3 hypertension receiving combination therapy and assessed by ABPM before and after Ramadan [42]. There were no statistically significant differences between the two monitoring periods, except for a slight BP elevation before dawn coinciding with the consumption of a morning meal. Likewise, in a study of 21 well-controlled hypertensive subjects, similarly evaluated by two ABPM recording periods before and during Ramadan, fasting did not alter the nocturnal dipping pattern [43].

In the light of the observations reported in these studies, the authors conclude that Ramadan fasting is safe in uncomplicated hypertension and can be observed regularly with the proviso of the continuation of prescribed antihypertensive medications. However, patients with severe or uncontrolled hypertension requiring multiple doses during the daytime should be counseled against fasting [25].

26.5 Licorice and Hypertension

Drinks in Ramadan have become part of the month's traditions. Licorice, a popular drink in many Arab countries during Ramadan, has been associated with an elevation in BP and or exacerbation of hypertension [44, 45].

Licorice is extracted from the roots of the licorice plant. The active ingredient, glycyrrhizinic acid, inhibits the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2), leading to reduced conversion of cortisol to cortisone with the subsequent increased half-life of the former [44]. The glucocorticoid cortisol has similar affinity to the mineralocorticoid receptors in epithelial cells in several target tissues such as the kidney, colon, and vascular smooth muscle (VSM). By accessing the mineralocorticoid receptors in the renal tubule, cortisol promotes renal sodium (Na^{2+}) retention and K^{+} excretion, with subsequent volume expansion, suppression of the renin–angiotensin system, and hypokalemic hypertension [45]. In addition, by promoting angiotensin II binding to the VSM, cortisol mediates a direct pressor effect, contributing to the licorice-induced hypertension [46].

Daily ingestion of licorice or licorice-flavored items (candy, chewing tobacco, or medications) can cause severe hypokalemic hypertension [44]. However, the effect is dependent on both dose and individual susceptibility [44]. In susceptible individuals, a regular daily intake of 100 mg of glycyrrhizinic acid, corresponding to 50 g of licorice produces adverse vascular reactions [44, 45].

No studies have evaluated the effect of licorice on BP control in Ramadan fasting subjects. However, because of uneven consumption and personal susceptibility, licorice drink may exacerbate hypertension. Therefore, it has been recommended that those who fast at Ramadan avoid or, at least, reduce licorice significantly, accompanied by frequent BP recordings.

26.6 Cerebrovascular Disorders

Most studies have reported that Ramadan fasting does not have a negative impact on the incidence of stroke. In a retrospective study of 1,579 stroke patients, the authors reported that stroke frequency during Ramadan was similar to that of other months of the year [47]. Similarly, in a cohort of 793 stroke patients admitted to a neurology service, Ramadan fasting did not influence the risk of stroke [48]. However, in those developing a stroke, the proportion of ischemic strokes was higher in diabetic patients, while the proportion of hemorrhagic strokes was lower in hypertensive subjects [48]. These interesting observations suggest that fasting in diabetic subjects may be associated with an increased risk of ischemic stroke [48].

In contrast to the lack of influence on stroke incidence, Ramadan fasting has been reported to be associated with an increased frequency of cerebral venous and sinus thrombosis [49]. Although it is unlikely that fasting in healthy individuals

would predispose to the latter cerebrovascular complications, patients with an underlying hypercoagulable state and women taking the contraceptive pill may be at increased risk [49].

26.7 Cardiovascular Disorders During Ramadan

Despite the fact that fasting is practiced by more than 1 billion Muslims worldwide, data on the incidence of cardiovascular disease during Ramadan fasting are sparse. Fasting may have a negative impact on cardiac patients because of the obligation to consume the daily calorie intake in 1–2 meals rather than the usually 3–5 meals, a heavy effort associated with physical worship practiced after a heavy meal, and the inability to take any medication during the daytime [25].

26.7.1 Ischemic Heart Disease

Several studies assessed whether Ramadan fasting has a negative influence on the incidence of acute coronary syndromes (ACS), such as acute myocardial infarction or unstable angina. In a retrospective analysis of a database of patients admitted to a cardiology department in Qatar, no significant differences were detected in the incidence of ACS before, during, or after Ramadan [50]. Similar observations were reported in an investigation involving 465 cardiac patients in several medical centers in the Gulf region [51]. Data revealed that fasting had minimal health effects. Further, in those patients developing an acute coronary event, symptoms tended to occur either in the early morning or late evening hours [51].

26.7.2 Congestive Heart Failure

Only few studies assessed whether Ramadan fasting enhances the risk of hospitalization for congestive heart failure (CHF) in cardiac patients. In a retrospective analysis involving 2,160 cardiac patients, the number of hospitalizations for CHF was similar in the months before, during, and after Ramadan [52]. Similar observations were reported in smaller studies. The authors of these various studies concluded that Ramadan fasting is safe in stable cardiac patients and does not increase the risk of cardiovascular events.

26.8 Diabetes Mellitus

The prevalence of diabetes mellitus in several Muslim countries is high, and is increasing yearly at a rate of 10 % as a result of urbanization and socioeconomic development [53]. Furthermore, Ramadan fasting poses a challenge to both physicians and patients.

Several studies have assessed the safety of Ramadan in type 1 and type 2 diabetic patients. A large multicountry population-based epidemiological retrospective study which included 12,243 diabetic subjects in countries with large Muslim populations revealed that 43 % of type 1 and 79 % of type 2 patients observe Ramadan fasting with a low overall incidence of hypoglycemic events [54]. However, severe hypoglycemic episodes requiring hospitalization were more frequent during Ramadan than during the preceding year and were frequently associated with a lack of compliance with treatment regimen (oral antidiabetic drugs and/or insulin therapy) [54]. Similar observations were reported in small studies. These data emphasize the need for closer monitoring in diabetic patients willing to observe Ramadan fasting and to avoid changing medications without the advice of health-care providers.

26.9 Sickle-Cell Disease

Ramadan fasting has been reported to enhance the risk of vaso-occlusive crisis in sickle-cell disease. In a study of 40 patients with sickle-cell disease followed up for 3 years, fasting was associated with a significant number of crises [55]. These complications, which frequently involved the kidney, have been attributed to sickling within and occlusion of small vessels in the hypertonic renal medulla resulting from severe daytime dehydration [55].

26.10 Symptomatology

Psychosomatic manifestations are frequent in Ramadan fasting subjects. There is an increased incidence of headaches, particularly in subjects prone to this ailment. In a study from Saudi Arabia, headaches were reported in 41 % of fasting subjects compared to only 8 % in nonfasting subjects [56]. Headaches are mild to moderate and increase in frequency and intensity with the duration of abstinence from food and fluids [56]. Several factors, such as caffeine and nicotine withdrawal and altered sleep patterns, have been postulated to influence the development of headache [1, 56]. However, several studies indicated that fasting itself may be the major contributor [56, 57].

Changes in mood and cognition have also been reported in Ramadan fasting subjects. Subjects are lethargic, less alert, and more irritable during the day, but become more active in the evening and at night after breaking the fast [58]. These psychosomatic symptoms have been attributed to alterations in the normal circadian pattern and to sleep deprivation [58]. However, smoking cessation, caffeine, and food and fluid intake may also be determining factors [58].

26.11 Management Recommendations During Ramadan Fasting

26.11.1 Hypertension

Formal recommendations on the management of hypertension during Ramadan fasting have been made by two professional organizations in the Arabian Gulf region [25, 59]. These include: (1) encouraging patients to seek medical advice before fasting to adjust the doses of medications; (2) advising and educating patients about the importance of strict compliance with nonpharmacological measures and antihypertensive therapy; (3) recommending a once daily schedule of a long-acting antihypertensive drug; (4) avoiding diuretics, especially in hot climates or, where diuretic therapy is indicated, reducing and administering the drug after the evening meal; and (5) avoiding salt intake and licorice drinks.

26.11.2 Diabetes Mellitus

Patients with type 2 diabetes mellitus can be controlled by adhering to the prefasting regimen by administering the whole morning dose of oral hypoglycemic agents at the break of the fast (Iftar) and for 25–50 % of the evening dose to be given before dawn (Suhoor) [25, 60, 61]. Administration of a long-acting metformin preparation may reduce the gastrointestinal side effects often associated with twice-daily dosing [25, 60]. Patients on a combination of insulin and sulfonylureas should take the oral hypoglycemic agents at Iftar and the basal insulin doses at about 22:00. Glitazones and incretin-based therapy may not need to be changed.

A recent observational study, the Vildagliptin Experience Compared to Gliclazide Observed during Ramadan (VECTOR) study indicated that, in type 2 diabetic patients, a combination of vildagliptin, a dipeptidyl peptidase 4 (DPP4) inhibitor, with metformin affords better glycemic control, weight reduction, and reduced hypoglycemic episodes compared to a combination of metformin and gliclazide, a sulfonylurea [62]. The American Diabetes Association has cautioned against the use of sulfonylureas during Ramadan fasting [63].

Patients with type 1 diabetes mellitus should be advised to abstain from Ramadan fasting. For those insisting on practicing, close monitoring for glycemic control and adjustment of insulin dosing as carried out by their physicians is highly recommended [25, 64].

26.11.3 Chronic Kidney Disease

To prevent or minimize rises in serum K^+ during Ramadan fasting, CKD patients (predialysis, hemodialysis, and renal transplant recipients) should be instructed to

reduce or avoid the consumption of items high in K^+ like those found in the traditional Ramadan familial meal, such as dates, apricot juice, and coffee [28].

26.11.4 Nonsteroidal Anti-Inflammatory Drugs

Short-term administration of nonsteroidal anti-inflammatory drugs (NSAIDS) during Ramadan has been shown to be safe and is not associated with any major adverse effects on renal function [25].

26.11.5 Anticoagulation Therapy

Studies indicate that anticoagulation therapy during the month of Ramadan is safe. Shifting from daytime to nighttime administration of a long-acting anticoagulant does not impair the anticoagulant process and does not increase the risk of atheroembolic events and hemorrhagic complications [19].

26.12 Conclusions

Ramadan fasting, an alternate day fasting event practiced by over 1 billion Muslims worldwide is characterized by repeated cycles of daytime fasting and nighttime feeding. The subject abstains from eating, drinking, medicating, smoking, and sexual intercourse during the day long fasting period.

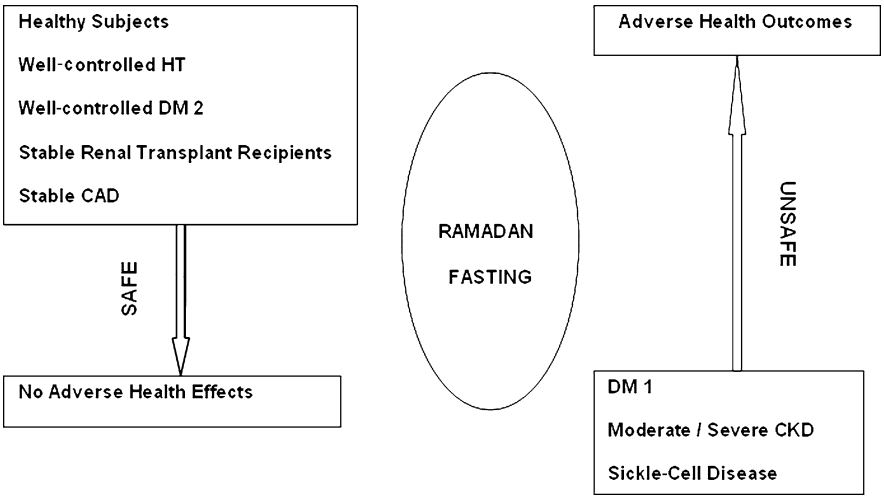

Fig. 26.1 The health effects of Ramadan fasting. *HT* hypertension, *DM 2* type 2 diabetes, *DM 1* type 1 diabetes, *CKD* chronic kidney disease, *CAD* coronary artery disease

Ramadan fasting may be associated with minor but reversible changes in several biochemical and hemodynamic parameters in healthy subjects and those suffering from stable metabolic and hypertensive disorders. However, alterations may become serious in patients with more serious cardiovascular and renal diseases, which may have a negative impact on the fasting subjects. It may be practiced safely in the former group, but may preferably be avoided in the latter subjects (Fig. 26.1).

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Postmenopausal Hormone Therapy and Blood Pressure

27

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27.1 Introduction

In 2008, the World Health Organization global status report estimated that 7.5 million deaths were attributed to high blood pressure (BP) [1]. High BP is responsible for 54 % of stroke and 47 % of ischemic heart disease cases. Overall, 80 % of the disease burden attributable to Hypertension occurred in low-income and middle-income economies, and over half in people aged 45–69 years [2]. While the prevalence of hypertension clearly increases with age in both genders (www.cdc.gov/bloodpressure/facts.htm), a comparison of cohorts from the third National Health and Nutrition Examination Survey (NHANES III) (1988–1994) with NHANES IV (1999–2002) reveals the proportion of hypertensive individuals to have decreased among men but increased among women over the time period from 1994 to 2002 [3]. Women are about as likely as men to develop high BP during their lifetime.

Although the condition affects more men than women in individuals under the age of 45 years, the age-related increase in BP accelerates in women around the menopause and this gender difference reverses after 45–55 years [4] (www.cdc.gov/nchs/data/hus/hus08.pdf), see Figs. 27.1a, 27.1b. Therefore, although the proportion of women with hypertension (elevated BP or on antihypertensive drugs) below the age of 45 years is one-third to one half to that of men,

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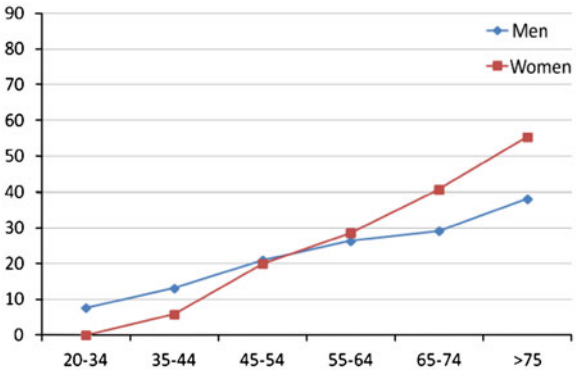

Fig. 27.1a Proportion of subjects with elevated BP by age and gender: 2003–2006. Reference www.cdc.gov/bloodpressure/facts.htm. CDC NHANES

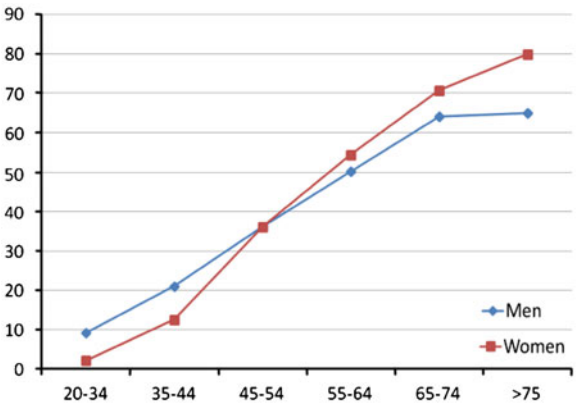

Fig. 27.1b Proportion of subjects with hypertension (elevated BP and/or on medications) by age and gender: 2003–2006. Reference www.cdc.gov/bloodpressure/facts.htm. CDC NHANES

numbers become identical in both genders in the 45–54 years age group and then increase further in women after the age of 65 years (Figs. 27.1a, 27.1b). Specifically, the proportions for women are 55 % at 55–64 years, 71 % at 65–74 years, and 80 % above the age of 80 years [4]. This pattern raises the possibility of differing pathophysiologies for hypertension in the two genders and a potential protective effect of sex steroids on the vascular system that is lost after the menopause.

The lower incidence of hypertension in premenopausal women and the increase in incidence following the menopause point to a gender-specific pathophysiology for postmenopausal hypertension. Vasodilation has been observed with fluctuating estrogen levels across the menstrual cycle, pregnancy, or 17β-estradiol supplementation [5–7], and in men after long-term estrogen administration [6]. Vasodilation has also been shown to increase during the luteal phase of the menstrual cycle and during pregnancy, at which time both estradiol and progesterone levels are higher. Endogenous progesterone has been shown to have a vasodilatory and diuretic effect in premenopausal women [8]. The substantial decrease in these endogenous vasodilators at the menopause may unmask a genetic predisposition to hypertension. In addition, menopause is associated with anthropometric, metabolic, and additional hormonal changes. These include weight gain, activation of the sympathetic nervous

system, alterations in the renin–angiotensin–aldosterone system (RAAS) and endothelin system, and an increased prevalence of metabolic syndrome, all of which may predispose to the development of hypertension [9–11].

In this chapter, we briefly review the potential mechanisms and modulators for the effect of hormone replacement therapy (HRT) on BP, detail its impact on BP in normotensive and then in hypertensive women, underscoring the results from major clinical trials in postmenopausal women.

27.2 Methodology for the Literature Review

A systematic review of the existing literature was implemented, and the topic of interest was divided into three main concepts: hypertension, hormone replacement therapy, and menopause. Each of these concepts was then searched on OVID Medline (www.ovid.com/site/catalog/DataBase/901.jsp) and also as synonyms or related terms to achieve a comprehensive literature review. The OVID Medline interface was used including MeSH terms, explode functions, keyword searching in title, abstract, and subject headings, adjacency, and publication types, in addition to using the AND and OR Boolean operators, and term truncation, to identify all relevant articles using the main terms and related terms. MeSH is used by the indexers at National Library of Medicine to describe the content of an article. These MeSH terms are also organized in a hierarchy or tree structure, and this allows users to explode a MeSH term to ensure that narrower MeSH terms are also included in the search results. The OVID Medline search was conducted from 2000–December 2011. Additional relevant studies and reviews before 2000 and those detailed in the papers retrieved and available in the authors' libraries were also used.

27.3 Effects of Estrogen and Progesterone on the Cardiovascular System

The effect of estrogen on the cardiovascular system can be through genomic and non genomic mechanisms and is mediated through two receptor isoforms, estrogen receptor (ER) alpha and ER beta [12], and a newly discovered seven transmembrane-spanning intracellular G-protein coupled estrogen receptor (GPER), that is expressed throughout the cardiovascular system [13]. The beneficial effect of estrogen on the cardiovascular system has been suggested in multiple studies evaluating different parameters. The effect on menopause-associated endothelial dysfunction has not been consistent across studies [9]. Similarly, estrogen's effect on the reinstitute renin angiotensin aldosterone system (RAAS) is complex and involves both stimulatory and inhibitory actions [14]. The increasing activity of the kinin–kallikrein [15] and sympathetic systems [16], an increase in atrial natriuretic

peptide, a reduction in oxidative stress [17] and inflammation [18], are all effects attributed to estrogen, which can result in BP lowering.

Furthermore, estrogen can play an important role on hypertension-associated complications. It has been shown that it can improve left ventricular function and mass [19, 20] and that it can induce a reduction in albuminuria [21], although the studies addressing this yielded differing results [22–24].

Progestins exist in different classes and differ in their metabolic, androgenic, glucocorticoid, and antimineralocorticoid effects. Medroxyprogesterone acetate (MPA), the most commonly used progestin in studies evaluating the impact of HT on cardiovascular outcomes, has been shown to attenuate estrogen's augmentation of endothelial-dependent vasodilation [25]. Drosperinone is a novel progesterone and spironolactone derivative with antimineralocorticoid and antiandrogenic activity [26]. The studies evaluating the combination of drosperinone and estradiol in hypertensive women showed a significant decrease in blood pressure [27, 28]. However, drosperinone has been associated with an increased risk of venous thromboembolism [29]. Additionally, dydrogesterone, which has minimal or absent effects mediated by receptors other than that of progesterone and a neutral activity on the glucocorticoid, androgenic, and aldosterone receptors [26], was shown to decrease BP when combined to estradiol in healthy and hypertensive postmenopausal women [30, 31].

27.4 Blood Pressure Changes Across the Menopause

A decline in estradiol levels is the cardinal hormonal marker of the menopause transition. Postmenopausal women have a distinctive pattern of blunted day–night BP reduction or *nondipping* [32] and certain ER polymorphisms have been associated with BP elevation in women [33]. The menopause transition is also characterized by significant changes in body composition, including increments in weight and fat mass [34], and a higher prevalence of metabolic syndrome, conditions associated with inflammation and an increased risk of hypertension [35, 36]. Studies evaluating the relationship between the menopause and hypertension yielded conflicting results, and an assessment of the role of sex hormones in this relationship is quite complex. The conflicting results could in part be explained by differences in study designs, the methods used to measure BP, office BP versus 24-h ambulatory BP monitoring (ABPM), the sample size used, the type of menopause (surgical vs. natural), and patients characteristics such as age, body mass index (BMI), years since the menopause, and general health status. Although there is a good correlation between ABPM and clinic measurements, provided a mean of three measurements is used, the power of ABPM to detect small changes in BP is higher, especially when small sample sizes are used [37]. In many studies, often a single BP measurement was taken, and it has been shown that office BP has a limited relationship with 24-h ABPM and that ABPM is a better predictor of end-organ damage and response to therapy [38].

An acceleration in age-related vascular stiffness in the large vessels occurs at menopause, as was shown in a study where the slope of the 24-h pulse pressure versus age was steeper in menopausal ($n = 149$) women than their premenopausal counterparts ($n = 166$), measured at 0.428 versus −0.066 mmHg per year ($p = 0.003$), and male controls ($n = 315$) 0.428 versus 0.188 mmHg per year ($p = 0.06$) [39].

In a 16-year longitudinal study of 408 premenopausal and 160 postmenopausal women, investigators were unable to demonstrate any difference in BP between the two study groups in age-adjusted analyses [40]. In a large cross-sectional epidemiological study evaluating the prevalence of hypertension across menopausal women in an Italian population [Study on Hypertension Prevalence in Menopause in the Italian population (SIMONA)], a significant increase in both systolic BP (SBP) and diastolic BP (DBP) (3.4 and 3.1 mmHg, respectively) was found in more than 18,000 Italian postmenopausal women, aged 46–59 years, compared to premenopausal and perimenopausal women. This finding was independent of age, BMI, smoking status, contraception, and HRT use [41], but was only evident for the younger end of the age range.

Finally, the Study of Women's Health Across the Nation (SWAN) is a multiethnic, community-based, longitudinal cohort study of the natural history of the menopause transition in 3,302 women, aged 42–52, and enrolled at seven sites throughout the United States. A subset of 949 women who had reached the menopause during the follow-up and who were not on HRT, were evaluated to investigate whether the incidence of metabolic syndrome increased during the menopause. The odds of developing metabolic syndrome per year were 1.45 (1.35–1.56) in perimenopausal women and 1.24 (1.18–1.30) after the menopause, $p = 0.001$. As secondary outcomes, all components of the metabolic syndrome, including BP, were assessed. SBP was found to slowly increase from 6 years before, peaking at 1.5 mmHg higher 1 year after the final menstrual period, but not significantly so ($p = 0.07$), leading the authors to report no effect of the menopause on BP [42].

The evidence for a putative protective role of sex steroids on BP as detailed earlier is compelling, but such effect is not conclusive from observational studies spanning the menopause. It thus deserves further examination through a careful scrutiny of the evidence provided from the clinical studies available to date, while future studies should be designed with BP as a primary end point.

27.5 Does Hormone Replacement Therapy Cause Hypertension in Normotensive Women? Case Control and Prospective Studies

Hypertension was the most common comorbidity reported in women on HRT in general [43], but whether this is simply an association or whether HRT is causal in increasing BP is controversial. Numerous studies have examined the effect of HRT on BP. In an extensive review from 1960 to 2004, Meuck described a somewhat

variable effect of oral HRT on BP in normotensive women, which may in part be explained by the various oral estrogen preparations used, and a more consistent beneficial effect when transdermal estradiol was used [44]. A more consistent BP-lowering effect of HRT became apparent when reviewing studies that used ABPM and in subjects receiving transdermal estrogen. In these studies, BP was lowered in 11 out of 13 studies using transdermal estrogen as opposed to only four out of 11 studies using oral estrogen formulations. In a more recent review, Ashraf and Vongpatanasian again underscored the beneficial effect of transdermal estrogen on BP; an effect, they proposed, which was likely due to the avoidance of the first-pass hepatic metabolism of estradiol [9]. In our update of the literature review since 2000, similar observations and conclusions were reached.

In a cross-sectional study of 35 normotensive postmenopausal women, Christ and colleagues showed that estrogen alone, either as oral 17β-estradiol or conjugated equine estrogen (CEE), over a 12-month period was associated with reduced ABPM systolic (−8 mmHg) and diastolic (−5 mmHg) daytime BP ($p < 0.05$), an effect that was offset when progestin, mainly in the form of oral medrogestone and norethisterone, was added [45]. In another cross-sectional study, Prelevic and colleagues studied 256 healthy postmenopausal women, divided into four groups according to the HRT used, i.e., tibolone, transdermal 17β-estradiol (with or without norethisterone acetate), oral CEE (with or without norgestrel), and control, and demonstrated a BP-neutral effect of all HRT combinations, in contrast to an increase in BP in the tibolone group, when compared to the controls [46]. Conclusions are limited, based on the varied estrogen and progestin compounds and combinations used.

Higashi and colleagues compared the impact of 0.625 mg CEE on forearm resistance artery endothelial function in three cohorts, including 10 hypertensive women, 35 normotensive women, 52 ± 4 years, BMI 22.6 ± 2.8 kg/m^2, compared to ten control subjects, 53 ± 4 years, BMI 23.1 ± 2.5 kg/m^2, over 12 weeks. The maximal forearm blood flow (FBF) response to reactive hyperemia increased over 12 weeks of CEE both in the hypertensive and normotensive groups whereas it remained unchanged in the control group. The augmentation of FBF response to reactive hyperemia evoked by the CEE was significantly greater in the hypertensive group than in the normotensive group (maximal FBF, 49 ± 8 vs. 17 ± 5 %, $p < 0.05$). The BP was measured before and after 12 weeks and did not reveal a difference between the two arms [47].

Sumino and colleagues examined the effect of 0.625 mg CEE with 2.5 mg MPA daily in 17 women, aged 53 ± 4 years, BMI 22.3 ± 2.4 kg/m^2, and 19 controls aged 52.6 ± 5.4 years, BMI 22.5 ± 2.4 kg/m^2, on clinic and ABPM. There were no differences in either clinic blood pressure, reported as the mean of three measurements after at least 10 min of rest, or on ABPM [48].

Lee and colleagues recently investigated the effect of 0.625 mg CEE daily on ABPM before and after 2 months of treatment in a noncontrolled study of 25 normotensive Korean postmenopausal women, mean age 56 ± 5.5 years, BMI 24 ± 1.64 kg/m^2, none of whom smoked or had diabetes. CEE increased both daytime SBP and DBP, an effect that tended to be abolished when micronized

progesterone was added [49]. Conversely HRT, in the form of oral and transdermal estrogen with progestin, diminished the rise in SBP over the years in healthy postmenopausal women compared to controls (7.6 vs. 18.7 mmHg, $n = 77$) in a longitudinal observational study, a difference that intensified at older ages [50]. Similarly, the proportion of postmenopausal women who experienced a nocturnal drop in BP (dippers) reached 80 % in HRT users, compared to 50 % in non-HRT users, $p = 0.048$ [51]. Finally, in the Rancho Bernardo cross-sectional study of 1,044 postmenopausal women, all estrogen users, with more than 80 % of participants on CEE, had a higher estimated glomerular filtration rate measured using the abbreviated modification of diet in renal disease equation and lower BP than non-users at study entry, after controlling for confounders. Similarly, at the 10-year follow-up, long-term current estrogen users showed an improvement in BP, with reduction in mean DBP among long-term current users, and an increase in mean SBP among those who never used HRT [21].

The neutral or beneficial effect of HRT on BP in postmenopausal women is in contrast to the clear elevations in BP that may occur when higher doses are given to younger women for oral contraception, especially with the oldest, first-generation birth control pills [52]. The difference in the results obtained in the studies mentioned may be explained by the different HRT preparations used (17β-estradiol vs. CEE, oral vs. transdermal, type of progestin used), the duration of HRT use, and the baseline characteristics of the study population.

27.5.1 Randomized Controlled Trials

The overwhelming evidence from large randomized controlled trials of HRT revealed a general neutral effect on BP, as detailed in Table 27.1. However, none of these studies were designed with BP as the primary outcome.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial [53] included 875 healthy normotensive postmenopausal women (mean age 56.1 years), who received various combinations of oral HRT with 0.625 mg CEE daily, either alone or in combination with various preparations of progestin (cyclic or continuous MPA, or cyclic micronized progesterone) for 3 years (see Table 27.1 for the details of the dose used). The study participants were mostly white with a mean age 56.1 $\pm$ 4.3 years, BMI 26 $\pm$ 4.5 kg/m^2, and 68.7 % had a natural menopause. SBP increased in all groups, whereas DBP remained uniform over time, though the BP effects did not differ significantly by treatment type. A distinctive characteristic of the PEPI cohort is the relatively high education level, 97 % of women graduated from high school, 41 % from college, and 29 % had additional post-college education. Furthermore 49 % were nonsmokers and two-thirds reported moderate physical activity.

In the Women's Health Initiative (WHI) 16,608 postmenopausal women (mean age 63.3 years) were randomized to treatment with 0.625 mg of CEE and 2.5 mg of MPA daily versus placebo. An increase in SBP of 1 mmHg was noted in those

Table 27.1 Randomized controlled trials of oral estrogen and/or progestin in healthy postmenopausal women

Study/reference (year of publication)	Age range/year (mean ± SD)	Study duration	Number	Estrogen type/dose	Progestin type/dose	Δ SBP versus control or placebo mmHg[a] (*p* value)	Δ DBP versus control or placebo mmHg (*p* value)
PEPI [53] (1995)	45–64 (56.1)	3 years	175	CEE[b] 0.625 mg	None	−1.7 (NS)	−1.5(NS)
			174	CEE 0.625 mg	MPA[c] 10 mg/d cyclical[d]	−1.3 (NS)	−1.4 (NS)
			174	CEE 0.625 mg	MPA 2.5 mg/d	0.4 (NS)	−0.3 (NS)
			178	CEE 0.625 mg	Micronized progesterone 200 mg/d[d]	−2.5 (NS)	−2.2 (NS)
			174	Placebo	placebo		
WHI [54] (2002)	50–79	5.2 years	8506	CEE 0.625 mg	MPA 2.5 mg/d	1.5[e] (NA[f])	No change
	(63.2 ± 7.1)		8102	Placebo	Placebo		
WHI–CEE arm [56] (2004)	50–79	6.8 years	5310	CEE 0.625 mg	None	1.1 (0.003)	No change
	(63.3 ± 7.3)		5429	Placebo	Placebo		
(DOPS trial) [57] (2003)	45–58	5 years	502[g]	E2[h] 2 mg	Norethisterone 1 mg	No change	No change
	(49.5 ± 2.7)		504	Control	Control		
EPAT [59] (2005)	46–81	2 years	93[i]	E2[h] 1 mg	None	No change	No change
	(61 ± 7)		88	Placebo	Placebo		

(continued)

Table 27.1 (continued)

Study/reference (year of publication)	Age range/year (mean ± SD)	Study duration	Number	Estrogen type/dose	Progestin type/dose	Δ SBP versus control or placebo mmHg[a] (*p* value)	Δ DBP versus control or placebo mmHg (*p* value)
Seely et al. [14] (2004)	50–72	16 weeks[j] cross over	21	CEE 0.625 mg	None	No change	−2 (NS)
	(57.2 ± 5.6)		21	Droloxifene 60 mg/day		AmBP (No change)[k]	AmBP (No change)
Sørensen et al. [60] (2000)	55 ± 6.3	24 weeks[l]	16	E2[h] 4 mg	Norethisterone acetate cyclic	No change	No change
						AmBP (No change)	AmBP (No change)
			16	Placebo	Placebo		

[a] Difference in systolic and diastolic blood pressure measured in clinic unless specified otherwise
[b] CEE – conjugated equine estrogen
[c] MPA –medroxyprogesterone acetate
[d] Given for 12 days per month
[e] Systolic blood pressure was, on average, 1.0 mm Hg higher in women taking estrogen plus progestin at 1 year, rising to 1.5 mm Hg at 2 years and beyond
[f] NA-data not shown
[g] 6.6 % were hypertensive, women with intact uterus (n = 407) received norethisterone 1 mg for 12 days per cycle, 95 hysterectomized women didn't receive any progestin
[h] E2-17- beta estradiol
[i] Healthy postmenopausal women with Low density lipoprotein cholesterol greater than 130 mg/dl
[j] Women received either CEE (0·625 mg/day) or droloxifene (60 mg/day) for 6 weeks and, after a 4-week washout, were restudied on the alternate medication, 12 days of MPA were administered at theend of the study to antagonize the effects of estrogen on the endometrium
[k] 24 hour ambulatory blood pressure was measured in 10 normotensive patients,
[l] cross over study in two 12-week periods separated by a 3-month washout

on HRT at 1 year, and of 1.5 mmHg at 2 years (p value not available), with no change in DBP [54], an increase that was considered substantial given the large study population. Women in the WHI trial were not all normotensive, nevertheless they were considered to be representative of the US population: 84 % were white, had a mean BMI 28 ± 5.9 kg/m^2, 40 % were previous smokers, 10 % were current smokers, 38 % had hypertension, 64 % were treated with antihypertensive medications, and BP was reported to be controlled in only 36 % of subjects [55]. We are unaware of any subgroup analysis by baseline BP status. Similarly, in the CEE-only arm of the WHI, 10,739 postmenopausal women, with similar baseline characteristics as detailed previously, were randomized to treatment with 0.625 mg of CEE. At 1 year, SBP was higher by 1.1 (0.4) mmHg ($p = 0.003$) in women receiving CEE compared with the placebo group, and remained so throughout the follow-up, while no differences in DBP were noted between the two groups [56].

In the Danish Osteoporosis Prevention Study [57] (DOPS), 1,006 early menopausal women ($n = 502$, mean age 49.5 years), of whom 6.6 % had hypertension at baseline, were randomized to HRT (2 mg oral estradiol combined with 1 mg norethisterone or not according to their hysterectomy status) or no HRT in an open label trial. HRT had no effect on either office SBP or DBP at any of the study time points (6 months, and 1, 2, and 5 years). HRT was terminated in three patients due to hypertension; in two of these, borderline hypertension was present before the initiation of HRT. High BP persisted after termination of HRT and normalized after the addition of antihypertensive therapy. In the third participant whose BP was normal before the initiation of HRT, BP normalized several years after termination of HRT.

The Estrogen in the Prevention of Atherosclerosis Trial (EPAT) trial randomized 222 healthy postmenopausal women, mean age 61 years, with low-density lipoprotein (LDL) cholesterol >130 mg/dL (but no pre-existing cardiovascular disease) to 1 mg of unopposed oral 17β-estradiol or placebo for 2 years. Fifty-six percent of study subjects were white, with a mean BMI of 29 ± 6 kg/m^2, 45 % nonsmokers, and 18 % on antihypertensive drugs. The primary end point was the overall rate of progression of subclinical atherosclerosis, measured by carotid artery intima-media thickness (IMT), which was slower in patients taking unopposed estrogen compared with placebo [58]. Office BP was a prespecified end point. SBP and DBP declined in both study arms, but there were no differences between the HRT and placebo groups [59] in the subset of normotensive women. Treatment effects on SBP differed significantly by age of the subject; younger women had a rise in SBP on estradiol, while older women had a drop in SBP. These trials used different estrogen and progestin HRT regimens, while the DOPS and EPAT trials used 17β-beta estradiol, and the PEPI and WHI trials used CEE; and while DOPS used norethisterone, PEPI and WHI used MPA, and EPAT used no progestin.

Smaller studies using ABPM have demonstrated conflicting results on BP. In a double-blind crossover trial lasting 16 weeks, Seely and colleagues [14] evaluated the impact of 0.625 mg CEE daily versus droloxifene 60 mg daily on clinic BP

levels in 21 postmenopausal women, and on ABPM in a subset of 10 women. Study subjects were almost exclusively white, mean age 57.2 ± 5.6 years, with a mean BMI 27.3 ± 4.2 kg/m^2. There was no impact of either oral CEE or droloxifene on either clinic BP or ABPM.

Sorensen and colleagues [60] studied 16 postmenopausal women with a mean age of 55 ± 6.3 years, in a randomized crossover design study. Women received 4 mg of oral 17β-estradiol plus 1 mg of norethisterone or placebo. The participants were evaluated at four visits in each treatment period, at baseline and in the second, ninth and 11th week. Office BP demonstrated a decrease in SBP (−5.1 mmHg, $p = 0.029$) and a decrease in DBP (−3.2 mmHg, $p = 0.057$) in the second week, but BP returned to baseline after 9 weeks of combined HRT. As for the ABPM, when compared with placebo, changes from baseline in mean, minimum, and maximum BP (daytime, nighttime and mean 24-h values) were not significant after 9 weeks of combined HRT.

27.6 Does Hormone Replacement Therapy Exacerbate Hypertension in Hypertensive Women? Case-Control and Prospective Studies

Older observational studies investigating the effect of HRT in hypertensive women are scarce, and either found no change or a decrease in BP [44]. In our literature search since 2000, very few additional studies investigated this issue.

In the Rancho Bernardo study, investigators evaluated the impact of long-term exposure to HRT, mainly as 0.625 mg oral CEE, on BP and parameters of kidney function in 1,044 community-dwelling postmenopausal women, divided into current users, past users, and those who never used HRT [21]. The mean age of the study subjects was 71.9 ± 7.8 years, BMI 24.7 ± 4.2 kg/m^2, 54.7 % met the criteria for hypertension, 5.4 % for diabetes, 28.5 % were on antihypertensive medications, 68.5 % exercised three times a week, and 50.9 % were ever-smokers. Current HRT users were younger, less likely to have hypertension, more likely to have had a hysterectomy, and had lower BMI and lower serum creatinine. In the cross-sectional analysis, SBP in current HRT users was 134.9 ± 22.4 mmHg, past users 140.4 ± 22.9, those who never used HRT 140.2 ± 23.0, $p = 0.001$, the significance of which was lost when adjusted for age, weight, hypertension, smoking, and presence of hypertension or hyperlipidemia. DBP in current HRT users was 74.6 ± 9.3 mmHg, in past users 74.4 ± 9.4, in those who never used HRT 74.9 ± 9.7, $p = 0.76$; the difference, however, became significant on multivariate analyses. Current users were also reported to have lower odds of having chronic kidney disease, odds ratio (OR) = 0.66 (0.48–0.90) in the adjusted analyses.

At the 10-year follow-up, DBP was highest in those who never used HRT when compared with past and current users (difference = −2 mmHg, $p = 0.04$), and over this follow-up period the DBP of those who never used HRT showed no significant age-adjusted change ($p = 0.1$). Past users and current users showed

similar drops in age-adjusted DBP compared to baseline (−3.4 mmHg, $p < 0.0001$ and −4.4 mmHg, $p < 0.0001$, respectively). The SBP increased among those who never used HRT (mean increase 6 mmHg, $p = 0.02$), but it did not differ in the past and current user groups. A firm conclusion for a protective effect of HRT and BP cannot be reached from this observational study because of the nature of the study design and the fact that it included relatively fit women, and thus the potential confounder of the *healthy user effect*.

Karalis and colleagues studied 161 early postmenopausal hypertensive women on different HRT preparations (39 % on CEE and MPA over 36 months. The mean age was 52.2 ± 6.6 years, 70 % were white, 44.1 % had surgical menopause, 76.9 % were overweight, and 21.7 % were smokers at study entry. Overall, there was no change in office SBP or DBP on HRT. However, seven subjects stopped HRT during the follow-up because of an excessive rise in BP noted on a single reading, and an increase in the average number of antihypertensive drugs taken was noted from 1.4 ± 1.1 to 1.7 ± 1.2, $p < 0.05$ [61].

Lee and colleagues [49] studied the impact of HRT on ABPM in 51 hypertensive women, aged 57.4 ± 5.1 years, BMI 25.8 ± 3 kg/m2, 50 % of whom were on antihypertensive medications, 8 % had diabetes, and were nonsmokers, who received HRT as CEE (with or without MPA) for 2 months. There was a significant decrease in daytime SBP from 143.6 ± 13.2 to 137.6 ± 13.1 mmHg, $p < 0.005$, and nonsignificant decrease in daytime DBP from 85.2 ± 9.6 to 83.4 ± 9.4 mmHg. The decrement in daytime SBP was more accentuated in the subset using micronized progesterone with CEE as opposed to CEE alone. Similarly, there was a significant decrease in nighttime SBP from 131.2 ± 17.4 to 126.6 ± 14.8 mmHg, $p < 0.05$, and a nonsignificant decrease in nighttime DBP from 76.5 ± 10.2 to 74.5 ± 9.5 mmHg after receiving HRT.

Sumino and colleagues [48] prospectively studied 61 Japanese early postmenopausal women, with mild-to-moderate hypertension, well controlled on antihypertensive medications for 3 years, for 1 year on 0.625 mg CEE and 2.5 mg MPA daily ($N = 31$), and 30 control subjects who did not want to take HRT. The mean age of the study subjects was 53–54 years and their BMI was 25 kg/m^2; they had clinic and ambulatory BP, as detailed earlier in the chapter in the subset of normotensive women. There was no significant decrease in office and 24-h ABPM in the HRT users.

Higashi and colleagues studied 18 hypertensive women, age 53 (± 4) years, 10 on HRT as 0.625 mg CEE and eight on no HRT therapy over 12 weeks. None of the study subjects were on any antihypertensive drugs, the entry SBP was 146–147 mmHg, and DBP was 90–91 mmHg. A nonsignificant decrease in SBP (Δ −1.4 mmHg) and DBP (Δ −2 mmHg) in the group receiving HRT versus control was reported [47].

Szcekas and colleagues [62] prospectively studied 34 postmenopausal women with treated hypertension (SBP 140–170 mmHg), mean age 53 years, on 2 mg 17β-estradiol and norgestrel (0.5 mg from day 12 to day 22) for 19 weeks, and demonstrated a significant drop in ABPM, with a mean SBP decreasing from 149.3 ± 6.1 mmHg to 140.3 ± 8.5 ($p < 0.001$) and in mean DBP from

95.4 ± 4.7 to 92.4 ± 7.2 ($p < 0.05$). Interestingly the decrease in BP was lowest in the subset of 11 women on calcium channel blockers.

In summary, the studies reviewed in this section show a neutral or slightly beneficial effect of oral HRT on BP in hypertensive women that is more likely to be detected in studies that used ABPM monitoring. A major limitation of these observational studies includes their small sample size, the variation in HRT regimens and combinations used, and a lack of control subjects. Hence, there is the need for randomized controlled trials to investigate the effect of HRT on this high-risk population.

27.6.1 Randomized Controlled Trials

There are no large clinical trials that studied the effect of HRT on BP in a population limited to hypertensive postmenopausal women. However, several of the large trials included a sizeable percentage of hypertensive women. Many of these studies, however, did not analyze the hypertensive women as a separate subset. These are detailed in Table 27.2 and are discussed in this section.

The Heart and Estrogen–Progestin Replacement Study (HERS) was a randomized placebo-controlled trial of 2,763 postmenopausal women with coronary heart disease (CHD), mean age 66.7 (±6.7) years, followed up for 4.2 years to determine the effect of HRT (CEE and MPA) in the secondary prevention of CHD [63]. Thirty-nine percent of the patients were hypertensive, 13 % current smokers, 23 % diabetic, 48 % of normal BMI, and 39 % exercised regularly. Clinic BP was determined and pulse pressure was calculated, but changes in BP were not the primary outcomes of the study. Mean SBP and DBP were 135 (±19) mmHg and 73 (±10) mmHg at study entry, and over 4.2 years there was an increase in SBP of 1 mmHg ($p = <0.0001$) with no change in DBP in women receiving HRT. There was a significant 2 mmHg increase in mean pulse pressure as compared to women in the placebo group (64 ± 17 mmHg vs. 62 ± 17 mmHg, $p = 0.04$) [64]. Changes in BP with HRT were not presented for the two subgroups of normotensive versus hypertensive women.

The Postmenopausal Hormone Replacement against Atherosclerosis (PHOREA) trial was designed to determine whether HRT can slow the progression of atherosclerosis, measured as carotid intima-media thickness (IMT) in 321 women, mean age 58.3 (±4.5) years. Study subjects were randomized to either oral 1 mg 17β-estradiol with standard-dose cyclic gestodene (0.025 mg gestodene on days 17–28 of each 4-week cycle), or oral 1 mg 17β-estradiol with low-dose gestodene (0.025 mg addition in each third cycle only), or no treatment. More than 50 % of subjects were hypertensive, on no antihypertensive medications, and had increased IMT in >1 segment of the carotid arteries at study entry. Office DBP decreased in the HRT groups as compared to the controls, by −4 mmHg in the standard gestodene group, $p = 0.027$, and −4.7 mmHg in the low-dose gestodene group, $p = 0.008$. During the follow-up, 29 subjects were started on antihypertensive

Table 27.2 Randomized controlled trials of oral estrogen and/or progestin In hypertensive postmenopausal women

Study/reference (Year of publication)	Age range (year) Mean ± SD	Study duration	Number	Estrogen type/dose	Progestins Type/dose	Δ SBP versus placebo or control mmHg[a] (p value)	Δ DBP versus placebo or control mmHg (p value)
HERS [64] (1998)	44–79	4.1 years	1380[b]	CEE 0.625 mg	MPA 2.5 mg/day	1 (<0.0001)	No change
	(66.7 ± 6.7)		1383	Placebo	Placebo		
PHOREA [65] (2001)	40–70	48 weeks	76[c]	E2[d] 1 mg	Standard gestodene dose[e]	3 (NS)	−4 (0.027)
			60	E2 1 mg		−1.2 (NS)	−4.7 (0.008)
				Control	Low dose gestodene[f]		
	(58.3 ± 4.5)		61		Control		
Kaya et al. [31] (2006)	51.2 ± 0.4	1 year	31[g]	E2 1 mg	Dydrogesterone 10 mg/day[h]	AmBP daytime	AmBP daytime −1.7 ($p < 0.01$)
			32	Control	Control	AmBP nightime −1.6 ($p < 0.01$)	AmBP nightime NS
Sumino et al. [66] (2006)	48–66	1 year	28	CEE 0.625 mg	MPA 2.5 mg/day cyclical[i]	−3.1 (NS)	0.3 (NS)
	(54.8 ± 3.6)		27	Control	Control		
EPAT*[59] (2005)	46–81	2 years	18[j]	E2 1 mg	None	No change	No change
	(61 ± 7)		23	Placebo	Placebo		
Manhem et al. [68] (2010)	51–65	1 year[k]	20	CEE 0.625 mg	MPA 0.5 mg/day	−4 (NS); AmBP 2 (NS)	−2 (NS); AmBP 1 (NS)
	(56)	Cross over	20	Placebo	Placebo		

(continued)

Table 27.2 (continued)

Study/reference (Year of publication)	Age range (year) Mean ± SD	Study duration	Number	Estrogen type/dose	Progestins Type/dose	Δ SBP versus placebo or control mmHg[a] (p value)	Δ DBP versus placebo or control mmHg (p value)
Harvey et al. [67] (2000)	48–60	16 weeks[l]	14	CEE 0.3 mg	MPA 10 mg/day cyclical[m]	−7 (<0.05); AmBP 1 (NS)	−2 (NS); AmBP 1 (NS)
			14	CEE 0.625 mg CEE 1.25 mg	MPA 10 mg/day cyclical	−7 (<0.05); AmBP -1 (NS)	−4 (<0.05); AmBP-1 (NS)
	(55)	Cross over			MPA 10 mg/day cyclical	−5 (NS); AmBP No change	−3 (NS); AmBP-1 (NS)
				Placebo	Placebo		

[a] Difference in systolic and diastolic measured in clinic unless otherwise specified
[b] Coronary heart disease patients, with 39 % being hypertensive
[c] Patients had increased intima-media thickness (IMT) in ≥1 segment in carotid arteries; blood pressure ranged from optimal to stage 2
[d] E2 = 17β-estradiol
[e] Standard dose gestodene—addition of 0.025 mg gestodene on days 17–28 of each 4-week cycle
[f] Low-dose gestodene (addition in each third cycle only)
[g] Newly diagnosed mild-to-moderate hypertension
[h] Dydrogesterone 10 mg per day for 14 days of each 28-day cycle
[i] MPA 2.5 mg/day for 12 days a month
[j] Hypertensive postmenopausal women with low-density lipoprotein cholesterol >130 mg/dL
[k] Crossover design: each subject received 6 months of HRT and 6 months of placebo
[l] Randomized double-blind four-phase crossover design. Each phase lasted 4 weeks. MPA 10 mg/day was added for the final 14 days of each 28-day cycle
[m] MPA was given for the final 14 days of each 28-day cycle

ABPM ambulatory blood pressure monitoring, *CEE* conjugated equine estrogen, *E2* estradiol, *EPAT* estrogen in the prevention of atherosclerosis trial, *HERS* heart and estrogen–progestin replacement study, *MPA* medroxyprogesterone acetate, *PHOREA* postmenopausal hormone replacement against atherosclerosis (trial)

medication: four subjects in the standard gestodene group, 12 in the low-dose gestodene group, and 13 in the control group (p = NS intervention groups vs. control) and these subjects were excluded from analysis [65].

In the hypertensive subset group of the EPAT trial [59], detailed previously, 18 hypertensive women, mean age 61 ± 7 years, received 1 mg 17β-estradiol and 23 women received placebo. No differences could be detected, either in office SBP or DBP, between the two groups.

Kaya and colleagues [31] studied 63 postmenopausal women, mean age 51.2 ± 0.4 years, with mild or moderate hypertension randomly assigned to receive either HRT with 1 mg/day micronized 17β-estradiol sequentially combined with 10 mg/day dydrogesterone (n = 31, BMI 37.4 ± 0.4 kg/m^2) for 14 days of each 28-day cycle, or no therapy (n = 32, BMI 38.1 ± 0.8 kg/m^2) over a 12-month period. Mean ABPM dropped significantly in the HRT group (−2.2 mmHg, $p < 0.01$); in addition, ambulatory daytime SBP remained unchanged whereas nighttime SBP decreased significantly by −1.6 mmHg ($p < 0.01$). Conversely, ambulatory daytime DBP decreased significantly by −1.7 mmHg ($p < 0.01$) in the HRT group whereas nighttime DBP remained unchanged.

Sumino and colleagues [66] randomly assigned women to one of three groups for a 12-month study: a continuous oral CEE (0.625 mg/day) plus a cyclic oral MPA (2.5 mg/day, for 12 days per month), n = 28, mean age 54.8 ± 3.6 years, BMI 22.7 ± 1.8 kg/m^2; continuous transdermal 17β-estradiol (absorption rate, 36 μg/day) plus cyclic oral MPA (2.5 mg/day, for 12 days per month), n = 28; mean age 55.2 ± 5.1 years; BMI 22.4 ± 3.3 kg/m^2; and a control group who did not receive HRT, n = 27; mean age, 55.9 ± 5.7 years, BMI 23.4 ± 2.0 kg/m^2. Eight untreated hypertensive subjects in the CEE + MPA group, seven subjects in the transdermal estradiol group, and seven subjects in the control group were included; information on whether the other participants were normotensive or controlled by antihypertensive medications was not available. There was no impact of the oral or the transdermal estrogen on BP.

Harvey and colleagues [67] studied 14 postmenopausal women, mean age 55 years, in a crossover 16-week study, where they used different preparations of CEE (0.3, 0.625, and 1.25 mg) combined with 10 mg/day MPA. Office SBP decreased significantly in the groups receiving CEE at the 0.3 and 0.625 mg doses, whereas office DBP decreased significantly only in the group receiving CEE at the 0.625 mg dose compared to placebo. ABPM remained unchanged.

In the randomized, double-blind, crossover study carried out by Manhem and colleagues [20], 20 well-controlled hypertensive postmenopausal women, mean age 56 years, BMI 27.6 kg/m^2, received 6 months of HRT (CEE 0.625 mg daily plus MPA 0.5 mg daily) and 6 months of placebo, on top of their antihypertensive treatment. None of the participants were smokers or diabetic and half of them were on RAAS-blocking agents. Office- and ambulatory-measured SBP and DBP did not change significantly.

There was no change or a decrease in BP with different preparations of HRT except for the HERS trial; this might be explained by the high-risk population and/or the large sample size of the study population.

27.7 Transdermal Estrogen and Blood Pressure

27.7.1 Case-Control and Prospective Studies

Transdermal estrogen enters the circulation directly, bypassing the first pass through the liver, and unlike oral estrogen, does not result in an unfavorable cardiovascular profile, i.e., an elevation in serum C-reactive protein and triglyceride levels, a decrease in LDL particle size, and an increase in the production of certain coagulation factors [68]. In addition, transdermal estradiol is not associated with an increase in angiotensinogen levels [69].

In a large-scale clinical surveillance study, the effect of transdermal estradiol on BP in 13,910 postmenopausal women, of whom 1,516 had hypertension, was evaluated over a 2-month observation period. The authors reported no effect of transdermal estradiol in the normotensive participants, whereas they noted a decrease in SBP and DBP in hypertensive women. In the subgroup of 1,397 women with DBP > 100 mmHg before HRT initiation, there was a mean decrease of 7 mmHg in SBP and 9 mmHg in DBP, but specific details regarding HRT preparations in terms of doses and p values for significance were not provided [70].

Zacharieva and colleagues studied 16 normotensive postmenopausal women, mean age 49.1 ± 3.5 years, BMI 24.1 ± 2.4 kg/m^2, who received transdermal estradiol 50 μg for 3 months. The participants were compared to 25 healthy young women with a mean age of 28.4 ± 1.4 years, BMI 23.87 ± 1.4 kg/m^2. No change was detected in office BP compared to baseline, whereas daytime, nighttime, and mean 24-h ambulatory SBP all decreased significantly by −6.75, −5.8, and −5.5 mmHg, respectively, $p < 0.05$ [71].

Kawecka-Jaszcz and colleagues studied 76 women with natural menopause, with mild-to-moderate hypertension for 5.9 ± 5 years, over 1 year: 40 women with a mean age of 52.5 ± 5.8 years, BMI 28.3 (± 4.8) kg/m^2, who took transdermal 17β-estradiol and oral norethisterone acetate, and 36 control subjects, with a mean age 53.6 ± 5.9 years, BMI 27.0 ± 3.6 kg/m^2. BP at 1 year did not differ significantly from baseline values in either group [72].

Randomized trials describing the effect of transdermal HRT in normotensive and hypertensive subjects, published since 2000, are described in Tables 27.3 and 27.4 and discussed in the following section.

27.7.2 Randomized Controlled Trials in Normotensive Women

Seely and colleagues studied the effect of transdermal estradiol (two 0.1 mg patches twice a week) with (intravaginal micronized progesterone 300 mg/day) and without progesterone on 24-h ABPM in a randomized, placebo-controlled, crossover study of 15 healthy postmenopausal women, mean age 56 ± 1.5 years, BMI 24.9 ± 0.9 kg/m^2. Nocturnal SBP (110 ± 3 mmHg), DBP (63 ± 2 mmHg), and mean BP (77 ± 2 mmHg) dropped significantly ($p < 0.02$) in the transdermal estradiol group compared with placebo. The mean decrease in SBP was −6 mmHg,

Table 27.3 Randomized controlled trials of transdermal estradiol in normotensive postmenopausal women

Study/reference (year of publication)	Age range (year) Mean ± SD	Study duration	Number	Dose of transdermal estradiol	Progestins type/dose	Δ SBP versus placebo or control mmHg[a] (*p* value)	Δ DBP versus placebo or control mmHg (*p* value)
Seely et al. [74] (1999)	56 ± 1.5	8 weeks	15[b]	200 μg/day	None	No change	No change
					Intravaginal Micronized Progesterone	AmBP-6 (night) (<0.02)	AmBP-5 (night) (<0.02)
							No change
			15	200 μg/day		No change	AmBP-7 (night)(<0.02)
				Placebo	Placebo	AmBP-8 (night)[c] (<0.02)	
Vongpatanasin et al. [75] (2001)	53 ± 2	8 weeks	12[b]	200 μg/day	None	AmBP no change	AmBP-2 (0.01)
			12	Placebo	Placebo		
Ichikawa et al. [76] (2008)	57 ± 8.1	24 months	22	36 μg/day	MPA 2.5 mg/day[d]	−9 (NS)	−7.1 (<0.01)
			10	Control	Control		

[a] Difference in systolic and diastolic blood pressure measured in clinic unless specified otherwise
[b] Cross over design
[c] No difference in daytime systolic or diastolic blood pressure was found
[d] MPA-Medroxyprogesterone 2.5 mg/day for 12 days per month
ABPM ambulatory blood pressure monitoring, *DBP* diastolic blood pressure, *MPA* Medroxyprogesterone, *SBP* systolic blood pressure

Table 27.4 Randomized controlled trials of transdermal estradiol in hypertensive postmenopausal women

Study/reference (year of puplication)	Age range (year) Mean ± SD	Study duration	Number	Dose of transdermal estradiol	Progestins type/dose	Δ SBP versus placebo or control mmHg[a] (*p* value)	Δ DBP versus placebo or control mmHg (*p* value)
Affinito et al. [76] (2001)	53.5 ± 4.5	6 months	30	50 μg/day	MPA 10 mg/day cyclical[b]	No change; AmBP-5.5 (<0.05)	No change; AmBP-6.5 (<0.05)
			30	Placebo	Placebo		
Sumino et al. [66] (2006)	48–66	1 year	28	36 μg/day	MPA 2.5 mg/day cyclical[c]	−6.6 (NS)	−3.6 (NS)
	54.8 ± 3.6		27	Control	Control		

[a] Difference in systolic and diastolic blood pressure measured in clinic unless specified otherwise
[b] 10 mg/day from day 17 to 28
[c] 2.5 mg/day for 12 days a month
ABPM ambulatory blood pressure monitoring, *DBP* diastolic blood pressure, *MPA* medroxyprogesterone acetate, *SBP* systolic blood pressure

in DBP it was −5 mmHg, and in mean BP it was −5 mmHg. The addition of progesterone resulted in no further drop in BP [73].

Vongpatanasin and colleagues [74] studied 12 postmenopausal women, mean age 53 ± 2 years, BMI 28.5 ± 1 kg/m^2 over 8 weeks. All subjects received each of the following three regimens in random order according to a single-blind crossover design: transdermal estradiol alone as two 0.1 mg patches twice a week (200 μg/day) for 8 weeks, oral CEE 0.625 mg for 8 weeks, and a placebo patch (two patches twice a week) plus oral placebo for 8 weeks. There was no change in BP on the oral CEE, whereas transdermal estradiol resulted in a significant decrease in 24-h BP by −2 mmHg ($p < 0.01$) compared to placebo, but no change was observed in SBP.

Ichikawa and colleagues studied 22 postmenopausal women, mean age 57.1 ± 8.1 years, BMI 22 ± 3 kg/m^2, randomized to transdermal HRT as continuous 17β-estradiol patch at 36 μg/day plus cyclic oral MPA 2.5 mg/day for 12 days/month for 24 months. DBP and mean BP were significantly decreased at 12 and 24 months. DBP decreased from 74.6 ± 9.4 to 67.5 ± 5.9 at 24 months; similarly, mean BP decreased from 90.1 ± 9.6 to 82.2 ± 7.0 ($p < 0.05$ for both), whereas SBP only tended to decrease [75].

27.7.3 Randomized Controlled Trials in Hypertensive Patients

Affinito and colleagues [76] randomized 60 postmenopausal women with treated mild-to-moderate hypertension, mean age 53.5 ± 4.5 years, BMI 25 ± 3 kg/m^{2,} to transdermal estradiol at a dose of 50 μg/day combined with MPA 10 mg/day or placebo over 6 months. Office and 24-h ABPM were measured. No change in office BP was observed, whereas mean 24-h ambulatory SBP and DBP decreased significantly in the treatment group, by −5.5 mmHg and −6.5 mmHg respectively, compared to placebo. The diurnal changes were analyzed separately and both SBP and DBP decreased significantly for the daytime, but not nighttime, measurements.

Sumino and colleagues [66] found in their study detailed earlier in the chapter a nonsignificant decrease in clinic SBP and DBP in 28 postmenopausal women, mean age 54.8 ± 3.6 years who received transdermal estradiol (36 μg/day) with MPA 2.5 mg/day for 12 months [66].

Ashraf and colleagues [9] reviewed the impact of transdermal estradiol in hypertensive women in eight prospective randomized trials and reported a trend for a decrease in SBP and DBP on 24-h ABPM measurements, with a weighted mean average change of −4.9 mmHg for SBP and −2.3 mmHg for DBP [9].

In general, randomized trials of transdermal estrogen in hypertensive women are small and reveal either no change or a significant decrease in BP, with the latter most likely to be detected in studies that included ABPM monitoring. The pattern for the decrease in SBP, DBP, daytime, and nighttime, was not very consistent across studies, probably reflecting their suboptimal monitoring of BP changes and/

or low power. Of interest, studies comparing oral versus transdermal estrogen yielded somewhat different results, some of them showed a reduction in BP in the transdermal group versus the oral group [77, 78], while others found a similar decrease in BP in both groups [79]. Thus, larger trials with longer duration and more careful serial BP assessment on follow-up are needed.

27.8 Conclusions

Hypertension is a major risk factor for cardiovascular diseases in both genders and accounted for 12.8 % of all deaths worldwide in 2008. The proportion of subjects with hypertension clearly increases with age in both genders, being higher in men before the age of 45 years, and then in women after the age of 65 years. Observational studies that examined changes in BP across the menopause have, however, led to mixed results. Physiological studies evaluating the impact of HRT on regulators such as the RAAS, sympathetic system, and markers of endothelial function and inflammation, have not led to consistent results. Observational studies that examined changes in BP across the menopause, and which investigated the impact of HRT on BP in hypertensive and normotensive women, have also provided mixed results. The above illustrates the complexity of the homeostatic systems involved and the heterogeneity of the studies in terms of the HRT regimens used, subjects characteristics, and study duration. The ultimate evidence emerging from randomized controlled trials of HRT reveal an overall BP-neutral effect of the oral preparations and a BP-lowering effect of transdermal estrogen, and possibly micronized progesterone, dydrogesterone, and drosperinone, both in normotensive and hypertensive women. The BP-lowering effect of transdermal HRT is best illustrated in studies that assessed 24-h ABPM.

Although the use of HRT has declined substantially over the last decade due to cardiovascular concerns and cancer adverse events, as revealed in the HERS, PEPI, and WHI trials, HRT protects from menopause-associated bone loss, can be beneficial for several other menopause-associated morbidities (mood, sleep, memory, some quality of life measures), and remains the most effective treatment for the vasomotor symptoms associated with the menopause.

Scrutiny of the data presented in this review with regards to the impact of HRT on BP suggests an overall BP-neutral effect of oral HRT and a neutral and/or lowering BP effect of transdermal estrogen. As HRT provides relief from vasomotor symptoms, HRT may decrease BP in the subset of women with these symptoms, although this hypothesis remains to be tested. The International Menopause Society, with the participation of the Task Force on Gender of the European Society of Cardiology, in its consensus workshop stated that HRT is not contraindicated in women with hypertension and, in some cases, it may even reduce BP. However, it recommended that BP be carefully monitored and well-controlled in women on HRT [80]. In its 2010 position statement, the North American Menopause Society stated: “The benefit–risk ratio for menopausal HRT is favorable for women who initiate HRT

close to menopause [81]". Studies are, however, relatively scarce and have the major limitations detailed earlier, and thus there is a clear need for trials to be conducted in a younger population using different HRT preparations.

The ongoing Early versus Late Intervention Trial with Estradiol (ELITE) trial and the Kronos Early Estrogen Prevention Study (KEEPS) may provide some insight on the characteristics of individuals who are most likely to benefit from HRT [82, 83]. ELITE is a 4-year trial recruiting 643 postmenopausal women to be randomized to 1 mg of 17β-estradiol versus placebo (with 4 % vaginal progesterone in women with an intact uterus) in women within 6 years of the menopause versus >10 years post-menopause, with the primary end point being the rate of change of the distal carotid IMT and the secondary end points of neurocognitive function, coronary artery lesion, and calcium score by cardiac computed tomography. KEEPS is a 4-year trial recruiting 720 early postmenopausal women randomized to oral CEE 0.45 mg or 5 μg of transdermal estradiol, along with 200 μg micronized progesterone administered cyclically, with the primary end point of carotid IMT, and multiple secondary end points, including change in coronary calcium score by X-ray tomography, plasma lipid profiles, blood clotting factors, inflammatory markers, hormone levels, cognitive and affective scores on standard psychometric tests, and quality of life. None of the studies prespecified BP as an outcome, but it is hoped that it will be captured as part of a visit exams in both studies. If so, both studies may shed light on whether the HRT effects on BP differ according to time since the menopause.

The majority of women, be they hypertensive or normotensive, do not experience any change in BP on oral HRT, and on average show a consistent decrease on the transdermal preparations. Transdermal estrogen in combination with micronized progesterone, dydrogesterone, or drospirenone may be a preferred option for normotensive women, and even hypertensive women, with menopausal symptoms, with careful BP monitoring. Most individuals are anticipated to do well, though exceptions do exist. Therefore, the challenge is to identify individuals at risk for developing hypertension on HRT, and avoid its use in such cases, if possible. Risk profiling, at present, is through a careful clinical assessment of the patient's characteristics, including vasomotor symptoms, age, family history, and lifestyle. In the future, it is anticipated to be complemented by genotype profiling, to identify genes or polymorphisms that increase the risk, for some individuals, to develop hypertension in general and hypertension on HRT in particular, e.g., estrogen receptors and renin polymorphisms.

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Treating Pain and Inflammation in Hypertension

28

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28.1 Introduction

A significant proportion of patients with various forms of arthritis have a concomitant diagnosis of hypertension [1]. Pharmacological agents used by these patients, including traditional nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, and corticosteroids may have pressor effects resulting in the attenuation of the actions of certain antihypertensive drugs and are commonly administered concurrently [1]. Blood pressure elevation in hypertensive patients with arthritis using these drugs may be substantial and may have clinically relevant consequences.

28.2 Effects of Cyclooxygenase Inhibition on Blood Pressure

Cyclooxygenase (COX) is the rate-limiting enzyme in the metabolism of arachidonic acid. It catalyzes the initial biotransformation of arachidonic acid into prostaglandin H_2 (PGH_2), which is further converted into thromboxane A_2 by thromboxane synthase, prostacyclin [prostaglandin I_2 (PGI_2)] by prostacyclin synthase, or to prostaglandins E_2, D_2, or $F_{2\alpha}$ (PGE_2, PGD_2, or $PGF_{2\alpha}$) by their respective isomerases. Two similar COX isoforms have been identified, COX-1 and COX-2. Although, nearly 60 % homologous, they are derived from different genes and have distinct patterns and location of expression. Both isomers share a hydrophobic tunnel that allows the lipid substrate to bind the active site, although

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COX-2 includes a side pocket that is absent in COX-1. While traditional NSAIDs inhibit both COX-1 and COX-2, selective COX-2 inhibitors (e.g., celecoxib and etoricoxib) exploit this structural difference by carrying side chains that fit within the COX-2 channel but which are too large to block COX-1 with equal affinity [2].

COX-1 is constitutively expressed in the kidney, vascular endothelium, gastrointestinal epithelium, brain, spinal cord, and in mature platelets. Although the COX-2 isoform is generally undetectable, it may be induced by bacterial endotoxins, cytokines, and growth factors and plays a major role in the induction of the inflammatory response to injury as well as subsequent repair [3–5]. COX-2 is also constitutively expressed in the macula densa and renal medullary interstitium [6, 7]. COX inhibition results in the reduction in synthesis of PGE_2 and PGI_2 and is associated with both antinatriuretic and vasoconstrictor effects, which may cause elevated blood pressure in susceptible individuals [8–12]. PGE_2 reduces reabsorption of sodium at the thick ascending limb of the loop of Henle, and inhibition of PGE_2 may produce a 30–50 % acute relative reduction in daily urinary sodium excretion. This is subsequently corrected in healthy individuals due to augmented sodium excretion, thereby helping to maintain the homeostasis of sodium balance [11, 12]. Therapy with selective COX-2 inhibitors or traditional NSAIDs impair this process in patients with chronic kidney disease with subsequent salt and water retention—within 1–2 weeks of initiation, this phenomenon may lead to blood pressure elevation [11–15].

Prostacyclin has a vasodilatory effect on both systemic and renal vasculature. Traditional NSAIDs and selective COX-2 inhibitors reduce PGI_2 synthesis and curtail this beneficial vasodilatory effect. With an unaltered presence of numerous vasoconstrictors such as angiotensin II, catecholamines, and endothelin, reduction in PGI_2 may lead to increases in systemic vascular resistance and subsequently to increases in mean arterial pressure (MAP). Pharmacological inhibition or gene knockout of COX isoenzymes in mouse models to assess the effects of COX-1 and COX-2 on the pressor activity of angiotensin II have shown diverse results. COX-1 inhibition blunts the pressor effect of angiotensin II, while COX-2 inhibitors reduce renal medullary blood flow and urine flow and enhance the pressor effect of angiotensin II [16, 17].

Interestingly, PGE_2, which may interact with four separate receptors, could theoretically cause vasoconstriction depending on the available downstream receptor [15]. Similarly, thromboxane A_2 is a potent vasoconstrictor, although it does not seem to play a role in blood pressure homeostasis [15]. Potential differences in PGE_2 production by individual cells, and the availability of distinct downstream receptors that it may interact with, may explain the variability in the response to NSAIDs on blood pressure in different individuals [15].

Additionally, several nonselective NSAIDs, such as diclofenac, R- and S-ibuprofen, indomethacin, ketorolac, meclofenamic acid, and (S)-naproxen have been shown to inhibit the glucuronidation of aldosterone by renal microsomes and may theoretically elevate blood pressure through enhanced concentrations of aldosterone [18, 19].

28.3 Effects of Traditional (Nonselective) Nonsteroidal Anti-Inflammatory Drugs on Blood Pressure

The effects of traditional, nonselective NSAIDs on blood pressure in a variety of populations, including normotensive individuals, hypertensive individuals, and patients taking antihypertensive medications have been known for many years. Two meta-analyses published in the early 1990 s aimed to quantify these effects and have served as benchmarks in this area [20, 21]. The first meta-analysis by Pope and colleagues included 54 studies enrolling 1,324 participants, 92 % of whom were hypertensive [20]. They evaluated the impact of various traditional NSAIDs on MAP, adjusting the results for dietary salt intake. Indomethacin increased MAP by 3.6 ± 1.1 mmHg and naproxen by 3.7 ± 1.9 mmHg when compared to placebo ($p < 0.00001$ for both). Changes in MAP with agents such as piroxicam, sulindac, and aspirin did not achieve statistical significance. The authors did note that the populations in the included studies were relatively young (mean age = 46 years), and may not be representative of an older population [20]. A subsequently published meta-analysis by Johnson and colleagues included 50 trials, 38 of which were randomized, placebo-controlled studies and 12 randomized, active-controlled studies [21]. When results were pooled, NSAIDs increased supine mean systolic blood pressure by 5 mmHg [95 % confidence interval (CI) 1.2–8.7 mmHg]. Studies in which patients received antihypertensive therapy showed a greater increase in blood pressure with NSAIDs (4.7 mmHg) compared with studies in which no antihypertensive drugs were given (1.8 mmHg). Among the antihypertensive drug classes, NSAIDs produced greater increases in blood pressure in patients treated with beta-blockers and vasodilators compared with diuretics. The results of these two meta-analyses suggest that NSAIDs induce increases in blood pressure that are dependent on whether patients are hypertensive or not, treated with antihypertensive drugs or not, and on the type of antihypertensive therapy [21]. Subsequently published studies have attempted to further quantify these results, and are discussed next.

Various studies have evaluated the impact of NSAIDs on blood pressure in normotensive individuals. A post hoc analysis of the Nurses' Health Study reported on the impact of nonnarcotic analgesics, including NSAIDs, on incident hypertension in 51,630 women aged 44–69 years with no history of hypertension over 8 years of follow-up [22]. After adjusting for multiple confounders, they found that women using NSAIDs at least five or more days per month were at a significantly higher risk of developing hypertension [relative risk (RR) 1.21, 95 % CI 1.08–1.31]. The more frequently individuals took NSAIDs, the higher their risk of developing hypertension. Similar results were seen in a cohort of 8,229 apparently healthy male physicians in the Physicians' Health Study [23]. A subsequently published analysis of an older cohort ($n = 1{,}903$; 51–77 years) from the Nurses' Health Study I and a younger cohort ($n = 3{,}220$; 24–53 years) from the Nurses' Health Study II aimed to study whether the association between NSAID use and incident hypertension was dose-related [24]. Both cohorts of patients

showed higher relative risks of developing hypertension with an increasing average daily dose of NSAID. The relative risk increase in patients taking an average of >400 mg of NSAIDs (doses were converted to ibuprofen equivalents) was 1.78 (95 % CI 1.21–2.61) in the older cohort and 1.60 (95 % CI 1.10–2.32) in the younger cohort. Taken together, these large observational studies suggest that NSAID use was associated with an increased risk of developing hypertension in normotensive individuals, which increased with frequency of use and dose.

Conflicting evidence exists regarding the destabilization of blood pressure in patients with hypertension who are taking NSAIDs. An observational study by Wolfe and colleagues used data from the National Data Bank for Rheumatic Diseases and reported on 3,352 individuals with rheumatoid arthritis and osteoarthritis who had reported blood pressure increases during the previous 6 months [25]. After adjusting for multiple parameters, including age, sex, and history of heart disease and hypertension, there was no significant effect on self-reported difficulty to control blood pressure in patients taking nonspecific NSAIDs versus nonusers (OR 1.08, 95 % CI 0.87–1.33). A smaller study matched 184 hypertensive patients prescribed an NSAID to 762 hypertensive patients not on an NSAID to evaluate their impact on systolic and diastolic blood pressure [26]. While differences observed in systolic (adjusted difference 1.9 mmHg, 95 % CI − 0.7 to 4.5) and diastolic blood pressure (adjusted difference 1.0 mmHg, 95 % CI − 0.3 to 2.3) between NSAID and non-NSAID users were not significant, the study may have been underpowered.

Clinical trials have shown that the effect of NSAIDs on blood pressure in patients with hypertension depends on which antihypertensive drugs they are concurrently receiving. The destabilizing effects of NSAIDs on blood pressure seem particularly pronounced in patients receiving angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or beta-blockers. In a prospective, multicenter crossover trial of 120 patients with hypertension and chronic osteoarthritis, Fogari and colleagues showed that concomitant administration of indomethacin significantly increased both systolic and diastolic blood pressure in patients receiving lisinopril (5.45/3.22 mmHg) and valsartan (2.12/1.87 mmHg) [27]. A small, placebo-controlled crossover trial of 25 patients with uncomplicated hypertension randomized patients to receive indomethacin, sulindac, or placebo in patients controlled on labetalol [28]. Both indomethacin (6.3 mmHg, $p = 0.002$) and sulindac (5.5 mmHg, $p = 0.028$) significantly increased mean seated systolic blood pressure compared with placebo. Similarly, a larger study by Palmer and colleagues of 285 hypertensive patients controlled with an ACE inhibitor showed that ibuprofen significantly increased systolic and diastolic blood pressures compared with placebo over a 4-week period ($p < 0.01$ for both) [29]. Conversely, studies have not shown a significant effect of NSAIDs on blood pressure in patients with hypertension controlled by calcium antagonists [30, 31]. In a 3-week, placebo-controlled study by Houston and colleagues, neither ibuprofen nor naproxen significantly increased mean blood pressure in patients treated with chronic verapamil therapy [30]. Klassen and colleagues confirmed this finding when patients on nicardipine hydrochloride were treated with naproxen [31].

28.4 Effects of Selective COX-2 Inhibitors on Blood Pressure

As with nonselective NSAIDs, which lead to clinically relevant destabilization of blood pressure [32], the evidence base for the impact of COX-2 inhibitors on blood pressure in normotensive subjects is limited. A study of 40 normotensive subjects on a low-salt diet showed no significant difference in either systolic or diastolic blood pressure in patients taking either naproxen, celecoxib, or placebo [33]. Similar effects were seen in a study of 36 healthy older adults given either indomethacin, rofecoxib, or placebo for 2 weeks [34]. Diastolic blood pressure was increased from baseline by 1.7 mmHg by indomethacin, 2.6 mmHg by rofecoxib, and 1.6 mmHg by placebo, none of which reached statistical significance, possibly due to the small sample size. A large, retrospective, case–control study of 17,844 Medicare subjects (average age 82 years) evaluated the incidence of new-onset hypertension with COX-2 inhibitors [35]. Using multivariable logistic regression models, they showed that rofecoxib use was associated with a significantly increased risk of new-onset hypertension compared with patients taking celecoxib (OR 1.6, 95 % CI 1.2–2.1), taking a nonselective NSAID (OR 1.4, 95 % CI 1.1–1.9), or not taking any NSAID (OR 1.6, 95 % CI 1.3–2.0). This risk was higher if patients had a history of congestive heart failure or kidney or liver disease.

As with nonselective NSAIDs, early studies of COX-2 inhibitors were designed to assess their effects on blood pressure in patients with hypertension who were receiving antihypertensive medications. Our research group conducted a randomized, placebo-controlled study of 178 patients with essential hypertension who were controlled on the ACE inhibitor lisinopril to evaluate the impact of celecoxib on blood pressure using 24-h ambulatory readings [36]. No significant difference in systolic or diastolic blood pressure from baseline was seen between celecoxib (2.6/1.5 ± 0.9/0.6 mmHg) and placebo (1.0/0.3 ± 1.0/0.6 mmHg), $p = 0.34$ for systolic and $p = 0.45$ for diastolic blood pressure. An observation of a transient (1–2 h) increase in systolic blood pressure after celecoxib dosing was observed, which corresponded with peak inhibition of COX-2 (Fig. 28.1).

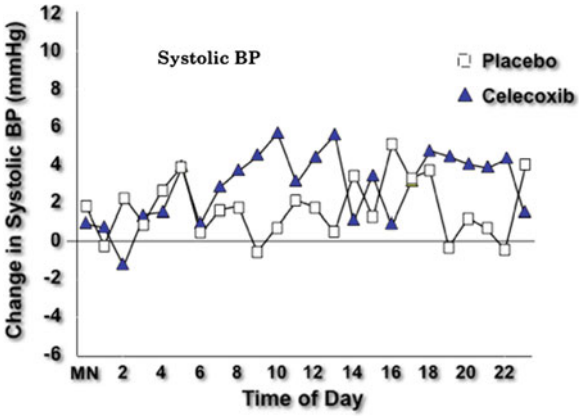

Fig. 28.1 Effects of celecoxib 200 mg twice daily versus placebo twice daily on hourly systolic blood pressure in hypertensive patients treated with the ACE inhibitor lisinopril (from Ref. [36] with permission). *BP* blood pressure, *MN* midnight

A larger parallel-group, double-blind, controlled trial randomized 1,092 patients on chronic stable doses of antihypertensive therapies to receive rofecoxib 25 mg/day or celecoxib 200 mg/day for a total of 6 weeks [13]. A significantly greater proportion of patients in the rofecoxib group (14.9 %) developed elevated systolic blood pressure (>20 mmHg from baseline and an absolute value ≥140 mmHg) compared with the celecoxib group (6.9 %, $p < 0.01$). The greatest differences between the groups were seen in patients receiving ACE inhibitor or beta-blocker monotherapy, whereas no differences were seen in patients on calcium channel blockers with or without concomitant diuretics (Fig. 28. 2).

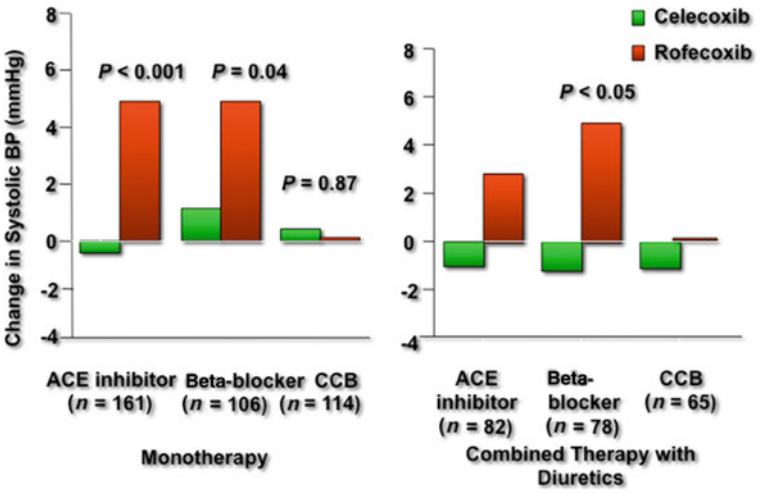

Fig. 28.2 Comparative effects of two COX-2 inhibitors, celecoxib 200 mg daily and rofecoxib 25 mg daily in older patients with osteoarthritis and hypertension according to antihypertensive treatment. Patients treated with ACE inhibitors and beta-blockers were observed to show blood pressure (BP) destabilization on rofecoxib while those treated with calcium channel blockers (CCBs) did not show BP destabilization. Additionally, celecoxib at 200 mg daily was not observed to increase systolic BP (from Ref. [13] with permission)

The Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT) randomized 396 patients with osteoarthritis, hypertension, and type 2 diabetes to celecoxib 200 mg/day, rofecoxib 25 mg/day, or naproxen 500 mg twice/day [1]. The primary end point was a change from baseline in the 24-h ambulatory systolic BP after 6 and 12 weeks of therapy. This study demonstrated that, at equally effective doses for osteoarthritis, treatment with rofecoxib induced a significant destabilization of 24-h systolic blood pressure control compared with celecoxib ($p = 0.005$) and naproxen ($p = 0.005$). Thirty percent of patients who were administered rofecoxib had a resultant 24-h systolic blood pressure of 135 mmHg compared with 16 % of patients randomly assigned to celecoxib ($p = 0.05$) and 19 % to naproxen ($p = 0.16$) (Fig. 28.3). It is noteworthy that no baseline clinical

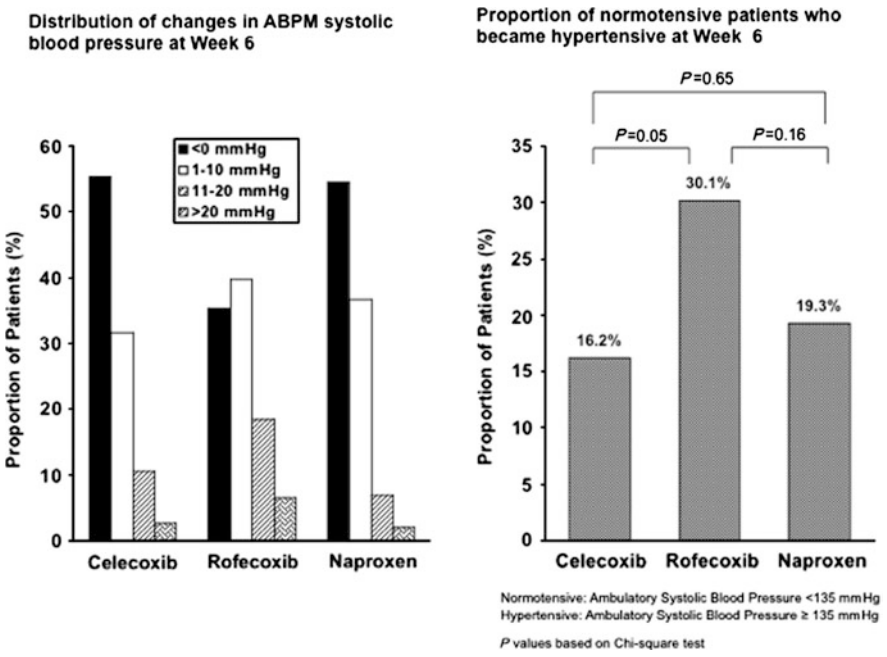

Fig. 28.3 Proportions of patients developing hypertension following treatment with celecoxib, rofecoxib, or naproxen for 6 weeks. Patients had osteoarthritis, hypertension, and type 2 diabetes. Development of uncontrolled hypertension was more common on rofecoxib than celecoxib or naproxen (from Ref. [1] with permission). *ABPM* ambulatory blood pressure monitoring

characteristic was predictive of the development of hypertension on the NSAID or COX-2 selective inhibitor. During the course of the study, significantly more patients developed peripheral edema while taking rofecoxib compared with the other two treatment groups, but no patient developed kidney dysfunction.

An updated meta-analysis of 51 randomized controlled trials was recently published with the objective of ascertaining the blood pressure response to COX-2 inhibitors and how they differ from placebo and nonspecific NSAIDs [37]. The COX-2 inhibitors increased systolic blood pressure by 3.18 mmHg compared to placebo and by 0.91 mmHg compared to nonspecific NSAIDs. The COX-2 inhibitors significantly increased the risk of new hypertension versus placebo (RR 1.49, 95 % CI 1.18–1.88) but not compared to nonspecific NSAIDs (RR 1.12, 95 % CI 0.93–1.35). When the COX-2 inhibitors were examined individually, rofecoxib and etoricoxib caused larger blood pressure increases than celecoxib.

Based on these clinical data, NSAIDs and COX-2 inhibitors should be used with caution in hypertensive patients who are taking ACE inhibitors, angiotensin receptor blockers, or beta-blockers, as well as in patients who have diabetes or mild kidney disease. Of particular concern is that some patients are susceptible to the development of congestive heart failure. Data from population-based cohort studies have

demonstrated that patients who are prescribed NSAIDs and some COX-2 inhibitors develop a substantially increased relative risk of hospitalization for heart failure compared to nonusers of NSAIDs [38]. Thus, hypertensive patients, especially those with a history of left ventricular hypertrophy and diastolic dysfunction should be seen relatively soon in clinical follow-up (e.g., 1–3 weeks) after anti-inflammatory therapy is initiated.

28.5 Effects of Acetaminophen on Blood Pressure

Acetaminophen, also known as paracetamol, is one of the most commonly used nonprescription analgesic drugs worldwide. Although it has been in use for nearly a century, its mode of action of relieving pain has been poorly understood. In addition, unlike traditional NSAIDs and selective COX-2 inhibitors, there are little data about the effect of acetaminophen on blood pressure, and in fact it has historically been considered *safe* at therapeutic doses. Most consensus guidelines recommend acetaminophen as the first-line analgesic in osteoarthritis, particularly in patients with high CV risk [39].

Several hypotheses regarding the mode of action of acetaminophen that could theoretically elucidate a pressor effect have been reported [40–44]. Acetaminophen appears to reduce the conversion of arachidonic acid to prostaglandin H_2 via indirect COX-2 selective inhibitor action on a peroxidase site on prostaglandin H_2 synthase 2, which could in turn theoretically increase vascular resistance [40]. It has also been proposed that the analgesic effect of acetaminophen occurs through an indirect activation of the cannabinoid receptors via a metabolite of acetaminophen, *N*-arachidonoyl phenylamine, which has been shown to indirectly stimulate endogenous cannabinoid release [41, 42]. However, activation of the cannabinoid system seems to lower blood pressure modestly, rather than increase it [43]. Another theory is that acetaminophen could affect blood pressure by the inhibition of *N*-methyl-D-aspartic acid receptors, which play a role in pain neurotransmission and in vasodilatation [44, 45]. When stimulated, *N*-methyl-D-aspartic acid receptors release nitric oxide as a neurotransmitter in the spinal cord, which may modulate arachidonic acid metabolism by altering cyclooxygenase activity [45].

More recently, acetaminophen has been shown to have selective COX-2 inhibitor properties [46]. The drug acts to reduce active oxidized COX to an inactive form, unlike traditional NSAIDs and selective COX-2 inhibitors, which inhibit COX by competing with arachidonic acid [46, 47]. Acetaminophen has decreased potency in the presence of arachidonic acid and peroxide, which would explain its reduced anti-inflammatory effect, as inflamed tissue contains high extracellular concentrations of both. Endothelial tissue, on the other hand, has low peroxidase concentrations compared to inflamed tissue and thereby would allow unabated COX-2 inhibition by acetaminophen, which could lead to elevated blood pressure [47–49].

Table 28.1 Effects of various non-steroidal anti-inflammatory agents on ambulatory blood pressure

Study [ref.]	Design and trial duration	Patient population	N	Age (years)	Study drugs	Baseline 24-hour BP (mmHg)	Change in 24-hour BP (mmHg)
Izhar M [51]	Randomized, cross-over Active controlled, 2 weeks	Hypertensive	25	58	Celecoxib 200 mg BID	129/80	1.6/1.9
		Non-arthritis		58	Diclofenac 75 mg BID	129/79	**4.2/3.0**
MacDonald T [52]	Parallel, double-blind active-controlled, 6 weeks	Osteoarthritis	787	65	Lumiracoxib 100 mg QD	127/74	−2.7/−1.5
		Hypertensive		64	Ibuprofen 600 mg TID	127/74	**2.2/0.5**
Morgan TO [8]	Parallel, randomized, double-blind, cross-over, 6 weeks	Hypertensives non arthritis	41	69	Amlodipine + indomethacin 50 mg BID	141/77	1.0/0.0
				72	Enalapril + indomethacin 50 mg BID	134/73	**12.0/5.0**
Polonia J [53]	Randomized, cross-over, single-Blind, 1 week of NSAID	Hypertensives non-arthritis	18	53	Nifedipine + indomethacin 75 mg	135/88	0.3/0.6
				53	Enalapril + indomethacin 75 mg	135/87	**6.8**/1.3
Schwartz J [54]	Parallel, double-blind, placebo-,and active-controlled, 15 days	Elderly normal controlled diet	85	66	Etoricoxib 90 mg QD	NR	**7.7/3.2**
				65	Celecoxib 200 mg BID	NR	**2.4**/1.1
				67	Naproxen 500 mg BID	NR	**3.6/1.4**
				66	Placebo	NR	−2.4/−0.8

(continued)

Table 28.1 (continued)

Study [ref.]	Design and trial duration	Patient population	N	Age (years)	Study drugs	Baseline 24-hour BP (mmHg)	Change in 24-hour BP (mmHg)
Sowers J and White WB [1]	Parallel, double-blind, active-Controlled, 6 and 12 weeks	Osteoarthritis,Hypertension, type 2 DM	404	64	Rofecoxib 25 mg QD	132/76	**4.2/1.5**
				62	Celecoxib 200 mg QD	132/76	−0.1/−0.1
				64	Naproxen 500 mg BID	134/76	−0.8/−1.0
Sudano F & Flammer AJ [50]	Randomized, double-blind cross over, placebo-controlled, 2 weeks	Coronary artery disease	33	61	Acetaminophen 1 g TID	122/73	**2.9/2.2**
				61	Placebo	123/74	-0.5/0.2
White WB [36]	Parallel, double-blind, placebo-Controlled, 4 weeks	Hypertensive on ACE inhibitor	178	55	Celecoxib 200 mg BID	135/84	2.6/1.5
				53	Placebo	131/82	1.0/0.3

The **bold**typeface indicates the values that are statistically greater than the comparator
ACE angiotensin-converting enzyme, *BID* twice daily, *DM* diabetes mellitus, *NR* not reported, *NSAID* nonsteroidal anti-inflammatory drug, *QD* once daily, *TID* three times daily

A randomized, double-blind, placebo-controlled crossover study in patients with coronary artery disease recently evaluated the effects of acetaminophen (1 g three times/day) versus placebo in addition to standard CV therapy for 2 weeks [50]. This study demonstrated that acetaminophen induced a significant increase in ambulatory BP (mean systolic pressure from 122.4 ± 11.9 to 125.3 ± 12.0 mmHg, $p = 0.02$ and diastolic pressure from 73.2 ± 6.9 to 75.4 ± 7.9 mmHg, $p = 0.02$). These findings are actually not dissimilar from the results on a variety of NSAIDs on the destabilization of ambulatory BP (Table 28.1) [1, 8, 36, 50–54]. Results of the targeted biomarkers and functional vascular assessments studied in the trial were not conclusively related to the blood pressure increase associated with acetaminophen administration [50, 55]. As exposure to acetaminophen was limited to only 2 weeks and as subjects had no pain indication, results of the trial may not necessarily reflect the effects of the agent in patients with treated hypertension [50]. In fact, one concern is that longer-term use of acetaminophen might induce more substantial increases in blood pressure than were observed in the study [55].

28.6 Effects of Glucocorticoids on Blood Pressure

Exogenous glucocorticoid administration forms the basis of treatment of many inflammatory, allergic, and immunological disorders [56]. There are wide ranges in dosage and frequency of administration that depend on the type and severity of the underlying rheumatological disease [56]. Glucocorticoid excess as a result of exogenous use induces a dose-dependent elevation of blood pressure, similar to endogenous excess seen in Cushing's syndrome [57–59]. Additionally, recent observational data indicate an association between glucocorticoid use and the incidence of heart failure [60]. In a meta-analysis assessing adverse events on intravenous high-dose pulse glucocorticoids (≥250 mg prednisone equivalent) for inflammatory diseases, nearly 15 % of patients were found to have an increased blood pressure [61]. Similarly, a retrospective study evaluating patients receiving low-dose glucocorticoids for polymyalgia rheumatica noted that there was a small, but significant, association between the duration of treatment and systemic hypertension (adjusted OR 1.03, 95 % CI 1.01–1.06) [62]. Nevertheless, there are few data regarding the long-term effect of glucocorticoids on blood pressure and CV health, suggesting that further studies examining the exact mechanism by which glucocorticoids exert their pressor effect are needed.

Cortisol and aldosterone have similar binding affinities to mineralocorticoid receptors [63]. Although the circulating levels of cortisol have been shown to be 2–3 times higher than those of aldosterone, only aldosterone has mineralocorticoid agonist properties. This is due to the presence of the microsomal enzyme 11β-hydroxysteroid dehydrogenase. The enzyme converts cortisol to receptor-inactive cortisone in mineralocorticoid-producing cells, especially proximal renal tubular cells, thus protecting mineralocorticoid receptors from endogenous glucocorticoids [64]. Exogenous administration of glucocorticoids may saturate 11β-hydroxysteroid dehydrogenase,

thereby allowing unconverted cortisol to stimulate mineralocorticoid receptors, producing an aldosterone-like pressor effect due to excessive sodium and water retention [65]. Theoretically, spironolactone should be able to reverse exogenous cortisol-induced hypertension due to its mineralocorticoid receptor antagonist properties [66, 67]. However, as this property is based on competitive inhibition of the mineralocorticoid receptor binding substrate, large-enough cortisol dosages could overcome this protective effect [65–68]. Studies in mice have demonstrated that spironolactone, while countering glucocorticoid-induced weight gain, does not prevent hypertension [68]. This presents the possibility that glucocorticoids induce a pressor effect through additional mechanisms. Preliminary studies using animal models have demonstrated the presence of glucocorticoid receptors in vascular smooth muscle cells, thereby allowing glucocorticoids to cause a pressor effect by direct action on systemic and renal vascular resistance [66].

28.7 Conclusions

The data that have accumulated in the past several years underscore the importance of analyzing the risks and benefits of traditional NSAIDs and COX-2 selective inhibitors when making decisions for the management of chronic arthritis pain and inflammation. Since the majority of patients with moderate-to-severe arthritis who might benefit from NSAID or COX-2 therapy are likely to be old, they are also likely to have hypertension and an increased risk for CV disorders. Selecting a combination of therapies that provide relief from arthritis-related symptoms, while minimizing the risk of blood pressure destabilization and preserving the gastrointestinal mucosa is complex. Recent developments that could potentially improve the safety of NSAIDs have included the development of new classes of anti-inflammatory and analgesic agents, such as COX-inhibiting nitric oxide donators [69] and selective E-prostanoid receptor antagonists [70]. These agents appear to induce less blood pressure destabilization, particularly in patients on antihypertensive therapies.

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Sexual Function in Untreated and Treated Hypertension

29

Margus Viigimaa and Michael Doumas

29.1 Introduction

One of the most implicit dangers for public health that physicians have to detect early and treat is, without doubt, hypertension. Hypertension affects >25 % of the general population but its frequency is rapidly increasing with future projections being very discouraging. As the westernized way of living is rapidly expanding and as life expectancy increases, it has been estimated that by the year 2025 around 1.5 billion people worldwide will be hypertensive, thus making hypertension a major and alarming threat to public health [1]. This danger can be better perceived if we take into account the fact that long-standing high blood pressure severely affects all of the major organs of our body and that as such, its major health complications include: heart disease (left ventricular hypertrophy, heart failure, myocardial infarction), stroke, retinopathy, nephropathy, and structural and functional of blood vessel deformities [2].

For many decades, sexual dysfunction has been thought to have either a psychological or anatomical origin; however, accumulating data point toward a vascular disease in the vast majority of affected patients. Since hypertension affects all the vessels of the body, it could be assumed that the genital vessels would also be affected. In addition, the treatment of hypertension includes several different classes of antihypertensive drugs, so one could argue that sexual dysfunction could actually be a pharmacological side effect. This opened the way for more extensive

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scientific research to discover whether sexual dysfunction is more prevalent in hypertensive patients than in normotensive subjects, and if so, whether sexual dysfunction is the result of hypertension per se, a side effect of antihypertensive treatment, or a combination of both [3–6].

In order to establish a firm association between hypertension and sexual dysfunction, we have to consider whether (1) sexual dysfunction is more frequently encountered in hypertensive patients than in normotensive subjects, and (2) whether there is a pathophysiological link between high blood pressure and sexual dysfunction, suggesting a causal relationship and not an epiphenomenon.

To delineate the effect of hypertension per se or the effect of antihypertensive drugs, we should consider whether: (1) sexual dysfunction is more prevalent in untreated hypertensive patients than in normotensive subjects of similar characteristics; (2) sexual dysfunction is more prevalent in treated than in untreated hypertensive patients; and (3) initiation of antihypertensive therapy worsens sexual function and results in sexual dysfunction.

It would then be very interesting, from a clinical point of view, to examine whether the various antihypertensive drug classes exert different effects on sexual function, and if so, whether a change in administered antihypertensive drugs could in fact ameliorate or even restore sexual function. Therefore, we did so by critically evaluating the available data.

29.2 Sexual Dysfunction in Hypertension Compared to Normotension

Sexual dysfunction is defined by the World Health Organization as "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish [7]." Since sexual dysfunction affects both genders, a more specific definition has emerged to clarify what sexual dysfunction means for men and women, respectively. Regarding men, erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse [8]. On the other hand, sexual dysfunction for women is considered as the "persistent or recurrent decrease in sexual desire or in sexual arousal, or the difficulty or the inability to achieve an orgasm, or the feeling of pain during sexual intercourse [9]."

Considering the structural and functional alterations that hypertension can provoke to the penile vasculature (discussed in the next section of the chapter) [10], one would expect that the prevalence of sexual dysfunction in hypertensive individuals of both sexes would be much higher than in the normal normotensive population.

However, the first large study to investigate the prevalence of sexual dysfunction in hypertensive subjects, the Treatment of Mild Hypertension Study (TOMHS), seriously challenged this belief since it showed a low prevalence of sexual dysfunction in individuals with hypertension (14.4 % in men compared to 4.9 % in women) [11]. Nevertheless, this study had several significant limitations: (1) it was not designed to specifically assess sexual dysfunction and thus only one

question was used for evaluating sexual dysfunction; (2) it included only patients with mild hypertension whereas patients with severe hypertension and diabetes mellitus were excluded; (3) participating patients were aged between 45 and 69 years, and older patients were excluded; and (4) the study took place when both patients and physicians were not accustomed or even reluctant to discuss and reveal issues like sexual dysfunction.

Despite some initial doubts, several other well-conducted studies have, over the years, proved and supported the initial correlation between hypertension and a higher prevalence of sexual dysfunction. Furthermore, it has been shown that individuals with hypertension have up to a sevenfold higher incidence of erectile dysfunction than their normotensive counterparts, with a relative risk from 1.3 to 6.9 [12]. Overall, the existing data indicate that erectile dysfunction is on average twice as prevalent in hypertensive subjects compared with normotensive subjects.

Similar findings have been observed in hypertensive women, although the existing data are far from being conclusive. An increased frequency of sexual dysfunction in hypertensive women was also supported by a small case–control study of 104 US women with mild hypertension compared with 107 normotensive women [13]. In this study, hypertensive women reported a higher rate of pain during sexual intercourse, decreased vaginal lubrication, and a lower rate of successful orgasm than normotensive women. Another study of 417 women demonstrated that sexual dysfunction was evident in 42.1 % of hypertensive women compared with 19.4 % of their normotensive counterparts, with an odds ratio of 3.2 [14]. Nonetheless, further studies are needed to establish an association between hypertension and female sexual dysfunction, an association which is remarkably ignored and understudied.

Altogether, the available data clearly indicate that sexual dysfunction is more frequently encountered in hypertensive patients than in normotensive individuals. More importantly, the prevalence of sexual dysfunction in hypertensive patients is considerably high, highlighting the clinical significance of this feature of hypertension.

29.3 Pathophysiology of Sexual Dysfunction in Hypertension

Taking into account male erectile physiology, which is primarily a vascular phenomenon, and the beneficial role of nitric oxide and the detrimental role of angiotensin II in male erection, it can be concluded that an intact penile vasculature with an efficient level of vasodilation and blood flow are the prerequisites for a firm and successful erection to occur [15]. As such, it would be expected that any lesion of the vessels or a lack of ability to distend would lead to impaired blood flow to the penis and the inability to achieve or maintain an erection, thus leading to sexual dysfunction. Hypertension is a clinical entity that primarily targets the vessels, so it is not surprising but rather anticipated that a strong and close association between hypertension and sexual dysfunction has been observed.

More specifically, it has been proved that hypertension results in structural and functional abnormalities which lead to sexual dysfunction. The most prominent structural abnormality is atherosclerosis. An increase in blood pressure has been highly implicated in the atherosclerotic process. Penile arteries are also affected, which results in reduced blood supply to the cavernous bodies of the penis, thereby preventing the acquisition of a full erection [16]. Apart from atherosclerotic lesions, three other structural abnormalities have been implicated in the pathogenesis of sexual dysfunction in men due to hypertension: smooth muscle hypertrophy of the wall of the cavernous arteries, as well as hypertrophy of the smooth muscle layer of the cavernous space, and an increase in type III collagen fibers in the extracellular matrix [17].

Additionally, several studies have demonstrated the functional abnormalities that are due to hypertension, the most important being a blunting of the nitric oxide-induced relaxation mechanism of the penile vasculature, due to decreased nitric oxide bioavailability [18]. Another important contributing factor is the activation of the renin–angiotensin system in hypertension. Angiotensin II not only causes vascular hypertrophy but also provokes the contraction of the corporeal smooth muscle through its action on angiotensin type 1 receptors. The significance of angiotensin II in sexual function can be better understood if we take into account that production of angiotensin II is increased during the detumescence phase of an erection [19]. Furthermore, an intracavernosal injection of angiotensin II in experimental animals has been shown to terminate the erection whereas injection of an angiotensin receptor blocker (losartan) has the opposite result. Apart from angiotensin II, several other hormones and peptides have been implicated in the pathophysiology of sexual dysfunction in hypertensive patients. These include: sex hormones, bradykinin, endothelin-1, catecholamines, and Rho–Rho kinases.

Structural and functional abnormalities affecting the clitoris and the vagina have also been observed in hypertensive females and follow a similar pattern to the one observed in males [20]. The role of angiotensin II and that of decreased nitric oxide bioavailability should also be taken into account as the two main pathophysiological mechanisms underscoring female sexual dysfunction. The relative lack of data regarding sexual dysfunction in hypertensive women calls for further systematic research in this field.

Although the prevalence of sexual dysfunction in hypertensive patients is higher than in normotensive subjects, another important issue should be considered: whether the increased prevalence of sexual dysfunction in hypertensive individuals is due to hypertension per se or whether it is a side effect of antihypertensive drugs, or maybe a combination of both factors.

29.4 Sexual Dysfunction in Untreated Hypertension Compared to Normotension

Data regarding the prevalence of sexual dysfunction in hypertensive patients who have never received treatment are quite limited and regard mainly male patients. However, all available data point toward an increased prevalence of sexual

dysfunction in untreated hypertension compared to normotension [12]. In a study of men with untreated hypertension, though free of cardiovascular disease or other cardiovascular risk factors, and normotensive men of similar characteristics, it was found that hypertensive patients who had never received treatment had an almost 40 % higher prevalence of erectile dysfunction compared to normotensive individuals [21]. Likewise, in a similar study in women, it was found that female sexual dysfunction was significantly more prevalent in hypertensive than in normotensive women [14]. The available data are, however, far from conclusive and further studies are needed to clarify this issue.

29.5 Sexual Dysfunction in Treated Versus Untreated Hypertension

Available data come from observational studies that consistently suggest a higher prevalence of erectile dysfunction in treated than in untreated hypertension. In summary, treated hypertensive patients are twice as likely to suffer from erectile dysfunction as untreated patients [12]. Indeed, an observational study carried out in Greece revealed that the prevalence of erectile dysfunction in treated patients was double than the prevalence seen in patients who had never been treated (40.4 % versus 19.8 %) [21]. These findings would suggest that treating hypertension contributes to sexual dysfunction. It could be assumed that antihypertensive drugs may be implicated in this phenomenon [22]. However, it cannot be excluded from the existing data that treated patients had more severe hypertension, significantly higher target organ damage, or more comorbidities than untreated patients and that these factors may be the actual contributors to sexual dysfunction rather than the antihypertensive drug therapy.

29.6 Sexual Dysfunction with Antihypertensive Treatment: Potential Differences Between Drug Classes

Data regarding the effects of antihypertensive drugs on sexual function come from various studies: (1) animal studies; (2) observational studies; (3) small clinical studies; (4) large randomized trials; and (5) meta-analyses. The vast majority of available data concern male sexual function, with fewer data sets reporting female sexual function. Since several studies compared the effects of specific antihypertensive drug classes on sexual function, data regarding the effects of antihypertensive therapy and the differences between drugs is presented together in this section, first for erectile dysfunction and second for female sexual dysfunction.

Several lines of evidence from animal studies point toward diverse effects of antihypertensive drug classes on erectile function. It has been shown that the structural changes in penile vessels induced by hypertension can be reversed by some drugs, while remaining unaffected by others [23, 24]. In particular,

angiotensin receptor blockers and nebivolol exert beneficial effects on the structural and functional alterations induced by hypertension in spontaneously hypertensive rats, while such effects are not observed with calcium antagonists or atenolol, suggesting differences between antihypertensive drug categories, but also suggesting that such differences exist even between drugs of the same class.

Data from observational studies unveiled differences on sexual function in patients taking various antihypertensive drugs. Hypertensive patients taking beta-blockers and diuretics show significantly worse sexual function than patients who are administered newer drugs such as angiotensin receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists [21].

A few small clinical studies supported both the experimental and observational data [25–27]. They showed the detrimental role of beta-blockers on sexual function, since the number of sexual intercourses per month was significantly lower with beta-blockers than with placebo. This property is shared not only by the first-generation beta-blockers, such as atenolol, but also by the newer vasodilating agents, such as carvedilol. In contrast, angiotensin receptor blockers not only do not prove detrimental to sexual function compared to placebo, but they significantly improve the number of sexual intercourses per month in hypertensive patients compared to placebo, suggesting a beneficial role for this class of agents.

Data from large clinical trials evaluating the role of antihypertensive drugs on sexual function is significantly limited. Available data come from older studies Medical Research Council (MRC); Trial of Antihypertensive Interventions and Management (TAIM), Treatment of Mild Hypertension Study (TOMHS), Aliskiren Effect on Plaque Progression In Established Atherosclerosis Using High Resolution 3D MRI (ALPINE)] that were not specifically designed to explore the effects of antihypertensive agents on sexual function, not even as a secondary end point [12, 28–30]. In the MRC and TAIM trials, diuretics had a significantly worse effect than beta-blockers, which in turn had a significantly worse effect than placebo [28, 29]. TOMHS showed a much higher incidence of sexual dysfunction in the group of patients receiving chlorthalidone over a period of 2 years compared to placebo (17.1 % versus 8.1 %; $p = 0.025$); however, the statistical significance was lost during the following 2 years [12]. In contrast to previous findings, sex life satisfaction was similar with hydrochlorothiazide and candesartan in the ALPINE trial [30]. Only a substudy of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomised Assessment Study in Angiotensin converting Enzyme inhibitor intolerant subjects with Cardiovascular Disease (TRANSCEND) studies was specifically designed to assess erectile function by using a validated questionnaire [31]. In the ONTARGET study, sexual function remained practically unaltered with ramipril, telmisartan, and their combination, with no significant differences between treatment arms, while in the TRANSCEND study there were no differences in sexual function with telmisartan or placebo. It has to be considered, however, that the individuals participating in these trials were high-risk patients with significant cardiovascular comorbidities, and that renin–angiotensin system inhibitors were added on top of prior multidrug therapy; therefore, definite conclusions regarding

the effect of angiotensin receptor blockers on sexual function in untreated hypertensive patients cannot be drawn from these studies. Another study specifically designed to assess sexual dysfunction in hypertension, the Nitric Oxide, Erectile Dysfunction and Beta-Blocker Treatment (MR-NOED) trial, showed that nebivolol significantly ameliorates sexual function in hypertensive patients [32].

Data from meta-analyses are also restricted. Due to limited available data, no specific meta-analysis exists that examines the role of antihypertensive drugs on erectile function. Relevant information comes from meta-analyses assessing the adverse effects of older antihypertensive drugs. Sexual problems are frequently encountered when diuretics are used in combination with other drugs, and similar problems frequently affect patients taking beta-blockers [33, 34].

The negative effects of beta-blockers on sexual function have been recently debated [35]. The findings from two European studies suggest that erectile dysfunction following treatment with beta-blockers is mainly due to a placebo effect, and that beta blocker-induced erectile dysfunction is perceived and not real [36, 37]. It is noteworthy that the three randomized crossover studies carefully designed and conducted by Fogari and colleagues [25–27], whose aim is to specifically evaluate the effect of antihypertensive treatment on erectile function, provide strong evidence for a detrimental effect of beta-blockers. Although a placebo effect, at least in some patients, cannot be entirely excluded, available data indicate that a negative effect of beta-blockers on sexual function cannot be excluded [35].

Data regarding female sexual dysfunction associated with antihypertensive drugs are significantly scarcer than data regarding erectile dysfunction. Only a few studies address this aspect, which remains considerably understudied, possibly due to lack of familiarity by treating physicians and the absence of available drugs to effectively manage female sexual dysfunction. Existing data from experimental and observational studies and small clinical studies point toward similar effects of antihypertensive drugs in male and female sexual function [14, 20, 38]. However, the available data are far from conclusive and further research is needed in this area.

29.7 The Effect of Changing Antihypertensive Drugs on Sexual Function

According to the recommendations issued by the second Princeton Consensus, a change in class of antihypertensive medication rarely results in the restoration of sexual function [39]. However, the available data suggest significant benefits in sexual function when existing antihypertensive therapy is switched to either angiotensin receptor blockers or nebivolol [40–43]. It is noteworthy that the relevant data come from open-label, so definite conclusions cannot be reached until information from randomized controlled trials becomes available.

29.8 Conclusions

As the interaction between doctor and patient becomes closer and closer by the years, it will allow conditions such as sexual dysfunction to be discussed more frequently and openly. Formerly a taboo subject, sexual dysfunction unarguably plays a very important role on patients' and their partners' sexual lives thus exerting a major impact on quality of life. However, the strong association between hypertension and sexual dysfunction and the impact of antihypertensive drugs on sexual function have called in question whether sexual dysfunction in hypertensive individuals is the result of hypertension per se, a side effect of antihypertensive treatment, or a combination of both factors. Many lines of evidence indicate that hypertension per se is indeed associated with sexual dysfunction, while the drugs used in the treatment of hypertension can indeed have a deleterious effect on sexual function, although this is generally true of older generation drugs (beta-blockers, diuretics) than newer drugs, such as angiotensin receptor blockers and nebivolol, which might even improve sexual function. Therefore, a combination of both factors may frequently be encountered by doctors; it is the responsibility of the treating physician to uncover any underlying contributing factors to effectively manage hypertensive patients who also present with sexual dysfunction.

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Cognitive Function and Dementia in Hypertension: Epidemiologic and Therapeutic Aspects

30

Jun Hata, Hisatomi Arima, Craig S. Anderson and John Chalmers

30.1 Introduction

Although hypertension is well established as a risk factor for major cardiovascular events, in particular stroke, it is the recognition of its association with dementia and the related societal burden that is of concern in aging populations around the world. While the prevalence of dementia is estimated at 8 % in people aged 65 years and over [1], the figure rises to almost one in five of the very old (≥80 years), which is the fastest growing segment of the population in most high-income countries.

The syndrome of dementia is typically characterized by chronic or progressive deterioration in multiple higher cognitive functions, including memory, thinking, orientation, calculation, language, and judgment, and there are variable degrees of impairment of emotional control, motivation, and social behavior. Alzheimer's disease, which has a characteristic neuropathological profile, is the most common cause of dementia (in 50–70 %), followed by vascular dementia (20–30 %) with the more

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frequent occurrence of *stroke-like* features and large and small vessel-related, ischemic or hemorrhagic, cerebrovascular lesions [2]. Given the common overlap in the manifestations of Alzheimer's disease and vascular dementia, and that hypertension is an established risk factor for diffuse cerebral white matter disease and ischemic and hemorrhagic stroke, it seems reasonable to suppose that hypertension is either a direct etiological risk factor or an indirect trigger/precipitant of dementia. Moreover, the traditional view that Alzheimer's disease is primarily a neurodegenerative disorder (i.e., the amyloid hypothesis) has been challenged by accumulating evidence for the involvement of vascular factors in the underlying pathology (i.e., the vascular hypothesis) [3], with cerebral ischemia/infarction and/or hypoperfusion causing or accelerating the neurodegeneration of Alzheimer's disease [3]. In addition, imaging and pathological changes of Alzheimer's disease and vascular dementia often coexist in the brains of people with mild cognitive loss or overt dementia [4]. Thus, population-wide risk modification and targeted blood pressure-lowering treatment might be able to preserve cognitive function and reduce the risk of both major subtypes of dementia, associated with aging and the consequences of cerebrovascular disease.

In this chapter, we first review major longitudinal observational studies which have investigated the effects of blood pressure or hypertension on the risk of dementia and its major subtypes. We then review observational comparative studies and randomized controlled trials of blood pressure-lowering treatment on the risks of dementia or cognitive impairment.

30.2 Blood Pressure and Dementia: Data from Observational Studies

Although there have been multiple longitudinal studies that have investigated the effects of *late-life* blood pressure (measured around the age of ≥65 years) on the risk of dementia [5–18] (Table 30.1), their conclusions are inconsistent. Some studies reported positive associations of late-life high blood pressure on the risk of dementia [5, 6], while others reported no significant associations [7–9], and several have even reported inverse associations between blood pressure and the risk of dementia [10–12]. Whereas inverse associations might reflect adverse effects of cerebral hypoperfusion from low blood pressure on disease risks in that particular patient group [19], *reverse causality* (whereby mild cognitive impairment lowers blood pressure [20] and is independently a major risk factor for dementia) has been identified as a plausible alternative explanation. To more reliably observe the long-term effects of blood pressure and to avoid the possibility of reverse causality, several studies have investigated the relationship between *midlife* blood pressure (measured at the age of approximately 40–64 years) and late-life onset of dementia [9, 21–25] (Table 30.2). The Hisayama Study [9], for example, demonstrated that higher midlife blood pressure levels, which had been measured 15 years previously, were associated with an increased risk of dementia in Japanese people, whereas there was no clear association for late-life blood pressure levels.

Table 30.1 Effects of blood pressure or hypertension in late life on the risk of dementia: observational studies

Study (references)	Sample size	Age and follow up	Results [relative risk (95 % confidence interval) for each outcome]
Hisayama, Japan [13]	828	Age 65–98 years Follow-up 7 years	SBP per 1 standard deviation (23 mmHg) increments: No significant association with AD; 1.61 (1.19–2.19) for VD
Göteborg, Sweden [5]	382	Age 70 years Follow-up 15 years (at age 75, 79, and 85 years)	Higher SBP at age 70 and higher DBP at ages 70 and 75 were associated with an increased risk of dementia at age 79–85 years Higher DBP at age 70 was associated with an increased risk of AD at age 79–85 years Higher DBP at age 75 was associated with an increased risk of VD at age 79–85 years
Cambridge, UK [7]	376	Age ≥75 years Follow-up 2.4 years (average)	History of hypertension: 1.06 (0.43–2.61) for dementia; 0.78 (0.34–2.92) for AD
Manitoba, Canada [14]	694	Age ≥65 years Follow-up 5 years	Self-reported high blood pressure: 1.14 (0.53–2.45) for AD
Rotterdam Study, The Netherlands and Gothenburg H-70 Study, Sweden [10]	6,985	Age ≥55 years Follow-up 2.1 years (average)	SBP per 10 mmHg increments in treated participants: 0.86 (0.78–0.95) for dementia; 0.91 (0.81–1.02) for AD; 0.77 (0.61–0.97) for VD; SBP was not associated with the risk of dementia in untreated participants

(continued)

Table 30.1 (continued)

Study (references)	Sample size	Age and follow up	Results [relative risk (95 % confidence interval) for each outcome]
East Boston, USA [15]	634	Age ≥65 years Follow-up 4 years	SBP ≥ 160 versus 130–139 mmHg: 0.22 (0.07–0.68) for AD; DBP < 70 versus 80–89 mmHg: 1.56 (0.60–4.07) for AD
Washington Heights-Inwood Columbia Aging Project, USA [16]	1,259	Age ≥ 65 years; Follow-up 7 years	History of hypertension: 0.9 (0.7–1.3) for AD; 1.8 (1.0–3.2) for VD
Canadian Study of Health and Aging, Canada [17]	4,088	Age ≥65 years Follow-up 5 years	Self-reported high blood pressure: 0.88 (0.62–1.27) for AD
Cardiovascular Health Cognition Study, USA [8]	3,608	Age ≥65 years Follow-up 7 years	History of hypertension 1.0 (0.94–1.27) for dementia; 0.9 (0.71–1.19) for AD; 1.4 (0.96–2.12) for VD
Bronx, USA [11]	488	Age ≥ 75 years Follow-up 21 years (median 6.7 years)	SBP per 10 mmHg decrements: 1.07 (0.99–1.15) for dementia; 1.09 (0.98–1.20) for AD; 1.01 (0.86–1.19) for VD; DBP per 10 mmHg decrements: 1.20 (1.03–1.40) for dementia; 1.23 (1.00–1.52) for AD; 1.15 (0.84–1.58) for VD
Kungsholmen, Sweden [12]	1,270	Age 75–101 years	SBP > 180 versus 141–180 mmHg: 1.6 (1.1–2.2) for dementia; 1.5 (1.0–2.3) for AD
		Follow-up 6 years (median 5 years)	DBP ≤ 65 versus 66–90 mmHg: 1.5 (1.0–2.1) for dementia: 1.7 (1.1–2.4) for AD

(continued)

Table 30.1 (continued)

Study (references)	Sample size	Age and follow up	Results [relative risk (95 % confidence interval) for each outcome]
Kame project, USA [18]	1,859	Age ≥65 years Follow-up 6.0 years (average)	SBP, DBP, and self-reported hypertension were not associated with AD
Adult change in thought study, USA (2007) [6]	2,356	Age ≥65 years Follow-up 10 years	SBP ≥ 160 mmHg versus < 140 mmHg in the age group of 65–74 years: 1.60 (1.01–2.55) for dementia; 1.38 (0.71–2.70) for AD. The association declined with increasing age
Hisayama, Japan [9]	668	Age 65–79 years Follow-up 17 years	Stage 2 hypertension (≥160/100 mmHg) versus normal (<130/85 mmHg): 1.16 (0.68–1.98) for dementia; 0.67 (0.33–1.37) for AD; 7.26 (1.54–34.17) for VD

AD Alzheimer's disease, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *VD* vascular dementia

Table 30.2 Effects of blood pressure or hypertension in midlife on the risk of dementia in late life: observational studies

Study (references)	Sample size	Blood pressure measurement and assessment of dementia	Results [relative risk (95 % confidence interval) for each outcome]
Honolulu-Asia Aging Study, USA [21]	3,703	Blood pressure measured in 1965–1968 (age 45–68 years) Dementia assessed in 1991–1993 (mean age 77.9 years)	SBP ≥ 160 versus 110–139 mmHg in untreated men: 3.88 (1.50–10.02) for dementia; 1.22 (0.37–4.04) for AD; 11.80 (3.52–39.50) for VD; DBP ≥ 95 versus 80–89 mmHg in untreated men: 4.00 (1.56–10.25) for dementia; 4.47 (1.53–13.09) for AD; 2.49 (0.46–13.43) for VD; Blood pressure was not associated with the risk of dementia in treated men
Kuopio and Joensuu, Finland [22]	1,449	Blood pressure measured in 1972–1987 (mean age 50.4 years) Dementia assessed in 1998 (age range 65–79 years)	SBP ≥ 160 versus <140 mmHg: 2.8 (1.1–7.2) for AD DBP ≥ 95 versus <90 mmHg: 1.7 (0.8–3.6) for AD
Linxian, China [23]	602	Blood pressure measured in 1984 (age ≥50 years) Dementia assessed in 1999–2000 (age ≥65 years)	High blood pressure (≥160/95 mmHg): 1.971 (1.097–3.541) for AD
Adult Health Study in Hiroshima, Japan [24]	1,774	Blood pressure measured in 1965–1968 Dementia assessed in 1992–1997 (age ≥60 years)	SBP per 10 mmHg increments: No significant association with AD; 1.33 (1.14–1.56) for VD
Kaiser Permanente of Northern California, US [25]	8,845	Blood pressure measured in 1964–1973 (age range 40–44 years) Dementia assessed in 1994–2003 (mean age 68.5 years in 1994)	Hypertension (self-reported, use of drugs, or ≥140/90 mmHg): 1.24 (1.04–1.48) for dementia
Hisayama, Japan [9]	668	Blood pressure measured in 1973–1974 Dementia assessed in 1988–2005 (age range 65–79 years in 1988)	Stage 2 hypertension (≥160/100 mmHg) versus normal (<130/85 mmHg): 1.95 (1.18–3.24) for dementia; 1.05 (0.50–2.22) for AD; 10.07 (3.25–31.25) for VD

AD Alzheimer's disease, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *VD* vascular dementia

The Honolulu-Asia Aging Study [21] similarly demonstrated a strong relationship between blood pressure in midlife (measured about 25 years before the assessment of dementia) and elevated risks of dementia in later life among Japanese-Americans without blood pressure-lowering drugs, while the Framingham Heart Study [26] reported that higher blood pressure levels in midlife (measured about 20 years previously) and a longer duration of hypertension were associated with a poorer cognitive performance in late life, particularly among participants without blood pressure-lowering treatment. Therefore, midlife blood pressure is likely to predict the risk of dementia better than late-life blood pressure. On the basis of observational data of midlife blood pressure, reverse causation as a result of the confounding effects of disease on blood pressure would appear to be the most likely explanation for the inconsistent results for late-life blood pressure. In conclusion, the findings obtained from observational studies suggest that, in the long term, patients with untreated hypertension or poorly controlled blood pressure are at a higher risk of developing dementia.

30.3 Blood Pressure and Major Subtypes of Dementia: Data from Observational Studies

As shown in Table 30.2, several observational studies have investigated the association of midlife blood pressure and the two major subtypes of dementia, namely Alzheimer's disease and vascular dementia [9, 21–24]. Most studies are consistent in showing strong associations between midlife blood pressure and the risk of vascular dementia [9, 21, 24]. Conversely, there is less certainty surrounding the association of blood pressure with the risk of Alzheimer's disease [9, 21–24]. In the Honolulu-Asia Aging Study [21], elevated diastolic blood pressure in midlife was clearly associated with an increased risk of Alzheimer's disease among Japanese-Americans without blood pressure-lowering drugs. The positive association between midlife blood pressure and the risk of Alzheimer's disease was also reported from studies in Finland [22] and China [23]. These results support the vascular hypothesis for Alzheimer's disease, whereby chronic untreated or undertreated hypertension might accelerate the progression of cerebral atherosclerosis and result in cerebral hypoperfusion and neurodegeneration in later life [19]. However, other observational studies [9, 24] have shown no significant associations between midlife blood pressure levels and the risk of Alzheimer's disease. The discrepancy between such studies might be explained on the basis of the considerable difficulty in the in vivo classification of dementia subtypes. Although standard diagnostic criteria for various types of dementia exist and have been applied in most studies [1], the predictive accuracy is 80–90 % at best and dementias often have mixed neurodegenerative and vascular pathologies, which contributes to misclassification. Other possible explanations involve the different background characteristics, including ethnicity, and the contributions of other possible risk factors such as diabetes and dyslipidemia, of study populations, and the different epidemiological designs,

sample sizes, and statistical methods used in each study. In summary, these findings would suggest that midlife hypertension is more of a risk factor for vascular dementia than Alzheimer's disease in later life.

30.4 Blood Pressure-Lowering Treatment and Dementia: Data from Observational Studies

Blood pressure-lowering treatment has the potential to prevent the development of dementia. Several longitudinal observational studies have investigated the effects of blood pressure-lowering treatment on the risk of dementia [12, 15, 17, 27–32]. As shown in Table 30.3, patients with blood pressure-lowering treatment had lower risks of dementia than those without blood pressure-lowering in most observational studies [12, 27–31]. The Honolulu-Asia Aging Study [27] and the Rotterdam Study [28] also demonstrated that a longer duration of blood pressure-lowering treatment was associated with increased protection against dementia. Furthermore, the benefits obtained from blood pressure-lowering were larger in younger (aged $\leq$75 years) than older (aged >75 years) patients [28]. When the outcome of dementia was subdivided into vascular dementia and Alzheimer's disease, most studies have demonstrated the beneficial effects of blood pressure-lowering treatment on the former [27, 29] and uncertainty on the risk of the latter [12, 15, 17, 27–30, 32].

30.5 Blood Pressure-Lowering Treatment and Dementia: Data from Randomized Controlled Trials

To date, nine large-scale randomized controlled trials have assessed the effects of blood pressure-lowering treatment on the risks of dementia [33–41]. Among them, eight [33–41] involved active versus placebo comparisons and one, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [33], was a head-to-head comparison of active agents involving different approaches to the inhibition of the renin–angiotensin system. Figures 30.1, 30.2 show the results of a meta-analysis and meta-regression analysis of these trials [33]. The study outcome for the meta-analyses was cognitive impairment, which was defined according to the scores obtained with the Mini-Mental State Examination (MMSE), or dementia if cognitive impairment was not reported. In the meta-analysis, the risk of cognitive impairment was not reduced significantly by active treatment (Fig. 30.1), which could possibly be attributed to the relatively short intervention periods (2–5 years) and which provided insufficient power to detect potentially modest but beneficial effects of blood pressure-lowering on this outcome. The meta-regression analysis showed that a 5 mmHg reduction in systolic blood pressure was associated with a 3.4 % reduction in the

Table 30.3 Effects of blood pressure-lowering treatment on the risk of dementia: observational studies

Study [Reference]	Sample size	Age and follow up	Results: relative risk (95 % confidence interval) for each outcome
Kungsholmen, Sweden [31]	1,301	Age ≥75 years Follow-up 3 years (average)	Users of any blood pressure-lowering treatment versus non-users: 0.7 (0.6–1.0) for dementia
Rotterdam, The Netherlands [29]	6,416	Age ≥55 years Follow-up 2.2 years (average)	Users of any blood pressure-lowering treatment versus non-users: 0.67 (0.45–1.00) for dementia; 0.77 (0.49–1.24) for AD; 0.30 (0.09–0.92) for VD
East Boston, USA [15]	634	Age ≥65 years Follow-up 4 years	Users of any blood pressure-lowering treatment versus non-users: 0.66 (0.68–2.61) for AD
Canadian Study of Health and Aging, Canada [17]	4,088	Age ≥65 years Follow-up 5 years	Users of any blood pressure-lowering treatment versus non-users: 0.91 (0.64–1.30) for AD
Kungsholmen, Sweden [12]	1,270	Age 75–101 years Follow-up 6 years (median 5 years)	Users of any blood pressure-lowering treatment versus non-users: 0.8 (0.6–1.0) for dementia; 0.7 (0.5–0.9) for AD
Cache, USA [32]	3,297	Age ≥65 years Follow-up 3 years	Users of any blood pressure-lowering treatment versus non-users: 0.64 (0.41–0.98) for AD
Honolulu-Asia Aging Study, USA [27]	1,294	Age ≥72 years Follow-up 6 years	Duration of blood pressure-lowering treatment (per 1 year): 0.94 (0.89–0.99) for dementia; 0.96 (0.93–0.99) for AD; 0.94 (0.89–0.99) for VD
Rotterdam, The Netherlands [28]	6,249	Age ≥55 years Follow-up 13.3 years (average 8.0 years)	Duration of blood pressure-lowering treatment (per 1 year): 0.95 (0.90–0.99) for dementia; 0.94 (0.90–0.99) for AD
Veteran Affairs, USA [30]	819491	Age ≥65 years Follow-up 4 years	Angiotensin receptor blocker versus lisinopril: 0.81 (0.73–0.90) for dementia; 0.81 (0.68–0.96) for AD; Angiotensin receptor blocker versus other cardiovascular drugs: 0.76 (0.69–0.84) for dementia; 0.84 (0.71–1.00) for AD

AD Alzheimer's disease, *VD* vascular dementia

risk of cognitive impairment, but again this association was also modest and did not reach statistical significance (Fig. 30.2).

Among the individual trials, the Hypertension in the Very Elderly Trial (HYVET) [34] undertaken in 3,336 very high-risk patients, defined by age (80 years or older) and hypertensive status, who received active treatment based

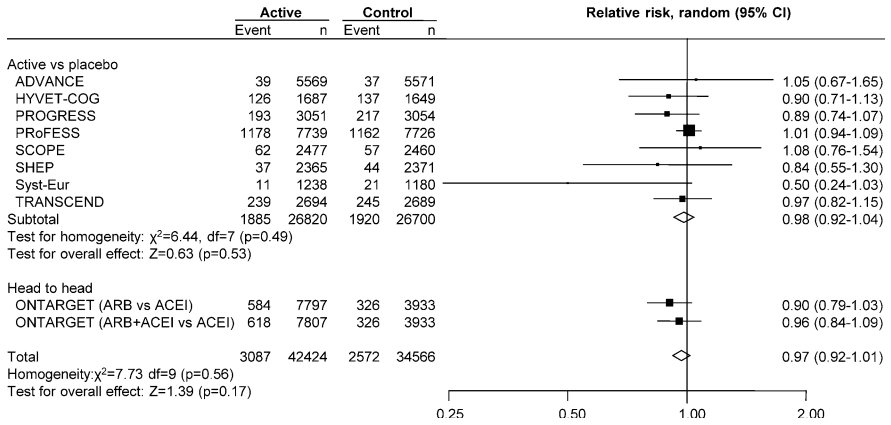

Fig. 30.1 Meta-analysis showing the effects of blood pressure lowering on cognitive impairment. Boxes and horizontal lines represent relative risk and the 95 % confidence intervals for each trial. The size of the boxes is proportional to the inverse of variance of that trial result. Diamonds show 95 % confidence intervals for pooled estimates of effect and are centered on pooled relative risk. Half of the patients in the *ACEI* group were included in each comparison of ONTARGET. *ARB* angiotensin-receptor blocker, *ACEI* angiotensin-converting enzyme inhibitor. Reproduced with permission from Elsevier [33]

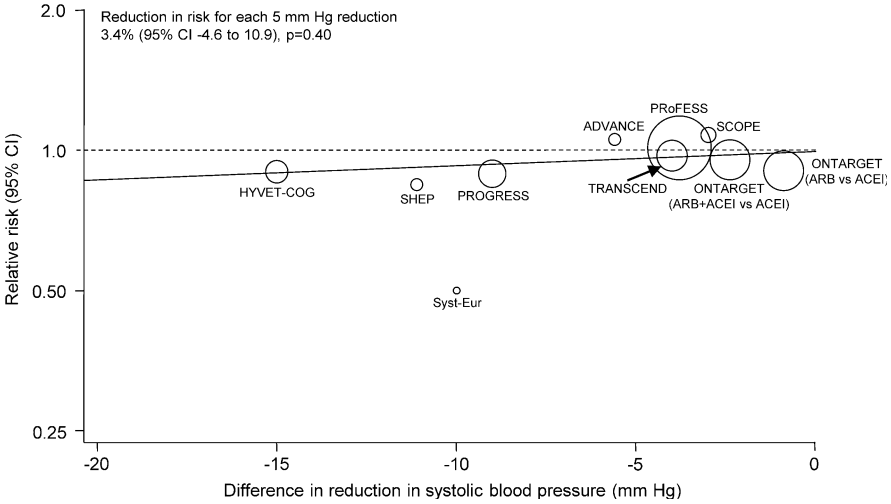

Fig. 30.2 Meta-regression showing the association of reduction in systolic blood pressure with risk reduction for cognitive impairment. The area of each circle is proportional to inverse variance of log relative risk. The fitted lines represent a summary meta-regression. Half of the patients in the *ACEI* group were included in each comparison of ONTARGET. *ARB* angiotensin-receptor blocker, *ACEI* angiotensin-converting enzyme inhibitor. Reproduced with permission from Elsevier [33]

on the diuretic indapamide with/without the angiotensin–converting enzyme inhibitor perindopril (or matching placebo(s)) showed no reduction in the risks of vascular dementia or Alzheimer's disease over a mean follow-up of 2.2 years. The most impressive effect on dementia was seen in the Systolic Hypertension in Europe (Syst-Eur) trial [35], where 2,418 patients with isolated systolic hypertension were randomly assigned to active treatment based on the calcium blocker nitrendipine or matching placebo(s). During a median follow-up of 2 years, active treatment reduced the overall risk of dementia by 50 %, with beneficial effects observed for both Alzheimer's disease and vascular dementia although the number of events was relatively small [36]. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [37], 6,105 patients with prior stroke or transient ischemic attack were assigned to either active treatment (perindopril with/without indapamide) or matching placebo(s). During a mean follow-up of 3.9 years, dementia was documented in 6.3 % of the active treatment group and 7.1 % of the placebo group. This reduction in the overall risk of dementia was not significant. However, dementia occurring in association with a recurrent stroke was observed in 1.4 % of the active treatment group and in 2.1 % of the placebo group, a 34 % reduction. There was no clear treatment effect on dementia without recurrent stroke. This suggests that in patients with established cerebrovascular disease, the protective effect of blood pressure-lowering treatment against dementia is mainly related to the prevention of recurrent stroke in treated patients [37].

In conclusion, pooled analyses with meta-regression techniques of large-scale randomized trials have failed to show any appreciable benefits of blood pressure lowering on dementia over several years of treatment. However, the findings from the Syst-Eur and PROGRESS trials suggest that blood pressure lowering may be beneficial for the prevention of dementia due to vascular causes. It is possible that the effects of treatment depend on the type, degree, and duration of blood pressure-lowering treatment, with effects likely to be more modest and require longer periods to manifest than for major *large vessel*-related cardiovascular events.

30.6 Conclusions

Longitudinal observational studies are nearly consistent in indicating that long-term untreated hypertension is associated with an increased risk of dementia, particularly of vascular dementia, and that blood pressure-lowering treatment is likely to be beneficial, especially for vascular dementia. There is, however, insufficient direct evidence from randomized controlled trials to confirm any definitive beneficial effects of blood pressure-lowering treatment on the risks of dementia. Despite this, the well-established evidence that this treatment reduces

stroke and stroke-associated dementia suggests, as more evidence is gathered, that blood pressure-lowering treatment will be confirmed to reduce the risk of vascular dementia at least, and possibly also Alzheimer's disease. It is clearly important that measures of cognitive function and of subtypes of dementia be included in future trials of blood pressure-lowering treatment.

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Can Hypertension Be Prevented?

31

Charlotte Jones and Norm R. C. Campbell

31.1 Is Hypertension Inevitable?

31.1.1 Introduction

The World Health Organization has estimated that increased blood pressure is the leading risk for death [1]. Hypertension currently affects approximately 25 % of the world's adult population [2]. Blood pressure increases with age, with hypertension occurring in over 50 % of adults after the age of 60 in most countries [3–7]. In the Framingham Study, over 90 % of people with *normal* blood pressures at age 55–65 develop hypertension if they lived for another 20 years [8]. Further, blood pressure-related disease occurs at levels below those considered to be hypertensive, with approximately half of disease occurring in those considered to have normal but not optimal blood pressure [9]. A relatively small proportion of the population has blood pressure remaining at an optimal level as they age [8]. Nearly all seem destined to develop hypertension with age and are at risk for blood pressure-related diseases.

However, on a population level, blood pressure and hypertension prevalence is malleable. Specifically, age-related increases in blood pressure and high rates of hypertension are not present in all populations [10–12]. Hunter-gatherer societies, which consume minimal salt in their diet, have little to no increase in blood pressure with age and little if any hypertension within their populations [10, 12]. Studies from

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most regions in the world including Africa, Asia, Central and South America, Europe, the Middle East, North America, and Polynesia, have shown that rural inhabitants with more active lifestyles and who eat largely unprocessed foods generally have lower rates of hypertension than do urban dwellers [13, 14]. In highly developed countries, where rural dwellers are inactive and have pathogenic diets, the rates of hypertension are similar or higher than those of urban dwellers [13, 15, 16]. Further, immigrants to areas of high blood pressure from areas of lower blood pressure experience increases in blood pressure and hypertension similar to those in their new environment [17–21]. For example, Punjabi and Gujarati people living in the United Kingdom had higher blood pressures rates than their siblings or similar nonmigrant populations in India, respectively [18, 20]. Furthermore, increasing hypertension rates have been reported for recent vs. more acculturated South Asian and Chinese immigrants from health surveys in Canada [22], the United States [23], and in a record-linkage study in the United Kingdom [24]. Although not fully explained, much of the migration-hypertension link is thought to be attributable not only to genetics, but socio-economic, cultural, literacy, and environmental pressures including suboptimal lifestyle behaviors, and possibly psychological stress [25–28].

Societies in developmental transition that adopt a more westernized way of life in general have increases in blood pressure and in the prevalence of hypertension [29]. Along with the benefits, economic development unfortunately has seen low- and middle-income countries evolve from having lower average population blood pressure to now having the highest average population blood pressure [29]. However, not all economic and social development has been marked by increases in blood pressure and hypertension. In Finland, following the introduction of the North Karelia project, there were large reductions in population blood pressure that were not explained by the modest improvements in antihypertensive treatment [30]. In Canada, rates of hypertension have been stable from 1985 to 2009 and North American countries have lower rates of hypertension than most European countries. Systolic blood pressure worldwide is trending downward, although the decreases are highly region-specific, with some regions exhibiting increases in systolic blood pressure [29]. These latter observations counter the perception that hypertension and age-related increases in blood pressure are inevitable and suggest that hypertension is preventable, even on a population scale.

31.1.2 Factors Implicated in Causing Hypertension on a Population Level

Animal studies and randomized controlled trials in humans have demonstrated that much of hypertension can be explained by modest changes in very common lifestyle factors (Table 31.1) [31–36]. From a causal perspective in humans, excess body weight (adiposity in particular), pathogenic eating patterns [usual/pathogenic diet versus a Dietary Approaches to Stop Hypertension (DASH) diet, and especially excess dietary salt and deficient potassium], lack of physical activity,

Table 31.1 The attributed risk of various lifestyle risks for hypertension[a]

Risk factor	Approximate attributable risk for hypertension (%)
Increased salt in diet	32
Decreased potassium in diet	17
Westernized diet	31
Overweight/Obesity	32
Sedentary lifestyle	17
Excess alcohol	3

Modified from Ref. [85]
[a] The attributable risk will be related the prevalence and distribution of the risk factor in the population

smoking tobacco products, and excess alcohol consumption are all implicated as the major factors associated with increasing blood pressure. There may be many other dietary or environmental factors that increase or decrease blood pressure (e.g., cadmium or lead) [37–39].

Numerous lifestyle interventions have been found to both prevent and treat hypertension [31–36]. Targeted lifestyle changes can lower blood pressure in those with normal blood pressure and prevent hypertension [40–47], while the same lifestyle changes can also lower and in some cases normalize blood pressure in those with hypertension. Arguably this may represent at least a temporal *cure* [33, 34].

Based on such evidence, models have been developed to predict the onset of hypertension based on individual characteristics [48, 49]. However, the exact driving forces behind increases in blood pressure with age and within and between populations have not been widely studied. It is assumed that time trends in the prevalence of hypertension and national differences in hypertension prevalence relate to differences in the causal risks for hypertension (i.e., obesity, pathogenic diet, lack of physical activity, excess alcohol consumption) [50].

Guided by this evidence and the understanding that hypertension and many other noncommunicable diseases (NCDs) are preventable and driven for the most part by obesity, a pathogenic diet, physical inactivity, tobacco, and unhealthy alcoholconsumption, and in support of the United Nations Millennium Development Goals, the World Health Organization (WHO) produced a Global Strategy on Diet, Physical Activity, and Health [51] and the 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Non-Communicable Diseases [52]. The overall goal of the strategy on Diet, Physical Activity, and Health is to "promote and protect health by guiding the development of an enabling environment for sustainable actions at individual, community, national and global levels that, when taken together, will lead to reduced disease and death rates related to unhealthy diet and physical inactivity." Similar encompassing strategies have been developed in the Expanded Chronic Care Model in Canada [53, 54] and the Model to Achieve Healthy People 2020 [55] in the United States.

These strategies have in common a framework to guide efforts aimed at preventing and reducing hypertension and other NCDs. They emphasize five areas of need: prioritization of NCD into policy change across all levels of government,

Table 31.2 United Nations recommendations to prevent chronic disease that would be likely to influence blood pressure

Policy
Implement multisectoral public policies that create equitable, health-promoting environments that empower individuals, families, and communities to make healthy choices and lead healthy lives
Develop, strengthen, and implement multisectoral public policies and action plans to promote health education and health literacy
Implement the WHO set of recommendations on reducing the marketing of foods and nonalcoholic beverages to children, including foods that are high in saturated fats, trans fats, free sugars, or salt
Increase and prioritize budgetary allocations for addressing noncommunicable disease risk factors and for the surveillance, prevention, early detection, and treatment of noncommunicable diseases
Call on the private sector to reduce the marketing of foods to children, produce foods consistent with a healthy diet that are affordable and easily accessible, promote and create an enabling environment for healthy behaviors among workers, work toward reducing the use of salt in the food industry to lower sodium consumption
Interventions
Implement multisectoral, cost-effective, population-wide interventions to reduce the impact of tobacco use, an unhealthy diet, physical inactivity and the harmful use of alcohol through the implementation of relevant international agreements and strategies, and education, legislative, regulatory, and fiscal measures
Scale up proven effective health promotion and primary prevention approaches
Implement cost-effective interventions to reduce salt, sugar, and saturated fats, and eliminate industrially produced trans fats in foods
Research
Actively promote national and international investments and strengthen national capacity for quality research and development, for all aspects related to the prevention and control of noncommunicable diseases
Surveillance/monitoring
Strengthen information systems for health planning and management … to facilitate appropriate and timely interventions for the entire population
Promote the use of information and communication technology to improve program implementation, health outcomes, health promotion, and reporting and surveillance systems
Partnerships/collaboration
International cooperation in support of national, regional, and global plans for the prevention and control of noncommunicable diseases through the exchange of best practices in the areas of health promotion, legislation, and regulation, and health systems strengthening and training of health personnel

(continued)

Table 31.2 (continued)

Policy
Promote multisectoral and multistakeholder engagement to reverse, stop, and decrease the rising trends of obesity in child, youth, and adult populations
International organizations to continue to provide technical assistance and capacity-building to developing countries, especially to the least developed countries, in the areas of noncommunicable disease prevention and control
Promote the capacity-building of noncommunicable disease-related nongovernmental organizations at national and regional levels, to realize their full potential as partners in the prevention and control of noncommunicable diseases

Adapted from www.who.int/nmh/events/un_ncd_summit2011/en/index.html (accessed 16 July 2012)

increased uptake and implementation of proven lifestyle interventions, research, surveillance, and evaluation focusing on the prevention and control of NCDs such as hypertension. Finally, to achieve these lofty outcomes, they advocate for broad collaborative partnerships across all sectors (see Table 31.2 for some of the key recommendations).

31.1.3 So, If it is so Easy to Explain and Preventable, Why Does Hypertension Remain Such a Pervasive Problem?

Given the worldwide *epidemic* of overweight/obesity, the widespread consumption of pathogenic foods, and sedentary lifestyles, it is not surprising that hypertension is so common. Globally, health is being influenced by three major factors: population aging, urbanization, and globalization, all of which contribute to the development of unhealthy or pathogenic environments and behaviors. With urbanization (and westernization in low- and middle-income countries), there has been a marked increase in consumption of energy-rich, highly processed, higher salt-containing foods, and a decrease in energy expenditure (through less physical activity). Increased mechanization in agriculture and the increasing use of automobile and bus transportation in rural areas are also leading to a decrease in physical activity. The global influences (television and the increased availability of processed food) on lifestyles perceived to be desirable or modern are changing the types of food consumed in both urban and rural areas [15, 16].

Obesity is reaching epidemic proportions in both developed and developing countries and is affecting not only adults but also children and adolescents. Over the last 20 years, excessive caloric consumption resulting in obesity has become one of the most prevalent nutritional problems in the world, overriding that of malnutrition and infectious diseases as a contributor to morbidity and mortality. The WHO estimates that in 2008, 1.5 billion adults, aged 20 years and older, were overweight. Of these, over 200 million men and nearly 300 million women were obese.

Widespread addition of saturated and trans fats, simple sugars, and salt to foods has been estimated to be the major contributor to premature death and disability, in part through hypertension. In particular, the high amounts of salt added to foods during industrial processing is estimated to be the second leading risk for death in a developing economy (Chile) and the seventh leading risk for death in a developed economy (USA), largely by increasing blood pressure and causing hypertension [56]. Most of the research on the public health impact of the changing food environment has focused on obesity; however, there is also an independent and very large effect on blood pressure and hypertension. It has been estimated that processed foods contribute to 40 % of premature non communicable death and are expected to decrease the life expectancy of the next generation [57, 58]. Table 31.1 indicates that a substantive proportion of hypertension is caused by the unhealthy processing of foods and is both dependent on and independent of the effects of obesity.

Physical inactivity is now identified as the fourth leading risk factor for global mortality [59]. In 2008, the prevalence of physical inactivity was highest in the WHO region of the Americas and in the Eastern Mediterranean region. Almost 50 % of women were considered inactive, while the prevalence for men was 40 % in the Americas and 36 % in the Eastern Mediterranean. The lowest prevalence (15 % for men and 19 % for women) was seen in the Southeast Asian region. In all WHO regions, men were more physically active than women.

Higher-income countries have at least twice the prevalence of physical inactivity compared to low-income countries for both men and women. Forty-one percent of men and 48 % of women were physically inactive in high-income countries compared with 18 % of men and 21 % of women in low-income countries. It is speculated that increased mechanization/automation of work and life in higher-income countries leads to an environment that promotes physical inactivity.

31.1.4 What Steps Can the Hypertension Community Take to Prevent Hypertension?

Successful population-wide health promotion and disease prevention programs such as the North Karelia project [60] mandate the inclusion of multisectoral policymakers and experts, the health-care system, health-care providers, community members, and nonhealth partners such as those in the food industry, education, recreation, and urban planning. Collective action requires the integration of multilevel interventions that target and achieve buy-in from individual community members, and must include change in social and physical environments, public policy, and need to be delivered with a sufficient *dose* of prevention [60].

The international and national hypertension scientific and professional healthcare communities (the World Hypertension League, national hypertension organizations, and the International Society of Hypertension) are well positioned to provide leadership in the effort to reduce the prevalence of hypertension. Guidance is provided by the WHO Global Strategies [51, 52, 61–67], the Model to Achieve

Healthy People 2020, and in Canada, the Expanded Chronic Care Model [54, 68]; all provide a consistent framework for action at the level of the community, health provider, and health system. They all advocate that a working partnership between communities, practitioners, researchers, decision- and policymakers will provide the mechanism to develop and implement the constituents of these frameworks along with enacting the policies and information/surveillance systems, research, and interventions that reduce blood pressure (and other NCDs) (Table 31.2). Pivotal to achieving these goals is the need to build capacity to change our pathogenic environments, enhance community resources, and support health-care providers and the health system to address the prevention needs of our community members.

A simple start would be to ensure that national and international hypertension meetings have a strong and integrated public health content that will provide for a greater understanding of the need for changes to public policy and health systems. National hypertension organizations could unite in preventing hypertension and in making health promotion a substantive part of their mandate.

31.1.5 Support for Changing the Pathogenic Environment

In Canada, a partnership between national health and scientific organizations has formed under the banner of hypertension prevention and control to work toward improving the food environment. The multidimensional approach includes efforts to reduce dietary salt, restrict the advertising of pathogenic foods to children, encouraging the widespread use of policies to buy and sell healthy foods (healthy food procurement policies), reducing the impact of commercial conflicts of interest in food policy development and implementation (i.e., Salt Institute, food processing companies) and regulations to provide easy-to-understand front of package food labeling that contains health connotations.

When effectively implemented, these policies will *denormalize* pathogenic eating patterns and create healthy environments where people can live longer, healthier lives with much less risk of NCDs, including hypertension. In contrast to health-care interventions, policy interventions may be cost-saving or highly cost-effective and form the basis of efforts to develop sustainable health systems.

31.1.6 Support to Build Community Capacity

The ability of the person to implement lifestyle changes is influenced by community resources that are available to support the desired change [69]. Communities may lack recreational facilities to support physical activity, safe and pleasant places to walk or be physically active in, and lack trained people to guide appropriate exercise regimes. Many communities may also lack affordable and easily accessible healthy foods, and trained people to guide dietary change and weight loss.

Changing the way communities are built and restructuring older communities to encourage active living and providing community-based programs to prevent hypertension can be effective in supporting individuals adopt lifestyle changes to prevent hypertension. Advocating for government policies that support these changes together with promoting the widespread availability of affordable healthy foods throughout the community is important. This may be particularly important for children and in school environments where lifelong eating and activity habits are learned.

Health literacy is "the degree to which an individual can obtain, process, and understand the basic health information and services they need to make appropriate health decisions [70]." Some have suggested that health literacy is at least as strong or stronger a predictor of health status than age, income, employment status, education level, self-efficacy, race, or ethnic group [71]. However, research on the relationship between literacy and health has been limited by the inability to separate out these complex factors that covary with literacy. Enhancing health literacy particularly that of at-risk vulnerable groups, is an imperative step in improving hypertension prevention. Unfortunately, many places around the world still do not have culturally adequate and literacy relevant public education materials on lifestyles to prevent and control hypertension [72]. Ensuring high-quality, up-to-date information on the prevention of hypertension to all populations of the world could be a priority and could be led by the national and international hypertension community.

31.1.7 Support for Health-Care Providers to Adopt Interventions for Healthy Lifestyles: Health System Change and Health-Care Provider Education

Hypertension is largely managed by general health-care workers who are not part of the *hypertension expert* community. Many health-care professionals are inadequately trained in how to facilitate lifestyle changes in their patients. Further, many physician remuneration systems do not support the time-consuming efforts required for effective lifestyle interventions, especially those with a large volume of patients. On the other hand, patients most frequently attend health-care professionals for specific symptoms or concerns and may not desire uninvited advice or preventive interventions based on their current lifestyle. Fueled by patients' beliefs about hypertension and its treatment, depression and other cognitive dysfunction, low health literacy, the challenges associated with competing comorbidities, patient motivation, coping, and lack of social support coupled with low rates of patient interest in and adherence to lifestyle change, [73, 74] even following intensive interventions, it is not surprising that clinicians may not perceive the overall utility of these interventions and therefore may not incorporate them into routine clinical practice.

Different models of providing health-care professionals with services have the potential to circumvent these barriers and provide routine lifestyle interventions for prevention and treatment. In particular, designs for health-care delivery using interdisciplinary health-care professional teams have been shown to be effective [75]. The optimal primary care system might include primary care interdisciplinary

teams working with community health workers and family members to achieve optimal blood pressure control [76–80]. Specially trained members of the health-care team can enhance the physician's ability to manage hypertension in their patients. They can be assigned to provide comprehensive evidence-based lifestyle interventions that include setting behavioral goals, assessing barriers and facilitators to behavior change, assessing patient motivation and confidence, and planning for follow-up visits to assess progress toward behavioral goals, all of which are quality indicators as recently assessed in a study of hypertension-related visits [81]. Even without specialized training, having dedicated staff provide lifestyle interventions is as effective as brief advice (about 3 min) and has been shown to double the chances of adherence to some lifestyle interventions [44, 82–84].

Incorporating training techniques for lifestyle interventions (e.g., motivational interviewing) into clinician training, emphasizing the importance of preventive interventions (including the impact of *small* changes in blood pressure on outcomes) in training programs, and teaching independent clinicians to routinely use brief lifestyle interventions, can be part of an effective solution to help address the failure of clinicians to adopt intervention for healthy lifestyles.

The hypertension community can play a significant role in ensuring health-care professionals have adequate skills, resources, and information to intervene to prevent hypertension. National hypertension organizations could forge partnerships with the health-care professional organizations that care for most people with hypertension to ensure they have opportunities to understand the importance of blood pressure as a determinant of health and provide expertise and training in the prevention of hypertension along with resources to disseminate to the people they care for.

31.2 Conclusions

With a current worldwide prevalence of 25 % and estimates of 90 % of those living an average lifespan developing hypertension, there is an increasing perception that hypertension is inevitable. Yet the major causes of hypertension (a pathogenic diet, lack of physical activity, obesity, tobacco use, and excess alcohol consumption) are known and are potentially amenable to interventions at an individual or even a societal level. Changing approaches to health-care delivery to ensure the routine provision of effective preventative interventions, providing culturally and literacy level-appropriate educational resources, ensuring communities are designed to support healthy lifestyles, and that the national governments implement well-known and highly recommended public policies to ensure the places people live and work are healthy, could markedly reduce the prevalence of hypertension. Because increased blood pressure is a major determinant of premature disability and death, clinicians and scientists interested in hypertension should play a much greater role in leading and supporting the changes that are required.

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Atrial Fibrillation. Modern Epidemiologic and Therapeutic Aspects

32

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32.1 General Considerations: Atrial Fibrillation, Hypertension, and Related Disorders

Atrial Fibrillation (AF) is the most common, clinically significant, sustained cardiac arrhythmia, occurring in 1–2 % of the general population. The adjusted incidence and prevalence of AF doubles for each added decade of life [1]. At age 40, the lifetime risks for AF are 26.0 % for men and 23.0 % for women (due to their additional longevity) [2]. Direct expenditures for AF in the USA are estimated to be about US$7 billion [3] and its prevalence is estimated to double in the next 50 years due to the expected longer life expectancy. On the other hand, hypertension (HTN) is the most common cardiovascular (CV) disorder, affecting 20–50 % of the adult population in developed countries and its prevalence rises steeply after the age of 50. In the next decades it will become even more prevalent as the population ages.

Important risk factors and clinical conditions for the development of AF are HTN, diabetes mellitus (DM), obesity, sleep apnea, age, metabolic syndrome, left ventricular hypertrophy (LVH), coronary heart disease (CHD), and heart failure (HF). Although HTN increases the risk of developing AF by about twofold [1], due to its high prevalence in the general population, it is responsible for most cases of AF [4]. HTN is highly prevalent in patients with AF recruited in major AF clinical

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trials (49–90 %) [5]. HTN, if left untreated, eventually leads to the development of LVH, which leads to atrial remodeling. This in turn promotes and maintains AF, causing electrical, contractile, and generalized cardiac tissue remodeling [6]. In its timeline, AF becomes more persistent (it either lasts longer than 7 days or requires termination by cardioversion) than paroxysmal (self-terminating, usually within 48 h or in fewer than 7 days), and possibly more resistant to cardioversion and, eventually, permanent (exists for longer than 1 year).

In the Framingham Heart Study, the levels of systolic blood pressure (SBP) and the duration of HTN were predictive of adverse left atrial remodeling [7], while a wide pulse pressure was associated with an increased incidence of AF [8]. Both obesity and HTN are independent predictors of left atrial enlargement [9]. Obstructive sleep apnea (OSA), apart from contributing to the magnitude of HTN, increases the risk of AF through other HTN-independent mechanisms [10]. Furthermore, HTN as a major risk factor for chronic kidney disease can affect AF prevalence in hypertensive subjects, irrespective of LVH or left atrial dilatation [11].

AF is the most common arrhythmia in HF patients. A recent meta-analysis of 53,969 patients found that AF was significantly associated with increased all-cause mortality in HF patients with both preserved and impaired left ventricular systolic function [12].

Although heart disease and age are strong predictors for the development of AF, there is evidence that genetic factors play a substantial role. In a cohort of the Framingham population [13], AF in at least one parent tripled the risk of their offspring also developing AF, implicating a role for heritability. Many mutations responsible for AF (e.g., KCNQ1, connexin 40 Gap junction alpha-5 protein, etc) have been recognized [14], but none that could account for many cases in real life. The strong environmental impact and the etiological diversity of AF may distort any genotype–phenotype correlation, so further research in this field is warranted [15]. Despite the volume of literature regarding the predictors of AF, it is still difficult to determine an individual's risk of developing AF in a given time frame.

32.2 Consequences of Atrial Fibrillation

Compared to subjects with normal sinus rhythm (SR), those with AF have a 40–90 % higher risk of overall mortality [16]. AF increases the risk of stroke fourfold to fivefold, is responsible for 15–20 % of all ischemic strokes and is an independent risk factor for their severity and recurrence [17].

Other consequences of AF include deterioration of cognitive function, increased risk of hospitalization, and impaired quality of life. In the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study, patients with new-onset AF had an approximately threefold higher risk of fatal and nonfatal stroke, and fivefold increased rates of hospitalization for HF [18]. In the

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), there was an 2.5-fold increase in mortality risk when AF or flutter was present at baseline or developed during the trial [19].

In at least 33 % of AF patients, the arrhythmia could be silent [20]. Asymptomatic episodes of paroxysmal AF are 10–12 times more frequent than symptomatic ones [21], but the consequences are the same. Paroxysmal AF has a significant impact on a patient's quality of life independent of the frequency or duration of symptoms [22]. AF is independently and significantly associated with all dementia types [23]. In patients with AF and history of HTN there was a threefold increase in the annual incidence of stroke compared to those with no HTN [24].

Numerous risk factors have been used to formulate various AF stroke risk stratification scores. Due to its simplicity and ease of use, the $CHADS_2$ score has become the most commonly used one in clinical practice [25]. The $CHADS_2$ score assigned one point each for a history of HF, HTN, age >75 years, and DM, and two points for a history of stroke or transient ischemic attack. The annual risk of stroke with respect to $CHADS_2$ score ranges from 1.9 % ($CHADS_2$=0) to 18.2 % ($CHADS_2$=6). Acetylsalicylic acid (ASA) (81–325 mg) was recommended for low risk (score 0), ASA or anticoagulation (warfarin) for moderate risk (score 1), and for patients with a $CHADS_2$ score ≥2 oral anticoagulation with warfarin was recommended [target international normalized ratio (INR) 2.5, range: 2.0–3.0] unless contraindicated. A more recent version, uses older *less well validated, weaker stroke risk factors* (female sex, age 65–74, vascular disease) and emphasizes the better clarification of risk in the $CHADS_2$ score 1 category [26]. The CHA_2DS_2-VASc score assigns one point each for a history of HF, HTN, age 65–74, DM, vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque), and female gender, and two points each for age ≥75 years, or a history of stroke/transient ischemic attack.Those with CHA_2DS_2-VASc score ≥1 should be considered for oral anticoagulation therapy [either vitamin K antagonists (VKAs), or the newer oral antithrombotics, see the following section].

32.3 Atrial Fibrillation and Antihypertensive Treatment

Antihypertensive drugs reduce the risk for AF mainly by lowering high blood pressure and possibly through other mechanisms.

32.3.1 Renin–Angiotensin System Blockers (Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers)

In a meta-analysis by Schneider and colleagues ($n = 87{,}048$), renin–angiotensin system (RAS) inhibition reduced the odds ratio for AF by 33 % ($p < 0.00001$), but there was substantial heterogeneity among trials. In primary prevention, RAS

inhibition was effective in patients with HF and those with HTN and LVH but not in postmyocardial infarction patients. In secondary prevention, RAS inhibition further reduced the odds for AF recurrence after cardioversion by 45 % ($p = 0.01$) and in patients on medical therapy by 63 % ($p < 0.00001$) [27]. However, most of the trials included in the meta-analysis were not designed to specifically investigate AF.

In prespecified analyses of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) [28] and Losartan Intervention for End Point Reduction in Hypertension (LIFE) trials the use of ARB (valsartan or losartan vs. amlodipine or atenolol, respectively) was associated with a reduction in the incidence of new-onset AF (16 and 33 %, respectively) [29]. In the ALLHAT trial [40], new-onset AF or atrial flutter did not differ by antihypertensive treatment group.

The 2007 European Society of Hypertension–European Society of Cardiology (ESC) guidelines [30] summarized evidence from post hoc analyses of HF and HTN trials and suggested (after warning of the inherent bias of post hoc analyses) ARBs and ACE inhibitors as preferred drugs in HTN patients at risk of developing AF. The same approach is adopted in the 2010 ESC/European Heart Rhythm Association (EHRA) guidelines for the management of AF [31], i.e., using RAS blockers as upstream therapy to prevent or delay myocardial remodeling (associated with HTN, HF, or inflammation) and the development of new AF (primary prevention) or its rate of recurrence or progression to permanent AF (secondary prevention).

However, it should be emphasized that data do not consistently support this recommendation. In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) [32], new AF was just slightly less frequent with the ARB (telmisartan) than with the ACEI (ramipril), whereas in the Heart Outcomes Prevention Evaluation (HOPE) study with patients on high CV risk [33], there was no difference between ramipril and placebo in the incidence of new AF [odds ratio (OR) of 0.92, confidence interval (CI) 0.68–1.24, $p = 0.57$]. In the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) [34], patients with CV disease or DM with end-organ damage were randomized to telmisartan or placebo, and no significant effect on new-onset AF was found [hazard ratio (HR) 1.02, CI 0.83–1.28, $p = 0.829$].

Nevertheless, HOPE and TRANSCEND are not *pure* HTN trials, although they included large numbers of well-treated (for their blood pressure) HTN subjects (approximately 50 % and approximately 76 %, respectively) and this fact may explain why these trials failed to detect an additive beneficial effect of RAS-blockade.

In AF secondary prevention, the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study failed to demonstrate any benefit of candesartan over placebo for the preservation of SR after cardioversion in patients who did not receive antiarrhythmic drug therapy [35]. In the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico–Atrial Fibrillation (GISSI-AF), no effect of valsartan was observed on the time to first AF recurrence (HR

0.99; 95 % CI 0.85–1.15; $p = 0.84$) compared to placebo [36]. In the Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial, there was no significant difference between olmesartan and placebo on AF burden, or on the time to persistent AF in patients with paroxysmal AF without structural heart disease [37].

These conflicting results in outcomes showing benefit mainly in primary prevention may relate to the fact that inhibitors of the RAS prevent, but do not reverse, the development of the structural and electrical remodeling that provides the substrate for AF in HTN.

32.3.2 Beta-Blockers

Beta-blockers are undoubtedly effective in the control of AF rate and possibly in maintaining SR, especially in HF and in cardiac postoperative settings [38, 39]. In hypertension trials like LIFE, the ARB-based therapy was superior to beta-blockers in reducing the risk of new and recurrent AF. In the United Kingdom-based General Practice Research Database, it was found that ACEI, ARBs, and beta-blockers were more effective than calcium channel blockers (CCBs) in reducing the risk of AF [40].

32.3.3 Calcium Channel Blockers

CCBs are a heterogeneous group of drugs with antihypertensive properties. Nondihydropyridines (diltiazem and verapamil) are extensively used for rate control in AF. In the VALUE trial, valsartan outperformed amlodipine in preventing new-onset AF [28].

32.3.4 Diuretics

Diuretics are often included in antihypertensive treatment regimens, but their effect on new-onset AF has not specifically been investigated. Their electrolyte side effects can trigger AF and should thus be closely monitored.

32.3.5 Aldosterone Antagonists

The only available data from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial indicate that the rate of new-onset AF/atrial flutter was lower in patients who received eplerenone vs. placebo (HR 0.58, 95 % CI 0.35–0.96, $p = 0.034$) [41].

32.4 Rhythm Control for Atrial Fibrillation in Hypertensive Subjects

The list of arguments in favor of rhythm or rate control in patients with AF is beyond the scope of this review. In the long-term rhythm control strategy, according to the ESC guidelines, amiodarone is more effective in maintaining SR, but because of its toxicity profile should generally be used as a second-line option [31]. Whether there is significant heart disease or not, the use of RAS inhibition plus statins is encouraged to *upstream* prevention of atrial remodeling; a beta-blocker should be added where appropriate by other indications. In hypertensive subjects with no LVH, dronedarone, flecainide, propafenone, and sotalol can be used followed by amiodarone (in case of failure to prevent AF recurrences). When there is LVH, dronedarone followed by amiodarone is recommended. Nevertheless, in light of the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial results [42] and recent US Food and Drug Administration (FDA) and European Medicines Agency (EMA) warnings, dronedarone should be used only if other antiarrhythmic medicines have been considered and should not be used for rate control in permanent AF.

32.5 Antithrombotic Treatment

Anticoagulation treatment should be given not only to eligible patients (according to their risk for stroke) with persistent or permanent AF, but also to those with paroxysmal AF, who should be regarded as having the same risk. Oral anticoagulation (OAC) with VKA (with a target INR of 2–3) is the current recommended standard of care guideline for stroke prevention in AF in moderate- and high-risk patients. VKAs are highly effective when the INR is maintained at an appropriate therapeutic range (INR 2–3) for the majority of the time (60–70 %). The intensity of anticoagulation involves a balance between prevention of thromboembolism and hemorrhage. The use of the HAS-BLED score (Fig. 32.1) should be used to assess the risk of bleeding in AF patients and is a good occasion to consider correctable risk factors for bleeding (e.g., uncontrolled blood pressure, concomitant nonsteroidal anti-inflammatory drugs, etc.) [43]. A risk score ≥ 3 deserves caution. A meta-analysis of 29 trials with more than 28,000 patients showed that adjusted-dose warfarin reduces ischemic stroke by 64 % and all-cause mortality by 26 %. This reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes. ASA offers only modest protection against stroke for patients with AF [44]. When VKAs were compared to ASA in nine studies, there was a significant reduction of primary end point by 39 % in favour of VKAs alone. Even when clopidogrel was added to ASA in Atrial Fibrillation Clopidogrel Trial with Irbesartan for the Prevention of Vascular Events-Warfarin (ACTIVE-W), anticoagulation with warfarin was superior to the combination of clopidogrel plus aspirin (RR reduction for primary outcome 43 %) with no

HASBLED Hemorrhage Risk Score

	Risk Factors	Points
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1–2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (>65 y.o.)	1
D	Drugs or alcohol (1 point each)	1–2
		Max 9 points

Fig. 32.1 Risk scores for hemorrhage. Shaded cells highlight the presence of hypertension, stroke, and age as risk factors [43]

differences in bleeding events between treatment arms [45]. On the other hand, the addition of clopidogrel to ASA in AF patients who were considered unsuitable for therapy with VKA (ACTIVE A trial) reduced major vascular events by 11 % compared to ASA alone [46], but at the price of increased hemorrhagic risk.

Nevertheless, VKAs come with a long list of drawbacks that result in substantial mortality/morbidity and costs, as well as the underutilization of anticoagulation, particularly in the older patients and in secondary stroke prevention patients (under 60 % of eligible patients) [47]. The aforementioned disadvantages and drawbacks in the use of VKAs have led to the development of novel oral anticoagulants with the potential to change the approach of AF-related thromboembolism/stroke prevention.

32.5.1 New and Investigational Antithrombotic Agents

The new oral anticoagulants are direct thrombin (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and many trials examining their use in AF have been published or are in their final phase [Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), Apixaban for

Reduction In STroke and Other ThromboembolLic Events in atrial fibrillation (ARISTOTLE), Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES), and Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE-AF TIMI 48)].

32.5.1.1 Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial

Dabigatran was evaluated in an open-label, randomized trial in which it was compared with warfarin in 18,113 patients with nonvalvular AF [48]. The mean $CHADS_2$ score was 2.1. Two doses of dabigatran (110 mg and 150 mg BID) were evaluated. The 150 mg BID (twice daily) dabigatran regimen was superior to warfarin. The primary outcome of stroke or systemic embolism occurred in 1.71, 1.54 ($p = 0.34$), and 1.11 % ($p < 0.001$) of patients per year in the warfarin group, in the 110 mg dabigatran BID, and in the 150 mg BID dabigatran group, respectively. The rate of major bleeding was 3.57 % per year in the warfarin arm, 2.87 % in the 110 mg BID dabigatran arm ($p = 0.003$), and 3.32 % in the 150 mg BID dabigatran arm ($p = 0.31$). The rate of hemorrhagic stroke was reduced with both doses of dabigatran compared to warfarin treatment (0.12 % and 0.10 % per year with 110 mg and 150 mg BID, respectively, vs. 0.38 % with warfarin, $p < 0.001$). Myocardial infarction showed a trend to be more frequent (no statistical significance) with dabigatran 110 mg [relative risk (RR) 1.29; 95 % CI: 0.96–1.75; $p = 0.09$] and 150 mg (RR 1.27; 95 % CI: 0.94–1.71; $p = 0.12$). Dabigatran does not require INR monitoring. Nevertheless, there is no specific antidote for it ($t½ = 12–17$ h), but only supportive therapy for severe hemorrhage. It was approved by the FDA and EMA for the prevention of stroke and systemic embolism in patients with nonvalvular AF. The American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society focused update [49] gave dabigatran a class IB recommendation for AF. Thus, it was the first new oral anticoagulant to become available for clinical use in >50 years.

32.5.1.2 Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)

A total of 14,264 patients with AF (87 % with a $CHADS_2$ score of ≥3) were randomized in a double-blind, double-dummy manner to either rivaroxaban 20 mg OD (once a day) (15 mg if creatinine clearance = 30–49 mL/min) or dose-adjusted warfarin (INR 2.0–3.0) [50]. The primary end point of stroke and non-cerebral embolism occurred in 2.12 % per year of patients treated with rivaroxaban and in 2.42 % of patients treated with warfarin ($p = 0.117$). Overall, rivaroxaban was not inferior to warfarin. Although major bleeding occurred in comparable rates (3.6 % for rivaroxaban, 3.45 % for warfarin $p = 0.576$), rates of intracranial hemorrhage were significantly lower with rivaroxaban (0.49 % vs.

0.74 %, $p = 0.019$). On November 2011, the FDA approved rivaroxaban for stroke prophylaxis in patients with nonvalvular AF.

32.5.1.3 Apixaban for Reduction In STroke and Other ThromboembolIc Events in atrial fibrillation (ARISTOTLE) Trial

In a head-to-head comparison of apixaban, 5.0 mg twice daily, versus warfarin in patients with AF, the ARISTOTLE trial randomized 18,201 AF patients [51]. After a median follow-up of 1.8 years, apixaban was associated with a 21 % reduction in the risk of stroke or systemic embolism, a 31 % reduction in bleeding, and an 11 % reduction in all-cause mortality.

32.5.1.4 Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) Trial

The AVERROES trial was a double-blind, randomized comparison of the oral factor apixaban versus ASA for stroke prevention in patients with AF not suitable for OAC with a VKA. Patients were randomized to either apixaban 5 mg BID or ASA (81–324 mg daily). Patients on apixaban had lower rates of stroke and systemic embolism (HR 0.45; 95 % CI, 0.32–0.62; $p < 0.001$) and overall mortality (HR, 0.79; 95 % CI, 0.62–1.02; $p = 0.07$) compared to ASA. There was no significant difference in the rate of major bleeding (1.2 % for ASA and 1.4 % for apixaban, $p = 0.33$) or hemorrhagic stroke (0.2 % per year in both treatment groups) [52].

32.6 Conclusions

AF and HTN are common disorders, and in fact HTN is the most common disorder in AF trials. AF is a progressive disease with many predisposing factors (most of them related one way or another to HTN) that affects major outcomes, quality of life, and results in increased risk of thromboembolism. The comprehensive management of hypertensive subjects with AF includes antihypertensive, antiarrhythmic, and antithrombotic drugs. ACE inhibitors and ARBs seem to be more effective than other classes of antihypertensive drugs in the prevention of AF, although data are sometimes conflicting, and beta-blockers and nondihydropyridine CCBs are extensively used for rhythm control. Finally, novel oral antithrombotics overcome many warfarin drawbacks and are truly new weapons in the clinician's armamentarium for stroke prevention.

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Genetics and Hypertension: Which Information for Clinical Practice

33

Sandosh Padmanabhan and Anna F. Dominiczak

33.1 Introduction

Blood pressure (BP) is a quantitative trait that is normally distributed in the general population. In adults, there is a continuous, incremental risk of cardiovascular disease, stroke, and renal disease with increasing BP starting as low as 115/75 mmHg [1], though hypertension (HTN) is defined on the basis of an arbitrary cut-off point. It is clear that BP regulation and consequently HTN arises from a complex interaction of genetic and lifestyle factors. The evidence for lifestyle factors comes from multiple strands of epidemiological data that are described in this issue. Uncovering the genetic determinants of BP and HTN has been one of the most challenging fields in complex trait genetics. In this chapter, we describe the genetic basis of BP and HTN with the implications of these in current clinical practice.

In the 1950s, a technical controversy about the unimodal or bimodal distribution of BP led to the famous Platt-Pickering debate [2], where Pickering argued that "in every population there occurs a distribution of blood pressure values, more frequent around the midpoint of the range and less so at the high and low extremes, with no 'dividing line' to distinguish between abnormal and normal, or sick and well". Platt countered that "the highest blood pressure values in a population distinguished a discrete group who represented the disease, hypertension, and that this fact could potentially be explained by specific genetic characteristics of this group". Revisiting the Platt-Pickering debate [2] is a useful exercise to understand

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the assumptions that have driven genetic research of BP/HTN so far. Platt measured BP in normotensive and hypertensive probands and their relatives and argued that HTN was a qualitative abnormality and hence a simple Mendelian disease subject to the classic Mendelian laws of inheritance. On the other hand, Pickering studied systolic (SBP) and diastolic BP (DBP) distributions from the second to the eighth decades in first-degree relatives of normotensive probands and hypertensive propositi and concluded that BP was inherited as a *graded character*, and is hence a complex non-Mendelian trait [2, 3]. Empirically, the distribution of BP in the general population is a normal unimodal distribution, which supports the complex multifactorial determination of BP [4–6], and this can be extended to HTN, which can be considered as a dichotomization of the quantitative BP trait. Platt's theory would necessitate a bimodal distribution of BP which is not observed in the general population. However Platt's view cannot be discounted entirely, as there exists rare Mendelian forms of HTN and hypotension caused by highly penetrant, rare genetic variants with large effects [7].

From an evolutionary perspective, high BP may be an undesirable pleiotropic effect of a genotype that may have optimized fitness in an ancient environment. Thus, high BP is a disease of modern civilization with its abundance of dietary salt, processed foods, and longer lifespans [8]. Different populations show differing predispositions to the trait and this may reflect different evolutionary selection pressures as different populations do not necessarily share the same ancestral histories. For example, HTN occurs earlier and with more severity in people of African ancestry compared to those of European ancestry [9]. The rates of HTN and sodium sensitivity are generally higher in individuals carrying the ancestral alleles of sodium-conserving genes, which show strong latitudinal clines with the ancestral sodium-conserving alleles more prevalent in African populations and less so in northern regions [10–12]. It is also hypothesized that the renin–angiotensin–aldosterone (RAAS) system was initially adapted for sodium conservation and may be maladaptive in modern societies with ready access to dietary salt [13].

33.2 Heritability of Blood Pressure

Early evidence that BP as Pickering's quantitative trait can be attributable to genetic differences between individuals came from family studies showing BP to be highly heritable, with 15–40 % of clinic SBP, 15–30 % of clinic DBP, 69 and 51 %, respectively, of ambulatory nighttime SBP and DBP, and 50–60 % of long-term SBP or DBP [14–18]. Heritability reflects the degree of phenotypic resemblance between relatives and this depends not only on shared genetic factors contributing to the trait, but also includes environmental factors and interactions within the genome. Thus, heritability estimates can increase or decrease without any genetic changes, for example, when environmental variation decreases or increases respectively. Hence the observed heritability of BP does not reflect the

true magnitude of genetic effect, but instead reflects the amount of variation in genotypic effects compared to variation in environmental effects. Environmental conditions vary between populations and indeed between generations and hence heritability estimates only refer to specific populations under a specific environment. Another factor that influences heritability estimates is measurement error. This is clearly illustrated in the previous paragraph, where minimizing measurement errors by using ambulatory nighttime values or using long-term average BP results in higher heritability estimates. For HTN as a binary trait, the genetic contribution is calculated using the sibling recurrence risk ratio (λs), which is the relative risk of HTN given that one sibling is affected, and which is around 1.5. In summary, genetic factors have a role in the regulation of BP and development of HTN but the magnitude of effect is modest.

33.3 Monogenic Hypertension

The monogenic forms of HTN are usually associated with volume expansion and low plasma renin activity secondary to salt retention [7]. The causative genetic mutations responsible for a number of monogenic forms of human HTN have been discovered through positional cloning. This method required the recruitment of large kindreds with multiple affected family members, with the same disease showing a clear mode of inheritance (autosomal dominant, autosomal recessive, codominant, sex-linked, etc.). Linkage analysis is performed by genotyping equally spaced, highly polymorphic microsatellite markers, which are usually evenly spaced at 10 cM (centimorgan) intervals. This identifies a specific region of the chromosome that is linked to the trait and further fine-mapping of this region leads to the identification of the causative gene. Most of the monogenic forms of HTN are due to gain-of-function mutations and a majority of these mutations lead to increased mineralocorticoid activity or production which is clinically associated with volume expansion and suppressed plasma renin activity (Table 33.1).

Glucocorticoid-remediable aldosteronism or familial hyperaldosteronism type 1 (OMIM #103900) is an autosomal dominant syndrome in which HTN is caused by increased aldosterone secretion driven by adrenocorticotropic hormone (ACTH). It results from a chimeric gene containing the 5′ regulatory sequences of 11β-hydroxylase (*CYP11B1*) (which confers ACTH responsiveness) fused with the distal coding sequences of aldosterone synthase (*CYP11B2*) leading to the use of ACTH rather than angiotensin II or potassium as the main controller of aldosterone secretion [19]. In contrast, familial hyperaldosteronism type 2 (OMIM #605635) is an autosomal dominant syndrome due to hyperplasia or adenoma of the aldosterone-producing adrenal cortex. The genetic abnormality causing FH type II (FH-II) has been localized to chromosome 7p22 [20], though the causative gene has not yet been identified.

Table 33.1 Monogenic forms of hypertension

Disorder	Inheritance	Biochemistry	Genetics	Treatment
Familial hyperaldosteronism type 1 Glucocorticoid remediable aldosteronism (GRA)	Autosomal dominant	Plasma and urinary aldosterone responsive to ACTH; BP controlled by glucocorticoids within 48 h	Chimeric gene	Glucocorticoids
Familial hyperaldosteronism type 2	Autosomal dominant	Hyperaldosteronism; glucocorticoids have no effect on BP	Unknown linkage to chromosome 7p22	Spironolactone, eplerenone
Apparent mineralocorticoid excess	Autosomal recessive	Increased plasma ACTH, increased levels of corticosteroids	Type 2 11β-OHSD mutations	Spironolactone, dexamethasone
Mineralocorticoid receptor gain-of-function mutation	Unknown	Low plasma renin Low aldosterone Low K^+	Missense mutation (S810L) in the mineralocorticoid receptor	–
Liddle syndrome	Autosomal dominant	Low plasma renin, Low or normal K^+, Negligible urinary aldosterone	Constitutive activation of epithelial sodium transporter ENaC	Amiloride, triamterene
Pseudohypoaldosteronism type 2; Gordon syndrome; familial hyperkalemia	Autosomal dominant	Low plasma renin, normal or elevated K+	Abnormality in WNK1 or WNK4	Thiazide diuretic, low-sodium diet
Hypertension with brachydactyly; Bilginturan syndrome	Unknown	No specific biochemical findings	Inversion, deletion, and reinsertion at 12p12.2–p11.2	–

11β-OHSD 11β-hydroxysteroid dehydrogenase, *ACTH* adrenocorticotropic hormone, *BP* blood pressure, *GRA* glucocorticoid remediable aldosteronism *WNK1/2* serine/threonine-protein kinase WNK1/2

Apparent mineralocorticoid excess (AME; OMIM # 218030) is another low-renin HTN syndrome accompanied by hypokalemia and metabolic alkalosis. The main defect in AME is the absence or reduced activity of 11β-hydroxysteroid dehydrogenase (*HSD11B2*), resulting in HTN in which cortisol acts as if it were a potent mineralocorticoid [21]. Normally, both cortisol and aldosterone have mineralocorticoid receptor agonist activity and *HSD11B2* is protective by metabolizing cortisol to prevent its binding to the mineralocorticoid receptor. Another syndrome leading to severe early-onset HTN and HTN during pregnancy is caused by a gain-of-function serine-to-leucine mutation in the mineralocorticoid receptor (S810L). One possible mechanism is that cortisone, the main metabolite of cortisol in the kidney, can activate the mutation, conferring a potential permanent increase in renal sodium reabsorption [22, 23]. There is preliminary evidence of epigenetic regulation of *HSD11B2*, with the observation of increased methylation in the promoter region of the gene, in those with low expression of 11β-hydroxysteroid dehydrogenase with HTN development after glucocorticoid treatment [24, 25].

Finally, defects in the enzymes of cortisol biosynthesis result in a group of autosomal recessive disorders collectively called congenital adrenal hyperplasia [26]. In some of these syndromes, plasma ACTH will increase in an attempt to produce cortisol, and aberrant products will accumulate, some of which lead to HTN. Enzyme mutations that are associated with HTN include, in order of frequency: 11β-hydroxylase (OMIM #202010; *CYP11B1*), 3-β-hydroxysteroid dehydrogenase (OMIM #613890; *HSD3B2*), 17α-hydroxylase (OMIM #609300; *CYP17A1*), and cholesterol desmolase (OMIM #118485; *CYP11A1*).

Monogenic low-renin HTN syndromes can also be caused by mutations in the renal ion transporters. Pseudohypoaldosteronism type 2 (Gordon syndrome; familial hyperkalemia; OMIM #145260), an autosomal dominant form of HTN associated with hyperkalemia, non-anion gap metabolic acidosis, and increased salt reabsorption by the kidney, is caused by mutations in the serine/threonine-protein kinases (WNKs) [27]. Gordon syndrome thus results from either gain-of-function mutations in *WNK1*, or loss-of-function mutations in *WNK4*. Liddle syndrome (OMIM # 177200) is an autosomal dominant condition with a clinical picture of HTN and aldosterone excess, but with very low aldosterone and renin levels, caused by mutations in the genes coding the beta or gamma subunits of the epithelial sodium channel (ENaC; *SCNN1B* and *SCNN1G*) resulting in deletions of proline-rich regions [28, 29]. These regions facilitate binding of NEDD4-2 (*NEDD4L*), a regulatory repressor that promotes channel degradation. The inability of the beta and gamma subunits to bind NEDD4 results in constitutive expression of sodium channels and prolongs the half-life of ENaCs at the renal distal tubule apical cell surface, leading to increased rates of sodium reabsorption, volume expansion, and HTN.

Conversely, mutations that reduce salt retention, such as those associated with Bartter (*SLC12A1*, *KCNJ1*, *CLCNKB*, *BSND*, *CASR*, and *CLCNKA*) and Gitelman (*SLC12A3*) syndromes, tend to lower BP and protect against the development of HTN [7, 30].

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare neuroendocrine tumors of the adrenal glands and the sympathetic and parasympathetic paraganglia. The annual incidence of PCCs is around 2–4 per million. PCCs and sympathetic PGLs are very similar histologically as well as functionally and cause HTN, which may be either paroxysmal or sustained. About 30 % of PCCs and PGLs are currently believed to be caused by germline mutations. Autosomal dominantly inherited pheochromocytomas are due to a variety of *RET* proto-oncogene mutations. Other pheochromocytoma-susceptibility genes include the tumor suppressor gene *VHL* observed in families with von Hippel–Lindau syndrome, and the gene that encodes the succinate dehydrogenase complex subunits A, B, C, and D (SDHA, SDHB, SDHC, and SDHD, respectively) with heterozygous germline mutations of SDHB, SDHC, and SDHD causing the well-characterized familial pheochromocytoma–paraganglioma syndromes known respectively as PGL4, PGL3, and PGL1 [31]. Newer predisposing genes for pheochromocytoma/paraganglioma include *KIF1B*, *EGLN1/PHD2*, and *SDHAF2* [32]. Hereditary pheochromocytoma and/or PGL are frequent (28.2 %), but inheritance is evident at presentation only in 16.9 % of cases and only 13.6 % of apparently sporadic variants are genetically determined. Despite increased costs, systematic genetic screening might be useful because it might lead to a stricter follow-up, early diagnosis of recurrences in index cases, and presymptomatic detection of disease in relatives [33].

33.4 Essential Hypertension

In striking contrast to the success of linkage studies in identifying genes for monogenic BP syndromes, the search for genes for essential hypertension using linkage studies were largely unsuccessful as predicted [34]. Koivukoski and colleagues [35] analyzed nine genome-wide linkage scans of blood pressure or HTN and found susceptibility loci on chromosomes 2 (2p12-q22.1) and 3 (3p14.1-q12.3). A locus on the short arm of chromosome 2 was further found to be associated with a response to antihypertensive therapy in white subjects and to colocalize to a chromosomal region that was found to be associated with HTN in African–American hypertensive subjects [36, 37]. However, none of these loci have resulted in the identification of the causative underlying genes.

An alternative to linkage analysis is the genetic association study which tests whether single genotype or allele frequencies differ significantly between groups of individuals ascertained on the presence or absence of a trait. Recent advances in genotyping technology have led to the advent of single-nucleotide polymorphism (SNP) chip arrays that allow the interrogation of a large number of genetic variants cost-effectively, making genome-wide association studies (GWAS) possible. GWAS are large-scale association mapping studies which make no assumptions of the genomic location or function of the causal variant and which provide a comprehensive approach to testing the hypothesis that common alleles contribute

to heritable phenotype variation. GWAS rely on the linkage disequilibrium (LD) or correlation patterns of SNPs with functional variants and, therefore, the identified SNPs are usually proxies of untyped functional variants. A typical GWAS experiment consist of genotyping 500,000–1 million SNPs across the genome, as depending on the population this number of SNPs is adequate to interrogate 80 % of common SNPs with minor allele frequency greater than 5 %. To adjust for multiple testing and to decrease type I errors (false-positive rates), the statistical burden of proof relies on stringent p values, usually $p < 5 \times 10^{-8}$. To study a single gene of interest, the focus of the study can be restricted to a single gene or a few genes. This has the advantage of imposing a lesser penalty on multiple testing due to fewer tests being performed. Among the single candidate genes studied, successful associations have been seen in the natriuretic peptide *NPPA–NPPB* locus [38]. Initial successful GWAS into HTN derive from two large consortia, the Global Blood Pressure Genetics (Global BPgen) [39] and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) [40]. The Global BPgen consortium tested 2.5 million genotyped or imputed SNPs for association with SBP or DBP in 34,433 subjects of European ancestry and identified eight regions with genome-wide significance. The variants were near the *CYP17A1*, *CYP1A2*, *FGF5*, *SH2B3*, *MTHFR*, *ZNF652*, and *PLCD3* genes and chromosome 10 open reading frame 107 (*C10orf107*). CHARGE studied 2.5 million genotyped or imputed SNPs in 29,136 subjects and found significant ($p < 4 \times 10^{-7}$) associations with SBP for 13 SNPs, with DBP for 20 SNPs and with HTN for 10 SNPs. Meta-analysis of the data from the two consortia revealed genome-wide significance ($p < 5 \times 10^{-8}$) for *ATP2B1*, *CYP17A1*, *PLEKHA7*, *SH2B3*, *CACNB2*, *CSK–ULK3*, *TBX3–TBX5*, and *ULK4* for association with SBP, DBP or HTN. A number of subsequent GWAS have successfully built on these landmark studies and identified additional loci. After meta-analysis combining the Women's Genome Health Study with prior study results of CHARGE one gene expression-associated SNP, the BLK–GATA4 region, reached genome-wide significance [41]. Among non-European ancestry populations, the first large-scale GWAS meta-analysis for SBP and DBP in east Asians [42], confirmed seven loci previously identified in populations of European descent, but, much more importantly, also identified six novel loci: ST7L-CAPZA1, FIGN-GRB14, ENPEP, NPR3, a newly discovered variant near TBX3, and one near ALDH2. Two initial GWAS in African–Americans did not identify any genome-wide significant signals after the replication stages [43, 44].

More recently, the International Consortium for Blood Pressure Genome-Wide Association Studies (ICBP-GWAS) published results of a GWAS with a multi-stage design in more than 200,000 individuals of European descent, which is the largest BP GWAS to date [45]. This study identified 29 variants associated with SBP, DBP, or both, 16 of which were previously unidentified. Of these, six contain genes previously known or suspected to regulate blood pressure (*GUCY1A3–GUCY1B3*, *NPR3-C5orf23*, *ADM*, *FURIN–FES*, *GOSR2*, *GNAS–EDN3*) [45]. The first successful GWAS for hypertension used an extreme case-control design in a discovery sample of 1,621 HTN cases and 1,699 hypercontrols, representing the

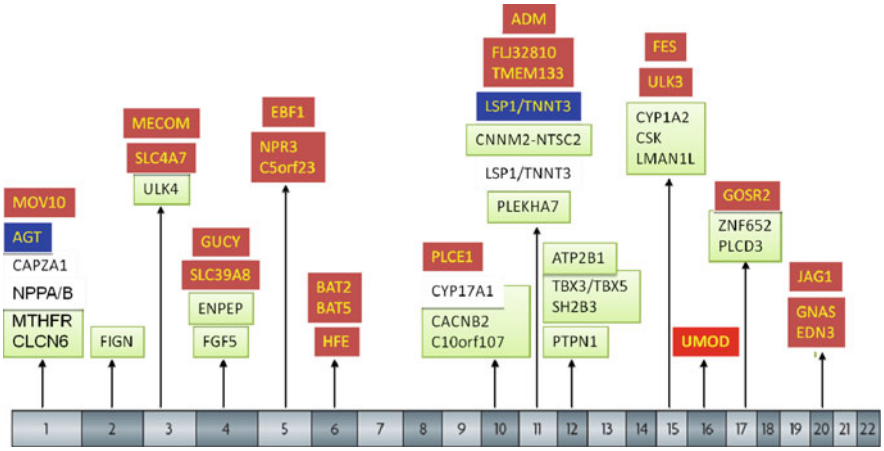

Fig. 33.1 Genetic loci that have attained a genome-wide significance (p value of 5×10^{-8}) with replication

top 2 % and bottom 9 % of the BP distribution in Sweden [46]. Combined with follow-up validation analyses in 19,845 cases and 16,541 controls, a locus near the uromodulin (*UMOD*) gene was identified. *UMOD* is exclusively expressed in the kidney, suggesting that the discovered variant may have an effect on sodium homeostasis. On a near-genome-wide scale, using gene-centric chips and applying the same rigorous criteria for evidence, significant SNPs were identified in *NPR3*, *HFE*, *NOS3*, *SOX6*, *LSP1/TNNT3*, *MTHFR*, *AGT*, and *ATP2B1* with some overlap with large GWAS meta-analyses [47]. The top replicated loci are summarized in Fig. 33.1 and Table 33.2.

It is striking that the signals from all the GWAS for HTN and BP do not contain genes from highly plausible pathways, for example, the RAAS or epithelial sodium channels. An important limitation of GWAS is that genome-wide significant SNPs often merely tag but do not provide direct information on the causal variants. To translate those signals to biological function, follow-up studies are necessary. The region around the top loci identified for BP and HTN do not show exclusive associations with the trait. Instead, looking at a 50 kb region flanking each of the top loci for BP/HTN (Fig. 33.2) shows a variety of phenotypes that colocalize to or near the BP loci in terms of replicated GWAS hits. Another issue arising from GWAS studies is the tiny fraction of population variance of BP (<1 %) and BP heritability (approximately 2 %) that are explained by the collective effect of all the GWAS loci identified so far [45]. The missing heritability conundrum [48] is not unique to BP genetics, but is observed in most of the common diseases. One approach to solve this has resulted in efforts directed toward the identification of additional rare variants of greater effect. This has been hypothesized before [49, 50] and there is early evidence of the relevance of rare variants in common essential HTN. Resequencing three candidate genes (*SLC12A3*, *SLC12A1*, and *KCNJ1*) involved in the Bartter and Gitelman syndromes in the Framingham Heart Study population identified 30

Table 33.2 Genes in genetic loci associated with blood pressure and HTN in GWAS and their function

Chromosome	Nearest gene	Function
1p36	*MTHFR* (*NPPA*, *NPPB*)	Methylenetetrahydrofolate reductase; has been associated with changes in plasma homocysteine levels and with preecclampsia. Atrial natriuretic and brain natriuretic peptides genes have been associated with hypertension
3q22	*ULK4*	Serine-threonine kinase of unknown function
3q26	*MECOM* (*MDS1*)	Myelodysplasia syndrome 1 protein
4q21	*FGF5*	Fibroblast growth factor 5; stimulates cell growth and proliferation and is associated with angiogenesis
5p13	*NPR3*	Natriuretic peptide clearance receptor
10p12	*CACNB2*	Subunit of voltage-gated calcium channel expressed in the heart
10q24	*CYP17A1*	Cytochrome p450 enzyme mediating the first step in mineralocorticoid and glucocorticoid synthesis. Also involved in sex steroid synthesis
11p15	*PLEKHA7*	Pleckstrin-homology domain containing family member A7; expressed in zonula adherens of epithelial cells
12q21	*ATP2B1*	Encodes plasma membrane calcium- or calmodulin-dependent ATPase expressed in the endothelium
12q24	*SH2B3*	Also known as lymphocyte-specific adaptor protein (*LNK*), may regulate hematopoietic progenitors and inflammatory signaling pathways in the endothelium
12q24	*TBX5–TBX3*	T-box genes involved in the regulation of developmental processes
15q24	*CSK*	Cytoplasmic tyrosine kinase involve in angiotensin II-dependent vascular smooth muscle cell contraction
16p12	*UMOD*	Uromodulin; Tamm-Horsfall protein. Specifically expressed in the thick ascending limb of the loop of Henle where 25 % of sodium reabsorption in the kidney occurs
17q21	*ZNF652*	Zinc-finger protein 652
20q13	*GNAS–EDN3*	*GNAS* encodes the α subunit of the G protein-mediating β-receptor signal transduction; *EDN3* encodes endothelin 3, the precursor for the ligand of the endothelin B receptor

distinct, potentially deleterious rare mutations present in 49 subjects. In the heterozygous state, these variants were associated with 5.7 mmHg lower BP at age 40 and by 9.0 mmHg at age 60, and in aggregate reduce the risk of HTN by 60 % at age 60 [30].

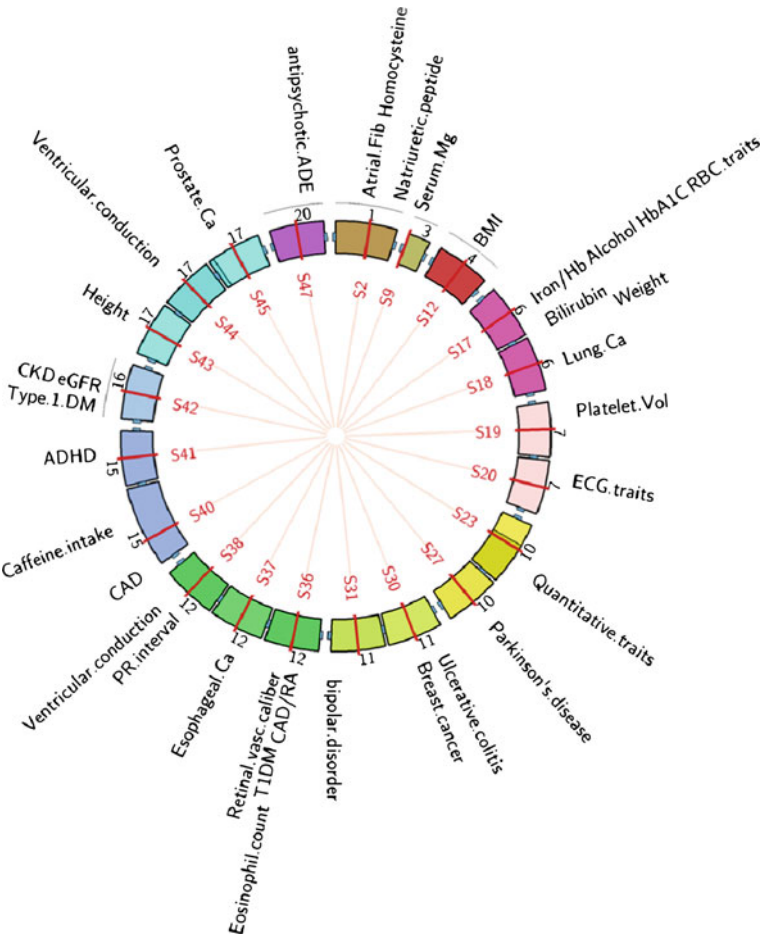

Fig. 33.2 Pleiotropy in the blood pressure loci from GWAS, [51]

Despite the increasing pace of discovery of variants associated with BP and HTN, the limited predictive utility of these variants, either singly or as part of a composite risk score, is striking. The population distribution of the number of BP-increasing alleles with nearly similar allele frequencies is normally distributed as each SNP is inherited independently and hence the number of individuals in the population expected to carry all harmful risk alleles would be vanishingly small. One way of maximizing information about the genetic signals is to create a composite genetic risk score coding for the presence or absence of risk alleles and their numbers for all the BP GWAS SNPs. In the ICBP-GWAS [45], between the top and the bottom quintiles of the risk score, a 4.6 mmHg SBP and 3.0 mmHg DBP difference was detected, and the prevalence of hypertension was 29 % compared to 16 % in the top and bottom deciles. The score was also associated

with early and advanced target organ damage including left ventricular hypertrophy, stroke, and coronary heart disease, but not chronic kidney disease or markers of renal function [45]. The lack of association between BP risk score and kidney function would indicate that high BP and renal disease do not necessarily have the same molecular origin and this opens a new avenue for research to validate or refute the observation. It is clear that using panels of genetic markers to predict risk has very poor discrimination and that the utility of GWAS approaches are primarily in the identification of novel pathways. The recent debate between Kurtz and Dominiczak summarizes the key issues and challenges in pursuing further large-scale genomic projects for complex traits [52, 53].

33.5 Conclusions

Unravelling the genetic basis of BP regulation and HTN has been more difficult than might be suggested by their high heritability; however, the progress in the cataloguing of common variants using GWAS is comparable to other common traits. Ongoing studies include the ongoing GWAS meta-analysis of BP extremes and exome sequencing of BP extremes to identify more sequence variants that are associated with BP. Indeed, it has been estimated that further increasing the GWAS sample size will identify 116 common variants for BP that have similar effect sizes to those found already, but these will collectively explain only about 2.2 % of the phenotypic variance [45]. A limitation of GWAS signals is that they rarely track to causal polymorphisms (a problem for linkage signals, as well), so the cataloguing effort with large-scale GWAS is just the first step in a long process of discovery [54].

Some important factors to be addressed in future studies of BP as a quantitative trait would be to more accurately model BP in subjects on antihypertensive treatment by taking into account the number of drugs, drug dosage, and compliance metrics, or the use of longitudinal BP data—for example, long-term average BP and BP variability (both visit-to-visit or 24-h intraindividual variability). Novel strategies are needed to efficiently discover causal and clinically useful genetic markers. This would require a move from pure BP quantitative traits in larger and larger cohorts to detailed studies of subjects selected on informative intermediate traits derived from the extensive interventional studies for high BP.

The limited predictive utility of common variants that have emerged from most GWAS studies would suggest that to build better predictive models it would be necessary to identify orthogonal (i.e., uncorrelated) genetic variants that are associated with new pathways, as suggested for biomarkers [55]. The next level of discovery will be more challenging as the molecular and functional dissection of the novel variants require more detailed low-throughput science in contrast to the high-throughput screening methods applied so far. While panels of SNPs are at the moment not clinically useful, identification of novel pathways and orthogonal biomarkers is likely to improve a multipronged approach to reducing the morbidity and mortality from elevated BP.

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Dual Blockade of the Renin–Angiotensin–Aldosterone System: Benefits Versus Adverse Outcomes

34

Michael R. Lattanzio and Matthew R. Weir

34.1 Introduction

Renin–angiotensin–aldosterone system (RAAS) blockade in patients with established heart or kidney disease provides an approximate 20 % relative risk reduction of disease progression, and cardiovascular (CV) or renal end points. There is minimal risk associated with this approach, especially with close monitoring. Whether dual RAAS blockade can provide incremental clinical benefit is of some debate. Overall, there is no CV benefit. However, dual RAAS blockade has not been well tested in patients with renal disease and there is some indication of therapeutic benefit in patients with systolic heart failure. The safety of dual RAAS blockade, especially in patients with kidney disease, is not well established. Not all dual RAAS blockade is the same in terms of efficacy and safety. With four available RAAS blocking drugs, the differences between combinations needs to be established from efficacy and safety standpoints.

Proteinuria is a powerful, independent predictor of progression of renal disease, cardiovascular disease, and mortality in people with renal disease, hypertension, diabetes, vascular disease, and in the general population. Blockade of the RAAS is the cornerstone of therapies aimed at reducing proteinuria. The blockade of multiple constituents of RAAS has been employed to amplify the proteinuria reduction achievable from single RAAS blockade. Does the use of dual RAAS blockade confer superior renal and cardiovascular outcomes compared to monotherapy? Although observational studies have suggested more substantial reduction of both proteinuria and blood pressure, long-term prospective studies with hard renal end points are lacking. The literature examining the cardiovascular

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outcomes of dual RAAS blockade in treating congestive heart failure is more concrete. Recently, the safety and efficacy of dual RAAS blockade has been challenged by the Ongoing Telmisartan Alone and in Combination with ramipril Global Endpoint Trial (ONTARGET), which suggested an increase in adverse renal outcomes associated with a combination therapy of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) in vascular patients. This chapter is a critical, evidence-based appraisal of dual RAAS blockade in the management of renal and cardiovascular disease, particularly focusing on potential benefits and adverse outcomes.

34.2 The Debate

The ONTARGET trial has sparked both efficacy and safety concerns within the hypertension community regarding the use of a dual RAAS blockade to achieve more desirable cardiovascular and renal outcomes. The trial was a multicenter, randomized, double-blind, controlled trial in patients with high-risk diabetes or vascular disease that examined the effect of telmisartan alone, ramipril alone, or a combination of both on the primary composite end point of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. At a median follow-up of 56 months, the primary outcome had occurred in 1,412 patients in the ramipril group (16.5 %), as compared with 1,423 patients in the telmisartan group [16.7 %; relative risk 1.01; 95 % confidence interval (CI), 0.94–1.09) [1]. In the combination therapy group, the primary outcome occurred in 1,386 patients (16.3 %; relative risk, 0.99; 95 % CI 0.92–1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8 % vs. 1.7 %, $p < 0.001$), syncope (0.3 % vs. 0.2 %, $p = 0.03$), and renal dysfunction (13.5 % vs. 10.2 %, $p < 0.001$) [1]. The conclusion of the authors was that the combination of ACEI and ARB was associated with more adverse outcomes without an increase in cardiovascular benefit.

The renal outcomes of the ONTARGET study were also analyzed. The primary renal outcome was a composite of dialysis, doubling of serum creatinine, and death. The number of events for the composite primary outcome was similar for telmisartan [$n = 1{,}147$ (13.4 %)] and ramipril [$n = 1{,}150$ (13.5 %); hazard ratio (HR) 1.00, 95 % CI 0.92–1.09], but was increased with combination therapy [$n = 1{,}233$ (14.5 %); HR 1.09, CI 1.01–1.18, $p = 0.037$] [2]. The secondary renal outcome, dialysis, or doubling of serum creatinine, was similar with telmisartan [189 (2.21 %)] and ramipril [174 (2.03 %); HR 1.09, CI 0.89–1.34] and more frequent with combination therapy [212 (2.49 %): HR 1.24, CI 1.01–1.51, $p = 0.038$] [2]. The estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan [−2.82 (SD 17.2) mL/min/1.73 m^2 vs. −4.12 (17.4), $p < 0.0001$] or combination therapy [−6.11 (17.9), $p < 0.0001$] [2]. The increase in urinary albumin excretion was less with telmisartan ($p = 0.004$) or with combination therapy ($p = 0.001$) than with ramipril [2]. The study suggested that

combination therapy in high-risk diabetes or vascular disease reduces proteinuria to a greater extent than monotherapy, but it worsens major renal outcomes overall.

ONTARGET ignited a firestorm of debate regarding the utility of dual RAAS blockade for the treatment of renal and cardiac conditions, leading some to endorse an indiscriminate refrain from dual RAAS blockade use [3, 4]. Alternatively, others highlighted that ONTARGET was largely underpowered to examine renal outcomes and that altering clinical practice based on this study would be immoderate, particularly since the incidence of adverse events was very low [5]. Based on the trial, the use of dual RAAS blockade to achieve superior renal outcomes in nonproteinuric individuals with diabetes or vascular disease appears dubious. The essentialness of large-scale, randomized controlled trials investigating the value of dual RAAS blockade in proteinuric chronic kidney disease (CKD) is self-evident. With this background, the authors, herein provide the most recent literature on the potential risks and benefits associated with dual RAAS blockade in various renal and cardiovascular conditions.

34.3 Benefits

34.3.1 Proteinuric Chronic Kidney Disease

Reduction of proteinuria is associated with delayed progression of CKD. The combined administration of ACEI and ARBs may be more effective in reducing proteinuria than either drug alone, particularly in diabetic nephropathy. In a recent meta-analysis, the effect of monotherapy and combination with inhibitors of the renin–angiotensin system (RAS) on proteinuria in renal disease (particular diabetic nephropathy) was studied. The combination of ACEI and ARB reduced proteinuria more than either drug alone. The ratio of the means for combination therapy vs. ARBs was 0.76 (CI 0.68–0.85) over 1–4 months and 0.75 (CI 0.61–0.92) over 5–12 months [6]. Similarly, the ratio of the means for combination therapy versus ACEI was 0.78 (CI 0.72–0.84) over 1–4 months, and 0.82 (CI 0.67–1.01) over 5–12 months [6]. In total, combination therapy reduced proteinuria by 20–25 % more than either drug alone [6]. The antiproteinuric effect achieved through combination therapy appeared consistent among all subgroups. Unfortunately, safety data was not available on most studies included in this meta-analysis, which limits its broad clinical application.

The addition of a mineralocorticoid receptor antagonist (MRA) to conventional ACEI or ARB therapy may also be a useful strategy in the treatment of proteinuric chronic kidney disease. A recent study examined the renoprotective effects of adding an MRA, spironolactone, to maximal ACE inhibition in patients with diabetic nephropathy [7]. Despite no differences in blood pressure, albuminuria decreased more in the low-dose spironolactone group than in the losartan group, when compared with placebo (34 % vs. 16.8 %) [7]. Similarly, the coadministration of eplerenone with enalapril substantially reduced albuminuria compared with enalapril alone in patients with diabetes without significant increases in

potassium levels [8]. Additional data suggest that adding a MRA to ACEI therapy yields decreases in proteinuria without adverse effects of hyperkalemia and impaired renal function [9]. Targeting different components of the RAAS may be a safe and powerful strategy for reducing proteinuria in patients with diabetic nephropathy.

Is proteinuria reduction a valid surrogate end point for improved cardiovascular and/or renal outcomes in dual RAAS blockade? A recent post hoc analysis of ONTARGET demonstrated that changes in albuminuria predict mortality, cardiovascular outcomes, and renal outcomes in vascular patients, regardless of baseline albuminuria [10]. A greater than or equal to twofold increase in albuminuria from baseline to 2 years, observed in 28 %, was associated with nearly 50 % higher mortality (HR 1.48; 95 % CI 1.32–1.66), and a greater than or equal to twofold decrease in albuminuria, observed in 21 %, was associated with 15 % lower mortality (HR 0.85; 95 % CI 0.74–0.98) compared with those with lesser changes in albuminuria, after adjustment for baseline albuminuria, blood pressure, and other potential confounders [10]. These findings suggest that the benefit of dual RAAS blockade may be most pronounced in individuals with proteinuric forms of CKD, and that the greater reduction in proteinuria, the greater the overall benefit. Moreover, the inferior renal outcomes associated with dual RAAS blockade in the ONTARGET trial may not be applicable to all forms of CKD, since the majority of the study population had nonproteinuric CKD.

Unfortunately, there is a dearth of prospective, randomized controlled trials examining the renal outcomes of patients on dual RAAS blockade. The Combination treatment of Angiotensin-II Receptor blocker and Angiotensin-converting enzyme inhibitor in non-diabetic renal disease (COOPERATE) trial was a long-term, prospective study that demonstrated improved renal survival in nondiabetic kidney disease with the combination of ACEI and ARB therapy versus either drug alone [11]. The article was later repudiated by the *Lancet* due to author improprieties related to data reporting [12]. As a consequence, the results of COOPERATE can no longer provide an insight into the utility of dual RAAS blockade. Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) and Combination Angiotensin Receptor Blocker and Angiotensin Converting enzyme inhibitor for treatment of diabetic nephropathy (VA NEPRON-D) are two ongoing trials examining the long-term renal effects of dual RAAS blockade in patient with diabetic kidney disease [13, 14]. Although the ALTITUDE trial has been stopped, the VA NEPHRON-D trial will provide more clarification on the value and safety of dual RAAS blockade in the management of proteinuric kidney disease, when using an ACEI and an ARB.

34.3.2 Hypertension

Most of the short-term blood pressure studies have shown an additional drop in systolic and diastolic pressure when an ARB was added to an ACEI and vice versa, regardless of the dose level of the first drug. Overall, the combination of an ACEI

and an ARB reduced ambulatory blood pressure by 4.7/3.0 mmHg (95 % CI 2.9–6.5/1.6–4.3) compared with ACEI monotherapy and 3.8/2.9 mmHg (CI 2.4–5.3/0.4–5.4) compared with ARB monotherapy [15]. Clinic blood pressure was reduced by 3.8/2.7 mmHg (CI 0.9–6.7/0.8–4.6) and 3.7/2.3 mmHg (CI 0.4–6.9/0.2–4.4) compared with ACEI and ARB, respectively [15]. Whether the additional blood pressure reduction afforded from the combination of ACEI and ARB provides a safe and effective strategy for reducing cardiovascular and/or renal outcomes in all patient populations remains unclear.

Although the blood pressure-lowering effect of a dual RAAS blockade is modest compared to the combination of a single RAAS blocker and calcium channel blockers or diuretics, studies show that the antiproteinuric effects of dual RAAS blockade may occur independently of blood pressure control. Why would dual RAAS blockade confer an additive renoprotective effect in patients with proteinuric CKD? In regards to diabetic nephropathy, Park and colleagues identified the *non-ACE* pathways responsible for the majority of angiotensin II production in the type 2 diabetic, leptin receptor-deficient mouse kidney [16]. Inhibition of these *non-ACE* enzymes abolished the afferent arteriole response for the intrarenal conversion of angiotensin I to angiotensin II in the diabetic kidney, but not the control kidney [16]. These studies provide a plausible explanation for the superior effects of combining an ACEI with an ARB relative to ACEI therapy alone so as to provide additional protection from diabetic nephropathy in humans.

Resistant hypertension is defined as blood pressure that remains above target despite the concurrent use of a diuretic plus two additional antihypertensive agents of different classes prescribed at optimal doses. The use of dual RAAS blockade, including either an ACEI or ARB combined with a MRA has demonstrated efficacy for the treatment of refractory hypertension. The Addition of Spironolactone in Patient with Resistant Arterial Hypertension (ASPIRANT) trial was a randomized, double-blind, placebo-controlled trial that studied the effect of the addition of 25 mg of spironolactone on blood pressure in patients with resistant hypertension compared to placebo [17]. The treatment arm ($n = 55$) included 42 patients (76.4 %) on ACE inhibition and 25 patients (45.5 %) on angiotensin receptor blockade [17]. At 8 weeks, the primary end points, a difference in mean drop in blood pressure on daytime ambulatory blood pressure monitoring (ABPM), between the groups was −5.4 mmHg (95 % CI −10.0 to −0.8) for systolic blood pressure [17]. The ABPM nighttime systolic, 24 h ABPM systolic, and office systolic blood pressure were significantly reduced by spironolactone (difference of −8.6, −9.8, and −6.5; $p = 0.011$, 0.004, and 0.011) [17]. The adverse events in both groups were comparable. In summary, the addition of a MRA to either an ACEI or ARB may be a powerful strategy to achieve blood pressure control in refractory hypertension.

34.3.3 Congestive Heart Failure

34.3.3.1 Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Combination

There is convincing evidence that dual RAAS blockade with ACEI and ARB is valuable in reducing cardiovascular events in select populations. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study evaluated individuals with New York Heart Association (NYHA) functional class II–IV congestive heart failure (CHF) and left-ventricular ejection fraction $\leq$40 %, and who were being treated with an ACEI. The addition of candesartan to ACE inhibition resulted in significant reductions in each of the primary outcomes, which included cardiovascular death and hospital admission for CHF [483 (38 %) patients in the candesartan group and 538 (42 %) in the placebo group experienced the primary outcome (unadjusted HR 0.85; 95 % CI 0.75–0.96, $p = 0.011$; covariate adjusted $p = 0.010$)] [18]. Similarly, Hamroff and colleagues found that the addition of losartan enhances peak exercise capacity, alleviates symptoms, and improves NYHA classification in patients with CHF who are severely symptomatic, despite treatment with maximally recommended or tolerated doses of ACEI [19]. The value of the ACEI/ARB combination in the treatment of CHF appears substantial.

34.3.3.2 Angiotensin-Converting Enzyme Inhibitor/Aldosterone Receptor Antagonist Combination

The Randomized Aldosterone Evaluation Study (RALES) investigated the role of spironolactone in treating individuals with NYHA Class IV Heart Failure and depressed left-ventricular (LV) function (EF $\leq$35 %). Of note, 95 % of the individuals in this study were on ACE inhibition during the study period. The addition of low-dose spironolactone conferred significant reduction (by about 30 % relative risk) in death and hospitalizations among the treated patients [20]. The median creatinine concentration in the spironolactone group increased by approximately 0.05–0.10 mg/dL and the median potassium concentration increased by 0.30 mmol/L, neither adverse event that would be considered clinically significant [20]. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), studied the effect of eplerenone (a selective aldosterone receptor blocker) combined with optimal medical therapy (including ACEIs and ARBs) on morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure. In the group treated with eplerenone, 86 % of the patients were receiving either ACEI or ARB therapy as part of optimal medical therapy [21]. At the 16 months follow-up, the eplerenone group had a significant reduction in all-cause and cardiovascular mortality (relative risk 0.85; 95 % CI 0.75–0.96, $p = 0.008$ and relative risk 0.83; 95 % CI 0.72–0.94, $p = 0.005$, respectively) [21]. Additionally, eplerenone use was associated with a reduction in the rate of sudden death from cardiac causes [21]. The benefits of eplerenone plus optimal medical therapy, including ACEIs and ARBs, was associated with only a small increase in serum potassium in the treatment group.

34.3.3.3 Beyond Angiotensin-Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker Combinations

MRAs and direct renin inhibitors (DRIs) are gradually finding their niche within the available armamentarium of RAAS blocking agents. In regards to DRIs, the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial was a multinational, randomized, double-blind study in which patients received 100 mg of losartan daily, patients were randomly assigned to receive 6 months of treatment with aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months) or placebo, in addition to losartan [22]. The primary outcome was a reduction in the ratio of albumin to creatinine. Treatment with 300 mg aliskiren daily, as compared with placebo, reduced the mean urinary albumin-to-creatinine ratio by 20 % (95 % CI 9–30; $p < 0.001$), with a reduction of 50 % or more in 24.7 % of the patients who received aliskiren as compared with 12.5 % of those who received placebo ($p < 0.001$) [22]. A small difference in blood pressure was seen between the treatment groups by the end of the study period (systolic: 2 mmHg lower, $p = 0.07$; diastolic: 1 mmHg lower, $p = 0.08$ in the aliskiren group) [22]. The total numbers of adverse and serious adverse events were similar in the groups [22].

A recent study examined the antiproteinuric effects of adding the MRA spironolactone, vs. losartan, to ACE inhibition (lisinopril 80 mg daily) in patients with diabetic nephropathy. Despite no differences in blood pressure, albuminuria decreased more in the spironolactone group than in the losartan group, when compared to placebo (34 % vs. 16.8 %) [7]. Similarly, the coadministration of eplerenone with enalapril substantially reduced albuminuria compared to enalapril alone in patients with diabetes without significant increases in serum potassium levels [8]. A recent meta-analysis evaluated the benefits and harms of adding selective and nonselective MRA in CKD patients already on RAAS blockade. In comparison to ACEI and/or ARB plus placebo, MRA along with ACEI and/or ARB significantly reduced 24 h proteinuria [7 trials, 372 patients, weighted mean difference (WMD) -0.80 g, 95 % CI −1.27 to −0.33] and BP [23]. This did not translate into an improvement in GFR (WMD −0.70 mL/min/1.73 m^2, 95 % CI −4.73–3.34) [23]. There was a significant increase in the risk of hyperkalemia with the addition of a nonselective MRA to ACEI and/or ARB (relative risk 3.06, 95 % CI 1.26–7.41) [23]. In two trials, addition of a selective MRA to an ACEI resulted in an additional reduction in 24-h proteinuria, without any impact on BP and renal function. The authors concluded that MRAs reduce proteinuria in CKD patients already on ACEIs and ARBs but increase the risk of hyperkalemia. The long-term effects of these agents on renal outcomes, mortality, and safety need to be established.

MRAs combined with either ACEIs or ARBs have proven beneficial for blood pressure control, albuminuria reduction, and regression of left ventricular hypertrophy (LVH). Krum and colleagues found that adding eplerenone to either ACEI or ARB in individuals with poorly controlled blood pressure resulted in improved systolic blood pressure control [24]. Moreover, adverse events were generally not

severe and did not significantly differ between the eplerenone and placebo groups [24]. The 4E study showed that the combination of eplerenone and enalapril resulted in a greater reduction in LV mass, albuminuria, and blood pressure than monotherapy [25]. Further clinical trials are necessary in this population to confirm the long-term, beneficial effects of dual RAAS blockade on renal outcomes.

34.4 Ongoing Clinical Trials

There are two large, well-powered, ongoing randomized clinical trials that will test the effects of dual RAAS blockade in diabetes populations at high risk for progressive kidney disease. The US Veterans Affairs NEPHRON-D is an ongoing randomized clinical trial designed to assess the effect of combination losartan and lisinopril, compared with losartan alone, on the progression of kidney disease [13]. The study aims to enroll 1,850 US veterans with type 2 diabetes and overt proteinuria, defined as a urine albumin creatinine ratio (ACR) >300 mg/g [13]. The primary outcome is the time to a composite end point of reduction in estimated GFR, end-stage renal disease (ESRD), and death. Follow-up is planned for up to 5 years [13].

Another trial, ALTITUDE, aims to determine whether aliskiren (a DRI), reduces the progression of kidney disease, cardiovascular disease, and death when added to conventional treatment, including an ACEI or ARB [4]. The study aims to enroll 8,600 participants with type 2 diabetes and macroalbuminuria (urine ACR $\geq$200 mg/g) or impaired GFR (estimated GFR <60 mL/min/1.73 m^2) [14]. The primary outcome is the time to first occurrence of the composite end point of cardiovascular death, resuscitated death, myocardial infarction, ESRD, or doubling of baseline serum creatinine concentration [14]. The planned follow-up time was 48 months. However, the data monitoring committee overseeing ALTITUDE recommended stopping the trial because patients were unlikely to benefit from the addition of aliskiren, and there was a higher incidence of adverse events with aliskiren compared to placebo [26]. Particularly, the use of aliskiren in addition to either ACEI or ARB was associated with an increased risk of nonfatal stroke, renal complications, hyperkalemia, and hypotension [26].

34.5 Adverse Events

Tolerability is one factor that restricts the broad application of dual RAAS blockade, particularly in individuals with chronic kidney disease. The main factors contributing to dual RAAS blockade intolerability are: reduction in renal function, hypotension/syncope, and hyperkalemia. Do these adverse events warrant more judicious use of dual RAAS blockade? To accurately answer this question, one must consider that not all patient populations have the same risk of adverse events associated with dual RAAS blockade, and, moreover, that the combination of

different RAAS blocking agents may not confer the same adverse event risk. Lastly, the threat of adverse events must be weighed against the potential benefit in reducing cardiovascular and renal events within select groups. A determination on the safety of dual RAAS blockade within various patient populations requires a thorough understanding of the adverse events reported in the available *dual RAAS blockade* trials.

In the ONTARGET trial, the primary outcome (death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure) occurred in 1,386 patients (16.3 %; relative risk 0.99; 95 % CI 0.92–1.07) in the combination group; when compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8 % vs. 1.7 %, $p < 0.001$), syncope (0.3 % vs. 0.2 %, $p = 0.03$), and renal dysfunction (13.5 % vs. 10.2 %, $p < 0.001$) [27]. In the renal outcomes of ONTARGET, the composite of dialysis, doubling of serum creatinine, and death was higher in the combination group [1233 (14.5 %); HR 1.09, CI 1.01–1.18, $p = 0.037$] [10]. Additionally, the secondary renal outcome (dialysis or doubling serum creatinine) was more frequent with combination therapy [212 (2.49 %); HR 1.24, CI 1.01–1.51, $p = 0.038$] [10]. Estimated GFR declined the least with ramipril compared with telmisartan [−2.82 (SD 17.2) mL/min/1.72 m^2 vs. −4.12 (17.4), $p < 0.0001$] or combination therapy [−6.11 (17.9), $p < 0.0001$] [10].

Previous studies have shown a risk for hyperkalemia in individuals with advanced proteinuric nephropathy requiring dual RAAS for proteinuria or blood pressure reduction. In a recent study, however, the risks for hyperkalemia associated with dual RAAS blockade were highest among those already on a maximal ACEI or ARB and an appropriately dosed diuretic that had a second RAAS agent added [28]. Specifically, those with an estimated GFR <45 mL/min and a baseline potassium >4.5 mEq/L were at the highest risk [28]. In the ONTARGET trial, a serum potassium >5.5 mmol/L was observed in 3.3 % in the ramipril group, 3.4 % in the telmisartan group, and 5.6 % in the combination group ($p < 0.001$ vs. ramipril) [1]. In the much smaller IMPROVE trial; the incidence of hyperkalemia did not differ between combination therapy (2.9 %) and ramipril (3 %) [29]. In the RALES study, spironolactone, 25 mg/day, added to an ACEI and loop diuretic increased median serum potassium concentration by 0.3 mEq/L compared with placebo, although only 14 cases of serious hyperkalemia were reported (compared with 10 for placebo) [20]. The termination of the ALTITUDE trial, despite the lack of details, indicates that the risk of ACEI or ARB with a DRI may be a significant concern, particularly in patients with diabetic nephropathy.

Compared with the clinical trial setting, the risk of hyperkalemia with dual RAAS blockade may be greater in practice, in which the *eligibility criteria* may be less strict and follow-up may be less frequent. This concern was demonstrated using an analysis of temporal trends following the publication of the RALES trial, of which a minimum of 95 % of participants were on dual RAAS blockade. In the general Canadian population, the prescription rate of spironolactone for patients recently hospitalized for heart failure rose dramatically after the online publication of RALES in 1999 [30]. Parallel temporal trends were observed for rates of hospital admission for hyperkalemia and in-hospital death associated with

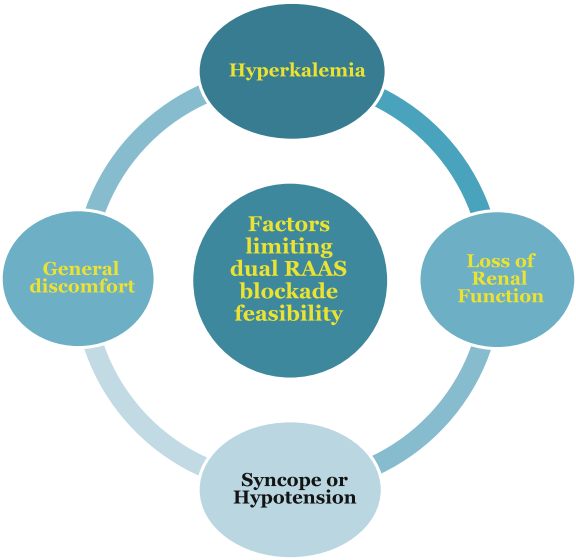

Fig. 34.1 Factors limiting the generalized use of dual RAAS blockade in CKD patients

hyperkalemia [30]. The rate of hospitalization for hyperkalemia rose from 2.4 per 1,000 patients in 1994 to 11.0 per 1,000 patients in 2001 ($p < 0.001$), and the associated mortality rose from 0.3 per 1,000 to 2.0 per 1,000 patients ($p < 0.001$). As compared with expected numbers of events, there were 560 (95 % CI 285–754) additional hyperkalemia-related hospitalizations and 73 (95 % CI 27–120) additional hospital deaths during 2001 among older patients with heart failure who were treated with ACEI in Ontario. Moreover, the addition of spironolactone did not reduce CHF readmission rates in this population. As is evident, increased vigilance is required of the physician when patients are treated with multiple RAAS blocking agents simultaneously.

Is the application of dual RAAS blockade feasible in individuals with chronic kidney disease? In a study to determine the feasibility of dual RAAS blockade (ACEI plus ARB), 47 CKD patients, mean age 59 years, with mean estimated GFR (eGFR) 26 mL/min/1.73 m^2 (range 13–49) and blood pressure 133/78 mmHg, were block randomized in an open study to 16 weeks of monotherapy with increasing doses of RAAS blockade aiming at enalapril 20 mg daily or candesartan 16 mg daily [31]. Thereafter, the complementary drug was added in incremental doses over a period of 5 weeks aiming at combined enalapril 20 mg and candesartan 16 mg for 3 weeks. Twenty-one patients (45 %) did not tolerate dual blockade in aimed dosages due to unacceptable plasma creatinine increase ($n = 12$, including two study withdrawals), hypotension ($n = 6$), general discomfort ($n = 2$), or unmanageable hyperkalemia ($n = 1$), see Fig. 34.1. Hyperkalemia >5.5 mmol/L was seen in 7 patients (15 %) [31]. The reduced dose group had baseline lower eGFR and diastolic blood pressure [31]. In short, 45 % of CKD stage 3–5 patients did not tolerate dual RAS blockade with 20 mg enalapril and

16 mg candesartan daily, primarily due to loss of renal function or hypotension. These risks must be weighed against the potential benefits of dual RAAS blockade in CKD populations and the soon to be described details behind the termination of the ALTITUDE trial with either ACEI or ARB with a DRI.

34.6 Conclusions

The emergence of safety concerns surrounding the use of dual RAAS blockade in the treatment of renal disease, especially in patients with diabetes, has evoked a more circumspect use of this treatment strategy to achieve desirable renal outcomes. Based on the current literature, the use of dual RAAS blockade for the treatment of nonproteinuric kidney disease seems dubious. In regards to proteinuric kidney disease, multiple observational studies have demonstrated that dual RAAS blockade reduces proteinuria to a greater degree than a single agent alone, particularly in diabetic nephropathy. Whether proteinuria reduction alone will equate to improved renal outcomes remains uncertain. Additionally, the ability of a dual RAAS blockade to confer cardiac protection in individuals with CHF has been substantiated. These benefits are evident in the literature whether looking at the ACEI/ARB combination or a combination of these drugs with a MRA or DRI. These benefits will have to be balanced against the potential risk of reduced renal function and altered potassium homeostasis, particularly in individuals with kidney disease.

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The Long-Term Effects of RAAS Blockade on Renal Function

35

César Cerezo and Luis Miguel Ruilope

35.1 Introduction

The existence of chronic kidney disease (CKD), described as albuminuria and/or an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, is particularly prevalent in the hypertensive population. The presence of elevated blood pressure (BP) significantly contributes to the development and evolution of cardiovascular (CV) and renal disease, and all the scientific guidelines recognize the need to achieve tight BP control [1, 2]. Moreover, the term *cardiorenal continuum* has come to substitute that of *CV continuum* [3], as originally described by Victor Dzau and Eugene Braunwald.

The requirement for a strict BP control was firstly proposed two decades ago in a meta-analysis of all available trials where antihypertensive drugs (mainly diuretics and beta-blockers) were compared to placebo [4]. The appearance of angiotensin-converting enzyme inhibitors (ACEIs) and, several years later, angiotensin receptor blockers (ARBs) [5] showed that their effects consisted not only of diminishing BP in an increment similar to that attained by other antihypertensive drugs, but also in their ability to protect the CV and renal systems beyond the advantage reached by a decline in BP. This benefit was first proven with regard to heart failure and postmyocardial infarction, but then also in CKD (particularly diabetic nephropathy with proteinuria) [5].

The success of ACEIs and ARBs in preventing and regressing target organ damage [particularly albuminuria and left ventricular hypertrophy (LVH)], together with their proven benefits when CV disease is established, have expanded the use of renin–angiotensin–aldosterone system (RAAS) blockers to the earlier stages

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of the cardiorenal continuum, particularly in patients with a high added risk due to the clustering of three or more CV risk factors, the presence of metabolic syndrome and diabetes, and the discovery of early target organ damage [1]. As a consequence, RAAS suppressors have became the most widely used form of monotherapy and combination therapy in the hypertensive population and have greatly contributed to improve the quality and duration of life for hypertensive patients with a high global CV risk profile [6].

However, recent data have suggested that CV disease could yet progress under chronic RAAS blockade [7], and that the progression of predictors of both CV and renal disease under chronic RAAS suppression, such as microalbuminuria, should be examined.

35.2 Renal Effects of Chronic Renin–Angiotensin–Aldosterone System Blockade

Renal disease has been widely recognized as an important complication of diabetes. Renal disease and hypertension constitute the two most common causes of end-stage renal disease (ESRD) [6]. On the other hand, growing evidence has continued to reveal the continuous relationship between worsening of renal function and CV disease, greatly and sharply increasing the risk of CV morbidity and mortality [8]. Indeed, renal dysfunction, including proteinuria and microalbuminuria, is nowadays considered an excellent predictor for the development of renal and CV complications, both morbidity and mortality [9, 10]. It reinforces the need to consider simultaneously CV and renal damage and treatment [11].

Since the initial description in 1985 of the capacity of captopril to reduce the amount of protein excreted in urine, the ability of RAAS suppression to reduce albuminuria has been sufficiently proven and RAAS blockade has been widely accepted as a positive therapy in terms of renal outcomes, especially in reducing micro- and macroalbuminuria. A group of placebo-controlled, randomized trials and meta-analyses published in the last decade have shown that both ACEIs and ARBs can have renoprotective properties and can also reduce all-cause mortality, especially in patients with diabetic nephropathy.

Two good examples are the Irbesartan Type II Diabetic Nephropathy Trial (IDNT) [12] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) [13] trials, which included patients with type 2 diabetes and nephropathy. In both trials, randomized treatments were administered on top of previous antihypertensive schedules, which excluded ACEIs, ARBs, and in the case of IDNT, calcium channel blockers. In the IDNT trial, irbesartan treatment was associated with a 20 % reduction, compared with placebo, in the primary renal end point (the composite of doubling of serum creatinine, end-stage renal disease, and all-cause death), essentially due to a 33 % reduction in the doubling of serum creatinine and a 23 % lowering in end-stage renal disease. During the 3.4 years of follow-up in the RENAAL trial, losartan obtained a

significant 16 % decrease in the primary renal end point (the same composite as in the IDNT trial), with important reductions in the doubling of serum creatinine and in end-stage renal disease. Losartan also caused a mean drop in proteinuria (measured as urinary albumin-to-creatinine ratio) of 35 % from baseline, while it showed an increased tendency in the placebo group ($p < 0.001$ for treatment effect).

Interestingly, the dose of RAAS suppressor used for treating hypertensive patients with albuminuria seems to play an important role in renoprotection. This is illustrated by the results of the Irbesartan Microalbuminuria in Type 2 Diabetic Subjects (IRMA 2) trial, which compared two doses of irbesartan (150 or 300 mg/day) with placebo in 590 patients with type 2 diabetes and persistent microalbuminuria [14]. The primary efficacy end point was the onset of overt nephropathy, defined as a urinary albumin excretion rate >200 μg/min and ≥30 % higher than at baseline. The level of urinary albumin excretion was reduced by 38 % in the irbesartan 300 mg group compared with a reduction of 2 % in the placebo group ($p < 0.001$). Irbesartan delayed the progression from micro- to macro-albuminuria, but the difference between the treatment and placebo group achieved a significant level only with the highest dose of irbesartan in the presence of equivalent BP reductions.

Recently, therapeutic intervention has taken place in the early stages of the cardiorenal continuum. Thus, in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial, 4,447 patients with type 2 diabetes and normoalbuminuria were randomly assigned to receive olmesartan (40 mg once daily) or placebo, with the possibility of adding other antihypertensive drugs (except for RAAS suppressors) as required to obtain BP target levels below 130/80 mmHg for a mean follow-up of 3.2 years [15]. Olmesartan delayed the time to new-onset microalbuminuria by 23 % ($p = 0.01$), and an adequate BP control was associated with a significantly lower occurrence of albuminuria in the active treatment group. The total number of CV events was low and was the same with both treatments. Nevertheless, there was an excess of coronary events in the olmesartan group compared with placebo, especially for those in the lowest quartile of systolic BP on treatment and those with the largest reductions in BP with treatment, which could at least partially explain the contributory role of excessive BP reduction resulting in the higher rate of CV events in these high-risk patients.

In conclusion, it is commonly accepted that a RAAS blockade is essential in patients with increased urinary albumin excretion with the dual aim of aiding BP control while reducing albuminuria [1]. This outcome has been shown to protect renal function and to delay the development of ESRD, principally in patients with macroalbuminuria [12, 13]. The absence of albuminuria when CKD is present (defined as an eGFR <60 mL/min) does not exclude the use of an ACEI or an ARB due to an increase in the global CV risk accompanying this situation [16].

35.3 Cardiovascular Aspects of Chronic Kidney Disease

The presence of CKD, usually considered as a form of target organ damage, can be detected throughout the CV continuum. There is a correlation between high levels of global CV risk and advanced CKD stages, affecting up to 35 % of the hypertensive population, and the high or very high added risk when presenting with an eGFR value below 60 mL/min/1.73 m^2 [17].

The coexistence of CKD and CV disease is accompanied by a significantly worse prognosis in conditions such as stable coronary artery disease, heart failure, coronary intervention, and peripheral arterial disease. The increasing progression of CKD, as defined by a continuous drop in eGFR, is accompanied by an increase in the amount of CV events and death.

Numerous data have been recently published highlighting the importance of the early detection of renal damage (including microalbuminuria) in the general population and in patients with essential hypertension independently of BP values, confirming the importance of microalbuminuria and CKD as CV risk factors in hypertensive patients. One of the most relevant, is a recent collaborative meta-analysis of general population cohorts involving more than 1 million participants, which has provided strong evidence for the direct relationship between renal dysfunction and CV risk. An estimated GFR rate <60 mL/min/1.73 m^2 and an albumin-to-creatinine ratio ≥1.1 mg/mmol (≥10 mg/g) were both independent predictors of mortality risk in the general population. These two parameters significantly augmented the mortality rate, without evidence of an interaction, verifying that an eGFR of 60 mL/min/1.73 m^2 and the lower limit of high-normal albuminuria [1.1 mg/mmol (10 mg/g)] are acceptable thresholds for risk estimation and for the definition and staging of CKD [18].

Additional subanalyses of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) trial [19] investigated the role of eGFR and albuminuria, but going further than conventional CV risk factor stratification and CV outcomes. Lower eGFRs and higher urinary albumin-creatinine ratios were related to the primary CV end point (the composite of CV death, myocardial infarction, stroke, and worsening kidney function). Albuminuria and eGFR were strongly associated with risk for long-term dialysis, while the results of the study greatly improved risk stratification for renal outcomes .

At the same time, the protective function of RAAS suppression in overt CV disease has been shown in patients with heart failure, post-myocardial infarction, and in individuals with high global CV risk, being especially relevant in those subjects with CV and renal disease. A good example of this issue is the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study [20], which included 9,193 patients with LVH and hypertension (average baseline BP 174/98 mmHg) that were assigned to receive losartan or atenolol (added to other antihypertensive treatments the patients were receiving, consisting mainly of diuretics) with the aim to evaluate the development of CV events and death. Considerable and similar BP reductions were obtained in both groups (30/17 mmHg in the losartan

group and 29/17 mmHg in the atenolol group). The risk of the primary end point (the composite of CV death, myocardial infarction, and stroke) was reduced by 13 % in the losartan group, with a significant decrease in risk of stroke of 25 % when compared with the atenolol group. CV and all-cause mortality were not significantly different between the treatment groups. However, in the subgroup of patients with diabetes at baseline, losartan treatment was associated with a reduction of 24 % in the primary end point, and significant reductions of 37 % in CV and 39 % in all-cause mortality [21]. In additional sub analyses in those patients, both the level of albuminuria at baseline and the reduction in albuminuria during treatment were predictors of CV events. Albuminuria decreased further with losartan than with atenolol, and significant reductions in CV and all-cause mortality with losartan were found only among patients in the highest quartile of baseline microalbuminuria [22].

In conclusion, CKD is frequently observed in arterial hypertension and is accompanied by a significant increase in CV risk that reinforces the need for a simultaneous protection of both renal and CV systems. Chronic RAAS blockade not only is effective in improving renal outcomes (especially albuminuria), but also protects from the development of atherosclerosis and established CV disease.

35.4 Limitations of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Blockade of RAAS is the elective treatment for managing high-risk hypertensive patients with or without diabetes, especially those patients in which albuminuria is already established or who are at an increased risk of developing renal damage.

Nevertheless, the initial demonstration of the beneficial effects afforded by ACEIs and ARBs has been shown to have limitations. Several different explanations could clarify why cardiorenal disease progresses under chronic RAAS suppression. First, the exact percentage of patients who do not respond to RAAS blockade is not yet known. Two good examples of nonresponders to this type of therapy are seen in the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) [23] and the ROADMAP [15] studies where a significant number of naive patients developed de novo microalbuminuria while being treated with an ACEI and an ARB at optimal doses. Additionally, RAAS suppression with only a single agent acting at one concrete location of the RAAS cascade may not be enough to prevent the evolution of target organ damage, and both angiotensin and aldosterone levels may return to pretreatment levels, or even increase in some patients, after an initial reduction (escape phenomenon); this has been observed in 30–40 % of hypertensive patients treated with an ACEI or an ARB, limiting their ability to block the RAAS and reducing the benefits afforded by a delay in the progression of CV and renal disease [7]. Finally, the use of RAAS suppressors at the highest recommended dose for hypertension would probably be insufficient to completely block the RAAS, failing the objective of delaying the development of

renal disease. Actually, several trials have suggested that very high doses of a single agent [24, 25] are much more effective in reducing proteinuria.

Additionally, current evidence has shown that CV and renal damage may develop even under long-term RAAS blockade [7], and the progression of predictors of both CV and renal disease, such as microalbuminuria, under chronic RAAS blockade seems to be ineffective in certain situations and in different groups of patients.

Clinical trials in patients with type 2 diabetes and normoalbuminuria have shown that the RAAS blockade can delay but not fully prevent the evolution of microalbuminuria, estimated at about 2 % per year [8]. In the BENEDICT trial, 1,204 hypertensive and normoalbuminuric subjects with type 2 diabetes were randomized to trandolapril, verapamil, trandolapril plus verapamil, or placebo for at least 3 years, with the aim to examine the development of persistent microalbuminuria. Although the ACEI, either alone or in combination, significantly reduced the albuminuria rate, there were still patients who developed microalbuminuria under ACEI (6.0 % of subjects receiving trandolapril alone and 5.7 % of subjects under combination therapy) [23]. In the ROADMAP study, although olmesartan significantly delayed the evolution of urine albumin excretion, microalbuminuria still developed in 8.2 % of patients receiving the ARBs vs. 9.8 % in the placebo group [15]. Likewise, in the ONTARGET trial, where the majority of participants had normoalbuminuria (including those with an eGFR 60 mL/min/1.73 m^2, who represented about 23 % of the population), albuminuria increased constantly during follow-up in all three groups of ramipril, telmisartan, and their combination [26].

The previous data relate to a retrospective study recently published concerning the evolution of albuminuria in a cohort of 1,141 normoalbuminuric patients who were treated at a hospital-based hypertension unit [27]. All patients had received a previous therapy for a minimum of 2 years before arrival at the unit of ACEI (47 % of patients) or ARB (53 %), at adequate doses, alone or in combination with other antihypertensive drugs (mainly diuretics or calcium channel blockers) for a minimum of 2 years before arriving at the unit. A 3 year follow-up was performed in all patients in whom RAAS suppression was maintained.

An elevated prevalence of albuminuria was observed at baseline (16.4 % microalbuminuric and 4 % macroalbuminuric) and new-onset microalbuminuria appeared in 16.1 % of normoalbuminuric patients while 1.0 % developed macroalbuminuria during the follow-up. The increase in microalbuminuria took place mainly during the first year, since 15 % of the normoalbuminuric patients at baseline were at the high-normal range of albuminuria (10–15 mg/day for men and 20–30 mg/day for women).

Of the cohort, 15.8 % of patients presented with previous CV disease at baseline and 4.6 % developed new CV events during the follow-up. Among patients with normoalbuminuria or high-normal albuminuria at baseline, the progression to micro- or macroalbuminuria was significantly higher in patients with previous CV disease than in those without it (17.2 % vs. 9.9 %, $p = 0.003$).

Progression to albuminuria was higher in patients presenting new CV events during the follow-up than in those without them (18.9 % vs. 10.7 %, $p = 0.057$).

Finally, the stronger predictors of microalbuminuria development were both glycemia and BP control (determined by the number of drugs needed to obtain the BP thresholds), but also the increase of baseline serum creatinine and baseline albuminuria at the high-normal level

35.5 The Concept of a Dual Blockade

The association of ACEI plus ARB was originally considered as a way to achieve a powerful blockade of the RAAS that would improve CV outcomes beyond BP reduction. Combined treatment with both has become an efficient therapeutic option against the development of CKD in patients with proteinuria, as well as against the progression to proteinuria in patients with microalbuminuria, but also in situations of congestive heart failure (CHF) with incomplete neurohormonal suppression (individuals without beta-blockers or intolerant of a sufficient dose of an ACEI) [28].

On the other hand, we have data which show that aggressive RAAS inhibition may produce harmful effects. The results of a meta-analysis published in 2007 demonstrated that combination therapy was more effective in reducing proteinuria, whereas there was a decrease in eGFR and a trend toward increased creatinine in the combination group. The conclusion of this meta-analysis is that proteinuria should be used as a surrogate marker for renal outcomes, limiting the use of combination therapy to diabetic nephropathy [29].

These data were confirmed by the results of the ONTARGET trial [30] where dual blockade with telmisartan and ramipril offered no benefit in patients with high global CV risk when compared to either of these drugs used in monotherapy, and it also showed an increase in the development of side effects. Therefore, combination therapy reduced the incidence of proteinuria, but produced a significantly increased risk of renal outcomes (dialysis or doubling serum creatinine), including a more rapid decrease in eGFR, and showed no benefit in terms of CV events or mortality. Moreover, BP control with this type of dual suppression has been widely described to be minor when compared to the one obtained by either ACEIs or ARBs used in combination with a diuretic or a calcium channel blocker.

The inhibition of renin activity offers a recent therapeutic option and has become helpful in limiting the first step of the RAAS cascade. Aliskiren, an oral direct renin inhibitor, has been shown to be not only effective in controlling BP alone or in combination with diuretics and calcium channel blockers in different stages of arterial hypertension in obese and metabolic syndrome patients [31], but also in reducing the progression of LVH and albuminuria when administered in addition to an adequate dose of an ARB, as published in the Safety and Efficacy of Aliskiren When Added to Standardized Losartan and Optimal Antihypertensive Therapy in Patients With Hypertension, Type 2 Diabetes and Proteinuria (AVOID) and

Aliskiren Left Ventricular Assessment of Hypertrophy (ALLAY) trials [32, 33]. However, the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) study, which was designed to evaluate the effects of a combination of aliskiren and ACEI or ARB versus ACEI or ARB used in monotherapy in patients with type 2 diabetes with increased urine albumin excretion and with an eGFR 30–60 mL/min/1.73 m^2 or a history of CV events, was cursorily concluded, following the advice of the monitoring committee [34], due to an increase in nonfatal stroke, renal complications, and hyperkalemia in the aliskiren group, which can basically reproduce the additive effects of hypotension and eGFR decline when adding powerful RAAS blocker in patients with previous optimal BP control.

The association of either ACEI or ARB with aldosterone receptor antagonists, both spironolactone and eplerenone, has been accepted as an important complementary management for CHF. The Randomized Aldactone Evaluation Study (RALES) trial revealed that treatment with spironolactone largely decreased morbidity and mortality in patients with severe CHF [35]. In the Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial (EPHESUS) study, eplerenone produced a significant reduction in the morbidity and mortality associated with left ventricular dysfunction and CHF in postmyocardial infarction patients when compared with placebo [36]. Similar positive effects with spironolactone when added to an ACEI and ARB for reducing proteinuria and preventing the progression of CKD [37], but also in subjects with true resistant hypertension [38], have been published. The growing evidence supports the notion that primary aldosteronism is more prevalent than usually considered. Nevertheless, low eGFR values might prevent its use because of the risk of hyperkalemia or worsening of renal function.

35.6 Conclusions

The treatment of hypertensive patients with RAAS suppressors has been extensively associated with positive CV and renal effects. An incomplete inhibition of the RAAS may be responsible for the residual organ damage and event incidence in patients with hypertension, diabetes, chronic kidney disease, and heart failure. Long-term RAAS suppression does not seem a reliable indicator in certain patients to avoid the progression of cardiorenal damage, mainly due to an escape phenomenon. Dual blockade with different RAAS suppressors has shown its ability to improve renal and cardiovascular outcomes, although recent data have raised doubts about of its safety. We need to know if the actual management of RAAS suppression is limited or whether it can be improved to better predict the outcome for these patients. Therefore, future randomized trials are needed to clarify which is the best way of improving RAAS suppression with the objective of reducing CV events, though with an adequate safety profile.

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