

YEAR IN CARDIOLOGY SERIES

The Year in Hypertension

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It has been a fruitful year in hypertension research, with many important publications since the previous review of the year in hypertension (1). This review distills some of the most important developments in the field of hypertension in the past year that will impact on the diagnosis and treatment of blood pressure (BP), as well as reviews some of the emerging concepts that will shape the approaches to treatment in the years to come.

Measurement of BP

Fundamental to the accurate diagnosis of hypertension is the method used to measure BP. Although office BP measurements have been the reference standard for many years, there is increasing use of self measurement of BP at home and 24-h ambulatory blood pressure measurement (ABPM). Unlike traditional office BP measurements, ABPM provides data on circadian variations of BP and the relative importance of nighttime versus daytime BP. In addition, disparities between office BP and ABPM have led to the concept of white-coat hypertension (i.e., BP elevated in the office but normal by ABPM), and more recently, masked hypertension (i.e., BP that is normal in the office but elevated by home BP measurement or ABPM). Important new information related to all of these issues and their prognostic significance has emerged in the past year.

Diagnostic thresholds using 24-h ABPM. These were revisited in a major study of ABPM in 5,682 participants (mean age 59.0 years, 43.3% women) in prospective population studies from Europe and Japan (2). Multivariate analyses were used to establish the ABPM thresholds, which yielded a 10-year cardiovascular risk similar to that associated with optimal (120/80 mm Hg), normal (130/85 mm Hg), and high (140/90 mm Hg) office BP measurements over a median follow-up of 9.7 years. After rounding the data, the approximate optimal 24-h average ABPM systolic/diastolic threshold was 115/75 mm Hg. The optimal daytime average was 120/80 mm Hg, and for nighttime was 100/65 mm Hg. Rounded thresholds for normal BP by

ABPM were 125/75, 130/85, and 110/70 mm Hg, respectively, and those for hypertension by ABPM were 130/80, 140/85, and 120/70 mm Hg, respectively (Table 1). These data suggest that population-based outcome-driven thresholds for optimal and normal ABP are lower than those currently proposed by international hypertension guidelines.

Home BP measurements—how often? How often should home BP be measured to obtain a standardized average for use in clinical practice? The authors of a recent study from Japan concluded that the average of single measurements twice per day (morning and evening) for 7 days was sufficient (3). However, an excellent accompanying editorial reviewed the dilemmas associated with standardizing the assessment of home BP measurement (4) and concluded that the recommendations of the European Society of Hypertension Working Group on Blood Pressure Monitoring should still be followed (5). Notably, duplicate morning and evening home BP measurements daily for 7 days. The measurements taken on the first day should be discarded, leaving at least 24 measurements to be averaged to obtain the home BP average.

The prognostic significance of office BP, home BP, and ABPM elevations. A common question relates to the significance of elevations of BP via one method but not another. A recent study addressed this important issue. Office BP, home BP, and ABPM were recorded between 1990 and 1993 in 2,051 people, and the individual and combined significance of these pressures with regard to cardiovascular outcomes was determined over 12 years of follow-up (6). Using a normal office and 24-h ABPM value as a reference, the hazard ratio for cardiovascular death progressively increased in those with an isolated office BP elevation (white-coat hypertension) or an isolated increase in 24-h ABPM (masked hypertension). Thus, white-coat hypertension and masked hypertension are not innocent entities, and those with elevations of BP recorded by all 3 measurement methods are at the highest risk of all (6).

Masked hypertension. This is defined as an elevated ABPM reading or home BP average but a normal office BP. It may occur in 10% to 30% of patients and was recently shown to carry a worse prognosis than white-coat hypertension (high office BP but normal ABPM or home BP) with regard to the development of atherosclerosis (7). Thus, it is important to recognize that a normal office BP does not exclude hypertension. Moreover, as home BP measurement

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Table 1 Proposed Outcome-Driven Reference Values for Ambulatory Blood Pressure Measurement

	24 h	Daytime	Nighttime
Optimal blood pressure, mm Hg	<115/75	<120/80	<100/65
Normal blood pressure, mm Hg	<125/75	<130/85	<110/70
Ambulatory hypertension, mm Hg	≥130/80	≥140/85	≥120/70

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becomes more popular, the detection of masked hypertension will increase. This diagnosis should be considered in patients who have clinical evidence of target organ damage but in whom office BP appears normal.

Central aortic pressure. Data from the CAFE (Conduit Artery Function Evaluation) study showed that different classes of BP-lowering drugs have a differential effect on brachial versus central aortic systolic and pulse pressures (8), and that central pressures may be a better predictor of cardiovascular outcomes in response to treatment when compared with brachial BP (8). Subsequently, data from the Strong Heart study have also shown that central aortic pressures may be a better predictor of target organ damage and outcomes than conventional brachial pressures (9). So should the assessment of central aortic pressures become a routine feature of the evaluation of the BP-modulating actions of drug therapies? The essence of this debate was captured in a recent consensus statement on central pressure measurements (10).

The Origins of Hypertension

Adiposity—an incubator for hypertension. There is little doubt that adiposity in young people predicts the risk of developing hypertension and associated metabolic risk factors. Longitudinal data from the Bogalusa Heart study tracked the association between obesity in childhood and the risk of developing hypertension (11). Excess adiposity, defined by a body mass index (BMI) or waist circumference, was present in one-fifth of those with normal BP, one-third of those with pre-hypertension, and more than one-half of those with hypertension. Moreover, these associations were evident in people as young as 4 to 11 years of age. These data suggest that the avoidance of obesity could markedly reduce the prevalence of hypertension in middle-aged adults. In support of the strength of the association between BMI and the risk of developing hypertension, a study of 36,424 Israel Defense Forces employees (mean age approximately 35 years) reported that BMI was the strongest predictor of pre-hypertension, with a 10% to 15% increase in risk for every 1 kg/m² increase in BMI (12). Recent studies have also highlighted that young people with pre-hypertension already have evidence of endothelial dysfunction (13) and cardiovascular structural damage (14,15).

Clinical significance of pre-hypertension. A study of 60,000 women followed up for 7 years in the Women's Health Study in the U.S. showed that pre-hypertension was associated with an almost doubling in risk of any cardiovas-

cular event, including death, myocardial infarction, stroke, or hospitalization for heart failure, when compared with those with normal BP (16). This risk in part relates to the elevated BP but also reflects the common association of pre-hypertension with features of the metabolic syndrome. In this regard, it was also reported that pre-hypertension is more common in people with diabetes and is associated with an almost 4-fold increase in risk of cardiovascular disease when compared with people without diabetes and normal BP (17).

A key question is whether earlier intervention with lifestyle intervention and/or BP-lowering therapy in younger patients would regress early structural damage and prevent further evolution of vascular structural changes. In this regard, a recent study of BP lowering in people with pre-hypertension showed improvement in markers of vascular damage (18). The importance of this kind of study is the acknowledgement that if we are to be effective at preventing the evolution of BP-mediated cardiovascular disease, rather than just treating the consequences of established damage, then treatment (lifestyle change and drug therapy) needs to begin earlier than currently advocated, and if drugs are used then they should be metabolically benign (19).

Arterial Structure and Function in Hypertension

Remodeling of small arteries linked to increased risk of cardiovascular disease and death. A previous study of patients with hypertension has suggested that the inward eutrophic remodeling of small arteries (resistance arteries), one of the earliest characteristics of hypertensive vascular structural change, is predictive of future cardiovascular events (20). A more recent study showed a clear link between an increased media/lumen ratio of small arteries from people with hypertension and an increased risk of cardiovascular events over a subsequent mean follow-up of 10 years (21). This remodeling link is most likely explained by the fact that such structural change is occurring throughout the cardiovascular system, as illustrated by the recent reports of an inverse relationship between BP status and coronary flow reserve (22) and between retinal arteriolar structural change and structural change elsewhere, that is, left ventricular hypertrophy (LVH), and the link between retinal vascular structural change (especially arteriolar narrowing) and the risk of death from ischemic heart disease and stroke (23).

Indices of large artery stiffness and cardiovascular outcomes. Adult ageing is associated with a progressive increase in systolic BP, a reduction in diastolic BP, and a widening of pulse pressure, consistent with a reduced compliance of large conduit arteries. It has been assumed that this stiffening process arises as a consequence of hypertension-mediated damage to elastic components of the arterial wall. However, it is also conceivable that inherent differences in arterial stiffness play a primary role in the development of systolic hypertension. In this regard, a recent report from Japan showed that brachial-ankle pulse wave velocity as an index of arterial stiffness predicted the likelihood of progression of BP status in younger patients over a 3-year period, from optimal through prehypertension to overt hypertension, thereby identifying arterial stiffness as an independent predictor for the development of hypertension (24). Increased arterial stiffness also seems to be more common in people with white-coat hypertension (25). Furthermore, other studies using an ambulatory arterial stiffness index as an index of arterial stiffness derived from ABPM identified arterial stiffness as an independent risk marker for target organ damage, cognitive function, and cardiovascular and renal outcomes (26–30).

Hypertension and the Heart

LVH. Left ventricular hypertrophy is associated with increased risk of cardiovascular morbidity and mortality in people with hypertension. Most of the data on this relationship have been derived in white Caucasian subjects. A recent large study from Northern Manhattan confirmed that LVH in Hispanic subjects had an approximately 3-fold increased risk of cardiovascular events when comparing those in the lowest and highest quartiles of left ventricular (LV) mass (31).

The association between traditional cardiovascular risk factors and the development of LVH has been clarified using magnetic resonance imaging to quantify LV mass and function in a population of 4,869 patients (mean age 62 years) without clinical cardiovascular disease. After adjustment for sociodemographic variables and height, higher systolic BP, increased BMI, diabetes, and current smoking were all associated with an increased LV mass and lower stroke volume and ejection fraction (32). Similar associations with an inappropriate LV mass were also reported from another study (33). As well as the BP load over 24 h, the rate of BP variation, that is, steeper BP oscillations, also seems to be an important determinant of LV wall stress and LVH (34), perhaps reflecting a stiffer cardiovascular system with less capacity to smooth variations in stroke volume.

Electrocardiographic (ECG) LVH is recognized to be a marker of poorer prognosis in people with hypertension. A recent study showed that LVH associated with a strain pattern on the ECG is associated with an even worse prognosis (35). A prolonged QRS duration is also associated

with greater LV mass, more wall motion abnormalities, and other markers of target organ damage in hypertensive patients, perhaps explaining why ECG QRS duration was shown to predict congestive heart failure (CHF) risk in a cohort of the Framingham population initially free of CHF (36).

LV functional impairment in hypertension. Recent findings suggest that diastolic and systolic function in people with hypertension is impaired earlier than anticipated in the evolution of hypertensive injury (37). The study used tissue Doppler imaging to derive systolic and diastolic velocities from the mitral annulus—a recognized early marker of subclinical LV dysfunction. The study reported a continuous relationship between reduced mitral annulus systolic and diastolic velocities with increasing LV mass in people with hypertension, beginning at LV mass values clearly within the current normal range (37). A study subsequently examining the impact of antihypertensive therapy on diastolic function in people with hypertension was evaluated over 38 weeks. There was improvement in diastolic relaxation time with BP lowering, but there was no obvious drug-specific benefit in this short-term study comparing an angiotensin receptor blocker (ARB) with treatment that avoided inhibition of the renin-angiotensin system (RAS), illustrating that BP lowering is overwhelmingly important to improving diastolic function, irrespective of the presence of LVH, baseline BP, or age (38).

Left atrial (LA) size. There has been recent interest in LA size in hypertension and its prognostic significance for the development of atrial fibrillation (AF). It is clear that AF is more likely to develop in hypertensive patients with LVH and an increased LA size. Evidence from recent trials with regard to the prevention of AF with angiotensin receptor blockade was recently reviewed (39). Of related interest, the pathophysiological determinants of LA size, methods of assessment, and prognostic significance of LA size were also comprehensively reviewed (40).

In light of the aforementioned associations between the magnitude of LV structural changes and the functional and electrophysiological consequences, it is reassuring that more effective regression of ECG LVH with antihypertensive therapy reduces the risk of developing AF (41) and also reduces the risk of sudden cardiac death (42).

BP and heart failure. There has been recent interest in the relationship between BP and heart failure in 2 contexts. First, the prognostic significance of systolic BP and outcomes in patients admitted to hospital with acute heart failure, and second, BP as a risk factor for the development of heart failure. In a major study of over 48,000 patients admitted with acute heart failure in the U.S., patients in the lowest quartile of systolic pressure <120 mm Hg had the highest in-hospital and 3-month post-discharge mortality rate (43). These findings of systolic BP as an important prognostic indicator for people admitted to hospital with acute heart failure, consistent with previous studies that have reported adjusted relative risks for mortality from 0.78 to 0.90 for each 10-mm Hg increase in SBP (44).

It is well accepted that elevated BP is a risk factor for the development of CHF. However, the diurnal pattern of BP may also be important. In a prospective community study from Sweden in relatively healthy men, free of LVH, heart failure, or vascular disease at baseline, an increased nocturnal pressure on ABPM, especially when associated with “non-dipping” of nocturnal BP, conveyed additional risk of developing CHF beyond conventional office BP measurements (45). It is intriguing to speculate whether more effective interventions to lower nocturnal BP would ultimately provide greater protection against the development of CHF.

Hypertension and Stroke

The treatment of hypertension in patients with ischemic stroke and hemorrhagic stroke has been specifically addressed in 2 recent comprehensive guidelines (46,47). Both guidelines acknowledge the great uncertainty that remains about when and how to optimally intervene with BP-lowering treatment in the setting of acute ischemic or hemorrhagic stroke.

With regard to acute ischemic stroke, a number of important therapeutic conundrums are discussed in detail (46) and the guideline panel concludes that definite answers to the key questions about the clinical management of BP in the acute stroke setting are not available. However, pragmatic recommendations are provided and the guideline panel did suggest that emergency treatment to lower BP would be indicated when systolic BP >220 mm Hg and/or diastolic BP >120 mm Hg and that BP lowering should be cautious, aiming for a 15% to 25% reduction in the first day. For those patients who were previously treated for hypertension, treatment should generally be reinstated, usually approximately 24 h after the acute event (46).

With regard to spontaneous intracerebral hemorrhage (ICH) (47), BP is correlated with increased intracerebral pressure (ICP) and volume of hemorrhage. However, it is unknown whether this relationship is a cause or a consequence, and indeed, it could be either in different settings. There has also been concern that overaggressive lowering of BP, particularly in the setting of a raised ICP, might result in enhanced damage in the ischemic penumbra, that is, the edematous region around the hemorrhage. The case for BP lowering is strongest for those bleeding from a ruptured intracerebral aneurysm or arteriovenous malformation, in whom the risk of rebleeding is highest. However, whether more aggressive control of BP in the first few hours after ICH can reduce bleeding without compromising brain perfusion is still unclear. If systolic BP >200 mm Hg or mean arterial pressure >150 mm Hg, then aggressive BP lowering is recommended with intravenous therapy (47). This approach may also be warranted at lower BP levels with careful monitoring of ICP (4).

Mechanisms of enhanced stroke risk in hypertension.

Stroke risk increases in people with stiff conduit arteries, and this is likely to be a key mechanism accounting for an increase in ischemic stroke risk with age. The endogenous nitric oxide (NO) synthase inhibitor, asymmetric dimethyl-arginine (ADMA), increases vascular tone and functional stiffness in cerebral blood vessels. A study examined the impact of systemic subpressor dose of ADMA on arterial stiffness and cerebral perfusion in humans. This study showed that subpressor doses of ADMA increase vascular stiffness and decrease cerebral perfusion in healthy subjects, implying a potentially important role for vascular stiffness in the pathogenesis of cerebrovascular disease (48). Another study showed that arterial stiffening with age results in a reduction in carotid flow velocity but a marked increase in carotid systolic and pulse pressures, attributable to greater systolic pressure augmentation with age and arterial stiffening. These changes could account for enhanced risk of microvascular damage in the brain in older hypertensive patients (49).

These observations may provide a basis for more effective modulation of cerebral pressures by reducing the late systolic augmentation. Consistent with the aforementioned observations regarding ADMA, one way of doing this might be the use of drugs that enhance NO availability in the vessel wall, such as NO donors. A recent study examined the effect of the NO donor glyceryl trinitrate, administered via a transdermal patch, on cerebral blood flow (CBF) and cerebral perfusion pressure (CPF) in patients with recent stroke (50). They showed that glyceryl trinitrate lowered central systolic BP by 22 mm Hg but did not alter global CBF or CBF or CPF to the contralateral or ipsilateral hemispheres, or the area of stroke oligemia, penumbra, or core. Thus, the treatment was effective at reducing cerebral pressures without inducing cerebral steal. Clearly, these findings provide a pathophysiological basis for studies of the use of NO donors in acute ischemic stroke and in the prevention of stroke. With regard to the latter, the challenge will be to develop the means of delivering NO on a consistent basis, in sufficient quantities, without the development of tolerance.

Moving away from the acute stroke setting, a recent comprehensive review of the treatment of hypertension for the primary and secondary prevention of stroke concluded that the most important determinant of outcome was the quality of BP control, and that BP control usually remains suboptimal (51). This was underscored by a 5-year follow-up of patients who had suffered their first stroke in Australia; 82% of patients after suffering their first stroke were hypertensive, and that BP control remained suboptimal in 30% and the patient was unaware of their hypertension in 7% (52).

BP and cognitive function. Another important aspect of brain protection is the prevention of cognitive decline. The treatment of hypertension in the Honolulu Asia Aging Study of Japanese American men followed up since 1965

showed that the treatment of hypertension substantially reduced the risk of dementia by as much as 60% when compared with those with never-treated hypertension. Importantly, the benefit accrued in proportion to years of treatment, thus the earlier the treatment starts, the better (53). Another European study of elderly men with treated hypertension showed a similar reduction in risk of cognitive impairment and dementia when compared with untreated patients (54). These studies highlight the importance of hypertension in the pathogenesis of cognitive decline and dementia, and the power of effective treatment of BP to prevent it—this will become especially important as our populations age and focus shifts toward strategies to preserve cognitive function.

Hypertension and the risk of developing new-onset diabetes. It is well recognized that people with hypertension have an increased risk of developing diabetes, even when untreated. It is also recognized that this risk can be further influenced by antihypertensive therapy. A long-term follow-up study of patients from Sweden evaluated the risk of developing diabetes in a cohort of 754 men with hypertension, ages 47 to 54 years, screened for cardiovascular risk factors and followed up for 25 to 28 years (55). A total of 148 (20%) treated hypertensive patients developed diabetes during 25 years, and in a multivariate Cox regression analysis, body mass index, serum triglycerides, and treatment with beta-blockers were positively related with the development of new-onset diabetes. Importantly, the development of new-onset diabetes was associated with an increased risk of stroke (hazard ratio [HR] 1.67), myocardial infarction (HR 1.66), and mortality (HR 1.42). The time from onset of new diabetes to stroke or myocardial infarction was approximately 9 years. This is important because clinical trials are usually of shorter duration than this and most likely underestimate the enhanced cardiovascular risk associated with the development of new-onset diabetes. In another study, a network meta-analysis was used to assess the risk of developing new-onset diabetes with different treatment strategies for hypertension (56). A network meta-analysis makes a number of assumptions, that is, if drug A causes more diabetes than drug B, and drug B more than drug C, then it is assumed that drug A will cause more diabetes than drug C. Initial treatment with a diuretic was the reference standard for the comparison of the various drug classes. As shown in Figure 1 (56), the association of antihypertensive drugs with incident diabetes was lowest with ARBs and angiotensin-converting enzyme (ACE) inhibitors, followed by calcium channel blockers (CCBs) and placebo, beta-blockers, and diuretics in rank order. Together, these studies suggest that the risk of developing new-onset diabetes: 1) is influenced by the class of antihypertensive therapy used to lower BP, 2) is more likely in people with obesity, an elevated baseline blood glucose level, and features of the metabolic syndrome, and 3) is associated

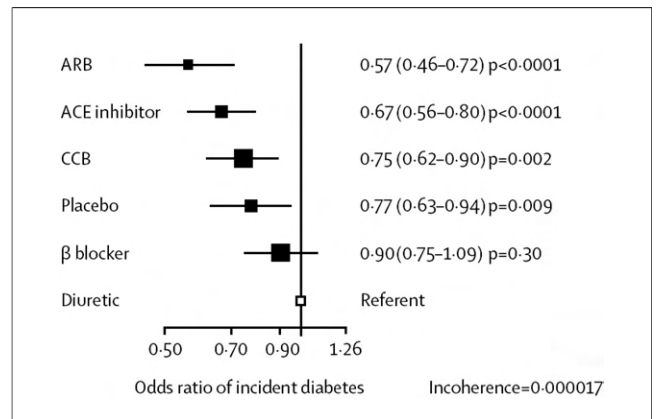


Figure 1 Network Meta-Analysis of New Onset Diabetes Associated With Antihypertensive Therapy

Initial diuretic therapy was used as referent agent (open box at odds ratio = 1.00). Size of squares (representing the point estimate for each class of antihypertensive drugs) is proportional to number of patients who developed incident diabetes. Horizontal lines indicate 95% confidence intervals. Odds ratios to the left of the vertical line at unity denote a protective effect (compared with initial diuretic). Individual pairwise comparisons between diuretic versus beta blocker were not significantly different (p = 0.30) and were significantly more likely to increase the risk of new diabetes when compared with other treatments, including placebo. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker. Reprinted with permission (56).

with an enhanced risk of developing major cardiovascular complications, if patients are followed up long enough for them to occur.

Genetics of Hypertension

An industry has grown around the genetics of hypertension, and there have been some spectacular discoveries of specific gene defects associated with rare causes of hypertension (e.g., Liddle and Gordon syndromes). Crucially, where progress has been made, the phenotype has been distinct. Tackling the genetic basis of essential hypertension would predictably be more of a challenge because the condition is heterogenous, the diagnostic criteria are a moving target, and there is a very strong lifestyle impact. Furthermore, even in well-characterized animal models (e.g., the spontaneously hypertensive rat), fed a mundane diet, and living a standardized lifestyle, identifying a genetic cause has proved elusive. Thus, although the results of the largest ever genome-wide association study of 7 common diseases (including hypertension) were eagerly awaited by the hypertension geneticists, the results were predictable to many (57). The study found no significant gene associations with hypertension. A number of reasons for this were discussed, including: 1) hypertension may indeed have fewer common risk alleles of larger effect sizes than some of the other complex phenotypes, 2) perhaps common susceptibility variants of large effect size were present but remained undetected by the specific single nucleotide polymorphism genotype sets used in this study, and perhaps more extensive screening of the genome would reveal more, and 3) the problem of accurate

identification of the hypertensive phenotype and the possibility that hypertensive patients may have been misclassified in both the affected and the control populations, thereby diluting the power of the study. The latter seems the most likely explanation. Blood pressure classification was based on office BP measurements—clearly some of these patients may have had white-coat hypertension, and some of the control subjects may have had masked hypertension, diluting the power of the study to find associations. It is remarkable that the genetic aspects of these studies are so rigorous and elegant and yet the phenotyping is so rudimentary—little progress will be made until this is addressed.

Lifestyle and Nonpharmacological Interventions

Sodium intake and cardiovascular risk. All international hypertension guidelines recommend dietary sodium restriction. However, the impact of this strategy on cardiovascular disease outcomes had been poorly defined until recently (58). This study used data from the long-term follow-up (10 to 15 years) of people originally allocated to 2 randomized, controlled trials of sodium restriction. Those allocated to sodium reduction had a 30% lower incidence of cardiovascular events in the next 10 to 15 years, irrespective of gender, ethnic origin, age, body mass, and BP. Interestingly, the people randomized into these studies were not hypertensive (BP approximately 125/85 mm Hg). It is conceivable that the benefits, impressive as they are, might have been even greater in a hypertensive population. Importantly, a recent meta-analysis has also highlighted the importance of salt intake in the genesis of hypertension in children and the effectiveness of sodium restriction at reducing BP (59). These findings reinforce current guideline recommendations and underscore the importance of education and national health policies to reduce dietary sodium.

Alcohol and BP. Using data from the National Health and Nutrition Examination Survey (NHANES) (1999-2000), the relationship between alcohol intake and BP for a sample of the U.S. adult population was examined. An alcohol intake of up to 2 drinks per day had no effect on BP. However, there was a gender-related effect of alcohol intake in excess of 2 drinks per day on BP, with increased BP observed only in men but not in women (60). Further information on the relationship between alcohol consumption, impact of consumption patterns, and types of alcohol consumed with regard to vascular function and hypertension subtypes was provided in a detailed review (61).

Sleep and BP. Characteristically BP decreases during sleep, and an absence of this nocturnal dip in BP has been associated with an increased risk of cardiovascular events. A recent longitudinal analyses of the first NHANES ($n = 4,810$) examined the impact of sleep duration on the risk of developing hypertension (62). This risk was increased by approximately 2-fold in adults in middle age who sleep ≤ 5 h each night. Even after adjusting for obesity and diabetes

(the risk of which also increase with sleep deprivation), the risk remained approximately 1.6-fold. There are a number of mechanisms that might account for this relationship; it may simply reflect a higher 24-h average BP load and longer duration of sympathetic nervous system activation as a consequence of less time asleep. In turn, this would give rise to a higher risk of longer-term cardiovascular structural damage, leading to sustained hypertension. Whatever the mechanism, doctors should consider sleep deprivation in their assessment of people developing hypertension.

Obstructive sleep apnea (OSA) and hypertension. There is a clear association between OSA and hypertension. An apnea-hypopnea index of ≥ 15 , (i.e., breathing decreases or stops ≥ 15 times per hour of sleep) is associated with a 3-fold increase in the risk of developing hypertension (63). Against this background, a recent randomized, double-blind study of patients with hypertension and OSA showed that 2 weeks of continuous positive airway pressure (CPAP) was effective in lowering both nighttime BP and to a lesser extent daytime BP when compared with sham CPAP (64). These findings further support the concept that chronic sleep disturbance can play a significant role in the pathogenesis of hypertension. Further studies will be required to determine whether such interventions in suitable individuals are also effective at reducing the risk of cardiovascular events as well as BP.

Diuretic Therapy for Hypertension

Although thiazide-type diuretics are often viewed as a single class, there has been much debate about the relative potencies of different thiazide-type diuretics. This was addressed in an 8-week cross-over study comparing treatment with chlorthalidone 12.5 mg/day (force-titrated to 25 mg/day) and hydrochlorothiazide 25 mg/day (force-titrated to 50 mg/day) in 30 untreated hypertensive patients (65). The main outcome was 24-h ABPM assessed at baseline and week 8. The decrease in BP was significantly greater with chlorthalidone 25 mg/day compared with hydrochlorothiazide 50 mg/day (24-h mean $-12.4/-1.8$ mm Hg vs. $-7.4/-1.7$ mm Hg); the differences were most notable for nighttime BP in favor of chlorthalidone. The incidence of hypokalemia was similar for both treatments. These data show that chlorthalidone is more effective in lowering systolic BP than hydrochlorothiazide, especially at night, reflecting a longer duration of action. Whether these differences are clinically important is unknown because there have been no head-to-head outcome trials with thiazide-type diuretics. However, it is intriguing that the majority of fixed-dose combination therapies that include a thiazide use hydrochlorothiazide rather than chlorthalidone; perhaps combinations with the latter would have been even more effective.

Diuretics for drug-resistant hypertension. Diuretic therapy is increasingly used for the treatment of drug-resistant hypertension. Low-dose spironolactone was recommended

as a step 4 treatment option in the British Hypertension Society guidelines in 2004 (66). In so doing, the guideline committee acknowledged a lack of clinical trial evidence to support this pragmatic recommendation. Spironolactone 25 mg once daily was the recommended fourth-line treatment for patients with uncontrolled BP in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) (67). In this setting, spironolactone, when added to existing therapy, which involved a mean of approximately 3 other drugs, resulted in an impressive approximately 22/10 mm Hg decrease in BP and was generally well tolerated, with 6% of patients discontinuing the treatment because of gynecomastia or breast discomfort and 2% because of hyperkalemia. Almost identical decreases in BP approximately 22/9 mm Hg were observed in another smaller observational study in which spironolactone 25 mg daily was added to the treatment of patients already receiving 3 or more drugs, one of which was an ACE inhibitor or an ARB (68). In a further retrospective study of 340 patients with uncontrolled BP despite treatment with at least 2 drugs in the U.S., 42 received add-on spironolactone therapy and the rest received a variety of other drugs (69). The decreases in BP in those receiving spironolactone averaged approximately 23.13 mm Hg, which was significantly greater than the decrease in those receiving other treatments, approximately 8/6 mm Hg.

Together, these data suggest that with appropriate monitoring of serum potassium and sodium levels and prior exclusion of patients with significant renal impairment, the addition of low-dose spironolactone therapy can be very effective at producing significant reductions in BP in people with drug-resistant hypertension. In those patients in whom this strategy is effective but the spironolactone is poorly tolerated because of breast discomfort, my practice is to use high-dose amiloride (typically 20 mg/day), or higher doses of thiazide-type diuretics. Further studies are required to build on these observations and define the optimal treatment strategies for patients with patients with drug-resistant hypertension.

Thiazide diuretics: hypokalemia and glucose metabolism. Thiazide diuretics are associated with an increased risk of developing diabetes in some people with treated hypertension. A long-held view has been that the underlying mechanism is related to diuretic-induced hypokalemia. This hypothesis was explored in a quantitative review of the relationship between thiazide-induced hypokalemia and glucose intolerance (70). The study used data from 59 clinical trials involving 83 thiazide diuretic study arms. The findings suggested that thiazide-induced hypokalemia was associated with increased blood glucose. This observation is intriguing and raises many thoughts. To my knowledge, there have been no studies that have formally reported a relationship between hypokalemia and incident diabetes in hypertension outcome trials—presumably this could be analyzed. Moreover, if thiazide-induced increases in blood glucose are driven by hypokalemia, then why has no relationship between chronic hypokalemia (e.g., in Conn

syndrome or Gittleman syndrome) and impaired glucose tolerance or risk of incident diabetes been reported? Moreover, could the protective effect of ACE inhibition or ARBs against the development of diabetes simply be a function of their capacity to increase serum potassium, or limit its decrease when used in combination with diuretics? In this regard, would the use of potassium-sparing diuretics in combination with thiazides reduce the risk of developing diabetes?

It is remarkable that as we enter the 50th anniversary of the launch of thiazide diuretics for the treatment of hypertension, so many fundamental questions remain unanswered. There is little doubt that novel, more effective, and better tolerated diuretic-based treatments could still emerge when clinical science rises to the challenge.

New Treatments and New Targets

There are already many effective drugs for the treatment of hypertension. It is therefore exciting to witness the emergence of new classes of drugs in a challenging market. The burden of disease is enormous, and it is unlikely that all therapeutic targets have been exhausted by existing treatments.

Direct renin inhibition. The renin system has been a popular target for drug therapy for hypertension dating from the discovery of the first ACE inhibitor, captopril, in 1977 and the first ARB, losartan, in 1988. Now the first direct renin inhibitor (DRI) for clinical use (aliskiren) has emerged. Renin was in fact the first target for inhibiting the renin system, with the description of pepstatin in 1971. However, progress in drug development was hampered by the fact that the first inhibitors were peptide analogues that had to be administered parenterally. The first orally active agents were bedeviled by problems of poor bioavailability (<2%), a short half-life, and poor BP-lowering efficacy (for review see reference 71). Eventually, aliskiren emerged as the first nonpeptide, orally active renin inhibitor to be launched as treatment for hypertension. Aliskiren has high specificity for renin and is a potent renin inhibitor. It still has low bioavailability (approximately 3%) but has a long half-life (approximately 24 h), which is attractive for the once-daily treatment of hypertension. Aliskiren is not metabolized by the cytochrome p450 system and is primarily eliminated unchanged in the bile, with <1% excreted in the urine. There seem to be no clinically important pharmacokinetic interactions. The adverse effect profile looks similar to placebo in phase II trials in humans, the main adverse effect being diarrhea at high doses, that is, at 600 mg/day, thus the recommended maximum dose is 300 mg/day (72). At these doses, aliskiren in monotherapy seems to have similar BP-lowering efficacy as other therapeutic approaches to blockade of the renin system. However, there are differences in the neurohumoral profile in response to blockade of the renin system with these different treatment strategies (Table 2). This has led to much speculation about the relative merits of each approach (73).

Table 2 Effects of Inhibitors of the Renin System on Enzymes, Substrates, and End Products

	Enzymes		Substrates			End Products	
	PRA	PRC	Angiotensinogen	Angiotensin I	Bradykinin	Angiotensin II	Aldosterone
Beta-blockers	↓	↓	NA	NA	NA	NA	NA
Renin inhibitors	↓	↑	NA	↓	NA	↓	↓
ACE inhibitors	↑	↑	↓	↑	↑	↓	↓
ARB	↑	↑	↓	↑	NA	↑	↓
ACE inhibitors plus ARB	↑↑	↑↑	↓↓	↑↑	↑	NA	↓
Renin inhibitors plus ARB	↓	↑↑	NA	NA	NA	NA	↓↓

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NA = data not available; PRA = plasma renin activity; PRC = plasma renin concentration (not including pro-renin). Adapted from Staessen et al. (71).

The most intense debate with DRIs has been about the role of pro-renin, the level of which increases after treatment with DRIs. Elevated pro-renin levels have been considered as a possible mediator of target organ damage because of an association in a number of studies between elevated pro-renin levels and diabetic microvascular disease and nephropathy. This area is complex, and recent data suggest that pro-renin may bind to a renin/pro-renin receptor that has been localized to the heart, liver, brain, and kidney. In vitro studies have suggested that binding of pro-renin to this receptor can generate angiotensin at the cell surface, supporting the hypothesis of increased tissue activation of RAS in the presence of high pro-renin levels. It has been suggested that the binding of aliskiren to the pocket in the prorenin/renin molecule may lead to a conformational change that prevents pro-renin binding to the receptor, thereby preventing tissue activation of RAS (for review of mechanisms, see reference 74). This hypothesis clearly needs testing in large-scale trials, and targeting the prevention of diabetic nephropathy and microvascular disease in this regard seems an attractive proposition.

With the availability of different methods of inhibiting the renin system, another concept that has been investigated is whether combining the DRI with another means of inhibiting the renin system, for example an ARB, in maximum recommended doses would be more effective than monotherapy with either at lowering BP. The combination of DRI and ARB was more effective at lowering 24-h ambulatory BP than either the DRI or ARB alone (approximately 4/3 mm Hg greater decrease in BP with the combination), with no significant increase in adverse effects with the combination (75). Moreover, the incidence of renal impairment or hyperkalemia was low in this group. There is little evidence to suggest that increasing the dose of the ARB or DRI beyond their recommended maximum would have achieved this magnitude of additional BP lowering, although few such studies have used ABPM to document the BP response. It should be added that the BP response to this combination is less than would be expected from combining the DRI with a thiazide diuretic or a CCB. So from a pure BP-lowering perspective, the DRI/ARB combination is unlikely to be the most effective option. However, if the speculated benefits of more complete blockade of

the renin system for target organ protection are real, then this may be the preferred strategy, both from a neurohumoral perspective and from a side effect profile—future trials will reveal all!

So, when to use DRIs for people with hypertension? They are likely to be as effective at lowering BP in monotherapy as other means of inhibiting the renin system, that is, ACE inhibition or ARBs, but with less side effects than ACE inhibition. The contraindications to their use are similar to other forms of RAS blockade. DRIs are likely to be especially effective in younger white patients who in general have a more active renin system, and in any patients receiving diuretics or CCBs, in whom their renin system will have been activated. They may also ultimately develop a role in other areas in which inhibition of the renin system has been effective, notably in heart failure and renal disease. The challenge will be to convert the promise for enhanced target organ protection into evidence.

A vaccine for hypertension? Furthering the efforts to develop techniques to inhibit the renin system, perhaps one of the most remarkable reports in the past year was of the preliminary results from a vaccination development program to immunize people with hypertension against angiotensin II (76). A construct of a virus-like particle linked to an angiotensin-like peptide was found to be highly immunogenic in mice and rats. Its administration to spontaneously hypertensive rats reduced systolic BP, similar to that with treatment with an ACE inhibitor (76). The investigators then immunized 12 healthy human volunteers with a similar construct to measure the immunogenicity of the antibody to angiotensin II. All subjects generated an antibody response, but no hemodynamic data were reported from this phase 1 study. Although the concept is intriguing, it is worth taking a step back and questioning whether a vaccine approach is safe and appropriate for people with hypertension, when it is unlikely to be reversible, could generate immune complex-mediated disease, and so many excellent therapeutic options are already available to inhibit the RAS. I would concur with the views expressed in the excellent critical editorial of Dr. Menard on the subject (77).

Acupuncture for treating hypertension? It has been claimed that the ancient Chinese art of acupuncture is an effective treatment for BP. Claims that have recently been

subjected to formal clinical trials. The SHARP (Stop Hypertension With Acupuncture Research Program) prospective, double-blind, randomized, sham-controlled, parallel-group study compared twice-weekly active acupuncture with an invasive sham acupuncture for 6 weeks in 192 patients who had been weaned off their BP-lowering medication 3 weeks previously. The conclusion of the study was that active acupuncture provided no greater benefit than the invasive sham procedure (78). Another study reported the results of a single-blind randomized controlled trial of 160 adult patients with grade 1 or 2 hypertension on stable BP-lowering therapy or no therapy from a single institution. The participants received BP-specific acupuncture or sham acupuncture on 22 occasions over 6 weeks. This study used ABPM to record the BP changes and reported that there was a significant 6 mm Hg greater reduction in ambulatory systolic BP at the end of the 6-week treatment period in the active acupuncture group. However, thereafter BP returned to pre-treatment values within 12 weeks (79). It seems at best that acupuncture may have a modest BP-lowering effect but that this effect may not be seen in all patients and does not persist beyond treatment withdrawal, thus continuous treatment (2 to 3 times per week) would be required to sustain the BP reduction. This may be a preferable option to drug therapy for a few patients, but the long-term efficacy is unknown and would need to be monitored, and recurrent treatments of this type will be costly and time-consuming. I cannot see it catching on!

Soluble guanylate cyclase (sGC) activators. Activation of sGC would be expected to increase cyclic guanosine monophosphate levels in target tissues, resulting in vasodilatation and an antiproliferative effect, properties that would be an attractive template for novel drug therapy for the treatment of hypertension. It was recently reported that BAY41-2272, a novel, orally active stimulator of sGC, can lower the BP and inhibit the cardiac hypertrophy and fibrosis in rats with angiotensin II-induced hypertension (80). I would also anticipate that this treatment would also reduce large artery stiffness and would be a particularly effective means of lowering central aortic systolic pressure, beyond the benefits observed on brachial BP. The only potential problem might be the fact that activation of sGC would be expected to inhibit platelet aggregation and thus prolong bleeding time. Although this would be beneficial in some patients, the impact of sGC activators on bleeding complications would be important to evaluate in phase II and III trials. Nevertheless, this is an exciting new approach to treatment and has the potential to be a very effective BP-lowering agent for older patients with systolic hypertension and others with stiff conduit arteries, that is, people with diabetes.

Targeting the Vascular Wall

Advanced glycation cross-link breakers. Increased stiffening of large conduit arteries with ageing and disease is

associated with a widening pulse pressure and increased brachial systolic pressure. It is also associated with a central aortic pressure relative to brachial pressure. A major mechanism accounting for the increased vascular wall stiffness with ageing is the accumulation of advanced glycation end-products (AGEs) within the vascular wall. The AGEs form abnormal cross-links with vascular wall collagen, reducing vascular compliance, thereby increasing arterial stiffness. The AGEs also quench nitric oxide, impairing endothelial function, which also increases arterial stiffness. Thus, targeting AGEs and reducing their presence within the vascular wall seems an attractive option. Such AGE cross-link breakers as alagebrium chloride previously have been shown to improve arterial stiffness in aged animal models and older humans with systolic hypertension. However, clinical trials of alagebrium for systolic hypertension have been disappointing with regard to brachial systolic pressure lowering (81). However, this does not preclude an important effect on endothelial function, arterial stiffness, and central aortic pressure and hemodynamics, which may be a more important target. A recent report supports this concept from a clinical study of 13 adults, mean age 65 years, who were administered oral alagebrium twice daily for 8 weeks (82). This resulted in marked improvements in endothelial function (as determined by flow-mediated dilatation) and central aortic hemodynamics and pressures, despite only a small but insignificant decrease in brachial pressure. It is surely too early to abandon hope of directly improving the functional characteristics of the aorta as a means of reducing cardiovascular risk. Importantly, brachial BP may not reveal such benefits, and the obsession of regulators with using brachial BP as the sole arbiter of drug efficacy in hypertension may prevent the development of novel and more effective strategies to reduce risk in these patients.

Marfan syndrome—a paradigm for vascular wall therapy. A natural model of degenerative aortic disease in Marfan syndrome, an autosomal dominant connective tissue disorder caused by mutations in the fibrillin-1 gene (FN1). Marfan syndrome is characterized by progressive aortic stiffening, dilatation, and rupture. The current recommendation for the treatment of hypertension in Marfan syndrome is with beta-blockade because of their effect to reduce the $\Delta P/\Delta T$ in the aortic root. It is noteworthy, however, that this recommendation is based on a single trial of 32 patients (83). Recent studies have directly implicated the RAS in the pathogenesis of the vascular wall changes in Marfan syndrome via a mechanism that involves transforming growth factor (TGF)-beta. The hypothesis is that FN-1 normally sequesters TGF-beta and deficiency in FN-1 because of its mutation leads to increased activation of TGF-beta. In a mouse model with a FN-1 gene mutation that mimics the Marfan syndrome aortic phenotype, an ARB (losartan) was more effective than a beta-blocker (propranolol) at preventing dilatation of the aortic root—indeed, the aortas of the animals treated with losartan were

indistinguishable from those of wild-type controls (84). These exciting developments were further evaluated in a small double-blind, placebo-controlled trial with an ACE inhibitor (perindopril) in patients with Marfan syndrome to measure its impact on aortic stiffness and root diameter over 24 weeks on a background of beta-blocker therapy. The ACE inhibitor reduced aortic stiffness and aortic root diameter and also reduced systemic markers of TGF-beta activation. (85). There now follows another clinical trial of young people with Marfan syndrome comparing a beta-blocker (atenolol) with an ARB (losartan) on progression of aortic root diameter over 3 years (86). The findings will be important, and whatever the outcome, this series of studies is an example of translational science at its best.

Strategies for improving the control of BP. Beyond the focus on monotherapy, a recent study has also highlighted the possibility of improving BP control by combining multiple BP-lowering drugs in low dose in a single pill (87). This study compared the BP-lowering efficacy of a single capsule containing a quarter of the standard dose of 4 antihypertensive agents (amlodipine, atenolol, bendroflumethiazide, and captopril) with standard doses of these agents in monotherapy in a parallel group design for 4 weeks. The reduction in mean arterial pressure with the combination of approximately 19 mm Hg was significantly greater than that with individual agents, ranging from 6 to 11 mm Hg. This small study establishes proof of principle for this approach to improving the magnitude and reducing heterogeneity in the BP response to therapy. Longer-term studies would be required to establish the tolerability of multidrug combinations and to define the optimal combination; nevertheless, the concept is an important pragmatic way to improve the BP response with a single BP-lowering pill.

Another way to improve long-term BP control is to encourage patients to continue to take their treatment! A recent study assessed the impact of the comprehensive pharmacy care program on medication adherence and BP and low-density lipoprotein cholesterol control (88). The comprehensive pharmacy program consisted of 3 elements: individualized medication education, medications dispensed using an adherence aid (blister packs), and regular follow-up with clinical pharmacists. Compared with usual care, the comprehensive pharmacy program substantially improved medication adherence and the control of systolic BP. However, it does seem that the intervention needs to be sustained for the adherence benefit to persist, and thus the cost effectiveness of this intervention would need to be evaluated.

Do statins reduce BP? Statins are very effective at reducing the risk of ischemic stroke and heart disease in people with hypertension. This has prompted the question of whether statins may exert some of this benefit by lowering BP. This question was addressed in a comprehensive meta-analysis of 20 trials and 828 patients receiving statin therapy in whom BP was recorded and concomitant BP-lowering therapy (if any) remained unchanged during treatment (89). Statins seemed to exert a small but significant effect on systolic BP

(−1.9 mm Hg) and a nonsignificant effect trend on diastolic BP (−0.9 mm Hg). The effect was greatest in those with higher BP at baseline. The BP response to statins was unrelated to age, changes in serum cholesterol, or length of the trial. Whether statins exert a greater effect beyond brachial BP on central aortic BP will soon be reported from the CAFÉ (Conduit Artery Functional Evaluation) study (90).

Recent clinical outcome trials of BP-lowering therapies.

There are a paucity of data on the impact of BP medications on cardiovascular outcomes in patients from Asia. The Jikei heart study contributed to the database with a randomized controlled trial, using a prospective randomized open blinded endpoint design, conducted in Japan (91). This study recruited 3,081 patients (mean age 65 years) who were receiving conventional treatment for hypertension and had coronary heart disease, heart failure, or a combination of these disorders. In addition to their conventional drug treatment (not including an ARB), the patients were randomly assigned to an ARB, valsartan (mean dose 75 mg/day) or other treatment, avoiding the use of an ARB. The primary end point was a composite of cardiovascular morbidity and mortality. At baseline, 67% of the patients were receiving a CCB, 35% an ACE inhibitor, 32% a beta-blocker, and approximately 10% a diuretic. The baseline BP was 139/81 mm Hg. After a median follow-up of 3.1 years, the primary end point was significantly reduced by 39% in the group assigned to valsartan, mainly because of a lower incidence of incidence of stroke and transient ischemic attacks, angina pectoris, and heart failure. There was no difference in mortality, and the effects on myocardial infarction and renal end points were neutral. Office BP at the end of the trial was similar in both groups, approximately 132/77 mm Hg. So, how can the results of the Jikei heart study be explained and reconciled with the results of the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) study (92), in which CCB-based treatment (with amlodipine) was associated with fewer myocardial infarctions and strokes when compared with therapy based on the ARB valsartan? In the VALUE study, the CCB-based therapy produced more effective BP lowering, especially in the early phase of the study, and this is the most likely mechanism accounting for the superiority of the CCB, especially at preventing stroke—the simple but important message is that putative drug-specific benefits of BP-lowering drugs can rarely if ever overcome superior BP control with regard to preventing major cardiovascular disease (CVD) events in large-scale clinical trials, it simply does not happen. In support of this conclusion, a recent post-hoc analysis of the VALUE trial that examined only those patients who remained on monotherapy was reported. This was interesting because the BP in the valsartan versus amlodipine treatment arms were similar throughout the trial, and in this case there was no difference in major outcomes, apart from heart failure, which was more effectively reduced by the ARB as expected (93). With regard to the Jikei heart study and mechanisms, it is also noteworthy

that the baseline treatment with RAS blockade (approximately one-third) was relatively low in this population at higher risk of CVD, and it is conceivable that the better coverage with blockade of the RAS in valsartan arm of the Jikei heart study provided the added protection beyond brachial BP. In this regard, it is also possible that more effective lowering of central aortic pressure in the valsartan arm could have driven some of the benefit, although this remains speculative in the absence of data on central aortic hemodynamics.

Further analyses of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) also emerged in the past year when data from a comparison of outcomes in the CCB (amlodipine, $n = 9,048$) versus ACE inhibitor (lisinopril, $n = 9,054$) arms of the trial were reported (94). To recap, the primary outcome of ALLHAT was combined fatal coronary heart disease or nonfatal myocardial infarction. The secondary outcomes included all-cause mortality, stroke, combined CVD, end-stage renal disease, cancer, and gastrointestinal bleeding. Over a mean follow-up of 4.9 years, BP control was similar in nonblack patients, but the CCB provided better BP control in black patients, consistent with the National Institute for Health and Clinical Excellence/British Hypertension Society (NICE/BHS) guideline recommendations (see the following text). No significant differences were found between treatment groups for the primary outcome, all-cause mortality, end-stage renal disease, or cancer. Stroke rates were higher on lisinopril in black subjects, consistent with the poorer BP control with the ACE inhibitor in this group, but were similar in nonblack subjects in whom BP control was similar. Overall, the rates of combined CVD events were higher with the ACE inhibitor because of higher rates for strokes, peripheral arterial disease, and angina. As expected, the rates of heart failure were lower with lisinopril. Gastrointestinal bleeds and angioedema were higher on lisinopril. This finding, along with the finding of a neutral effect on cancer rates between treatment arms, is important because it dismisses prior concerns about higher rates of cancer and gastrointestinal bleeding with CCBs that emerged from earlier case-control studies, highlighting that such studies are riddled with confounding factors that cannot be adequately controlled and should never be used to inform health policy, or worst, alarm patients. This analysis also suggests that the combination of an ACE inhibitor and a CCB might be a particularly happy marriage for BP lowering and CVD prevention.

Lowering BP in people with diabetes significantly reduces the risk of CVD morbidity and mortality and microvascular disease. The recently reported ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation) trial examined the impact of an ACE inhibitor (perindopril)/thiazide-type diuretic (indapamide) combination versus placebo on top of conventional therapy on vascular events in 11,140 people with type 2 diabetes (95). An important design feature of

this trial was the fact that the BP-lowering combination therapy was added irrespective of baseline BP levels or the use of other BP lowering drugs. The primary end point was a composite of major macrovascular and microvascular events, including death of cardiovascular disease, nonfatal stroke or nonfatal myocardial infarction, and new or worsening renal or diabetic eye disease, over a mean follow-up of 4.3 years. The active therapy was associated with a lower BP ($-5.6/-2.2$ mm Hg) versus placebo treatment. This modest BP reduction was associated a significant 9% risk reduction in major macrovascular and microvascular events, an 18% reduction in cardiovascular death, and a 14% reduction in all-cause mortality. Importantly, there was no evidence that the benefits of additional BP-lowering therapy differed according to initial BP level—in other words, even those within lowest BP strata at baseline experienced a similar relative risk reduction to those in the highest BP strata. Moreover, the lowest BP strata included patients whose BP was already below the currently recommended treatment target for type 2 diabetes ($<130/80$ mm Hg). It is also important to note that this result was achieved in a population of patients with high concomitant use of statins, antiplatelet drugs, ACE inhibition, and good glycemic control, in both arms of the trial. This trial provides the strongest evidence yet to support the safety, tolerability, and efficacy of a “lower is better” philosophy for BP control in people with diabetes and that the modern treatment goal should perhaps be “the lowest pressure the patient will tolerate without an adverse impact on function.”

Hypertension Treatment Guidelines

A number of treatment guidelines related to the treatment of hypertension have recently been published. In the United Kingdom, the NICE, working in collaboration with the BHS, issued an updated guideline for the treatment of hypertension in primary care in June 2006 (96,97). This guideline was the result of a comprehensive systematic review of clinical trial data and concluded that initial therapy for hypertension should be with an A drug (ACE inhibitor, or ARB if an ACE inhibitor was not tolerated) in younger, nonblack people, that is, <55 years, and a CCB (C drug) or thiazide-type diuretic (D drug) drug in older people, or black subjects at any age, to guarantee the most effective BP-lowering efficacy with initial therapy. This guideline went beyond usual guideline recommendations by providing very specific recommendations for preferred combinations of therapy if BP was not controlled with monotherapy, notably A + C or A + D at step 2, and A + C + D at step 3. Beyond step 3, further diuretic therapy, for example, higher doses of thiazide-type diuretic, or addition of another diuretic, for example, low dose spironolactone, was recommended. A bold and controversial recommendation of this guideline was the removal of beta-blockers as a preferred routine therapy for hypertension because the data analysis had suggested that this class of drugs was: 1) less

effective at preventing stroke than other treatments; 2) no more effective in the primary prevention of myocardial infarction (despite popular dogma); 3) was more likely to induce new-onset diabetes; and 4) the least cost-effective treatment option for routine hypertension. This does not preclude the use of beta-blockers at step 4, or in patients who had a specific indication for beta-blockade, for example, symptomatic angina, after myocardial infarction, or in chronic stable heart failure. This view of the NICE/BHS guideline regarding the routine use of beta-blockers for hypertension was supported by a subsequent Cochrane review (98) and other reviews and editorials (99–102). The metabolic effects of beta-blockers, and in particular their adverse effect on weight loss, also was recently reported (103).

The European Society of Cardiology (ESC), working in collaboration with the European Society of Hypertension (ESH), also released new guidelines for the treatment of hypertension in 2007 (104). This guideline provides a very comprehensive review of the assessment of hypertensive patients with regard to target organ damage and cardiovascular risk and also contains specific recommendations of BP measurement, investigations of secondary hypertension, and drug treatment in special situations, for example, pregnancy, the elderly, stroke, renal disease, and so on. This guideline does not define a preferred initial therapy for routine hypertension. An important aspect of the ESC/ESH guideline is continued recognition in Europe of the importance of targeting cardiovascular disease risk and not just BP when considering the treatment of hypertension in an individual patient—advocating the more widespread use of statin therapy in particular, and antiplatelet therapy when safe and appropriate, to optimize cardiovascular risk reduction.

The World Health Organization (WHO), in collaboration with the International Society of Hypertension (ISH), have also focused attention on the need to consider total CVD risk and have provided a new WHO/ISH CVD risk chart that could be readily applied to low-income and middle-income countries (105).

With regard to CVD risk, the recent position statement from the American Heart Association on the treatment of hypertension for the prevention and management of ischemic heart disease (IHD) was disappointing (106). This 27-page document focused on differences between BP-lowering drugs and addressed whether some drugs might “go beyond blood pressure” with regard to the prevention of IHD. Surely this missed a key opportunity to give prominence to the importance of statin therapy as the most effective means of going “beyond blood pressure” for the prevention of IHD and stroke in people with treated hypertension? Remarkably, the authors did concede that “There are no special contraindications in hypertensive patients to the use of . . . lipid-lowering agents for the management of STEMI [ST-segment elevation myocardial infarction].” Contraindications! I would suggest that a physician would struggle to justify not using statin therapy in such patients and in others with hypertension! A good example, if we needed another one,

why modern guidance must be focused on total CVD risk assessment and intervention.

Recent Reviews of Hypertension

In addition to the topics covered in this overview of the year in hypertension, there have been a number of very good reviews and topical overviews of different aspects of hypertension. The topics include atherosclerotic renovascular disease and related ongoing trials (107), clinical aspects of chronic hypertension in pregnancy (108), isolated systolic hypertension in the elderly (109), a review of the presentation and clinical diagnosis and treatment of pheochromocytoma (110,111), the effects of nonsteroidal anti-inflammatory drugs on BP (112), the role of the sympathetic nervous system in the pathogenesis of metabolic syndrome (113), and the eye in hypertension (114), along with a comprehensive seminar in hypertension (115).

Conclusions

The past year has been an eventful one for hypertension research, and 2008 promises to be an even more eventful year, with a record number of long-awaited major clinical outcome trials due to report their findings. Findings that should answer some key questions: 1) What is the preferred combination of antihypertensive therapy for hypertension, the routine use of an ACE inhibitor plus a thiazide diuretic or a more contemporary combination of ACE inhibition with a CCB? 2) Is there any difference between ACE-inhibitor-based versus ARB-based therapy for cardiovascular protection, and does the combination of these agents provide more (or less)? 3) What are the benefits of BP lowering in the very elderly? 4) What is the optimal treatment for diastolic heart disease in hypertensive patients? 5) Further major studies of BP lowering in acute stroke and the secondary prevention of stroke. Thus, there will be no shortage of information for next year’s review of the year in hypertension, which will focus on the implications of these key clinical trials.

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