Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 8, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.06.074

YEAR IN CARDIOLOGY SERIES

The Year in Hypertension

Bryan Williams, MD, FRCP, FAHA
Leicester, United Kingdom

This review focuses on published works in 2005, up to April 2006, that have implications for clinical practice in the clinical management of hypertension. It has been an eventful year with a number of key publications. We have gained new insights into the epidemiology of hypertension and better characterization of the "hypertensive phenotype" that poses challenging questions about when and how to begin treatment in people at risk of developing hypertension. We have also begun to gain a better understanding of the clinical significance of atrial fibrillation in people with hypertension and of the treatment strategies for its prevention. Further studies have yielded important new information about the differential impact of blood pressure (BP)-lowering drugs on central aortic pressure and its potential role in clinical outcomes. These studies have complemented new data from major clinical outcomes trials that have served to consolidate the evidence base for some aspects of existing hypertension treatment guidance but also have questioned the role of beta-blockade as a routine treatment for hypertension. This has been an invigorating year of discovery that has begun to shift the foundations that have previously provided a stable platform for current thinking. There seems little doubt that these new data will be the catalyst for new ideas and ultimately a reappraisal and revision of hypertension treatment guidelines in the year to come.

THE GLOBAL BURDEN OF HYPERTENSION

Recently, the global prevalence of hypertension (defined as an average systolic BP of 140 mm Hg or greater, a diastolic BP of 90 mm Hg or greater, or the use of antihypertensive medication) was estimated for the year 2000 and the data used to predict the global prevalence of hypertension by 2025 (Fig. 1) (1). More than 25% of the world's adult population was hypertensive by the aforementioned criteria in 2000. The estimated total number of people with hypertension in 2000 was 972 million, and this is projected to increase by 60% to a total of 1.56 billion by 2025, that is, 29% of the worldwide adult population. Most of this increase is expected to result from an increase in the number of people with hypertension in economically developing regions, so that almost 75% of the world's hypertensive population will reside in economically developing countries by 2025. Although hypertension is more common in economically developed countries (37.3%) than in those classified as undergoing economic development (22.9%), hypertension is a greater population burden in economically developing countries because of their much larger populations.

These projections for 2025 are based on the assumption that the country, age, and gender-specific prevalence estimates remain constant and are likely to be conservative, mindful of the rapidly changing lifestyles, and in particular the increasing prevalence of obesity and sedentary lifestyles in these regions, which increases the risk of developing hypertension. Overall, the prevalence of hypertension in all regions increases with age, more steeply in women. By the age of 60, more than half of adults in most regions of the world will be hypertensive, with the lowest current and projected rates in India and Asia and the highest rates in Latin America and the Caribbean, former Socialist Republics, and sub-Saharan Africa. These alarming figures highlight that high BP is set to remain the single most important preventable cause of premature death worldwide over the next 2 decades.

HYPERTENSION AWARENESS, DETECTION, AND CONTROL

Data on control rates for hypertension are periodically released worldwide, and the data for the U.S. were recently reviewed (2). The U.S. NHANES (National Health and Nutrition Examination Survey) studies have revealed a steady increase in awareness of hypertension (70%), up to 2000, an increase in treatment rates (~55%) but less progress in the percentage of those with hypertension whose BP is controlled to recommended goals on treatment, which continues to hover around 25% (Fig. 2). It should be noted, however, that the criteria for control have been tightened from <160/95 mm Hg in the earlier NHANES surveys to <140/90 mm Hg in the most recent. The Healthy People 2010 report (3) targets a control rate for the U.S. population of 50% in 5 years, which would only be reached if at least 80% of people with hypertension were aware of their condition, 90% were treated, and 70% of those treated had their condition controlled (4)—there is still much work to be done if these laudable aspirations are to be realized.

The reasons for the slow progress on BP control rates are many and have been recently comprehensively reviewed (2), but perhaps an important and less commonly appreciated reason is that the earliest indicators of the "hypertensive

From the Department of Cardiovascular Sciences, University of Leicester School of Medicine, Leicester, United Kingdom. Dr. Williams has received grant support for investigator-led research (Pfizer and Merck); honoraria for presentations at scientific meetings (Pfizer and Merck); and consultancy (Pfizer, Merck, and Novartis).

Manuscript received June 20, 2006; accepted June 28, 2006.

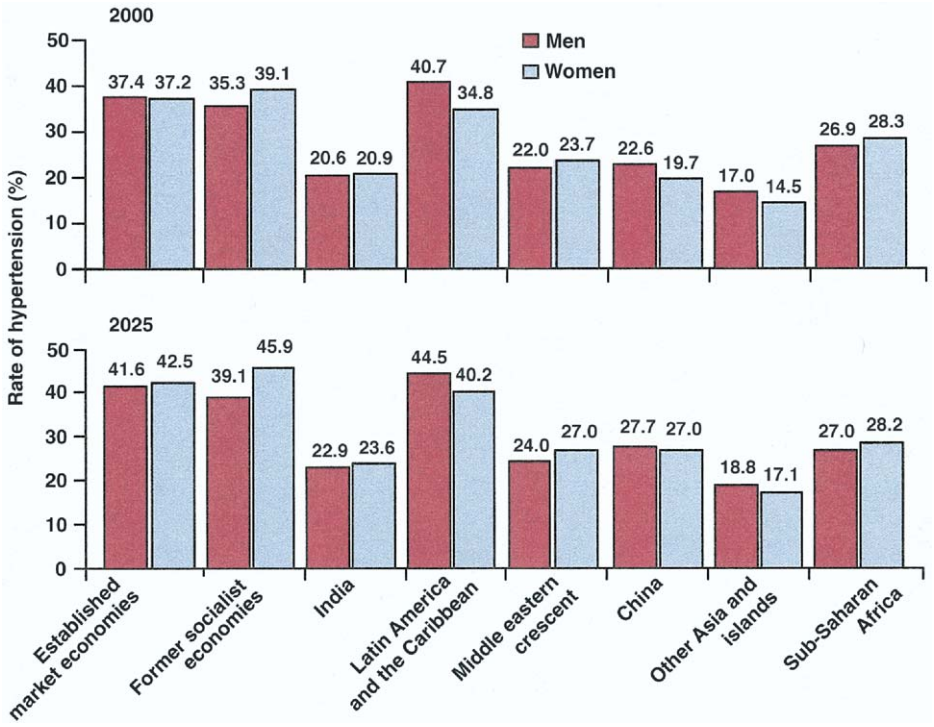

Figure 1. Frequency of hypertension in people ages 20 years and older by world region and gender in 2000 **(upper panel)** and projected to 2025 **(lower panel)**. Reprinted with permission from Kearney et al. (1).

phenotype" are overlooked until hypertension is well established and thus more resistant to treatment. This concept has been reinforced by the data discussed later.

THE HYPERTENSIVE PHENOTYPE

It has been suggested that the cumulative lifetime risk of developing hypertension approaches 90% in a Western population (5), a trend that is likely to follow in developing countries without lifestyle modification. This observation prompts 2 questions: 1) is there a hypertensive phenotype that could be identified early? 2) If there is such a phenotype, would early intervention in the "prehypertension" phase lead to the prevention of hypertension, or at least reduce the risk of developing more severe/resistant hypertension, and thereby help challenge the stubbornly poor control rates of more established hypertension? These are key questions that have begun to be addressed by studies in the past year.

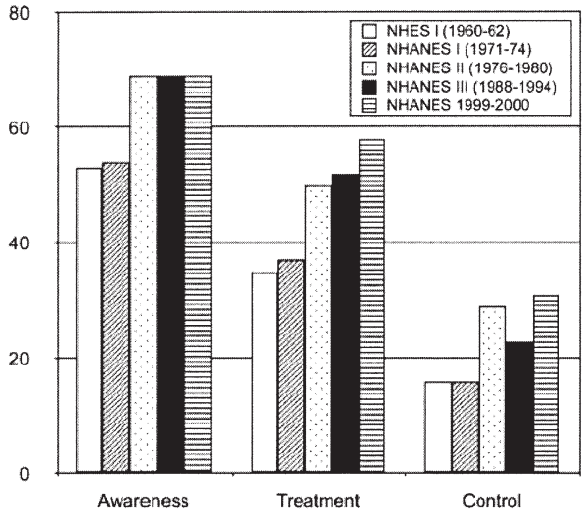

Figure 2. Trends in awareness, treatment, and control of hypertension in the U.S., 1960 to 2000. Definition of blood pressure control is <160/95 mm Hg for NHES (National Health Examination Survey), NHANES (National Health and Nutrition Examination Survey) I, and NHANES II and <140/90 mm Hg for NHANES III and NHANES 1999 to 2000. Reprinted with permission from Wang et al. (2).

The risk factors for developing hypertension in adults were recently evaluated from the Strong Heart Study, a population-based longitudinal cohort study of cardiovascular risk factors in Native Americans from 3 communities in Arizona (6). Unsurprisingly, initial BP was a strong predictor of incident hypertension. However, incident hypertension could also be predicted by a person's initial metabolic profile and unfavorable metabolic variations over time. Even in those with optimal initial BP levels (<120/80 mm Hg), increasing abdominal obesity and abnormal lipid profile were major predictors of the development of hypertension. The participants were examined at baseline, at 4 years, and at 8 years. In those with a normal baseline glucose tolerance, as well as an optimal BP, higher baseline waist circumference and systolic BP, as well as evidence of diabetes at 4 years, increases in systolic BP and waist circumference, and a decrease in high-density lipoprotein (HDL) cholesterol from baseline to the second examination predicted hyper-

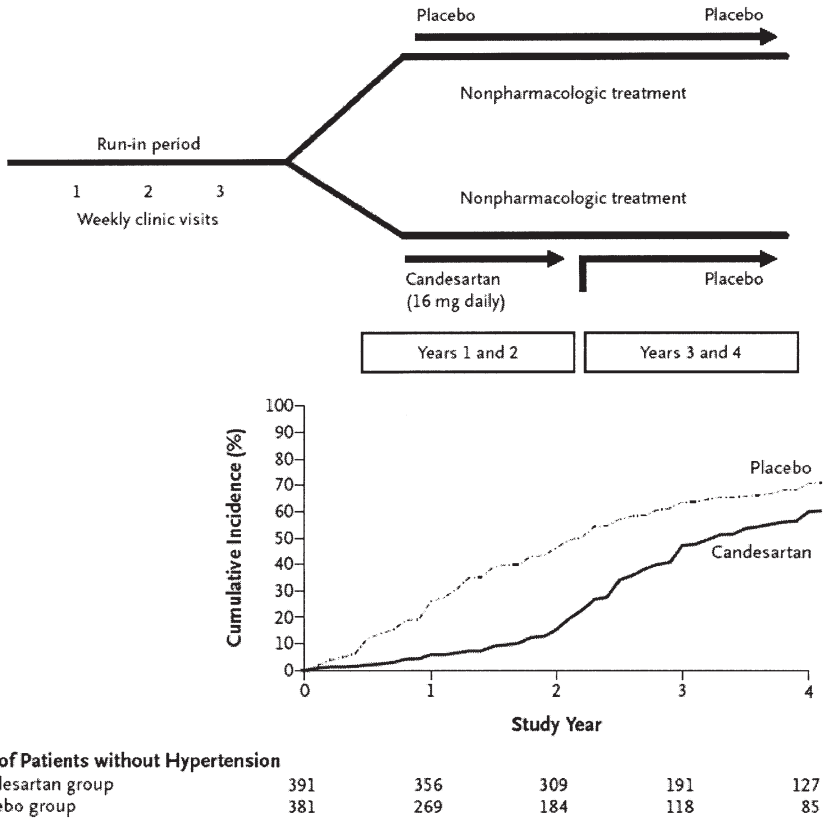

Figure 3. TROPHY (Trial of Preventing Hypertension) study design **(upper panel)** and Kaplan-Meier analysis **(lower panel)** of new-onset clinical hypertension. Reprinted with permission from Julius et al. (11).

tension at 8 years. It was also of interest that the 4-year decrease in HDL cholesterol was as strong an independent predictor of 8-year incident hypertension as the baseline level of systolic BP. Similarly, a recent report examining factors predicting development of hypertension from the Physicians' Health Study also reported a powerful association between disturbed lipid metabolism and the risk of developing hypertension (7). After following up this cohort for a mean of 14 years, using Cox proportional hazards modeling adjusted for lifestyle and clinical risk factors, men in the highest quintile of total cholesterol, non-HDL cholesterol, and the ratio of total to HDL cholesterol had increased risks of developing hypertension of 23%, 39%, and 54%, respectively, compared with participants in the lowest quintile. Moreover, men in the highest quintile of HDL cholesterol had a 32% decreased risk of developing hypertension compared with those in the lowest quintile.

Together, these observations support previous reports characterizing the prehypertensive phenotype (8–10) and highlight that this phenotype is a complex mix of dysregulated BP and metabolism that is potentially amenable to early lifestyle and/or drug interventions designed to prevent the development of hypertension.

The TROPHY study. With regard to early intervention aimed at preventing the development of hypertension, the TROPHY (Trial of Preventing Hypertension) study has provided some important insights (11). A total of 809 people with "prehypertension" (systolic BP 130 to 139 mm Hg; diastolic BP 89 mm Hg or lower) were all offered lifestyle advice for the duration of the study and randomized to treatment with either an angiotensin receptor blocker (ARB) (candesartan 16 mg once daily) or placebo for the first 2 years of follow-up, then placebo for both groups for a further 2 years of follow-up (Fig. 3). The objective was to determine whether drug treatment of prehypertension prevented or postponed the development of stage 1 hypertension. During the first 2 years, hypertension developed in 154 participants in the placebo group and in 53 of those in the candesartan group, a relative risk reduction of 66.3% ($p < 0.001$). The active treatment was then stopped and converted to placebo for a further 2 years. Thus, after a total follow-up of 4 years, hypertension had developed in 240 participants in the placebo group and 208 of those originally assigned to the candesartan group, a relative risk reduction of 15.6% ($p < 0.007$).

The TROPHY study highlights some key points: 1) Lifestyle intervention alone, as offered in the study, was disappointing at preventing the development of hypertension because stage 1 hypertension had developed in almost 2/3 of the patients in the placebo group after 4 years. 2) The transition rate from prehypertension to established hypertension was alarmingly high. 3) Early pharmacologic treatment markedly retarded the elevation of BP, but this benefit was lost after treatment was discontinued. 4) Continuation

of treatment would be required to maintain the retarded transition to stage 1 hypertension. It is tempting to speculate that had pharmacologic treatment continued long-term, this might have maintained a normal BP, thereby preventing progression to the well-recognized state identified by the surveys discussed earlier of poorer BP control resistant to treatment with multiple drug therapy.

It will be interesting to discover from subsequent analyses of the TROPHY data whether the pharmacologic treatment of the prehypertensive state also impacted on the metabolic disturbances mentioned earlier, or more intriguingly, looking to future studies, whether treatments targeting the metabolic disturbances per se that characterize the hypertensive phenotype might actually prevent the development of hypertension. The importance of the TROPHY study was not in the result, which was largely predictable, but that it served to highlight the potential of therapeutic strategies aimed at targeting the early hypertensive phenotype to prevent the development of more severe hypertension.

LIFESTYLE INTERVENTIONS FOR PEOPLE WITH HYPERTENSION

Having just reflected on how ineffective the lifestyle instruction offered in the TROPHY study was at preventing the development of hypertension, it may seem an inopportune moment to reflect on recent data with regard to lifestyle intervention for hypertension. It is important to note, however, that much of the predicted increase in the global prevalence of hypertension will have its origins in poor lifestyle choices, and that concerted efforts to adopt and reinforce the importance of healthier lifestyles remain the foundation for tackling the emerging global epidemic of hypertension and cardiovascular disease. In the past year, a detailed meta-analysis quantifying the impact of various lifestyle interventions on BP was reported (12). The American Heart Association has also issued an updated scientific statement on the role of dietary interventions to both prevent and treat hypertension (13), and this notes some important principles that are consistent with the findings of the meta-analysis and are worthy of reiteration: 1) Well-established dietary modifications that lower BP are reduced salt intake, weight loss, and moderation of alcohol consumption. 2) Black subjects are especially sensitive to the BP-lowering effects of a reduced salt intake and the DASH diet. 3) In those hypertensive patients already on drug therapy, lifestyle modifications should continue, particularly a reduced salt intake, because this can add to the BP-lowering effect of drug therapy.

However, in light of the high transition rates from prehypertension to stage I hypertension and beyond, in my view, it is questionable whether lifestyle intervention alone will continue to be regarded as sufficient for people with uncomplicated stage 1 hypertension.

AMBULATORY BP MEASUREMENT

There has been continuing debate about the relative merits of various methods for measurement of BP. A key question has been whether techniques such as ambulatory BP measurement (ABPM) offer anything more in terms of predicting mortality than conventional clinic BP measurements. This was addressed in 2005 by the Dublin Outcome Study (14). This was a prospective study of 5,292 untreated hypertensive patients referred to a single BP clinic. All patients had clinic BP and ABPM at baseline. There were 646 deaths (of which 389 were cardiovascular). This large number of deaths allowed this study to evaluate the prognostic significance of ABPM with regard to mortality for the first time.

After adjustment for gender, age, risk indices, and clinic BP, higher mean values of ambulatory BP were independent predictors for cardiovascular mortality. After correction for other risk factors, ambulatory BP was superior to clinic BP for prediction of cardiovascular mortality. Moreover, night-time BP was the most potent predictor of outcome (Fig. 4). This finding is consistent with another recent report from Japan that examined the relationship between ABPM and patterns of stroke. In 1,430 people followed up for an average of 10 years, cerebral infarction risk was significantly higher in "non-dippers" (i.e., people with a <10% decline in night-time BP). On the other hand, an increased risk of cerebral hemorrhage was observed in people with a large morning pressor surge (i.e., >25 mm Hg in the 2 h after waking) (15).

These findings add to a growing body of evidence showing that ambulatory BP per se and the diurnal characteristics of BP are stronger predictors of clinical outcomes than clinic BP. Furthermore, the observation that nighttime BP control is the strongest predictor of clinical outcome suggests that treatment strategies that deliver 24-h BP control are likely to be important.

So, when to use ABPM? The routine use for all patients is perhaps a step too far at this time, but ABPM is useful in the assessment of the untreated patient when there is uncertainty about the decision to treat and for assessing the quality of BP control in patients at high risk. Moreover, there needs to be greater use of ABPM and other strategies to record BP in clinical outcome trials to better characterize the effect of drugs on BP (16).

Ambulatory arterial stiffness index (AASI). In an endeavor to further refine risk stratification using ABPM, the data have been used to derive an AASI. The physiological principles underpinning the derivation of the AASI are that arterial stiffness varies nonlinearly with distending pressure throughout the day and that the relationship between systolic and diastolic BP will depend on the functional characteristics of large conduit arteries—in people with stiffer arteries, there will be a greater increase in systolic versus diastolic BP. It has therefore been proposed that the AASI is a surrogate measure of arterial stiffness. Using all of

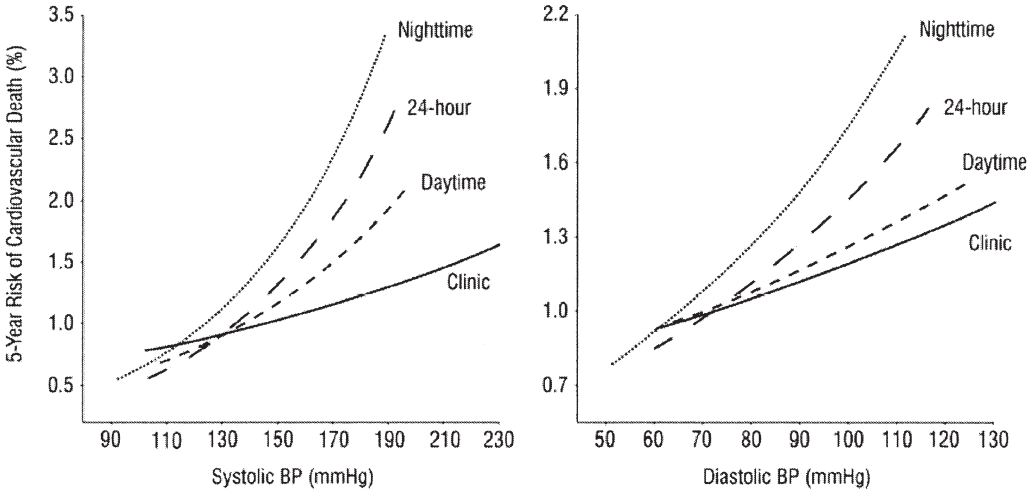

Figure 4. Adjusted 5-year risk of cardiovascular death in the study cohort of 5,292 patients for clinic blood pressure (BP) and ambulatory BP monitoring. Using multiple Cox regression, the relative risk was calculated with adjustment for baseline characteristics including gender, age, presence of diabetes mellitus, history of cardiovascular events, and smoking status. The 5-year risks are expressed as number of deaths per 100 people. Reprinted with permission from Dolan et al. (14).

the readings from a 24-h ABPM recording, the AASI is derived by plotting diastolic versus systolic BP and the regression slope for this relationship is calculated. The AASI has been defined as 1 − this regression slope (17). In support of the concept that the AASI is a surrogate for arterial stiffness, the AASI correlates with the pulse wave velocity and pulse wave augmentation index and correlates more with the augmentation index than 24-h pulse pressure (17).

The use of AASI as a prognostic indicator of total and cause-specific cardiovascular mortality was evaluated utilizing the Dublin Outcomes Study cohort described earlier. Baseline AASI was derived from ABPM recordings from 11,291 patients (mean age 54.6 years). Over a median follow-up of 5.3 years, before and after adjustment for other cardiovascular risk factors, the AASI and pulse pressure significantly predicted total cardiovascular mortality.

The AASI was a stronger predictor than pulse pressure for stroke. The AASI seemed to be a stronger predictor of stroke mortality than pulse pressure, especially in normotensive patients (18). Clearly, further physiological and clinical studies will be required to validate this novel risk index and to confirm the predictive value of the AASI over and above conventional risk stratification in other cohorts. If confirmed and validated, the AASI could be readily computed from standard ABPM recordings and may in future provide additional data for risk stratification. However, it is unfortunate that the term AASI was applied to this index. There is much misuse of the term arterial stiffness, as expertly reviewed in the accompanying editorial (19). The concept that the AASI is a measure of arterial stiffness is simplistic, and truer markers of arterial stiffness, such as pulse wave velocity, have a stronger predictive value for mortality than reported for the AASI (20). Perhaps a better and suitably vague term would have been an ambulatory vascular index.

TRIALS OF BP-LOWERING THERAPY

ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial). The BP-lowering arm of ASCOT (ASCOT-BPLA) was recently reported (21). The ASCOT was a multicenter prospective randomized controlled trial of 19,257 people with hypertension, and had a mean age of 63 years. The study had a factorial design that addressed 2 questions. The first question was whether the addition of a statin (atorvastatin 10 mg daily) would be more effective at reducing cardiovascular events than placebo in a cohort of ASCOT patients who would not otherwise have been treated with a statin. The results of the ASCOT lipid-lowering arm (ASCOT-LLA) were published in 2003 and clearly showed that the addition of a statin significantly reduced the risk of coronary heart disease by 36% and stroke by 27% when compared with placebo (22). The benefits of statin therapy were recently reported to be similar in the cohort of patients with hypertension and diabetes at baseline (23).

The second question addressed by ASCOT-BPLA was whether conventional BP-lowering therapy (atenolol ± bendroflumethiazide-K, as required) was sufficient for optimal cardiovascular disease prevention when compared with a more contemporary regimen of newer drugs (amlodipine ± perindopril, as required). The patients were predominantly male (77%), with a mean age of 63 years. Importantly, people with a prior history of myocardial infarction or treated angina were excluded; thus, this was a primary prevention trial. The ASCOT-BPLA was stopped earlier than anticipated (follow-up median 5.5 years) on the recommendation of the data safety monitoring board because of a clear benefit of the amlodipine-based therapy on most cardiovascular end points and total mortality (reduced by 11%) and in particular on cardiovascular mortality (reduced by 24%), even though the primary end point (fatal coronary heart disease or nonfatal myocardial infarction)

was nonsignificantly different at the time the study was terminated (21).

Some have argued that because most of the power of a clinical trial is invested in its primary end point, if this is not significantly different, then subsequent analysis of secondary end points should be viewed with caution. This seems unreasonable when a study is terminated because of safety concerns due to substantial and significant differences in key end points in favor of one of the treatment strategies. In ASCOT, when compared with atenolol-based treatment, amlodipine-based treatment significantly reduced stroke by 23%, all-cause death by 11%, cardiovascular death by 24%, and all cardiovascular events and procedures by 16%. There was also a significant 30% reduction in new-onset diabetes in favor of amlodipine-based therapy (21).

The BP control was better throughout ASCOT-BPLA with amlodipine-based therapy, especially in the first few months. Moreover, the differences persisted, albeit to a lesser extent throughout the trial, despite greater use of add-on therapy with the atenolol-based therapy. These differences in brachial BP between the treatment arms are likely to have been an important driver of the differences in clinical outcomes in ASCOT, but further analyses adjusting for BP and other variables throughout the study suggested that other factors were also important (24). The CAFE (Conduit Artery Function Evaluation) study (25,26), a substudy of ASCOT, suggested that the differential effects of BP-lowering therapy on central aortic pressures may also have been an important determinant of the beneficial effect of amlodipine-based therapy in ASCOT. This is further discussed later.

The ASCOT study confirmed the importance of initial drug selection in defining the subsequent quality of BP control. The ASCOT study also showed that those patients randomized to the most effective BP-lowering regimen (amlodipine-based therapy) and a statin had their risk of stroke and myocardial infarction reduced by half when compared with those randomized to conventional BP-lowering therapy without a statin. This is a very important message that reinforces a shift in thinking regarding the optimal management of risk in people with hypertension. The cardiovascular disease risk of the typical ASCOT patient was <20% over 10 years, thereby suggesting that the typical hypertensive (i.e., European or American men over 50 years old) would have sufficient cardiovascular disease risk to benefit from statin therapy, even if their cholesterol levels appear normal. This is a very significant development that is already impacting treatment guidelines (27).

Finally, ASCOT also reinforced data from previous studies suggesting that beta-blocker–based therapy, especially in older patients (i.e., >55 years) is less effective than alternative classes of therapy at reducing cardiovascular events, notably stroke, and is more likely, especially in combination with thiazide diuretics, to increase the risk of developing diabetes. The impact of these findings on the fate of beta-blockers for the routine treatment of hypertension is discussed later.

The CAFE study. The CAFE study was a large substudy of ASCOT that examined the hypothesis that the different BP-lowering drug regimens used in ASCOT could have had different effects on central aortic pressures despite similar effects on brachial BP (25,26). The CAFE study recruited 2,199 patients, and radial artery applanation tonometry and pulse wave analysis were used to derive central aortic pressures and hemodynamic indices. Despite a similar brachial systolic BP between treatment groups, there were significantly greater reductions in central aortic systolic and pulse pressures with the amlodipine-based treatment regimen when compared with the atenolol-based regimen (Fig. 5). Thus, BP-lowering drugs have the potential to differentially impact on central aortic pressures, despite similar effects on brachial BP. This important finding suggests that brachial BP does not always faithfully reflect the impact of different BP-lowering drugs on central aortic pressures and hemodynamics. A similar conclusion has been reached recently by other investigators using different drug treatments in much smaller, shorter-term studies (28,29).

The CAFE study showed that the more effective central aortic pressure lowering with the amlodipine-based therapy resulted from reduced pulse wave reflection, pointing to the importance of vasodilatation as an important mechanism for optimizing the reduction in central aortic pressures. Whether the same differential drug effects on central pressure would also have been observed in younger patients with more compliant arteries is unknown. Moreover, whether the result would have occurred with the newer generation of vasodilating beta-blockers is also unknown.

Using Cox proportional hazards modeling, the CAFE investigators went on to show that on-treatment central pulse pressure was significantly associated with clinical outcomes (26). These findings suggest that differential drug effects on central aortic pressures could be an important determinant of drug-related differences in clinical outcomes in clinical trials such as ASCOT and others that have often referred to drug benefits as "beyond blood pressure." The CAFE findings also suggest that drug development programs that are predicated on regulatory requirements for effective reductions in brachial pressure may be underestimating the potential benefit of drugs that favorably impact pulse wave reflection.

In another study, baseline pulse wave analysis was performed in small a subset of participants in the ANBP-2 (Australian National Blood Pressure Study 2) study to derive central aortic pressures (30). In this analysis, there were only 53 events (in contrast to CAFE's 305 events) during a median of 4.1 years of follow-up in 484 women. The ANBP-2 study did not show that higher baseline central aortic pressures were a significant predictor of clinical outcomes. However, the study was clearly underpowered to test this hypothesis and thus prone to a type 2

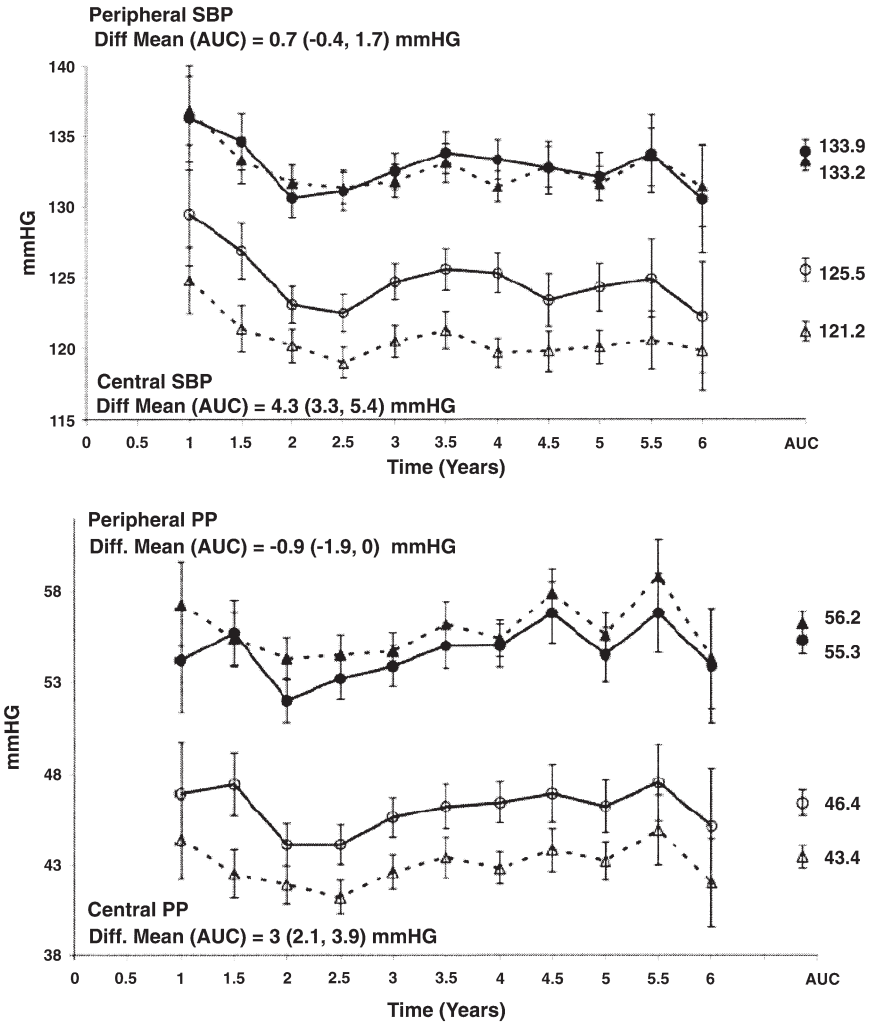

Figure 5. Brachial **(solid symbols)** and derived central aortic **(open symbols)** systolic blood pressure (SBP) **(top panel)** and pulse pressure (PP) **(lower panel)** with time (mean, 95% confidence interval) for patients randomized to atenolol- versus amlodipine-based therapy. Numbers below abscissa represent the number of patients seen at each time point. Time represents the duration from randomization into ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) to patient follow-up visit at which tonometry measurement was made in the CAFE (Conduit Artery Function Evaluation) study. Reprinted with permission from the CAFE Investigators (26). AUC = area under the curve.

statistical error, and differs from the CAFE study in that it did not examine on-treatment pressures.

Further analyses from ALLHAT. The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) investigators continue to generate important data from various subanalyses. The ALLHAT compared treatment with amlodipine or lisinopril with the reference drug chlorthalidone. The primary end point was fatal coronary heart disease or nonfatal myocardial infarction. Three reports have emerged in the past year looking at clinical outcomes from prespecified subgroup analyses: 1) black and nonblack patients (31), 2) people with diabetes (32), and 3) renal outcomes (33).

ALLHAT outcomes in black and nonblack patients. This was an important prespecified analysis because of the paucity of clinical outcome data in variety of ethnic groups with hypertension. In ALLHAT, 11,792 patients were black (35%). No significant difference was found between treatment groups for the primary coronary heart disease (CHD) outcome in either racial subgroup (31). For lisinopril versus chlorthalidone, systolic BP was lowered more effectively with the diuretic, and this coincided with more effective stroke prevention in black patients (relative risk [RR] 1.40 [95% confidence interval 1.17 to 1.68]) with the diuretic. The difference in stroke rate is likely to be caused by the differences in BP control. There was less difference in BP control between treatments in nonblack patients, and no significant difference in stroke rate (Table 1).

The comparison of amlodipine with chlorthalidone showed that despite slightly more effective control of systolic BP throughout the study with the diuretic, there were no differences in the primary and major secondary end points in black patients and nonblack patients (31). The exception is the higher rate of heart failure in black patients and nonblack patients with either lisinopril or amlodipine when compared with the diuretic. This is perplexing for two

Table 1. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) Clinical Outcomes in Blacks and Non-Blacks by Antihypertensive Treatment Group versus Chlorthalidone After Time-Dependent Blood Pressure Adjustment

	RR (95% CI)			
	Black		Non-Black	
Outcome	Amlodipine	Lisinopril	Amlodipine	Lisinopril
CHD	0.99 (0.82–1.19)	1.07 (0.90–1.28)	0.95 (0.85–1.08)	0.93 (0.83–1.05)
Mortality	0.97 (0.85–1.10)	1.07 (0.94–1.21)	0.92 (0.83–1.02)	0.96 (0.87–1.06)
Stroke	0.91 (0.72–1.15)	1.36 (1.10–1.68)	0.91 (0.76–1.10)	0.97 (0.81–1.17)
Combined CVD	1.03 (0.93–1.15)	1.17 (1.05–1.29)	1.01 (0.94–1.08)	1.04 (0.97–1.12)
Heart failure*				
First year	2.85 (1.75–4.66)	2.47 (1.49–4.10)	2.49 (1.68–3.68)	2.14 (1.43–3.20)
Beyond first year	1.23 (0.99–1.52)	1.13 (0.90–1.41)	1.16 (1.00–1.35)	1.01 (0.87–1.19)

*The proportional hazards assumption was violated for the heart failure outcome. From Wright Jr. et al. (31).
CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; RR = relative risk.

reasons: 1) The rates of heart failure are much higher in the first year, rather than in later years. This suggests that a likely cause was the withdrawal of previous diuretic therapy before randomization to lisinopril or amlodipine, unmasking fluid retention previously controlled by diuretic therapy. 2) The mortality in black patients and nonblack patients was not higher with amlodipine or lisinopril despite the reported high rates of incident heart failure. It is also worth noting that the rates of incident diabetes were highest in black patients and nonblack patients with the diuretic therapy.

The main conclusions to be drawn from this important report are: 1) achieved BP is a powerful determinant of outcome for black patients and nonblack patients, especially for stroke, and 2) a thiazide-type diuretic or calcium channel blocker (CCB) will deliver the most effective initial BP control in black patients.

ALLHAT outcomes in people with diabetes. The ALLHAT investigators have also reported a prespecified subgroup analysis of people with type 2 diabetes (n = 13,101) or normoglycemia (17,012) at baseline (32). This is by far the largest study of the treatment of hypertension in people with diabetes.

When comparing treatment arms, there was no significant difference in relative risk for the primary outcome of fatal CHD or non-fatal myocardial infarction in people with or without diabetes at baseline. These findings are important because: 1) ALLHAT does not support the superiority of angiotensin-converting enzyme (ACE) inhibition for the prevention of CHD in people with diabetes; 2) ALLHAT does not support the ill-founded concerns about the use of CCBs for people with diabetes generated in previous retrospective case-control studies, some meta-analyses, and much smaller prospective studies (34–37); 3) ALLHAT provides confirmation that thiazide-type diuretics are very effective and often an essential component of hypertension treatment in people with type 2 diabetes.

These findings support the conclusions of a recent meta-analysis of patients with diabetes and hypertension randomized into major clinical outcome trials (38). This meta-analysis also analyzed the outcome in those with "more versus less intensive" (ΔBP ~5/3 mm Hg) BP lowering in people with or without diabetes at baseline. There was clear benefit, reducing the risk of major cardiovascular events and total mortality, with the more intensive BP-lowering strategy in people with diabetes. The benefit of this strategy was less clear for those without diabetes at baseline. These findings provide retrospective support for the more intensive BP-lowering strategy advocated for people with diabetes in treatment guidelines.

ALLHAT renal outcomes in high-risk hypertensive patients. This post-hoc analysis of the ALLHAT database examined whether treatment with either a CCB or an ACE inhibitor influenced the likelihood of developing end-stage renal disease (ESRD) or a reduction in glomerular filtration rate (GFR) of at least 50%, when compared with treatment with a thiazide-type diuretic, over a mean follow-up of 4.9 years (33). Patients were stratified according to their baseline GFR (estimated by the simplified Modification of Diet in Renal Disease equation), into 3 categories: normal or increased GFR (≥90 ml/min per 1.73 m^2, n = 8,126), mild reduction in GFR (60 to 89 ml/min per 1.73 m^2, n = 18,109), or moderate-severe reduction in GFR (<60 ml/min per 1.73 m^2, n = 5,662). In 448 participants ESRD developed, and in 1,049 the composite end point developed, defined as a 50% or greater decline in GFR or ESRD. There was no difference in treatment effects for either end point for patients taking amlodipine or lisinopril compared with those taking chlorthalidone across the 3 GFR subgroups, either for the total group or for participants with diabetes at baseline.

These are important and intriguing findings. They challenge the view that renin angiotensin aldosterone system (RAAS) blockade is especially renoprotective in people with different categories of renal disease. The findings cannot be dismissed lightly because the number of patients in each category of mild and moderate renal insufficiency in ALLHAT exceeded the total number of similar patients in many renal outcome studies. Moreover, the number of patients who reached ESRD in ALLHAT was greater than in any previous renal trial. Furthermore, in previous studies examining renoprotection in which the benefits of RAAS blockade have been established, there has invariably been a lower

JACC Vol. 48, No. 8, 2006
October 17, 2006:1698–711

on-treatment BP favoring the RAAS blockade group. In ALLHAT, the converse was true. This supports the view that BP lowering is a key driver of renoprotection. Nevertheless, there are caveats. The ALLHAT did not measure urinary albumin excretion, and it is conceivable that the renoprotective benefits of RAAS blockade are more pronounced in people with significant albuminuria. Also, the ALLHAT investigators concede that it was likely that atherosclerotic or ischemic kidney disease (i.e., tubulointerstitial disease) accounted for much of the renal insufficiency in their patients and that this type of renal injury may be less amenable to the protective effect of RAAS blockade (33).

The MOSES study. The MOSES (Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention) study evaluated BP lowering for secondary prevention in patients who had suffered a computed tomography– or magnetic resonance imaging–documented cerebral event in the previous 24 months (39). The study compared BP lowering with either an ARB-based (eprosartan), or CCB-based (nitrendipine) therapy. Blood pressure control was similar with both treatment strategies. The primary end point of the MOSES study was the composite of all-cause mortality and the number of cardiovascular and cerebrovascular events, including all recurrent events. This was significantly reduced by eprosartan-based therapy (incidence density ratio 0.79, 95% confidence interval 0.66 to 0.96, $p < 0.014$). It is unusual not to focus the primary end point of an outcome trial on first event, rather than also counting additional events in the same patient. Nevertheless, when only first events were included in the analysis, a similar trend of benefit for the ARB was observed. Further studies of optimal timing and treatment strategies for BP lowering in the secondary prevention of stroke are needed.

ATRIAL FIBRILLATION IN HYPERTENSION

Hypertensive patients are at increased risk of developing atrial fibrillation and/or flutter (AF), and this further increases their risk of cardiovascular morbidity and mortality (40–42). Recent studies have suggested that the choice of BP-lowering medication can influence the risk of developing AF in people with hypertension. In a post-hoc analysis from the LIFE (Losartan Intervention for End Point Reduction in Hypertension) study, 8,851 patients with hypertension and electrocardiographic (ECG)-left ventricular hypertrophy (LVH) but without AF by ECG or history were followed up for almost 5 years, during which they were treated with either losartan-based or atenolol-based BP-lowering therapy (43). New AF occurred in 150 patients randomized to losartan versus in 221 randomized to atenolol (6.8 vs. 10.1 per 1,000 person-years, $p < 0.001$), a relative risk reduction of 33%.

The 4 main factors predicting the risk of developing AF in the LIFE study in order of effect size were: 1) age (each year of age associated with a 9% higher rate of new-onset AF), 2) male gender (56% increase in risk compared with women), 3) systolic BP (6% increase per 10 mm Hg), and 4) the magnitude of ECG-LVH by Cornell product (4% increase per 100 mV · ms) (Table 2). In addition, randomization to losartan rather than to atenolol was associated with a 33% lower rate of new-onset AF independent of other risk factors ($p < 0.001$). Furthermore, patients receiving losartan-based therapy tended to stay in sinus rhythm longer.

Table 2. Univariate Predictors of the Onset of Atrial Fibrillation in People With Hypertension and ECG-LVH From the LIFE Study

Variable	Hazard Ratio (95% CI)	p Value
Age (yrs)	1.09 (1.07–1.10)	<0.001
Male gender	1.3 (1.06–1.60)	0.011
Systolic blood pressure (mm Hg)	1.02 (1.01–1.02)	<0.001
Diastolic blood pressure (mm Hg)	0.99 (0.98–1.00)	0.046
Cornell voltage-duration (mV · ms/100)	1.013 (1.004–1.022)	0.006
Sokolow-Lyon voltage (mV)	1.01 (0.997–1.02)	0.170
Framingham risk score (%)	1.02 (1.01–1.03)	<0.001
Coronary disease (yes/no)	1.28 (0.99–1.67)	0.062
Total cholesterol (mmol/l)	0.89 (0.80–0.98)	0.014
Potassium (mmol/l)	0.78 (0.58–1.04)	0.091
Log UACR (mg/mmol)	1.44 (1.23–1.67)	<0.001
Treatment with losartan	0.67 (0.54–0.82)	<0.001

Heart rate, body mass index, diabetes, cerebral and peripheral vascular disease, high-density lipoprotein cholesterol, plasma glucose, and creatinine were not significant predictors ($p < 0.20$). From Wachtell et al. (43).

CI = confidence interval; ECG-LVH = electrocardiographic-left ventricular hypertrophy; UACR = urine albumin/creatinine ratio.

Another important finding in a companion report from the LIFE study was that the choice of BP-lowering therapy also influenced the risk of cardiovascular events in people with hypertension, ECG-LVH, and a history of AF (44). In patients with a history of AF, when compared with those without such a history, there were substantial increases in the risk of total and cardiovascular mortality, stroke, heart failure, and sudden cardiac death (Table 3A). This risk in people with AF was significantly reduced in those treated with losartan-based therapy compared with atenolol-based therapy (Table 3B).

The findings of a reduced risk of developing AF in people with hypertension treated with an ARB are supported by another recent study by Fogari et al. (45) that compared losartan with amlodipine therapy in people with hypertension but with a prior history of AF. The objective was to determine the influence of BP-lowering therapy on the risk of recurrent AF. In a double-blind study, the 222 patients were all in sinus rhythm at the time of randomization but had at least 2 ECG-documented episodes of AF in the previous 6 months and were currently treated with amiodarone to suppress further AF. Monthly 24-h ECGs were performed over a median follow-up of 299 days. Despite similar clinic BP control, at least 1 ECG-documented AF episode occurred less frequently in those receiving losartan-based therapy (13%) compared with amlodipine therapy (39%), $p < 0.01$.

Table 3. End Points in People: With and Without a History of AF (Panel A); and in Losartan- Versus Atenolol-Based Therapy in People With AF, From the LIFE Study (Panel B)

Panel A

End Points	Atrial Fibrillation (n = 342)			Nonatrial Fibrillation (n = 8,851)			Adjusted Hazard Ratio*		p Value	Unadjusted Hazard Ratio		p Value
	Rate†	n	(%)	Rate†	n	(%)		95% CI			95% CI	
Primary composite end point	70.0	103	30.1	23.5	993	11.2	2.23	1.81–2.74	<0.001	2.95	2.4–3.62	<0.001
Components												<0.001
Cardiovascular mortality	36.1	58	17.0	8.7	380	4.3	3.06	2.31–4.06	<0.001	4.19	3.18–5.52	<0.001
Stroke	35.8	56	16.4	11.2	485	5.5	2.44	1.84–3.25	<0.001	3.08	2.33–4.08	<0.001
Myocardial infarction	11.3	19	5.6	8.4	367	4.1	1.03	0.65–1.64	0.895	1.34	0.85–2.13	0.209
Other prespecified end points												
Total mortality	50.2	79	23.1	17.1	735	8.3	2.32	1.83–2.93	<0.001	2.99	2.37–3.78	<0.001
Hospitalization for												
Angina pectoria	7.1	12	3.5	5.6	247	2.8	0.95	2.16–4.24	0.866	1.26	0.7–2.24	0.440
Heart failure	24.1	41	12.0	6.1	265	1.0	3.02	1.56–3.59	<0.001	4.15	2.99–5.76	<0.001
Revascularization	15.6	26	7.6	4.7	205	2.3	2.37	1.56–3.59	<0.001	3.37	2.24–5.06	<0.001
Sudden cardiac death‡	15.5	26	7.6	3.7	164	1.9	2.93	1.92–4.48	<0.001	4.21	2.78–6.36	<0.001

Panel B

End Points	Losartan (n = 157)			Atenolol (n = 185)			Adjusted Hazard Ratio*		p Value	Unadjusted Hazard Ratio		p Value
	Rate†	n	(%)	Rate†	n	(%)		95% CI			95% CI	
Primary composite end point	50.3	36	22.9	88.8	67	36.2	0.58	0.39–0.88	0.009	0.58	0.39–0.87	0.009
Components												
Cardiovascular mortality	26.2	20	12.7	45.2	38	20.5	0.58	0.33–0.99	0.048	0.58	0.33–0.99	0.045
Stroke	24.1	18	11.5	46.5	38	20.5	0.55	0.31–0.97	0.039	0.55	0.31–0.97	0.038
Myocardial infarction	14.2	11	7.0	8.9	8	4.3	1.49	0.60–3.72	0.392	1.63	0.65–4.04	0.296
Other prespecified end points												
Total mortality	40.1	30	19.1	59.4	49	26.5	0.67	0.43–1.06	0.090	0.67	0.42–1.05	0.079
Hospitalization for												
Angina pectoris	7.7	6	3.8	6.5	6	3.2	1.18	0.38–3.69	0.778	0.65	0.34–1.22	0.182
Heart failure	19.1	15	9.6	30.1	26	14.1	0.66	0.35–1.25	0.206	1.14	0.37–3.53	0.824
Revascularization	14.2	11	7.0	16.9	15	8.1	0.82	0.38–1.79	0.615	0.83	0.38–1.82	0.647
Sudden cardiac death‡	11.4	9	5.7	19.3	17	9.2	0.57	0.25–1.29	0.179	0.59	0.26–1.33	0.204

*For degree of left ventricular hypertrophy, Framingham risk score, and treatment allocation. †Per 1,000 patient-years of follow-up; ‡Composite end point of resuscitated cardiac arrest, cardiac death within 24 h. From Wachtell et al. (44).
CI = confidence interval.

Previous studies have suggested that blockade of the RAAS with either ACE inhibition or an ARB can reduce the risk of developing AF (46–48), but these studies usually compared active drug with placebo, thus it was unclear whether the reduction in incident AF was related to BP lowering or to a specific drug effect. These new data from the studies cited earlier imply a drug treatment effect because there was no difference in BP reduction between the treatment arms. Moreover, the findings from the LIFE study will come as a surprise to many who have considered beta-blockade a preferred therapy for preventing AF as well as the preferred treatment for rate control in established AF (49).

It is tempting to speculate on the mechanisms underpinning these observations. At the cellular level, studies in animals have suggested the potential for blockade of the action of angiotensin II to prolong the action potential and prevent the acute electrical remodeling response to short-term rapid atrial pacing (50,51). Others have shown no effect on electrical remodeling to more chronic atrial pacing and no effect of angiotensin II infusions on electrical physiology in humans (52). Other possibilities relate to the beneficial effects of blockade of RAAS, or more specifically the angiotensin II receptor, on atrial fibrosis (53), LVH regression, remodeling, and left atrial size (54,55). Whatever the mechanism, these findings should prompt formal studies of the role of RAAS blockade (ACE inhibition, ARB or renin inhibition) in the prevention of new and recurrent AF in people with and without hypertension and in the role of routine RAAS blockade in the prevention of cardiovascular events in people with established refractory AF.

BETA-BLOCKERS AND HYPERTENSION

One of the most significant developments in the past year has been a re-evaluation of the role of beta-blockers as a routine initial therapy for the treatment of hypertension.

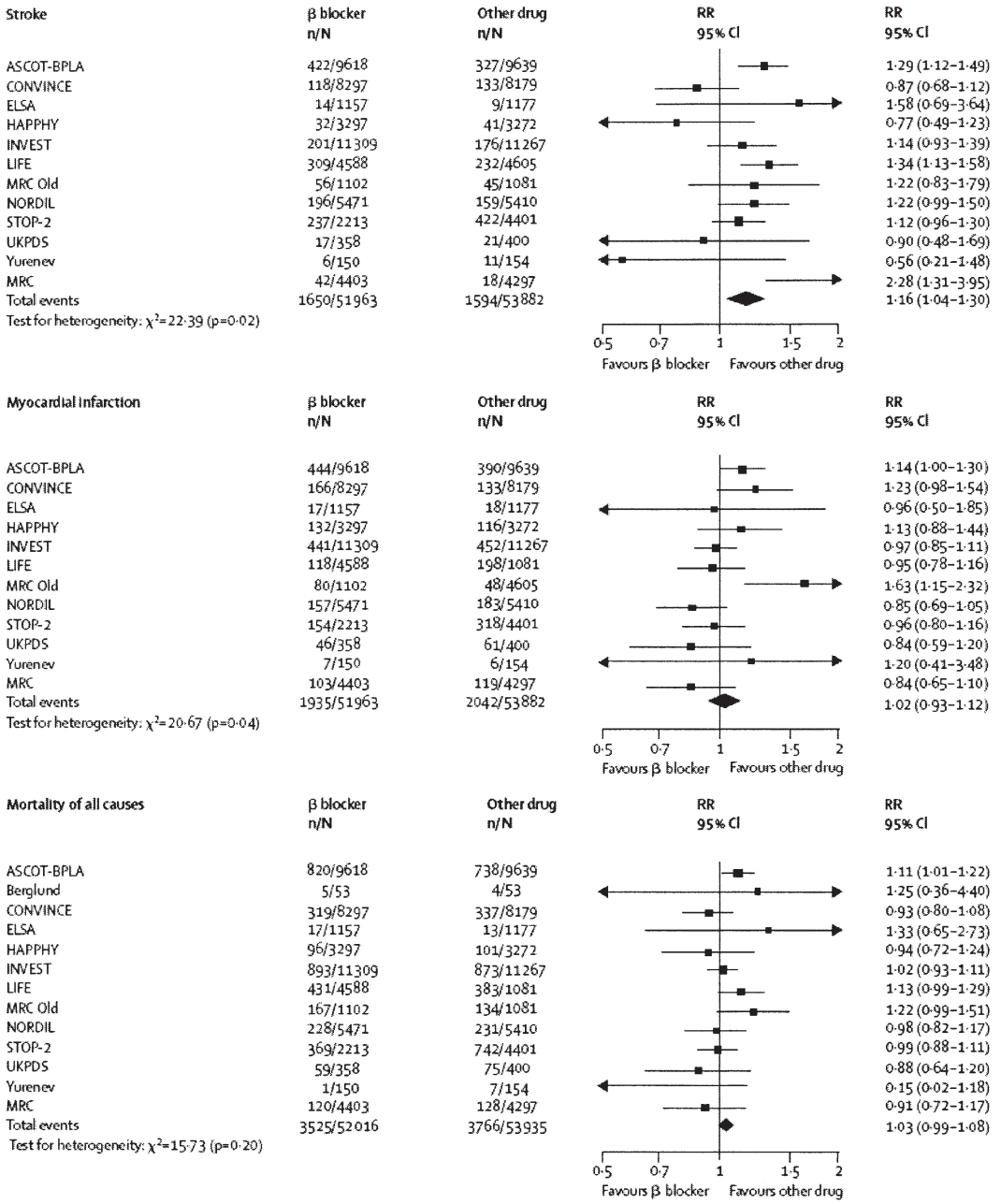

Figure 6. Clinical outcomes from a meta-analysis of hypertension trials comparing beta-blockers with other therapies for the treatment of hypertension. Reprinted with permission from Lindholm et al. (56). CI = confidence interval; RR = relative risk.

This was prompted by a meta-analysis that included 13 randomized controlled trials (n = 105,951) comparing beta-blocker–based therapy for hypertension with other antihypertensive drugs and 7 studies (n = 27,433) comparing beta-blockers with placebo or no treatment (56). When beta-blockers were compared with placebo or no treatment, the relative risk of stroke was reduced by 19% (95% confidence interval 7% to 29%) (Fig. 6), which is about half of that expected from an equivalent BP difference analyzed from previous hypertension trials (57). When compared with other BP-lowering therapies, the relative risk of stroke was 16% higher for beta-blockers. There were no differences in myocardial infarction or mortality (56).

These data suggest that beta-blocker–based therapy is much less efficient at reducing the risk of stroke when compared with other treatment options for hypertension. Why has the interpretation seemingly changed so suddenly? The principal reason is that data on almost 55% of patients included in the meta-analysis, specifically examining a beta-blocker as the initial therapy comparator, have been acquired since 2002 (i.e., the LIFE study [58] and ASCOT [21]). In both of these studies, the alternative therapy was unequivocally superior to the beta-blocker at reducing the risk of stroke. In addition, analysis of the effectiveness beta-blockers in prior studies was less clear-cut because therapy was often analyzed in combination with diuretics. A

further reason has been a reluctance to concede that beta-blockers may be less effective because of a popular but ill-conceived perception that they are especially cardioprotective when compared with other therapies. In addition to suboptimal stroke prevention, LIFE and ASCOT also showed a substantially increased risk of developing diabetes with beta-blocker–based therapy, 25% and 30% respectively, when compared with other treatment options. A recent meta-analysis showed that when compared with alternative treatments (often involving a thiazide), beta-blockers, especially when combined with a thiazide, increase the risk of developing diabetes by ~20% (59). These data, taken together with the observations that beta-blockers are less effective than alternatives at regressing cardiovascular structural changes and in preventing the development of AF than anticipated (discussed earlier), are likely to condemn beta-blockers when considering the preferred initial therapy options for the routine treatment of hypertension in future guidelines.

What are the potential mechanisms for less effective stroke prevention with beta-blockade? One possibility is that they are less effective at BP lowering than the alternatives. This is supported by the early months of ASCOT and may be part of the explanation in older patients (21). Nevertheless, it is not sufficient to explain ASCOT or the results of other studies such as LIFE. Another possibility highlighted by the CAFE study (see earlier) is that beta-blocker–based therapy may be less efficient at lowering central aortic BP, despite similar effects on brachial BP (26). Another consideration is that the adverse effects of beta-blocker therapy on the metabolic milieu, notably increased triglycerides, reduced HDL cholesterol, and impaired glycemic control, may all conspire to reduce their effectiveness at optimally reducing cardiovascular disease risk.

There are a number of important caveats to the anticipated demise of beta-blockers for the routine initial treatment of hypertension: 1) Most of the data for their role in the treatment of hypertension have been acquired with atenolol, the most popular beta-blocker used for the treatment of hypertension worldwide. It is unclear whether the outcomes would be similar with other beta-blockers, especially those with different pharmacologic properties. Nevertheless, in the absence of outcome data with other beta-blockers in people with hypertension, it would be difficult to support their routine use as a preferred initial therapy for hypertension. 2) There are specific indications for continued use of beta-blockers in people with hypertension, irrespective of their BP effect, notably, in patients with symptomatic angina, chronic stable heart failure and after myocardial infarction. 3) Most of the trials of BP-lowering therapy have been conducted in older patients, and it is unclear whether the same concerns would apply to younger people with hypertension, in whom their BP-lowering efficacy may on occasion exceed that of other classes of therapy. 4) There are also circumstances in which alternative treatments may be poorly tolerated or contraindicated, or ineffective at controlling BP, circumstances in which it would be perfectly reasonable to select a beta-blocker to lower BP, the benefits of which exceed no treatment at all. This is a debate of great importance and one that will continue to generate much interest.

SUMMARY AND REFLECTIONS

The past year has generated a wealth of new and important data. Increased awareness of the early hypertensive phenotype, its nonbenign nature, and the importance of considering earlier intervention with drug therapy is a milestone that should prompt new studies in this area. The new clinical trial data and ongoing analyses of important subgroups of patients continue to illuminate our understanding of BP-lowering therapies and have challenged well-entrenched dogma. The data from ASCOT showing the powerful complementary benefits of statin therapy in hypertensive patients at reducing cardiovascular disease risk is impressive and should lead to increased routine use of statins in people with hypertension. Moreover, the data showing that subtle disturbances to lipid profiles exist in the early evolution of hypertension suggests the need for a radical reappraisal of current thinking about when treatment should begin and whether early use of BP- and lipid-lowering drugs could prevent the onset of more severe, multi-drug–resistant hypertension.

However, let us not lose sight of how little we know about how current BP therapies may or may not work. The CAFE study and others have highlighted the importance of studies of human vascular function that will be further enhanced by the emergence of ever-improving imaging modalities. No doubt, this will cause us to lament the lost tribes of cardiovascular physiologists and will emphasize how studies of human physiology and its response to modern drug therapy need to be reinvigorated to better define how existing drugs work and how future novel therapies might be developed.

Around the corner is the launch of a new class of BP-lowering drugs—the renin inhibitors, and the late-stage evaluation in treatment-resistant hypertension of drugs that inhibit endothelin, new combinations of BP-lowering drugs, further analyses from recent clinical outcome trials, continuing debate about beta-blockers and the clinical significance of drug-induced diabetes, and ultimately the assimilation of these new data into hypertension treatment guidelines. Who said hypertension was sorted!

Reprint requests and correspondence: Dr. Bryan Williams, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester, LE2 7LX, United Kingdom. E-mail: www.bw17@le.ac.uk.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of world-wide data. Lancet 2005;365:217–23.
2. Wang TJ, Vasan RS. Epidemiology of uncontrolled hypertension in the United States. Circulation 2005;112:1652–62.
3. US Department of Health and Human Services. Healthy People 2010. 2nd edition. Washington, DC: US Government Printing Office, 2000.
4. Egan BM, Basile JN. Controlling blood pressure in 50% of all hypertensive patients: an achievable goal in the healthy people 2010 report? J Invest Med 2003;51:373–85.
5. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA 2002;287:1003–10.
6. deSimone G, Devereux RB, Chinali M, et al., for the Strong Heart Study Investigators. Risk factors for arterial hypertension in adults with initial optimal blood pressure. Hypertension 2006;47:162–7.
7. Halperin RO, Sesso HD, Ma J, Buring JE, Stampfer MJ, Gaziano JM. Dyslipidemia and risk of incident hypertension in men. Hypertension 2006;47:45–50.
8. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 2001;358:1682–6.
9. Bakx JC, van den Hoogen HJ, van den Bosch WJ, et al. Development of blood pressure and the incidence of hypertension in men and women over an 18-year period: results of the Nijmegen Cohort Study. J Clin Epidemiol 1999;52:531–8.
10. Dyer AR, Liu K, Walsh M, Kiefe C, Jacobs DR Jr., Bild DE. Ten-year incidence of elevated blood pressure and its predictors: the CARDIA study. Coronary Artery Risk Development in (Young) Adults. J Hum Hypertens 1999;13:13–21.
11. Julius S, Nesbitt SD, Egan BM, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med 2006;354:1–13.
12. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens 2006;24:215–33
13. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension 2006; 47:296–308.
14. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin Outcome Study. Hypertension 2005;46:156–61
15. Metoki H, Ohkubo T, Kikuya M, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama Study. Hypertension 2006;47:149–54.
16. Williams B, Lacy PS. Blood pressure and outcomes in clinical trials. J Hypertens 2005;23:487–8.
17. Li Y, Wang J-G, Dolan E, et al. Ambulatory Arterial Stiffness Index derived from 24-hour ambulatory blood pressure monitoring. Hypertension 2006;47:359–64.
18. Dolan E, Thijs L, Li Y, et al. Ambulatory Arterial Stiffness Index as a predictor of cardiovascular mortality in the Dublin Outcome Study. Hypertension 2006;47:365–70.
19. Laurent S. Surrogate measures of arterial stiffness: do they have additive predictive value or are they only surrogates of a surrogate? Hypertension 2006;47:325–6.
20. Mattace-Raso FUS, van der Cammen TJM, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113:657–63.
21. Dahlof B, Sever PS, Poulter NR, et al., for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895–906.
22. Sever PS, Dahlof B, Poulter NR, et al., for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58.
23. Sever PS, Dahlof B, Poulter NR, et al., for the ASCOT Investigators. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm. Diabetes Care 2005;28:1151–7.
24. Poulter NR, Wedel H, Dahlof B, et al., for the ASCOT Investigators. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial–BloodPressure Lowering Arm (ASCOT-BPLA). Lancet 2005;366:907–14.
25. Williams B, O'Rourke M. The Conduit Artery Functional Endpoint (CAFE) study in ASCOT. J Hum Hypertens 2001;15 Suppl 1:S69–73.
26. The CAFE Investigators. Differential impact of blood pressure–lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213–25.
27. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice, British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. Heart 2005;91 Suppl V:v1–v52.
28. Morgan T, Lauri J, Bertram D, Anderson A. Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004;17:118–23.
29. Dhakam Z, McEniery CM, Yasmin, Cockcroft JR, Brown MJ, Wilkinson IB. Atenolol and eprosartan: differential effects on central blood pressure and aortic pulse wave velocity. Am J Hypertens 2006;19:214–19.
30. Dart AM, Gatzka CD, Kingwell BA, et al. Brachial blood pressure but not carotid arterial waveforms predict cardiovascular events in elderly female hypertensives. Hypertension 2006;47:1–6.
31. Wright JT Jr., Dunn JK, Cutler JA, et al., for the ALLHAT Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. JAMA 2005;293:1595–608.
32. Whelton PK, Barzilay J, Cushman WC, et al., for the ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia. Arch Intern Med 2005;165:1401–9.
33. Mahboob-Rahman M, Pressel S, Davis BR, et al. for the ALLHAT Collaborative Research Group. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic. Arch Intern Med 2005;165: 936–46.
34. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies as first line agents. A systematic review and meta-analysis. JAMA 1997;277:739–45.
35. Cutler JA. Calcium-channel blockers for hypertension—uncertainty continues. N Engl J Med 1998;338:679–81.
36. Pahor M, Psaty B, Alderman MH, et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. Lancet 2000;356:1949–54.
37. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. N Engl J Med 1998;338:645–52.
38. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005,165: 1410–9.
39. Schrader J, Luders S, Kulschewski A, et al., for the MOSES Study Group. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). Stroke 2005;36: 1218–26.
40. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359–64.

41. Vidaillet H, Granada JF, Chyou PH, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med 2002;113:365–70.
42. Tsang TS, Petty GW, Barnes ME, et al. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. J Am Coll Cardiol 2003;42:93–100.
43. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005; 45:712–9.
44. Wachtell K, Hornestam B, Mika-Lehto M, et al. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005;45:705–11.
45. Fogari R, Mugellini A, Destro M, et al. Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. J Cardiovasc Pharmacol 2006;47:46–50.
46. Pedersen OD, Bagger H, Keber L, et al. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation 1999;100:376–80.
47. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation. A prospective and randomized study. Circulation 2002;106:331–6.
48. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreased the incidence of atrial fibrillation in patients with left ventricular dysfunction. Insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation 2003;107:2926–31.
49. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol 2001;38:1231–66.
50. Li Y, Li W, Xue J, et al. Effects of losartan on acute atrial electrical remodeling. Chin Med J 2004;117:643–6.
51. Nakashima H, Kumagai K, Urata H, et al. Angiotensin II antagonists prevents electrical remodeling in atrial fibrillation. Circulation 2000; 101:2612–7.
52. Kistler PM, Davidson NC, Sanders P, et al. Absence of acute effects of angiotensin II on atrial electrophysiology in humans. J Am Coll Cardiol 2005;45:154–6.
53. Kumagai K, Nakashima H, Urata H, et al. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol 2003;41:2197–204.
54. Gerdts E, Oikarinen L, Palmieri V, et al. Correlates of left atrial size in hypertensive patients with left ventricular hypertrophy. The Losartan Intervention for End point reduction in hypertension (LIFE) study. Hypertension 2002;39:739–43.
55. Devereux RB, Dahlof B, Gerdts E, et al. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol. The Losartan Intervention For End point reduction in Hypertension (LIFE) trial. Circulation 2004;110:1456–62.
56. Lindholm LH, Carlberg B, Samuelsson O. Should β-blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005;366:1545–53.
57. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively designed overviews of randomised trials. Lancet 2003;362:1527–45.
58. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995–1003.
59. Mason JM, Dickinson HO, Nicolson DJ, Campbell F, Ford GA, Williams B. The diabetogenic potential of thiazide-type diuretic and beta-blocker combinations in patients with hypertension. J Hypertens 2005;3:1777–81.