

STATE-OF-THE-ART PAPER

Recent Hypertension Trials

Implications and Controversies

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The pharmacologic treatment of hypertension has been extensively studied by clinical trials. These studies have provided definitive evidence of a treatment benefit, and the weight and consistency of the clinical evidence has led to uniformity in many aspects of treatment recommendations worldwide. However, controversies remain—in particular, whether specific classes of drug therapy offer benefits for cardiovascular disease prevention beyond the expected benefits of blood pressure lowering per se. Updated large-scale epidemiologic studies and the meta-analysis of clinical trial data have better informed this debate and emphasized that the main driver of clinical benefit from blood pressure-lowering therapy is the magnitude of blood pressure reduction and perhaps the speed at which it is achieved. However, clinical trials are of short duration, and there are more marked drug-specific differences in intermediate cardiovascular structure, functional, and metabolic end points. The challenge is to interpret their significance with regard to longer term outcomes. Finally, although blood pressure lowering is undoubtedly beneficial, the concepts of single risk factor intervention and arbitrary blood pressure thresholds and treatment goals are being challenged by the recognition that the real target is cardiovascular disease risk. Undoubtedly, the most effective way to “go beyond blood pressure” is to add a statin. (J Am Coll Cardiol 2005;45:813–27) © 2005 by the American College of Cardiology Foundation

The benefits of lowering blood pressure are no longer disputed and are supported by the most impressive evidence base in clinical medicine. The most recent World Health Organization report highlighted the importance of blood pressure as a major cardiovascular risk factor when it identified hypertension as the single most important preventable cause of premature death in developed countries (1). Consequently, international guidelines have advocated ever more aggressive screening and treatment strategies.

Despite the certainty of therapeutic benefit, numerous controversies have emerged and many remain. Are there drug-specific benefits that go beyond the powerful independent benefits of blood pressure lowering? Conversely, are certain classes of drugs potentially “harmful” with regard to specific outcomes, and does this offset the potential benefit of blood pressure lowering? Are clinical trials, which focus on higher risk patients and “hard clinical end points,” the best way to assess the potential benefits of drug treatments that are likely to be applied for half of a patient’s lifetime? Are we endeavoring to prevent events or prevent the evolution of a destructive disease process? In this regard, what is the role of surrogate or intermediate end points? And finally, just what is hypertension in 2005? Is it appropriate to have an arbitrary threshold to define “hypertension,” or should we instead consider the benefits of

“blood pressure-lowering” in the context of a patient’s overall cardiovascular disease (CVD) risk? These are key questions that have been addressed and in many instances generated by the results of recent clinical trials. The purpose of this review is to critically evaluate these important questions and concepts.

EVOLUTION OF CLINICAL TRIALS OF BLOOD PRESSURE-LOWERING DRUGS

To fully appreciate the complexity and challenges in interpreting hypertension trials, it is informative to review their evolution. The prospective, randomized, clinical trial has been the foundation for evaluating the effectiveness of blood pressure-lowering drugs. The duration of clinical trials rarely exceeds five years, and trials focus on so-called “hard end points”—notably, all-cause mortality and/or cause-specific morbidity and mortality due to CVD, usually coronary heart disease (CHD) and/or stroke, but more recently heart failure (HF) as well. The early clinical trials had the advantage of being able to compare “active therapy” with placebo and usually included patients with more severe hypertension, as compared with modern trials. Consequently, they generated more end points and had sufficient power to be conducted on a smaller scale than modern trials. As the benefits of blood pressure lowering became apparent, it became unethical to include a placebo group. This led to the modern “head-to-head” trials, which no longer focused on whether blood pressure lowering, per se, was beneficial, but whether treatment based on different drug classes would offer advantages “beyond blood pressure lowering.” This

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
AF	=	atrial fibrillation
ARB	=	angiotensin receptor blocker
CCB	=	calcium channel blocker
CHD	=	coronary heart disease
CI	=	confidence interval
CVD	=	cardiovascular disease
HF	=	heart failure
MI	=	myocardial infarction

approach aimed to minimize the blood pressure difference between the treatment arms, thereby reducing the power of the studies, which markedly increased the numbers of patients and the study duration to maximize power. This also led to the emergence of “the composite primary end point” (i.e., a combination of events), because despite their considerable size, trials rarely had the power to examine key cause-specific outcomes.

Trial design has been further complicated by the tightening of treatment thresholds, which has meant that most patients require multiple drugs to achieve the blood pressure goals. Thus, trials no longer compared individual drug classes, but rather, they compared treatment regimens. This complexity has been compounded by the fact that the majority of patients at high CVD risk also receive concomitant medications such as statins and aspirin, which further reduces the likelihood of major CVD events and further diminishes the power of the trial, thereby mandating trials of ever increasing size and cost. These considerations are hugely important when reviewing the results of clinical trials with regard to the certainty to which benefits can be attributed to individual drugs.

META-ANALYSIS OF BLOOD PRESSURE-LOWERING DRUG TRIALS

As indicated earlier, the more recent trials of blood pressure-lowering therapies have usually used a composite primary end point because of insufficient power to examine important individual cause-specific outcomes. To address important questions about drug safety and outcomes with specific drug classes, the data from recent trials have been pooled and subjected to meta-analyses (2–4). This aggregation of data provides much greater statistical power with which to examine drug-specific effects.

The Blood Pressure Lowering Treatment Trialists Collaborative (BPLTTC) published their most recent meta-analysis in 2003 (2). This incorporated data from 29 randomized, controlled trials involving 162,341 patients, and the mean duration of follow-up ranged from 2.0 to 8.0 years, providing over 700,000 patient-years of follow-up. The overall mean age of trial participants was 65 years, and 52% were men.

As expected, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) were both

more effective than placebo at reducing the risk of major cardiovascular events by 22% (confidence interval [CI] 17% to 27%) and 18% (CI 5% to 29%), respectively (Fig. 1). When the main drug classes were compared “head-to-head,” (i.e., conventional therapy [thiazide and/or beta-blocker], ACE inhibitors, or CCBs), there were no significant differences in major cardiovascular outcomes or cardiovascular mortality (Fig. 2). Similar conclusions were reached in a second independent meta-analysis conducted on behalf of the National Institute of Clinical Excellence (NICE) in the United Kingdom (Fig. 3) (4), and a quantitative overview of recent clinical trials (3), which included the more recently published Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) study (5).

PREVENTION OF CHD

When meta-analysis was used to examine the impact of ACE inhibitors or CCBs on CHD events, both reduced CHD risk to a similar order of magnitude versus placebo, by 20% and 22%, respectively (Fig. 1) (2,3). Moreover, when compared head-to-head, there was no evidence that any one class of drug was more effective than any other at preventing CHD events (Figs. 2 and 3) (2–4). This is important because it fails to confirm popular perception that ACE inhibition provides special protection against CHD events, or that conventional or CCB-based therapy is less effective than ACE inhibition at CHD prevention in people with treated hypertension.

Few data were available for the angiotensin receptor blockers (ARBs) when these analyses were conducted, but there is no evidence from existing data from three ARB-based trials (Study on COgnition and Prognosis in the Elderly [SCOPE], Losartan Intervention For Endpoint reduction in hypertension [LIFE], and Valsartan Antihypertensive Long-term Use Evaluation [VALUE]) that ARBs are any more or less effective at preventing CHD than can be expected from their action to lower blood pressure (6–9).

Thus, for CHD prevention, the benefits accrued from blood pressure-lowering appear to be directly attributable to the blood pressure reduction rather than the drug classes used to achieve it. This conclusion is endorsed by reference to specific trials such as the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT), the largest ever blood pressure-lowering therapy trial, with sufficient power to specifically examine CHD morbidity and mortality as its primary end point (10). In the ALLHAT study, the primary outcome occurred in 2,956 participants, and there were no differences between the rates with the reference drug, a thiazide-like diuretic; chlorthalidone (11.5%), a CCB; amlodipine (11.3%), an ACE inhibitor; or lisinopril (11.4%) (9).

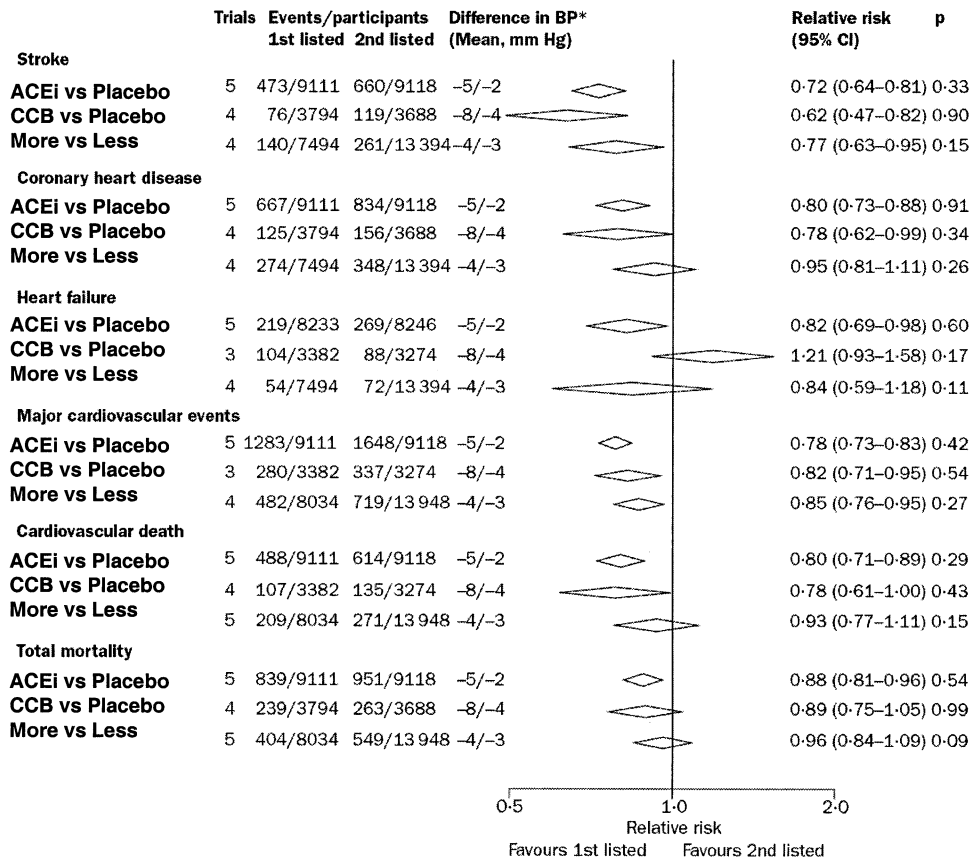


Figure 1. Effect of angiotensin-converting enzyme inhibitors (ACEi) and calcium channel blockers (CCBs) versus placebo and “more versus less” blood pressure (BP) lowering on cause-specific cardiovascular outcomes. The overall mean BP difference between treatments is shown. Negative values mean lower blood pressure values in the “first listed.” CI = confidence interval. Reproduced from the Blood Pressure Lowering Treatment Trialists’ Collaboration (2), with permission.

STROKE PREVENTION

With regard to stroke prevention, the BPLTTC meta-analysis revealed some interesting trends. Not surprisingly, ACE inhibitor or CCB-based therapy reduced the risk of stroke by 28% and 38%, respectively, as compared with placebo (Fig. 1) (2). Of interest, compared with conventional therapy, ACE inhibitor-based therapy was marginally less effective at preventing fatal/nonfatal stroke in both the BPLTCC and NICE meta-analyses (Figs. 2 and 3) (2,4). This may surprise many, mindful of the publicity surrounding ACE inhibitor-based studies such as the Heart Outcomes Prevention Evaluation (HOPE) study (11,12) and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) (13), which reported greater stroke prevention with ACE inhibitor-based studies and implied “drug-specific benefits beyond blood pressure lowering.” It is important to note that these two studies compared ACE inhibitor-based treatment with placebo—a comparison that inevitably resulted in greater blood pressure lowering with ACE inhibition. As discussed subsequently, these differences in blood pressure are more than sufficient to account for the cardiovascular benefits observed in these two trials. Moreover, when ACE inhibition has been compared “head-to-head” with other blood pressure-lowering drugs (the Captopril Prevention Project [CAPPP] [14], the Swedish

Trial in Old Patients with Hypertension-2 [STOP-2] [15], ALLHAT [10], the Second Australian National Blood Pressure Study [ANBP-2] [16]), there is no suggestion from any of these trials of superior stroke prevention by ACE inhibition.

In contrast to ACE inhibition, the BPLTTC and NICE meta-analyses showed that CCB-based therapy tended to be more effective than conventional therapy and ACE inhibition at stroke prevention (Figs. 2 and 3) (2,4). Similar trends have been reported by others (3,17,18).

A more marked benefit for stroke prevention was seen by meta-analysis of ARB-based therapy, as compared with other treatments (2). This relates to data from two trials: SCOPE and LIFE (6-8). The SCOPE trial is less informative with regard to “drug-specific benefits” because it randomized hypertensive patients to ARB-based treatment (candesartan) versus placebo, which inevitably resulted in a significant blood pressure difference between the treatment groups (6). However, a recent analysis of the cohort of patients with isolated systolic hypertension from the SCOPE trial revealed a patient population in whom the blood pressure difference was only -2/1 mm Hg in favor of candesartan and in whom there was a 42% reduction in stroke with the ARB-based treatment (7).

The LIFE study compared ARB-based treatment (losar-

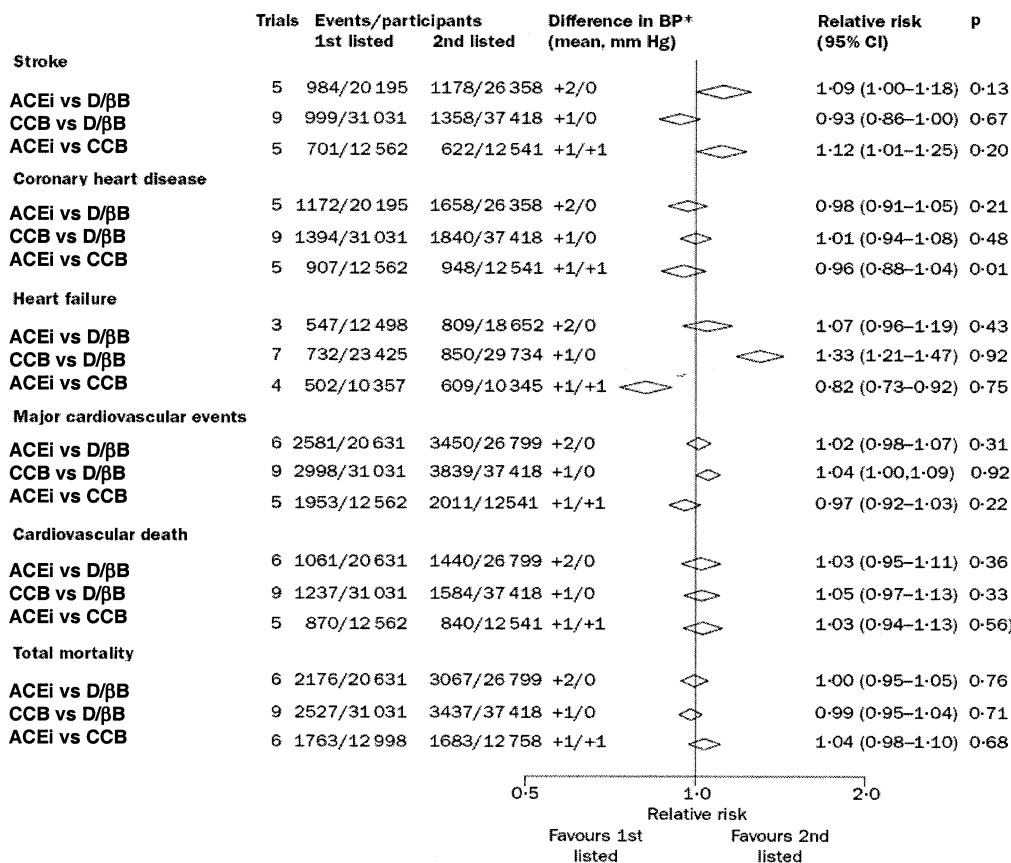


Figure 2. Comparison of blood pressure (BP)-lowering regimens based on different drug classes. Mean blood pressure differences between the first and second treatment regimens are shown. Negative blood pressure values indicate lower pressures with the first treatment listed. ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker; CI = confidence interval; D/βB = diuretic- and/or beta-blocker-based regimens. Reproduced from the Blood Pressure Lowering Treatment Trialists' Collaboration (2), with permission.

tan) with atenolol-based treatment in over 9,000 people with hypertension and left ventricular hypertrophy by electrocardiography. There was a significant 25% reduction in the rate of fatal or nonfatal stroke in those randomized to losartan-based therapy (8). Of interest, this benefit was not observed in hypertensive black patients within the LIFE study, the reasons for which remain unclear (19). In the more recent VALUE trial comparing ARB-based treatment (valsartan) with CCB-based treatment (amlodipine), there was no evidence of greater stroke prevention with the ARB-based therapy (9). On the contrary, there was a trend toward 15% fewer strokes ($p < 0.08$) in those randomized to the CCB-based regimen. In the VALUE trial, blood pressure was significantly lower throughout the trial with CCB-based therapy, perhaps explaining the trend toward better stroke prevention with CCB. In the LIFE trial, much smaller intergroup blood pressure differences were apparent, and mean arterial blood pressures appeared similar for both treatment arms throughout the study. Some have calculated observed and predicted odds ratios for stroke in clinical trials and concluded that even the small blood pressure differences in the LIFE trial are sufficient to account for the observed difference in stroke rates (Table 1) (3). Others have suggested that the benefit of losartan-based treatment in LIFE

may be due to the deficiency of beta-blocker-based treatment in preventing stroke, rather than a specific advantage of the ARB (20-22). This provocative hypothesis is not supported by the BPLTTC meta-analysis of stroke prevention with conventional therapy, which includes beta-blockade (2), or the NICE meta-analysis (4), both of which suggest that beta-blocker-based treatments prevent stroke in proportion to the blood pressure reduction they produce.

Another major trial will soon better inform this debate about the effectiveness of beta-blocker/thiazide diuretic-based therapy. The blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (23) has compared conventional blood pressure lowering based on treatment with a beta-blocker (atenolol) with or without a thiazide (bendroflumethiazide-K) with a more contemporary regimen based on a CCB (amlodipine) with or without an ACE inhibitor (perindopril) in almost 20,000 patients with hypertension. This study was recently stopped early based on the advice of the Data Safety Monitoring Board because of significant and important benefits with regard to major cardiovascular outcomes associated with the contemporary treatment regimen based on the CCB with or without ACE inhibitor. It has not yet been reported whether this relates to better blood pressure control with the

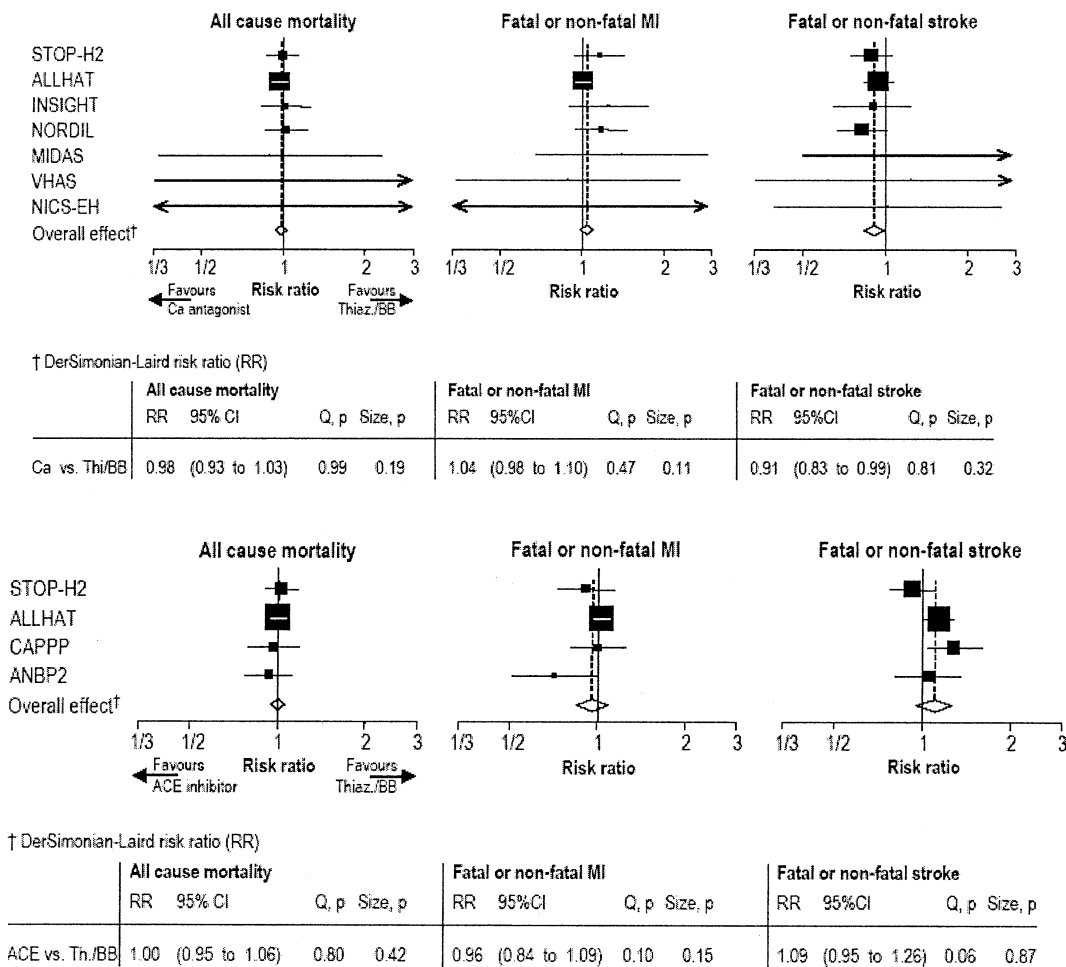


Figure 3. Effect of blood pressure lowering in different studies comparing calcium (Ca) channel blocker-based treatment regimens (top panel) or angiotensin-converting enzyme (ACE) inhibitor-based regimens (bottom panel) versus thiazide (Th/Thi/Thiaz.) and/or beta-blocker (BB)-based regimens on cardiovascular outcomes and all-cause mortality. CI = confidence interval; RR = risk ratio. Reproduced from the National Institute of Clinical Excellence Clinical Guideline 18 (4), with permission.

contemporary regimen. Whatever the mechanism, this finding from the ASCOT study, which will be reported fully later in 2005, suggests that modern treatments are more effective than the traditional beta-blocker/thiazide diuretic regimen at reducing major cardiovascular outcomes in people with hypertension.

HEART FAILURE PREVENTION

The end point of HF is not an easy diagnosis to validate outside the hospital and has been a contentious issue in hypertension trials. An example is the ALLHAT trial, where HF rates were much higher than those reported in other studies randomizing people of comparable baseline CVD risk (10). One possible explanation for this higher than usual rate of HF in the ALLHAT trial rests with the trial design—patients were crossed over from their usual antihypertensive therapy to the trial drug at randomization, without a washout period. The majority (90%) were treated hypertensive patients before randomization, and mindful of the mean age of the study population (67 years), it is likely

that many patients were receiving diuretic therapy before randomization. Subsequent randomization to drugs other than a diuretic means it is perhaps not surprising that HF was diagnosed significantly more often over six years in those randomized to either amlodipine or lisinopril, perhaps due to the unmasking of existing HF by diuretic withdrawal.

Using a definition of HF that caused death or admission to the hospital, meta-analyses suggest that there is a clear benefit of ACE inhibitor-based treatments over placebo (Fig. 1) (2,3). No such benefit has been demonstrated for CCB-based therapy as compared with placebo or compared with treatments based on ACE inhibition or conventional therapy (Figs. 1 and 2). Of interest, by meta-analyses, for the treatment of hypertension, there was no evidence that ACE inhibition was more effective at preventing HF than conventional therapy. However, this conclusion is strongly influenced by the data from the ALLHAT study, with all of the aforementioned caveats.

The ARBs appear to prevent HF more effectively than

Table 1. Observed Odds Ratios for Myocardial Infarction and Stroke From Specific Clinical Trials Versus the Odds Ratios Predicted by Intergroup Differences in Systolic Blood Pressure From Previous Trials Comparing Older Versus Newer Blood Pressure-Lowering Regimens

Study	Δ SBP (mm Hg)	Observed OR (CI)	Predicted OR (CI)	p Value
ALLHAT—thiazide (chlorthalidone) versus amlodipine				
Myocardial infarction	-1.1	0.99 (0.90-1.08)	1.06 (0.93-1.20)	0.37
Stroke		0.94 (0.82-1.07)	1.00 (0.89-1.12)	0.43
ALLHAT—thiazide versus lisinopril				
Myocardial infarction	-2.3	0.98 (0.90-1.08)	1.14 (0.98-1.34)	0.08
Stroke		1.15 (1.05-1.30)	1.08 (0.94-1.24)	0.51
ALLHAT—thiazide versus lisinopril in black Americans				
Myocardial infarction	-4.0	1.10 (0.94-1.28)	1.29 (1.05-1.59)	0.20
Stroke		1.4 (1.17-1.68)	1.23 (1.03-1.47)	0.31
ANBP-2—thiazide (hct) versus enalapril				
Myocardial infarction	-1.4	0.70 (0.49-1.00)	1.08 (0.95-1.23)	0.02
Stroke		1.05 (0.79-1.38)	1.02 (0.90-1.15)	0.83
CONVINCE—atenolol or thiazide versus verapamil				
Myocardial infarction	+0.1	0.81 (0.64-1.03)	0.99 (0.89-1.09)	0.14
Stroke		1.15 (0.89-1.48)	0.92 (0.83-1.02)	0.11
LIFE—atenolol versus losartan				
Myocardial infarction	+1.0	1.07 (0.87-1.31)	0.93 (0.85-1.02)	0.24
Stroke		0.75 (0.63-0.90)	0.87 (0.79-0.95)	0.15
SCOPE—placebo \pm thiazide (hct) (80%) versus candesartan				
Myocardial infarction	+3.4	1.11 (0.77-1.59)	0.84 (0.77-0.92)	0.96
Stroke		0.76 (0.57-1.02)	0.77 (0.71-0.84)	0.92

Δ SBP refers to the difference in treated systolic blood pressures between treatment groups. A negative value indicates better blood pressure control on "older" drugs, usually thiazides and/or beta-blockers. The observed odds ratios (OR) are shown \pm 95% confidence intervals (CI) calculated from the data in the specific trial. The 95% CI for the predicted ORs have been calculated by meta-regression analysis. The p value refers to the significance of the difference between predicted and observed OR between first- and second-listed initial therapies. Adapted from data in Staessen et al. (3).

the comparator drugs used in the LIFE and SCOPE trials (6,8). However, the VALUE study did not confirm a significant advantage of treatment based on the ARB valsartan compared with CCB-based treatment (amlodipine) for the prevention of HF (hazard ratio 0.89, 95% CI 0.77 to 1.03, $p < 0.12$) (9). In the VALUE trial, there was a late trend in favor of the ARB, but overall, the study is difficult to interpret because of greater diuretic use in the valsartan arm of the study and significant differences in blood pressure control in favor of amlodipine.

IMPACT OF GENDER

The impact of gender on the effectiveness of blood pressure lowering at reducing cardiovascular events was addressed by the INDANA Working Group using a meta-analysis of individual patient data from seven randomized clinical trials comprising 40,777 patients, of whom 49% were men (24). In this analysis overall, the risk ratios did not differ between men and women for any of the major outcomes, and there was no significant interaction between treatment effect and gender. This conclusion is supported by reference to the ALLHAT study, the largest study published since the INDANA analysis. The ALLHAT study showed no evidence of any significant difference in major cardiovascular

outcomes, including coronary events between men and women, irrespective of drug allocation at randomization (10).

IMPACT OF ETHNICITY

The effects of ethnicity on cardiovascular outcomes in blood pressure-lowering trials has been poorly studied. Until recently, most trials had predominantly included white Caucasians with poor representation from black, Asian, and Hispanic patients. This is an important consideration because of ethnic influences on the blood pressure-lowering efficacy of different drug classes. For example, people of black African descent more commonly have a "low renin" phenotype and in general exhibit a poorer blood pressure-lowering response to monotherapy with drugs that inhibit the renin system, such as ACE inhibition, ARBs, or beta-blockers, as compared with CCBs or thiazide diuretics (25,26). This almost certainly explains the outcome in the 10,702 black Americans (35% of study population) in the ALLHAT study in whom ACE inhibition was much less effective at preventing stroke compared with chlorthalidone, most likely due to poorer blood pressure control with ACE inhibition in the black American cohort (10).

There is no good evidence of significant heterogeneity in

response to blood pressure-lowering drugs in other ethnic groups—notably, Hispanic or Asian. The ALLHAT study randomized 5,246 Hispanic Americans (19% of study population), and there did not appear to be any heterogeneity in their cardiovascular benefits from different treatments (10). Much less data are available for Asian patients with hypertension, but modern trials are increasingly recruiting patients from the Asia-Pacific region, which will address this deficiency. From the limited data available, there does not appear to be any reason to anticipate major differences in drug-specific outcomes.

DRUG SAFETY: LESSONS LEARNED

The randomized clinical trial is as much a test of drug safety as it is of efficacy. This became important in the late 1990s when controversy first emerged about the safety of CCBs (especially short-acting CCBs) for the treatment of hypertension (27–29). This controversy was initially founded on a retrospective case-controlled study suggesting that CCBs, especially short-acting ones, may be associated with an enhanced risk of CHD, as compared with alternative treatments (27). Such analyses are fatally flawed by the enormous potential for confounding by drug indication. Further data from the premature stopping of a small clinical trial suggesting less effective prevention of CHD with CCBs in people with type II diabetes (30) fueled the controversy.

Subsequently, data from a series of large, prospective, randomized, clinical trials comparing CCBs head-to-head with other blood pressure-lowering therapies, such as the Intervention as a Goal In Hypertension Treatment (INSIGHT) study, the Nordic Diltiazem (NORDIL) study, ALLHAT, CONVINCe, the International Verapamil-Trandolapril Study (INVEST), and VALUE, have dismissed these concerns (5,9,10,31–33). The ALLHAT study was specifically powered to test the CHD hypothesis as its primary end point and definitively showed effective CHD prevention with a CCB (amlodipine), including in those with diabetes (10). More recently, the VALUE trial further tested this hypothesis and included CHD events in its primary end point. In the VALUE trial, amlodipine was actually superior to valsartan-based therapy at protecting against fatal and nonfatal myocardial infarction (MI), as well as reducing the frequency of angina (9). These two very large trials confirm the conclusions from the aforementioned meta-analyses (Figs. 2 and 3), notably that, for CHD prevention, no one class of blood pressure-lowering drug has been shown to be any less or any more effective than any other; their benefits are primarily determined by how effectively they lower blood pressure. The important message from this turbulent time is that case-control studies can be seriously misleading and must always be interpreted with great caution. There is no substitute at present for randomized, controlled trials for formulating health policy and treatment guidelines.

IMPORTANCE OF BLOOD PRESSURE CONTROL REVISITED

An improved understanding of the importance of blood pressure lowering has been a key advance from recent clinical studies. This issue has been central to the controversy and debate about whether drugs provide “benefits beyond blood pressure control,” which is discussed in more detail subsequently.

From an epidemiologic perspective, new data have clarified the importance of blood pressure as a risk factor for CVD. In the largest and most detailed analysis, information from one million adults with no known vascular disease at baseline, included in 61 prospective observational studies of the relationship between blood pressure and mortality, was examined (34). This meta-analysis related outcomes per decade of age to the estimated usual blood pressure at the start of that decade. At ages 40 to 69 years, each difference in usual systolic blood pressure of 20 mm Hg was associated with a more than two-fold difference in stroke death rate, as well as a two-fold difference in the death rate from CHD or other vascular causes (Fig. 4). These proportional differences in cardiovascular mortality were about half as extreme in those who were 80 to 89 years old as compared with those 40 to 49 years old (i.e., the relative risk is steeper in younger age groups), but the absolute differences in risk are of course greater in older age. Thus, throughout age, usual blood pressure is strongly and directly related to cardiovascular mortality across all blood pressure values, with no evidence of a threshold down to 115/75 mm Hg, below which there are insufficient data. Consistent with this conclusion, data from Framingham have shown a doubling in the cumulative incidence of cardiovascular events in those with a “high-normal” blood pressure (120 to 139/80 to 89 mm Hg), as compared with those with a “normal” blood pressure (<120/80 mm Hg) (35), observations that led to the emergence of the term “pre-hypertension” for those with high-normal blood pressures in Joint National Committee (JNC) VII (36).

With regard to intervention studies, meta-analyses have examined the impact of “more versus less” blood pressure lowering in clinical trials to determine whether there is evidence for substantial cardiovascular benefits with seemingly small blood pressure changes (Fig. 1) (2). Blood pressure difference of $-4/-3$ mm Hg in 20,888 patients produced a 23% reduction in the relative risk of stroke, as well as a 15% reduction in CHD events, a 16% reduction in HF, and a 14% reduction in total mortality. The weighted blood pressure differences between treatment groups seemed to be directly related to the differences in the risk of stroke, CHD, major CVD events, CVD death, and total mortality (2,3). In contrast, the magnitude of blood pressure difference in clinical trials did not appear to predict the risk of HF (2). These data suggest that in general and apart from HF, blood pressure differences between treatment groups in clinical trials predict differences in outcome for all major

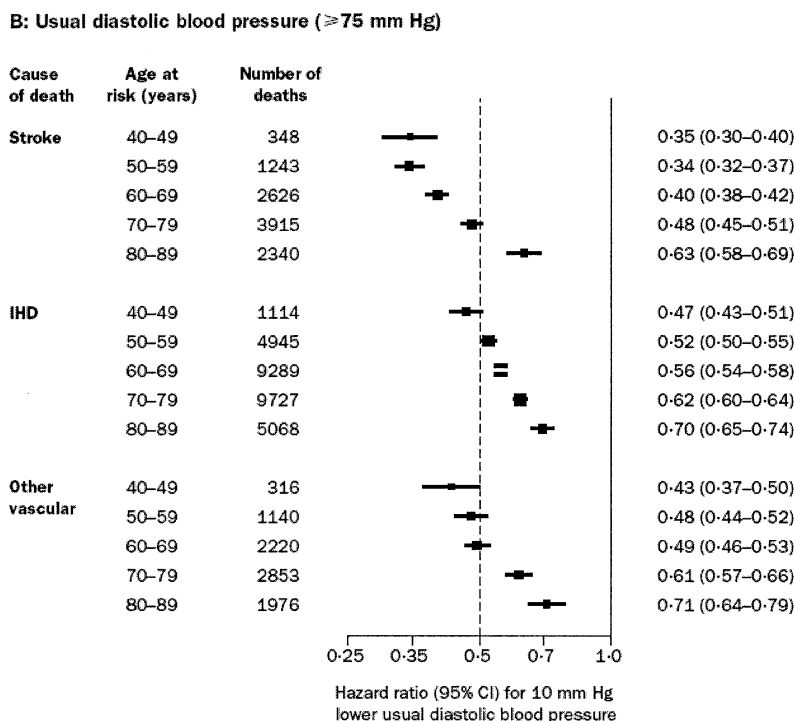
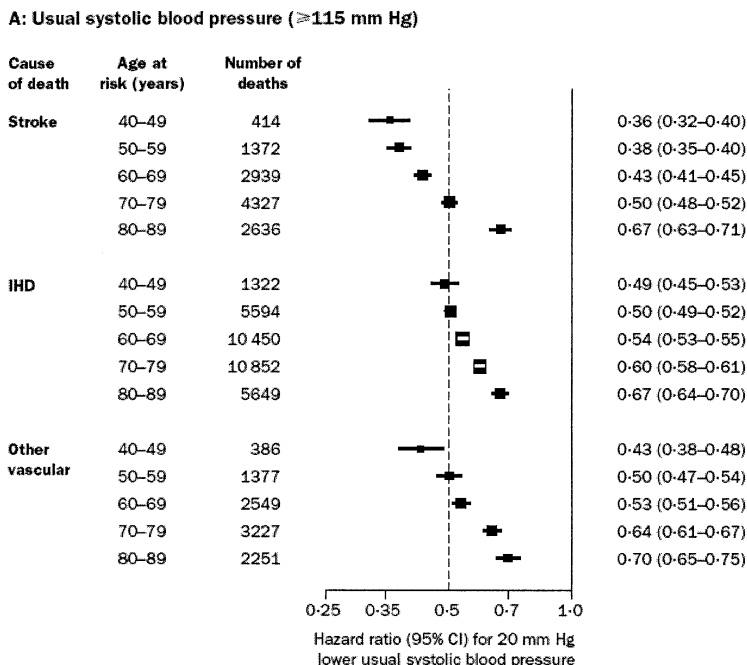


Figure 4. Age-specific hazard ratios for specified differences in usual systolic (A) and diastolic (B) blood pressures. Impact on stroke, ischemic heart disease (IHD), and other vascular events. Data from 61 prospective observational studies of blood pressure and mortality in one million adults with no vascular disease at baseline. CI = confidence interval. Reproduced from the Prospective Studies Collaboration (34), with permission.

cardiovascular events, even when blood pressure differences are seemingly small. Moreover, there is no blood pressure threshold below which benefits cease, down to 115/75 mm Hg. These latter two observations are critical to the debate of the “beyond blood pressure” hypothesis championed by the HOPE trial and the European trial On reduction of

cardiac events with Perindopril in stable coronary Artery disease (EUROPA) (11,37).

The VALUE trial strongly supports the blood pressure hypothesis. The VALUE trial compared ARB-based therapy (valsartan) with CCB-based therapy (amlodipine) in 15,245 patients with hypertension at high risk of cardiac

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events, in most cases by virtue of a history of coronary disease, stroke, or diabetes. It is informative to review the hard end points traditionally associated with hypertension trials—notably, fatal and nonfatal MI or stroke. There were 19% fewer MIs ($p < 0.02$) and a trend toward 15% fewer strokes ($p < 0.08$) in those randomized to the CCB-based regimen as compared with the ARB-based treatment. There were no significant differences in HF hospitalization or all-cause death (9).

The fact that blood pressure control was not equivalent in both arms of the VALUE trial provides an important insight into the power of seemingly small differences in blood pressure to drive major differences in end points in large clinical trials of people at high CVD risk. Closer examination of the data for the first few months of the VALUE trial reveals striking, indeed alarming differences in end point rates (at least two-fold differences) between the two treatment arms when there was the greatest disparity in blood pressure control (i.e., $\sim 3/2$ mm Hg) (Fig. 5) (9,38). Of note, these blood pressure differences are remarkably similar to those reported in many trials in which ACE inhibition was compared with placebo, and such blood pressure differences were dismissed as irrelevant to drug-driven differences in outcome (11,37).

“BEYOND BLOOD PRESSURE”

Accepting that: 1) the increased CVD risk attributable to blood pressure is linear and extends across a wide range of pressures down to 115/75 mm Hg; and 2) even small reductions in blood pressure have a dramatic effect in high-risk patients, what is the evidence to support the view that some classes of blood pressure-lowering therapy can provide benefits “beyond blood pressure” (i.e., benefits that cannot be accounted for by blood pressure reduction)? This hypothesis has been founded primarily on data from clinical trials with ACE inhibitors and on the flawed premise that when treating people with “normal blood pressures” (i.e. $<140/90$ mm Hg), blood pressure lowering is unlikely to be an important determinant of outcome.

In the light of all of the new data cited in this article, it is instructive to reflect on the interpretation of the HOPE study—the study that has provided the greatest impetus for the “beyond blood pressure” hypothesis (11). The HOPE study randomized a total of 9,297 patients ≥ 55 years old to treatment with either ramipril (10 mg/day) or matching placebo for five years. The patients were deemed to be at high CVD risk due to a history of CHD, stroke, peripheral vascular disease, or diabetes, plus at least one other cardiovascular risk factor. Almost 50% had treated hypertension. The mean baseline blood pressure was 139/79 mm Hg, suggesting a significant proportion of patients had a baseline blood pressure above that value. The primary outcome of the study was a composite of MI, stroke, or death from cardiovascular causes and was reduced by 22% ($p < 0.001$) in favor of ramipril. Compared with placebo, treatment with

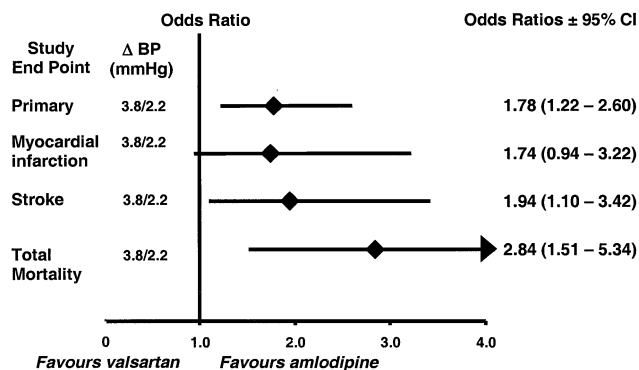


Figure 5. Odds ratios for the primary end point (composite of cardiac end points), major cause-specific outcomes, and total mortality during the first three months of the VALUE trial after patients had been randomized to either valsartan or amlodipine monotherapy. Change in blood pressure (Δ BP) at three months refers to the lower mean blood pressures in patients randomized to amlodipine. Data are expressed as the odds ratios \pm 95% confidence intervals (CI). Figure is adapted from data extracted from Julius et al. (9).

ramipril also reduced the rates of death from cardiovascular causes by 26% ($p < 0.001$), reduced MI by 20% ($p < 0.001$), stroke by 32% ($p < 0.001$), and death from any cause by 16% ($p < 0.005$). These risk reductions are remarkably similar to those reported in the BPLTTC meta-analysis, which compared ACE inhibitor therapy with placebo, for these specific end points (Fig. 1) (2).

There has been much controversy about the difference in blood pressure between the ramipril- and placebo-treated patients in the HOPE trial (39). The in-study clinic blood pressure difference was reported to be 3/2 mm Hg in favor of ramipril; however, a subsequent small study in HOPE patients reported mean 24-h ambulatory blood pressure differences of 11/4 mm Hg in favor of ramipril, even though the clinic pressure difference was similar to that reported for the main HOPE study population (40). Such substantial differences in 24-h pressure would more than account for the differences in cardiovascular outcomes reported for the HOPE study.

EUROPA, a more recent study, mimicked the HOPE study design by randomizing patients at high cardiovascular risk (i.e., documented coronary disease, 65% with previous MI) to the ACE inhibitor perindopril (8 mg/day) or placebo for five years of follow-up (37). The patients were “normotensive” at baseline (mean blood pressure 137/82 mm Hg) although 27% were treated hypertensives. Blood pressure was 5/2 mm Hg lower with perindopril than with placebo, and this was associated with a 14% reduction in total mortality and 24% reduction in MI. Once again, these risk reductions are similar to those reported from the BPLTTC meta-analysis when ACE inhibitors were compared with placebo, with an identical blood pressure difference (Fig. 1) (2).

A more conservative and perhaps more scientifically accurate interpretation of the data from the HOPE and EUROPA studies is that blood pressure lowering, even in

those patients with seemingly “normal” blood pressures (according to the arbitrary definition of hypertension) is beneficial, especially in patients at high baseline CVD risk, and moreover, that the benefit gained is entirely consistent with that expected from the magnitude of blood pressure lowering. This conclusion is further supported by an analysis comparing the observed odds ratios for risk reduction from clinical trials such as the HOPE and EUROPA studies from those predicted on the basis of blood pressure lowering in other trials. This analysis concluded that the observed odds ratios fell well within the 95% confidence interval of the odds ratio predicted by blood pressure fall alone (3).

More recently, the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study retested the HOPE trial hypothesis and compared the ACE inhibitor trandolapril with placebo in 8,290 patients at high risk of CVD with a mean baseline blood pressure of 133/78 mm Hg (41). There was no difference in the primary end point (death from cardiovascular causes, MI, or coronary revascularization) after a median follow-up of almost five years. This clear lack of benefit of ACE inhibition was observed despite a lower blood pressure ($-3/1$ mm Hg vs. placebo) in the ACE inhibitor-treated patients. This finding remained when the primary end point was adjusted to reflect the identical end point used in HOPE. This finding further refutes the popular notion that ACE inhibition provides benefit “beyond blood pressure” in patients without left ventricular dysfunction—in the words of one eminent commentator, may this concept “rest in PEACE” (42).

Finally, if ACE inhibition offered such “added value” beyond blood pressure with regard to CVD prevention, then this would have been observed in trials in which ACE inhibitors have been compared head-to-head with other active blood pressure-lowering drugs. This has not been the case. In trials such as the ALLHAT, CAPPP, and STOP-2 (10,13,14) studies, there was no evidence that ACE inhibition is superior to conventional blood pressure lowering for the prevention of CHD or stroke. The main “outlier” to this conclusion is ANBP-2, which showed a borderline significant benefit of ACE inhibitor-based therapy versus thiazide diuretic-based therapy for some end points but not others. Interestingly, where there was benefit, it was only seen in males (16)! The data from ANBP-2 have been included in the aforementioned meta-analyses and do not alter the conclusions from objective assessment of the totality of the evidence (2–4). Moreover, the recent Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared the effectiveness of an ACE inhibitor (enalapril), a CCB (amlodipine), or placebo on cardiovascular events in 1,991 patients with angiographically proven CHD and a normal average baseline blood pressure (129/78 mm Hg), over a two-year follow-up period (43). The primary composite end point of cardiovascular events was significantly reduced by amlodipine versus placebo (hazard ratio 0.69, 95% CI 0.54 to 0.88, $p < 0.003$), primarily because of a reduction in

hospitalization due to angina. Of interest, there was no significant difference between enalapril and placebo for the primary end point. The CAMELOT study provides two important insights: first, along with the VALUE trial (9), it further dismisses the ill-founded concerns about the safety of CCBs (at least amlodipine) in patients with CHD. On the contrary, both of these recent studies demonstrate a clear treatment benefit. Second, in a direct head-to-head trial with an active comparator, the CAMELOT study has failed to demonstrate any specific treatment benefit of ACE inhibition in patients with established CHD. Moreover, a substudy in the CAMELOT study used intravascular ultrasound (IVUS) to assess the impact of treatment on changes in coronary atheroma volume (43). The IVUS study (termed NORMALISE) showed progression of atheroma over two years in the placebo group and a trend toward progression of atheroma in the group treated with enalapril. In contrast, there was a trend toward less progression of atheroma in the group treated with the CCB amlodipine, which was significant in those with a systolic blood pressure above the mean at baseline.

This assessment of all of the recent head-to-head trials does not support the view that ACE inhibition prevents major cardiovascular events beyond the benefits attributable to blood pressure lowering in clinical trials.

REPORTING BLOOD PRESSURE PARAMETERS IN CLINICAL TRIALS: THE NEED FOR CLARITY

Another important caveat to the “beyond blood pressure” debate is that the information provided with regard to “in-trial” blood pressures is often very limited and invariably inadequate. The data emphasized in study reports usually refer to mean blood pressure parameters at the end of the study (i.e., in those patients who complete the study). This provides no information with regard to potentially greater “in-trial” differences before the end of the study, perhaps best exemplified by the much larger blood pressure differences early in the VALUE study (9). Concentrating on blood pressure data at the end of the study clearly has the potential to minimize the true “in-trial” blood pressure differences between treatment comparisons. Moreover, by definition, the data at the end of the study represents the cohort of study participants who have survived the study and thus does not include the patients who suffered major end points earlier in the study. Thus, we have little or no data on the blood pressures of the patients we are most interested in (i.e., those who suffered a major clinical event). As a minimum requirement it would be helpful to know patients’ blood pressure parameters immediately before their clinical events or at least at the clinic visit preceding the event. This would surely be more informative to better understand the relationship between achieved blood pressures and clinical outcomes. The powerful relationship between achieved blood pressures and clinical outcomes in high-risk patients highlights the need for trialists to develop more sophisti-

cated analyses of individual patient blood pressure data, integrated throughout the trial. Without such data, it is impossible to dismiss the impact of blood pressure differences on outcome.

PREVENTING DISEASE VERSUS PREVENTING EVENTS

Although clinical trials have been important in confirming the potent efficacy of blood pressure lowering, there is a downside to our dependence on clinical trials to validate long-term treatment. To prevent CVD, many people will be treated for decades, whereas the clinical trial is of relatively short duration. Moreover, to ensure adequate end points, clinical trials recruit older patients at high CVD risk, often with established and severe CVD. In effect, trials are designed to assess the prevention of “events” rather than the “evolution of the disease process” that will ultimately culminate in events. In this regard, it is perhaps not surprising that it has been difficult to show drug-specific benefits with regard to preventing acute CHD events in patients with such advanced disease.

Much of the experimental data postulating a direct role for the renin-angiotensin-aldosterone system (RAAS) in the development of CVD have advocated mechanisms that are more relevant to the evolution of structural changes, vascular inflammation, and the development of atheroma (44–48). Indeed, most studies in animal models using RAAS blockade are studies of “disease prevention” (i.e., preventing the development of atheroma or reversal of structural changes, rather than preventing cardiovascular events) (44,46–48). Conceptually, it is easier to envision how subtle but important and favorable effects on vascular structure and function, over a prolonged time, may ultimately have an impact on survival, rather than influence the terminal stages of the disease process over a shorter duration of time. Clearly, lowering blood pressure appears to be able to influence the entire spectrum of the disease process (i.e., disease evolution and short-term events), whereas drug-specific benefits and, in particular, blockade of the RAAS may provide a more subtle but prolonged benefit. This is speculative but highlights the difficulties in endeavoring to translate clinical trial data from older, high-risk patients in the truncated time frame of a clinical trial, to a broader more heterogeneous population at various stages of disease evolution. Consequently, it would be premature to dismiss the potential nonhemodynamic benefits of specific drugs altogether.

This concept is particularly relevant to younger patients who have the potential to be exposed to drug therapy for many decades and for whom there is limited outcomes data. Most clinical trials, to ensure adequate event rates, limit recruitment to patients above the age of 55 years and have usually reported a mean age of the study populations of more than 65 years. Thus, younger patients are poorly represented in outcome trials. This is a concern as modern CVD prevention strategies increasingly advocate the impor-

tance of primary prevention and treatment of an increasing number of younger patients. It is conceivable that in younger patients, subtle differences in drug effects on various surrogate or “intermediate” disease markers could have an important beneficial impact over the longer term.

SURROGATE OR INTERMEDIATE DISEASE MARKERS: DO THEY MATTER?

Recent clinical studies have examined the impact of different blood pressure-lowering drugs on resistance vessel structure (44), intima-medial thickness in larger arteries (49), left ventricular mass and structure (8,45), new-onset atrial fibrillation (AF) (50–52), systemic inflammatory markers (53), albuminuria (54–57), and metabolic changes culminating in new-onset diabetes (see subsequent text). These studies have consistently shown that blockade of the RAAS has favorable effects on these surrogate parameters beyond that attributable to blood pressure lowering alone. In many instances, this potential benefit has not necessarily translated into a reduction in cardiovascular events in clinical outcome trials, perhaps because their impact on the disease process takes more time to evolve than the typically shorter duration of a clinical trial. A good example of this comes from the ALLHAT study, in which treatment with chlorthalidone was associated with significantly more new-onset diabetes than treatment with amlodipine or lisinopril (10). The CHD event rates were little different, despite the fact that diabetes is usually associated with at least a doubling in CHD risk. One explanation for this apparent anomaly is that there was insufficient time within the trial for the new-onset diabetes to exert its impact on CHD outcomes.

Another example relates to new-onset AF. Atrial fibrillation occurs more commonly in people with hypertension and greatly increases the risk of all cardiovascular events, especially stroke (58). In the ALLHAT study, patients with AF at baseline experienced a three-fold increased risk of mortality, a doubling in risk of fatal or nonfatal CHD, and a four-fold increase in the risk of stroke, as compared with those without AF at baseline (10). In the LIFE trial, new-onset AF was reduced by 28% ($p < 0.001$) with losartan-based therapy, as compared with atenolol-based therapy, suggesting a role of angiotensin II in the induction of AF (51), a conclusion supported by some (50) but not other recent studies (9).

It seems reasonable to conclude that if such surrogate benefits were maintained over the longer term, that they might ultimately translate into a reduced morbidity and mortality. As longer term trials are unlikely to be performed, we are left with the challenge of trying to weigh the relative importance of these surrogate benefits alongside the proven benefits of blood pressure lowering. Perhaps that weighting should be greater when considering treatment of younger patients in whom the opportunities for preventing structural

damage will be greater and in whom avoiding the induction of new-onset diabetes is particularly important.

NEW-ONSET DIABETES: IMPACT OF BLOOD PRESSURE-LOWERING DRUGS

Diabetes is reaching epidemic proportions in westernized societies, and hypertension and diabetes are a lethal duo (59). Moreover, hypertension, per se, is associated with a doubling of risk of developing type II diabetes (60). Previous studies have suggested that newer drugs (often in combination with a thiazide) are associated with a significantly reduced likelihood of developing type II diabetes in people treated for hypertension as compared with people treated with conventional therapy, especially when a beta-blocker and thiazide/thiazide-like diuretic are used in combination (6-11,14,16,31-33). These are summarized in Table 2. This is not cosmetic, and previous studies have emphasized that the development of diabetes in people with treated hypertension is associated with an enhanced CVD risk, beyond the period of observation traditionally associated with a clinical outcomes trial (61,62). A more recent long-term cohort study has quantified the risk associated with new-onset diabetes in people with treated hypertension (63). In 795 initially untreated hypertensive patients, 6.5% had type II diabetes at baseline, and new diabetes developed in 5.8% during follow-up. Cardiovascular event rates in those without diabetes, developing new diabetes, or diabetes at baseline were 0.97, 3.90, and 4.70 × 100 person-years, respectively (p < 0.0001). Blood glucose at baseline and the use of a thiazide diuretic were independent predictors of new diabetes developing during follow-up. After adjustment for various confounders, including blood pressure control, the relative risks of a cardiovascular event with new diabetes or previous diabetes were 2.92 and 3.57, respectively, as compared with those who did not develop diabetes (63). Thus, the development of diabetes during the treatment of hypertension appears to substantially enhance cardiovascular risk if patient follow-up is sufficiently long to recognize it. Further work in this important area is necessary.

There are clearly differences in the likelihood of develop-

ing new diabetes with the major classes of blood pressure-lowering drugs, and a hierarchy of risk for new diabetes can be developed from the results of recent clinical trials. Drugs that block the renin-system (i.e., ACE inhibition and ARBs) have been shown to reduce the risk of new diabetes, as compared with conventional therapy (7-10,14-16). The CCBs have also been shown to reduce new diabetes compared with conventional diuretic-based therapy (9,10,31-33). In the ALLHAT study, the rates of new diabetes were chlorthalidone > amlodipine > lisinopril (10). In the VALUE trial, ARB-based therapy (valsartan) was associated with less new diabetes than CCB-based therapy (amlodipine) (9). All of this suggests that conventional therapy (i.e., thiazide and/or beta-blocker), especially when combined, is associated with the highest rate of new diabetes. Blockade of the renin system with ACE inhibition or ARBs appears to be associated with the lowest rate of new diabetes, with CCBs sitting between the two extremes. This conclusion has been supported by a recent similar analysis (64). Two key questions that need to be addressed prospectively are: 1) whether certain drugs (i.e., ACE inhibitors or ARBs) can reduce the anticipated high rate of new diabetes in people with hypertension; and 2) whether it matters. Current data cannot provide a definitive answer to these questions, but a suggested hierarchy is emerging which suggests that conventional therapy (beta-blocker and/or thiazide diuretics) probably enhances the baseline risk of developing diabetes, CCB-based therapy is probably neutral, and ACE inhibition or ARB-based therapy may diminish the risk of developing diabetes.

The potential for conventional therapy to unfavorably influence the development of diabetes in people with treated hypertension has recently been incorporated into national treatment guidelines in the United Kingdom (4,65). These guidelines recommend avoiding the combination of thiazide and beta-blockers in people at higher risk of developing new diabetes (i.e., people with a strong family history of diabetes, obesity, impaired fasting glucose levels, or those within ethnic groups that have high rates of diabetes). This is an important example of how the differential effects of drugs on

Table 2. Percentage of Patients Developing Diabetes in Randomized Clinical Trials of Blood Pressure-Lowering Therapy

Study (Ref.)	Risk Profile	Treatment Comparison	New Diabetes Rates (%)	Risk Reduction	p Value
HOPE (11)	High CVD risk	ACEi vs. CT	3.6 vs. 5.4	-32%	<0.001
CAPP (14)	Hypertension	ACEi vs. CT	6.5 vs. 7.3	-13%	<0.05
ALLHAT (10)	High-risk hypertension	ACE vs. CT	8.1 vs. 11.6	-33%	<0.001
ANBP-2 (16)	Elderly hypertensive	ACE vs. CT	4.5 vs. 6.6	-31%	<0.0005
INSIGHT (31)	High-risk hypertension	CCB vs. CT	5.4 vs. 7.0	-23%	<0.05
NORDIL (32)	High-risk hypertension	CCB vs. CT	4.3 vs. 4.9	-8%	0.14
INVEST (31)	Hypertension + CHD	CCB vs. non-CCB-based	7.0 vs. 8.2	-15%	<0.05
ALLHAT (10)	High-risk hypertension	CCB vs. CT	9.8 vs. 11.6	-16%	<0.04
SCOPE (6)	Elderly hypertension	ARB vs. CT	4.9 vs. 6.0	-20%	0.09
LIFE (8)	Hypertension + LVH	ARB vs. CT	6.0 vs. 8.0	-25%	<0.001
VALUE (9)	High-risk hypertension	ARB vs. CCB	13.1 vs. 16.4	-23%	<0.0001

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CHD = coronary heart disease; CT = conventional therapy, usually thiazide and/or beta-blocker-based; CVD = cerebrovascular disease; LVH = left ventricular hypertrophy.

a surrogate end point have influenced prescribing recommendations in a sensible and pragmatic way; as the evidence supporting this approach strengthens, it is likely to be adopted elsewhere.

IMPLICATIONS FOR MODERN TREATMENT: TARGETING CVD RISK RATHER THAN HYPERTENSION?

The key debate over the next few years will not be whether one class of blood pressure-lowering drug is better than another, but rather what is the most effective therapeutic strategy to reduce the overall CVD risk burden of individual patients. The aforementioned evidence that blood pressure is a potent risk factor for CVD across the full range of blood pressure, extending from 115/75 mm Hg, questions the logic of thresholds for “normotension,” “pre-hypertension,” and “hypertension” (36). In people at high CVD risk, lowering their blood pressure will produce a benefit irrespective of whether they are hypertensive by any of the current definitions. What is the logic of treating such a patient with drugs if their systolic blood pressure is 143 mm Hg, but not if their systolic pressure is 138 mm Hg? There is no biologic plausibility for such thresholds. The sole justification for thresholds is to decide when to use blood pressure-lowering drugs in people at low CVD risk and with no preexisting CVD in whom the strategy would be designed to prevent the evolution of hypertensive injury.

It is also impossible to target treatment appropriately without assessing the total CVD risk burden of the patient, ideally formally by risk charts or calculators (e.g., based on Framingham). After all, the purpose of treatment is to reduce the risk of stroke and CHD, not just blood pressure! This concept is important because many patients with elevated blood pressure exhibit features of the metabolic syndrome and dyslipidemia that magnify their risk of stroke and CHD, beyond that crudely attributed to blood pressure alone (66).

GOING BEYOND BLOOD PRESSURE? ADD A STATIN

Just as it is not necessary to be “hypertensive” to benefit from blood pressure lowering, it is also not necessary to have a high blood cholesterol level to benefit from statin therapy. The data from the Heart Protection Study (67) and the ASCOT study (68) are very important complementary data with regard to CVD prevention. Both have both shown that irrespective of baseline cholesterol or blood pressure, statin therapy reduces the risk of stroke and CHD. Thus, from a pragmatic and evidence-based perspective, the new target should be CVD risk, not its individual components. Consequently, most people with treated hypertension, especially males over the age of 50 years, are at sufficient CVD risk to benefit from the addition of statin therapy which, they may further substantially reduce their risk of CHD by an additional 30% and stroke by an additional 25%. In my view, statins should and will become routine therapy in people with treated hypertension, especially those at highest

CVD risk, because they potentially complement the primary objective of antihypertensive therapy—notably, to reduce the risk of CHD and stroke. This is undoubtedly the most effective way to “go beyond blood pressure.”

This concept of targeting CVD risk has been endorsed by European guidelines (69) and further advocated by the “polypill” concept (70). The latter was an important stimulus for debate in this area, but in my view, is limited by the complexity of the proposed pill and the lack of outcome data supporting the use of some of its constituents.

The guideline issue is important because guidelines frame the messages adopted by the clinicians in primary care, where most of the preventive medicine strategies are undertaken. Recent statements have appropriately advocated ever more aggressive cholesterol lowering (71,72). Nevertheless, in my view, the “silo approach” to risk factor management adopted by specialist societies and exemplified by JNC VII (36) will ultimately become an obstacle to effective CVD risk factor management. The evidence demands a single unified, evidence-based approach to identifying those with sufficient CVD risk to benefit from effective and proven multifactorial interventions. Patients are only interested in having their risk reduced, and for most, this will require more than one drug, each targeting different aspects of risk. In this regard, due credit must be given to the HOPE trial and its investigators for highlighting that, irrespective of arbitrary thresholds, drugs that lower risk factors ultimately lower risk—not exactly rocket science but still too bold for some.

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