

NEPHROLOGY

Rounds®

Controversies in Blood Pressure

By JOHN P. FORMAN, MD, MSc.

Clinicians caring for patients with hypertension must determine how – and how aggressively – to treat this disease. Forty years ago, with the publication of the first randomized trial in individuals with “essential hypertension,” clinicians were encouraged to use thiazide diuretics to treat patients whose diastolic blood pressures (DBPs) were ≥ 115 mm Hg.¹ Since then, there has been strong evidence that lowering BP reduces morbidity and mortality and treatment targets have progressively lowered. Furthermore, with the recent identification of a “pre-hypertensive” population by the Joint National Committee, it has been recognized that there is significant morbidity associated with BPs below treatment targets.² In fact, given the continuous association between BP and cardiovascular (CV) morbidity and mortality, a “hypertension” vs. “normal” dichotomy seems inappropriate; rather, “BP-related disease” appears to be more apt terminology.³ Also, since 1967, the armamentarium of drugs available to clinicians has grown, as have claims that certain agents may have beneficial effects independent of BP lowering. In 2006, therefore, the appropriate initial treatment strategy, as well as the intensity of treatment, is an area of active debate.

This issue of *Nephrology Rounds* attempts to frame these debates using the existing evidence. Part 1 addresses the controversy surrounding the appropriate initial treatment strategy; specifically – is one drug superior to another, given similar BP control? A point vs. counterpoint approach is used, as if two individuals, using their interpretations of the same available data from the medical literature, present opposing arguments. These hypothetical sparring partners follow similar trains of thought, interpreting the same randomized trials and similar recent meta-analyses, yet they arrive at polar conclusions. The debate is followed by my own thoughts and arguments regarding this controversy. Part 2 presents evidence that calls into question whether our current guidelines for the treatment of BP-related disease are sufficiently aggressive in various populations.

Part 1: “Is it the drug, or is it the blood pressure?”

It is important to clearly state the question at the center of this controversy, which is: Among individuals with BP-related disease, does 1 antihypertensive agent confer additional benefit “beyond BP control” in the prevention of CV outcomes? Given that older and less expensive medications (eg, beta-blockers and diuretics) used to be standard first-line therapy, the question alternatively posed is whether newer drugs like the angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or calcium channel blockers (CCBs) are superior to the older drugs.

It is also important to put this question in its appropriate context. As stated, this controversy applies to the prevention of CV outcomes among patients with BP-related disease. It does not apply to the prevention of renal outcomes among patients with established chronic kidney disease (CKD), which is discussed later.

The outcome of interest matters: renal vs. cardiovascular

The controversy over whether the choice of agent is, or is not, important does not pertain to patients with CKD when renal outcomes are considered. In these situations, angiotensin blockade has proven advantages. The African American Study of Kidney Disease and Hypertension (AASK) serves as a prime example. In AASK, a 3×2 factorial designed, randomized trial of 1,094 patients with nondiabetic CKD attributed to elevated BP, comparisons were not only made between ramipril, metoprolol, and amlodipine, but also between intensive BP control (mean 128/78 mm Hg) and conventional BP control (141/85 mm Hg).⁴ Intensive BP control did not reduce the risk of the combined clinical outcome of death, end-stage renal disease (ESRD), or a 50% decline in glomerular filtration rate (GFR); (RR = 0.98; 95% CI, 0.78-1.21). In contrast, ramipril was associated with a significantly lower risk of this clinical outcome compared to both metoprolol (RR = 0.78; 95% CI, 0.62-0.99) and amlodipine (RR = 0.62; 95% CI, 0.44-0.86). This dramatic superiority to amlodipine occurred despite the fact that the achieved mean systolic BP

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was 2 mm Hg lower during the study in the amlodipine compared to the ramipril group.⁴

Similar findings in non-diabetic CKD were found in the Ramipril Efficacy In Nephropathy (REIN) trial, where significant reductions in the risk of ESRD were observed with angiotensin blockade compared to other drugs in patients with nephrotic proteinuria,⁵ and non-nephrotic proteinuria,⁶ even after statistical adjustments were made for differences in BP. Likewise, among patients with diabetic nephropathy, both the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) demonstrated that angiotensin blockade, compared to other therapy, significantly reduced the risk of a composite endpoint of doubling of serum creatinine, ESRD, and death by 16% and 20%-23%, respectively.^{7,8} IDNT included a head-to-head comparison of irbesartan vs amlodipine. Despite a mean systolic BP discrepancy of just 1 mm Hg during the study, irbesartan was associated with a 23% lower risk of the primary endpoint.⁸ A careful reading of a recent meta-analysis by Casas et al, in spite of its tenor that angiotensin blockade remains an unproven therapy for preventing renal outcomes, actually provides further confirmation that angiotensin blockade is indeed an effective approach to prevent renal function decline and ESRD.⁹

It must be noted that neither AASK nor REIN specifically examined non-renal outcomes.⁴⁻⁶ In both RENAAL and IDNT, although angiotensin blockade reduced the risk of the composite endpoint, it did not significantly reduce the risk of death alone, nor was it associated with a lower risk of a combined CV outcome.^{7,8} Furthermore, these trials enrolled patients with established CKD. Thus, we arrive at a controversial issue: Does drug choice impact the risk of CV disease outcomes among individuals with BP-related disease, or rather, are all CV benefits derived from the magnitude of BP lowering?

Debate: Does the drug matter?

To frame the debate, two hypothetical individuals will give their interpretations of randomized trials and meta-analyses of randomized trials. The randomized trials include 15 large (ie, >1000 participants) drug vs. drug comparisons (13 independent trials with 1 trial containing 3 drug vs drug comparisons). While some placebo-controlled trials achieved similar BP in both arms and, thus, theoretically could be included when considering a specific drug effect (independent of BP), there is typically a greater BP discrepancy in placebo-controlled trials compared with drug-vs-drug trials. The discrepancy in SBP is very often >2 or 3 mm Hg. This is a critical issue, given what has been learned from observational data. In a 2002 analysis that combined individual data from almost one million participants with no baseline CV disease from 61 prospective studies, there was a linear association between both SBP and DBP and risk of CV mortality down to 115 mm Hg SBP and 75 mm Hg DBP.¹⁰ Every 10 mm Hg lower usual systolic or 5 mm Hg lower usual diastolic pressure was associated during long-term follow-up with a 40% reduction in the risk of death from stroke and a 30% reduction in the risk of death from coronary heart disease (CHD). A 2 mm Hg lower usual SBP was associated with a 10% lower risk of death from stroke and a 7% lower risk of death from CHD.¹⁰

The randomized trials comparing drug-vs-drug are shown in Table 1. For the purposes of this discussion, ALLHAT is treated as 3 separate trials, including its com-

Table 1: Randomized trials describing drug-vs.-drug comparisons

- Captopril Primary Prevention Project (CAPPP)¹¹
- Swedish Trial in Old Patients with Hypertension (STOP-2)¹²
- Nordic Diltiazem trial (NORDIL)¹³
- International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT)¹⁴
- Losartan Intervention for Endpoint Reduction (LIFE)¹⁵
- Systolic Hypertension in the Elderly Long-term Lacidipine trial (SHELL)¹⁶
- Australian National Blood Pressure Trial 2 (ANBP-2)¹⁷
- Controlled Onset Verapamil Investigation for Cardiovascular Endpoints (CONVINCE)¹⁸
- International Verapamil SR/Trandolapril Trial (INVEST)¹⁹
- Valsartan Antihypertensive Long-term Use Evaluation (VALUE)²⁰
- Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BLPA)²¹
- Morbidity and Mortality After Stroke: Eprosartan Compared with Nitrendipine in Secondary Prevention (MOSES)²²
- Antihypertensive and Lipid-lowering to Prevent Heart Attack Trial (ALLHAT)^{23,24}

parisons of chlorthalidone with doxazosin (ALLHAT-1),²³ amlodipine (ALLHAT-2),²⁴ and lisinopril (ALLHAT-3).²⁴ The primary endpoints that these trials were designed to study range from more specific outcomes (eg, fatal and non-fatal CHD in ALLHAT and ASCOT-BLPA), to more broad outcomes (eg, all-cause death plus a myriad of CV events in ANBP-2). Most of the trials reported rates of stroke, CHD, and CV mortality in addition to the primary endpoint.

Pro – “The drug matters”

The simplest and most straightforward way of examining whether drug choice matters is to examine large-scale randomized drug-vs-drug trials in individuals with BP-related disease. Because of the strong association between BP and risk of CV events, one would anticipate that trial results would always favor the drug in which a lower BP was achieved, particularly if that BP difference was substantial (ie, ≥ 2 mm Hg systolic, which is associated with lower CV risk in observational data).¹⁰ Therefore, to observe a drug effect beyond the BP, discordance between achieved BP and risk of CV outcomes should be sought and taken as the strongest evidence. Alternatively, significant trial results *despite no* substantial BP difference and equivalent trial results *despite a* substantial BP difference should also serve as evidence of a drug effect, although not as robustly as discordant results. The results of these 15 large-scale comparisons are summarized in Table 2.

Examining Table 2 for discordant results, the NORDIL trial stands out. Despite the fact that the beta-blocker/diuretic arm achieved a ≥ 3 mm Hg lower SBP, it was the diltiazem arm that was associated with a 20% lower risk of stroke (RR=0.80; 95% CI, 0.65-0.99).¹³ In ANBP-2 and MOSES, although SBP differences between treatment arms were <2 mmHg, the results favored angiotensin blockade despite slightly inferior BP control.^{17,22} Although enalapril compared to hydrochlorothiazide achieved a higher SBP by 1.4 mm Hg in ANBP-2, it was associated with significantly fewer events (RR=0.89; 95% CI, 0.79-1.00 for the primary composite endpoint), a finding that was driven primarily by a much lower risk of myocardial infarction (RR=0.68, 95% CI, 0.47-0.98).¹⁷ In MOSES, post-stroke patients randomized to

Table 2: Concordance between SBP lowering and outcome among drug vs. drug randomized hypertension trials that enrolled >1000 Participants

Primary outcome of the trial	SBP difference between trial arms		CV mortality	SBP difference between trial arms	
	<2 mm Hg	≥2 mm Hg		<2 mm Hg	≥2 mm Hg
Statistically significant result favoring better SBP control	LIFE		Statistically significant result favoring better SBP control		ASCOT-BLPA
No difference	STOP-2 CONVINCE INVEST ALLHAT-2 SHELL INSIGHT	CAPP NORDIL VALUE ASCOT-BLPA ALLHAT-1 ALLHAT-3	No difference	STOP-2 CONVINCE INVEST INSIGHT MOSES LIFE	CAPP NORDIL VALUE
Statistically significant result favoring worse SBP control	ANBP-2 MOSES		Statistically significant result favoring worse SBP control		
Stroke	SBP difference between trial arms		CHD	SBP difference between trial arms	
	<2 mm Hg	≥2 mm Hg		<2 mm Hg	≥2 mm Hg
Statistically significant result favoring better SBP control	LIFE	CAPP ASCOT-BLPA ALLHAT-1 ALLHAT-3	Statistically significant result favoring better SBP control		VALUE
No difference	STOP-2 CONVINCE INVEST ALLHAT-2 SHELL INSIGHT ANBP-2 MOSES	VALUE	No difference	STOP-2 CONVINCE INVEST ALLHAT-2 SHELL INSIGHT MOSES LIFE	CAPP NORDIL ASCOT-BLPA ALLHAT-1 ALLHAT-3
Statistically significant result favoring worse SBP control		NORDIL	Statistically significant result favoring worse SBP control	ANBP-2	

eprosartan suffered fewer CV events and death compared to patients treated with nitrendipine (RR=0.79, 95% CI, 0.66-0.96), despite a 1.5 mm Hg higher achieved SBP.²² Thus, discordance between achieved BP and outcome in these large-scale trials favor the newer agents (ACEIs, ARBs, CCBs). There were no instances where diuretics and beta-blockers led to more favorable outcomes despite less favorable achieved BP.

In the LIFE trial, treatment with losartan achieved better BP control than treatment with atenolol.¹⁵ However, the difference in SBP was only 1.3 mm Hg, which would not be expected to lead to large differences in outcomes within a trial involving several thousand individuals. Recall that with observational data, a statistically significant decrease in CV outcomes among approximately one million individuals was observed when the usual SBP was decreased by 2 mm Hg.¹⁰ In LIFE, losartan was associated with a 13% lower risk (95% CI, 0.77-0.98) of the primary endpoint of MI, stroke, and CV death, and a 25% lower risk of stroke (95% CI, 0.63-0.89).

Finally, trials with equivalent results, despite substantially better BP control in one of the treatment arms, should be examined as evidence. If achieved BP was the only factor that mattered in preventing CV outcomes, then one would expect chlorthalidone to be significantly better than lisinopril in the ALLHAT trial (by far the largest randomized BP lowering trial) because achieved SBP was ≥2 mm Hg lower with chlorthalidone throughout most of the study.²⁴ While fewer strokes occurred with chlorthalidone, there was, in fact, no difference in the primary outcome of MI and fatal CHD (RR=0.99, 95% CI, 0.91-1.08), demonstrating that lisinopril was equal to chlorthalidone in preventing CV disease, despite a less favorable achieved BP.

One can also examine meta-analyses of randomized trials to note a difference in drug effect. In a recent meta-analysis of 28 randomized trials comparing newer drugs (ACEIs and CCBs) to older drugs (diuretics and beta-blockers) or placebo, ACEIs were found to be superior in preventing CHD (RR=0.87; 95% CI, 0.79-0.96), while CCBs were superior in preventing stroke (RR=0.84; 95% CI, 0.76-0.94).²⁵ More importantly, using meta-regression, the authors adjusted for treatment-arm differences in achieved BP, and the chief finding persisted. Specifically, ACEIs are superior agents for preventing CHD events and CCBs are superior for preventing stroke.²⁵

To summarize, the NORDIL trial demonstrated that initial therapy with a CCB may lead to fewer strokes despite less optimal achieved BP control, while the ANBP-2 trial argues that angiotensin blockade confers better protection against CHD despite inferior achieved BP control.^{13,17} A recent meta-analysis of multiple trials lends support to this finding.²⁵ While achieved BP is no doubt a critically important factor in determining CV outcomes among individuals with BP-related disease, a careful review of large-scale head-to-head randomized trials provides evidence that BP is not the only factor.

Con - "The drug does not matter"

The simplest and most straightforward way of examining whether or not drug choice matters is to examine large-scale randomized drug vs. drug trials in individuals with BP-related disease. Because of the strong association between BP and the risk of CV events, one would anticipate that trial results generally favor the treatment arm that achieves better BP control.¹⁰ The results of 15 large scale trials are summarized and segregated in Table 2. Given the relatively similar achieved BP between the treatment arms in these head-to-

head trials, and the relatively small sample sizes compared to the available observational data, it is not surprising that most did not find significant differences in CV outcomes.

However, among the trials that did observe significant outcome differences, there was concordance between a lower achieved SBP and a lower event rate in the majority: LIFE, CAPP, VALUE, ASCOT-BLPA, ALLHAT (chlorthalidone vs. doxazosin), and ALLHAT (chlorthalidone vs. lisinopril).^{11,15,20,21,23,24} The 3 studies that found discordant results include ANBP-2, MOSES, and NORDIL.^{13,17,22} The interpretation of ANBP-2 and MOSES must be tempered by features of design and methodology (discussed later). In NORDIL, in which the achieved SBP was worse in the diltiazem vs the beta-blocker/diuretic arm, there were more total CV outcomes with diltiazem (5.2 vs. 4.5 per 1000 person-years), and a trend towards an increased risk of MI (RR = 1.16, 95% CI, 0.94-1.44).

ANBP-2 should be interpreted with caution. The original description of the study protocol in 1997 defined the primary endpoint as total CV events.²⁶ However, by the time of the final publication in 2003, the primary endpoint was altered, re-defined as a combination of total CV events and all-cause mortality.¹⁷ Post-hoc outcome definitions may be biased and should raise concern. In fact, there was no statistically significant difference between treatment groups in terms of the *a priori* defined primary outcome. Another major issue with ANBP-2 was the method in which events were accrued. In the principal analysis, the investigators included recurrent CV events; however, if they had used standard time-to-first-event methodology, then participants would have dropped out of the analysis when they achieved case status. Keeping these individuals in the analysis and counting subsequent events can bias the results because “first” events may greatly impact the risk of “second” events. When only first events were included in the analysis, only non-fatal MI remained significantly different in favor of enalapril (RR = 0.68; 95% CI, 0.47-0.99).¹⁷ On the other hand, fatal stroke was more common with enalapril than with hydrochlorothiazide (RR = 1.91; 95% CI, 1.04-3.50). There was no differences in fatal MI or total CV mortality between the two treatment arms.¹⁷

The MOSES study should also be cautiously interpreted for several reasons. First, the patient population was substantially different from that in most of the other trials, in that it was clearly a secondary prevention trial. All participants had previously suffered a stroke or transient ischemic attack (TIA).²² Second, like ANBP-2, the investigators included both first events and subsequent events in their analysis. When only first events were counted, no significant differences were found between the eprosartan and nitrendipine groups.²²

One can also examine meta-analyses of randomized trials to see that there really is no drug effect beyond the BP. A recent meta-analysis of 27 randomized trials comparing newer drugs (ACEIs, ARBs, and CCBs) to older drugs (diuretics and beta-blockers) and placebo demonstrated that angiotensin blockade and CCBs lead to a reduced risk of CV endpoints only when compared to

placebo.²⁷ In these placebo-controlled studies, the differences in achieved SBP between the active and placebo treatment arms differed by 2.9 to 9.3 mm Hg in favor of active treatment. However, when drug vs. drug trials were pooled using meta-analysis (SBP differences ranged from 0.5 to 2.5 mm Hg), there was no benefit for the newer drugs over the older drugs. Specifically, the RRs (95% CI) for comparisons of ACEI vs. older drugs were 1.08 (CI, 0.96-1.21) for stroke; 0.96 (CI, 0.87-1.07) for CHD, and 1.03 (CI, 0.95-1.11) for CV mortality. Among comparisons of ARB vs. older drugs, the RRs (95% CI) were 0.87 (CI, 0.70-1.08) for stroke, 1.00 (CI, 0.83-1.19) for CHD, and 1.00 (CI, 0.86-1.15) for CV mortality. For comparisons between CCB vs. older drugs, the RRs (95% CI) were 0.92 (CI, 0.85-1.00) for stroke, 1.01 (CI, 0.94-1.08) for CHD, and 1.05 (CI, 0.97-1.15) for CV mortality.

In summary, a simple examination of the large-scale drug vs drug-randomized trials reveals that initial drug choice is hardly relevant and that better outcomes correlate with better BP control. Furthermore, pooling all available data using meta-analysis demonstrates that when achieved BP is similar, there are no advantages to ACEIs, ARBs, and CCBs compared to older and less expensive alternatives. In conclusion, achieved BP is not just a critically important factor in determining CV outcomes; rather, it is the only factor.

Arbitration: Does it really matter if the drug matters?

We have just examined two competing arguments in which, despite interpreting almost exactly the same data, polar conclusions were reached. Despite 15 large-scale drug vs. drug trials, with >160,000 patients enrolled and many years of follow-up, the verdict to this controversy remains elusive. In fact, the principal analysis comparing one drug to another in 12 of the 15 trials was null, and methodological questions surround 2 of the remaining 3. While several of these studies reported statistically significant results among a variety of secondary endpoints, it is important to focus on the primary endpoint of each study and pay less attention to the secondary endpoints. Trials are designed *a priori* to examine the primary endpoint, and focusing on 1 significant result among multiple secondary comparisons increases the risk of drawing conclusions based on chance findings. For example, in the time-to-first-event analysis of ANBP-2, enalapril was associated with a 32% reduction in nonfatal MI and a 91% increase in risk of fatal stroke; yet, the enalapril arm had a nonsignificant 20% lower fatal MI rate and a nonsignificant 7% decrease in nonfatal strokes. Are we to believe then that enalapril prevents only nonfatal MI, and increases the risk of stroke death without increasing the risk of nonfatal strokes? Most studies that report results from these multiple secondary endpoints do not adjust the p-values for multiple testing, but rather add a cautionary note to the discussions about the interpretations of secondary findings. I would argue that although both sides of the debate can make compelling arguments, we do not have a clear winner.

Perhaps a more important point to make is that the debate over which agent is the best initial therapy is

moot. In addition to the lack of consensus that the results of these trials provide, the majority of participants were treated with more than one drug; therefore, these trials that compare drug vs. drug are really comparing drug combinations. To achieve current treatment targets, most patients with BP-related disease require combination therapy.² Unfortunately, of the 15 large-scale trials, only ASCOT-BLPA achieved adequate BP control and also prevented cross-contamination of secondary and tertiary agents between the study arms such that true drug combinations were being compared. Thus, if there is to be any future research devoted to whether one regimen is better than another regimen, perhaps the appropriate question is whether one combination is superior to another.

Another important consideration is that the *central controversy* (ie, whether, for prevention of CV outcomes, certain drugs have effects beyond BP control) might not really matter. Let us assume that such effects beyond BP control do exist. The fact that this conclusion remains elusive despite millions of research dollars and years of investigation suggests that any such effects are relatively small. Thus, in the economy of research dollars and the labor of research scientists, the controversy might be summed up using the proverb: “penny wise, pound foolish.”

This advice can be taken quite literally, especially given the existence of 2 incontrovertible pieces of information: first, BP reduction *per se* has a tremendous beneficial effect on CV events, as noted in the earliest randomized trials, as well as in very large observational datasets.^{1,10,28} Second, only about 30% of individuals in the United States with BP-related disease have adequately controlled BP.^{29,30} Taking these facts into account, perhaps instead of laboring to determine whether 1 drug is marginally superior to another, we should focus our efforts to improving BP control in the community, resulting in more profound public health improvements.

Finally, it is not at all clear whether the current BP targets are adequate, since many studies have shown that achieving BPs well below current recommendations incurs additional benefit (see below). Thus, the ultimate answer to the question “Does the drug matter for the prevention of CV outcomes?” is: “It does not matter if it matters.” Instead, our research should focus on what the appropriate BP targets should be and how best to help all individuals with BP-related disease reach those targets.

Part 2: “How low is low enough?”

As discussed, this controversy is more pressing and perhaps even more relevant. Currently, the treatment target for patients with BP-related disease is a BP <140/90 mm Hg.² For individuals with diabetes mellitus and CKD, a BP of <130/80 mm Hg is recommended.² As we shall see, currently available data argues that <140/90 mm Hg may not be low enough for a larger portion of the population (beyond patients with diabetes). In addition, studies that have examined the lower BP target in patients with CKD are conflicting.

The patient with diabetes: Patients with type 2 diabetes mellitus (T2 DM) with baseline BPs <140/80 mm Hg were randomized in the normotensive ABCD trial to placebo or active treatment with either enalapril or nisoldipine.³¹ During 5 years of follow-up, the

incidence of stroke was 70% lower in the active treatment group ($p=0.03$) compared to the placebo group (whose mean BP was 137/81 mm Hg compared to 128/75 mm Hg in the active treatment group).³¹ Among a subset of these patients with peripheral vascular disease in addition to diabetes, aggressive BP treatment also reduced the risk of a combined CV endpoint of CV death, nonfatal stroke, and nonfatal MI by approximately two-thirds.³² Treatment of “normotensive” diabetics with ramipril in the HOPE study also resulted in a reduction of CV events.³³

The patient with coronary artery disease: The CAMELOT study randomized 1,991 individuals with angiographically-confirmed coronary artery disease and a mean baseline BP of 129/78 mm Hg to either placebo or active treatment (10 mg of amlodipine or 20 mg of enalapril).³⁴ The difference between the BP in the active treatment group vs the placebo group was about 5/2.5 mm Hg. During 2 years of follow-up, the occurrence of the CV endpoint was reduced by 30% with amlodipine therapy. Enalapril therapy lowered the risk by 20%, but this was not statistically significant. Among participants with known coronary artery disease in the EUROPA study, active treatment led to a 20% lower CV event rate, along with an average 5/2 mm Hg reduction in BP compared to placebo; the results were consistent whether participants were “hypertensive” or “normotensive” at baseline.³⁵

The patient with cerebrovascular disease: The PROGRESS study included 3,189 “normotensive” participants with a prior stroke history and a mean entry BP at baseline of 136/79 mmHg.³⁶ They were randomized to either perindopril (resulting in a 5/3 mm Hg fall in BP), a combination of perindopril and indapamide (resulting in a 12/5 mmHg fall in BP), or placebo. All vascular events were reduced by 24% with active therapy in this “normotensive” group. However, combination therapy, concomitant with its greater effect on BP, appeared more effective: combination therapy reduced the risk of recurrent stroke by 42% in these individuals.

The patient with multiple cardiac risk factors: Participants in the HOPE study had known CV disease or diabetes at baseline, and 53% had BPs <140/90 mm Hg at entry.³³ BP separation with ramipril compared to placebo was 3/2 mmHg at the 4 study visits but, in fact, may have been more substantial given the results of a substudy that measured ambulatory BP.³⁷ Among the “normotensive” group, the combined CV endpoint was reduced by 20% with active treatment.

The patient with renal disease: Whether targeting a lower BP goal of <130/80 mm Hg compared to <140/90 mm Hg reduces the risk of CV outcomes in another high-risk population, namely those with non-diabetic CKD, remains undetermined. So far, 3 randomized trials have examined this question.^{4,38,39} Although 2 did not show a significant benefit with lower targets within the “normal” range, the study with the longest follow-up and highest degree of statistical power demonstrated a significant reduction in both ESRD and all-cause mortality.³⁹ The Modification of Diet in Renal Disease Study (MDRD) achieved a BP separation of approximately 8/3 mmHg (126/77 vs. 134/80 mm Hg) over 2 years; during an average of 6 years of follow-up, ESRD and all-cause death was reduced by 23% in the group with lower BP.³⁹

Conclusions

Among individuals with CKD, the data supports using angiotensin blockade for the prevention of renal endpoints; however, whether more intensive BP control to <130/80 mmHg rather than <140/90 mmHg leads to superior outcomes in nondiabetic CKD is not clear. In contrast, among individuals with BP-related disease in general, it is not clear whether one antihypertensive agent is superior to another for the prevention of CV disease outcomes. More pressing is the finding that our current treatment targets for this population are suboptimal and that intensive control is likely warranted. Perhaps the most important public health issues in the field are the high prevalence of BP-related disease and the fact that the vast majority of those with BP-related disease are inadequately treated.

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