Blood Pressure Control and Benefits of Antihypertensive Therapy
Does It Make a Difference Which Agents We Use?

Luis M. Ruilope, Ernesto L. Schiffrin

Abstract—This article debates the important question of whether blood pressure lowering alone is responsible for the benefits accrued from antihypertensive therapy as demonstrated in many multicenter randomized clinical trials with different antihypertensive agents or whether there is evidence that some agents have special properties that result in benefits that go beyond those resulting from lowering blood pressure. Over the past 30 years, it has been demonstrated that lowering blood pressure in severe forms of hypertension, and more recently in systolic and even mild hypertension, will result in reduced incidence of stroke and slower progression of heart and renal failure. These effects have been easier to demonstrate in sicker patients, because enough end points may be counted in the 3 to 5 years that these clinical trials last. However, risk attributable to high blood pressure comes, to a greater degree, from the much larger group of hypertensive individuals who have less severe forms of hypertension. Blood pressure lowering offers less protection from coronary heart disease, which is highly prevalent in hypertensive patients, than from stroke. With the introduction of agents such as renin-angiotensin system inhibitors or calcium channel blockers, it has been demonstrated that hypertensive vascular remodeling and endothelial dysfunction may be corrected. It has therefore been suggested that benefits beyond blood pressure lowering may be achieved with the use of specific drugs to lower blood pressure. Although some evidence suggests that this may be the case, it is difficult to extrapolate from mechanistic studies to prevention of hard end points in outcome trials and vice versa. The question remains for the time being largely unanswered. (Hypertension. 2001;38[part 2]:537-542.)

Key Words: hypertension, arterial blood pressure renal disease angiotensin-converting enzyme inhibitors calcium channel blockers

The benefit of outcome trials in hypertension has been steadily accumulating since the era of multicenter hypertension trials was initiated with the Veterans Administration studies. Numerous multicenter randomized double-blind clinical trials have since been performed, with some initially against placebo, until it was apparent in the 1990s that it was no longer ethical to perform studies against placebo. Thus, benefits of antihypertensive therapy for most categories of hypertensive patients seem well proven. However, it has never been clear whether benefits could be attributed exclusively to lowering of blood pressure or whether some agents had properties that resulted in cardiovascular protection beyond the benefit provided by blood pressure control. The following reviews this debate.

In Favor of the Position That Blood Pressure Lowering Is Responsible for All the Benefit That Can Be Attributed to Antihypertensive Agents

The association of arterial hypertension with cardiovascular and renal disease was established a long time ago. The goal of antihypertensive therapy thus consists in reducing cardiovascular morbidity and mortality associated with arterial hypertension by a strategy focused on lowering blood pressure while minimizing the impact of other associated cardiovascular risk factors. The conclusion drawn from the initial studies was that the reduction of cardiovascular events and death observed in hypertensive patients was mainly related to the magnitude of the fall in BP achieved by treatment. Benefit could not be ascribed to a given class of therapy because studies were not designed to compare agents but rather to determine whether active therapy differed from placebo in preventing cardiovascular morbidity and mortality. Evidence of benefit of ACE inhibitors (ACEIs) and calcium channel blockers (CCBs) to prevent cardiovascular events and death compared with placebo has also been demonstrated in placebo-controlled trials. True benefits of lowering BP may have been however underestimated in these trials for a number of reasons, which are mentioned in Table 1.

Although high blood pressure is among the most common reasons for outpatient medical visits, in Europe and the...
TABLE 1. Possible Reasons for Underestimation of the True Benefits of Antihypertensive Therapy by Intervention Trials

<table>
<thead>
<tr>
<th>Reason</th>
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<tbody>
<tr>
<td>Mislabeling of patients (and inclusion of patients with isolated clinic hypertension)</td>
<td>Late intervention (irreversible damage when therapy started)</td>
<td>Too short of a trial duration</td>
</tr>
<tr>
<td>Inadequate blood pressure control (more aggressive control is needed)</td>
<td>Overly aggressive therapy (J-shaped curve in patients with previous coronary artery disease)</td>
<td>Switching of patients (cross-over active therapy from the placebo group)</td>
</tr>
<tr>
<td>Harm from drugs</td>
<td>Noncompliance with therapy</td>
<td></td>
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</table>

United States, many individuals with established hypertension have poorly controlled BP with ≤1 out of 4 hypertensive patients having BP levels <140/90 mm Hg. Improvement in BP control independent of the type of therapy is therefore warranted to further improve prognosis in hypertension. Better control could be facilitated by proposals included in most recent guidelines, such as the sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) and the guidelines of the World Health Organization–International Society of Hypertension (WHO-ISH), that have established more precisely the level of both threshold and goal BP depending on risk (lower with higher risk).

The Problem of Systolic BP Control
Systolic BP (SBP) is the most important BP parameter generating cardiovascular risk in hypertensive patients, particularly after 60 years of age. The benefit of reducing BP in the elderly with isolated systolic hypertension has been recently subject of a meta-analysis. A difference of 10.4 mm Hg in SBP and 4.1 mm Hg in diastolic BP (DBP) between active therapy and placebo was associated with 13% reduction in total mortality, 18% reduction in cardiovascular mortality, 26% reduction in all cardiovascular complications, 30% reduction in stroke, and 23% reduction in coronary events. However, recently published trials have confirmed that control of SBP is achieved in a significantly lower number of patients compared with that of DBP. In the Hypertension Optimal Treatment (HOT) trial, a SBP >140 mm Hg was observed during follow-up in >50% of patients, whereas DBP <90 mm Hg was observed in 90% of cases. In the Swedish Trail in Old Patients With Hypertension-2 (STOP-2) study, SBP remained =160 mm Hg throughout the study, which is clearly above the goal BP of <140 mm Hg.

Current guidelines recommend diuretics and calcium antagonists (long-acting dihydropyridines) as first-step therapy for isolated systolic hypertension. ACEIs do not differ from diuretics, β-blockers, or CCBs in their capacity to control SBP, both in systo-diastolic and in isolated systolic hypertension. However, in all the recently published trials, the percentage of patients achieving adequate SBP control was always <50%, although combination therapy was often used. The risk of elevated SBP is particularly high when accompanied by normal DBP, that is, when a widened pulse pressure is found. This is particularly prevalent in elderly hypertensives and is an excellent predictor of cardiovascular risk in hypertensive and cardiac patients. Better BP control is therefore warranted.

The Case of Diabetes Mellitus, a Condition With Particular Sensitivity to BP Elevation
The UK Prospective Diabetes Study (UKPDS) and the HOT study have favored considering a goal BP of <130/80 mm Hg for diabetic patients. When compared with placebo, all drug classes, with the exception of β-blockers, have been particularly effective in diabetics. Small drops in BP have been accompanied by very substantial reductions in cardiovascular risk. In the HOT study, a mean difference of only 4/4 mm Hg for SBP and DBP among patients with DBP of 90 mm Hg and 80 mm Hg was accompanied by 43% reduction in mortality, 30% reduction in stroke, and 38% reduction in cardiac events. In the Systolic Hypertension in Europe (SystEur) trial, a difference of 8/3 mm Hg was associated with a 64% reduction in mortality, 86% reduction in stroke, and 58% reduction in cardiac events. Comparison of different classes of antihypertensive agents in hypertensive diabetics does not provide clear-cut evidence of superiority of any class of agent. In most studies, many patients were treated with drug combinations, which will be needed in practically all cases to achieve goal BP according to the most recent guidelines.

Renal Disease, Another Condition Particularly Sensitive to BP Levels
Recently published guidelines have established that goal BP in the presence of renal failure should be <130/85 mm Hg, or even lower (<125/75 mm Hg) if proteinuria >1g/day is found. Strict BP control has to be achieved to protect the kidney from the consequences of arterial hypertension. Does it matter how this control is obtained? During the last decade, a series of studies showed the apparently beneficial effects of ACEIs, compared with placebo, to arrest or at least retard the progression of renal failure. However, in only one of these studies was BP control not different between placebo and the ACEI arm. In the remaining trials, BP was significantly lower in the active therapy arm compared with the placebo arm. Furthermore, available data on BP control in these studies show that BP remained far from goal BP. This is particularly so for systolic BP. Strict BP control has been shown to be specially important for patients with proteinuria. It is also known that good BP control can be accompanied by a decrease in proteinuria. However, ACEIs are the only drugs that significantly lower proteinuria in the absence of reduction in BP. The decrease in proteinuria greatly contributes to arresting the progression of decay in renal function in patients with renal failure. This effect of proteinuria on progression of renal functional loss is independent of changes in BP.

Recently the African American Study of Kidney Disease (AASK) showed that evolution of renal function in African
Americans with chronic renal failure greatly differs when initial therapy is a dihydropyridine (amlodipine) compared with an ACEI. A significantly more rapid fall in glomerular filtration rate (GFR) accompanied by increased in proteinuria was seen in the group treated with the CCB. However, the possible combination of an ACEI plus a CCB, widely used in daily clinical practice, remains to be tested.

Evidence in Favor of Drug-Specific Effects Beyond BP Control

Since their introduction, ACEIs and CCBs have been widely used in clinical practice to treat all stages of essential hypertension. In many countries, ACEIs are the most commonly used drugs, either as monotherapy or in association with other antihypertensive agents. Their clinical use has been based on efficacy (which is not different from diuretics and β-blockers), tolerability, and easy combination. Their popularity among physicians treating hypertensive patients has also derived from the beneficial effects of the drugs on intermediate or surrogate end points such as regression of left ventricular hypertrophy31,32 or the ability of the drugs to diminish proteinuria.29 Beneficial effects of ACEI in secondary prevention after acute myocardial infarction and congestive heart failure,33 as well as in diabetic and nondiabetic nephropathy,24–26 have further contributed to increment their use.

Recent experimental and human studies have generated the hypothesis that drugs that protect the vasculature and correct both arterial remodeling and endothelial dysfunction may result in better prognosis in hypertension. It has been demonstrated that treatment with ACEIs,34–38 with ARB,39 and with CCBs40 results in regression of small artery remodeling and endothelial dysfunction present in hypertensive patients. Mechanisms involved in these effects include the reduction in oxidative stress in the vascular wall, heart, and kidney; the decrease in cell migration and cell growth; diminished interstitial fibrosis; and an improvement in endothelial dysfunction. All of these mechanisms and others are involved in some of the cardioprotective, vasculoprotective, and renoprotective actions of blockers of the renin-angiotensin system and of some of the calcium channel antagonists.41 These effects have been demonstrated in both experimental animals and humans and provide strong experimental support to the idea that these actions may improve prognosis in hypertension beyond BP lowering. However, it must be admitted that there is a quantum leap from mechanistic studies to outcome trials and hard end points such as regression of left ventricular hypertrophy or the ability of the drugs to diminish proteinuria. Nevertheless, only a minority of the hypertensive population falls into this category. The population with high BP may be seen as a risk pyramid, with the largest number of people at the base and the smallest number at the top, where relative risk because of BP is highest. The largest absolute number of complications and the highest excess of deaths attributable to high BP thus occur at the base of the pyramid in subjects with high-normal (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg) or mild hypertension (SBP 140 to 149 mm Hg or DBP 90 to 99 mm Hg). These considerations highlight the necessity of reducing BP below these values (at least <140/90 mm Hg) to achieve a substantial reduction in complications caused by elevated BP.8,9

The expected differences among antihypertensive drug classes are probably difficult to detect in studies performed on patients with mean baseline BP within the limits of stages 2 and 3 or arterial hypertension and with a follow-up of only 3 to 5 years, as has been the case in the great majority of comparative studies. The relative risk due to BP elevation in the population of patients studied in multicenter clinical trials is high, and with marked falls in blood pressure, the decrease in risk could be mainly because of BP reduction independent of the type of therapy. On the contrary, if BP-independent effects are to be observed, it is in long-term studies starting at lower BP levels. In the Heart Outcomes Prevention Evaluation (HOPE) study,44 in which 9500 patients with high cardiovascular risk (53% normotensive, 39% diabetics) were treated with a high dose (10 mg) of the ACEI ramipril for 4 years; a 22% (P<0.01) reduction in mortality and morbidity was obtained with the ACEI compared with placebo. Initial BP values were 139/79 mm Hg (high-normal blood pressure). It has been claimed that results of this study cannot be extrapolated to hypertension. In fact, 46% of patients had a history of high blood pressure. However, three quarters of patients were receiving, at baseline, ≥1 drug capable of lowering BP, which confirms that most patients entering such studies today should achieve strict BP control (<130/85 mm Hg) to obtain the most favorable outcome. Patients randomized to placebo in the HOPE study exhibited no change in SBP, whereas a fall of 2 mm Hg was observed in DBP at the end of the study. Patients who received ramipril presented a reduction of 3 mm Hg in SBP and DBP. Thus, within the range of high-normal blood pressure, high cardiovascular risk patients benefit from treatment with an ACEI, even if this is associated with small BP reductions. The clinical advantage of such a therapy was even more independent of BP changes in diabetic subjects,20 in whom the BP drop was negligible. Further evaluation of the ability of different antihypertensive drugs to reduce cardiovascular events and death in subjects with baseline BP similar to that of the subjects who participated in the HOPE study is
TABLE 2. Incidence of Type 2 Diabetes in the ARIC Study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>ACEI</td>
<td>0.98 (0.72–1.34)</td>
</tr>
<tr>
<td>(\beta)-Blocker</td>
<td>1.28 (1.04–1.57)</td>
</tr>
<tr>
<td>Calcium-channel antagonist</td>
<td>1.17 (0.83–1.66)</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>0.91 (0.73–1.13)</td>
</tr>
</tbody>
</table>

*P<0.05 vs no antihypertensive medication.

warranted to demonstrate specific effects of drug classes on cardiovascular risk in the absence of the confounding effects of BP reduction that may hide BP-independent benefits of therapy.

Mechanisms underlying beneficial cardiovascular effects of antihypertensive therapy within the short period of a clinical trial (3 to 5 years) may be different from mechanisms operating in longer time periods. The former may relate to plaque stabilization and may be achieved by all antihypertensive agents via adequate BP lowering. The latter may be the result of arresting the progression of atherosclerosis or other processes. Recent studies, summarized in Tables 2 and 3, have highlighted the potential of some agents, such as \(\beta\)-blockers and diuretics, to induce the development of diabetes.15,16,20,45 Diabetes places hypertensive patients automatically in the highest risk category because of the enhancement of vascular and renal injury and its consequences.8,9,46 An enhanced risk for developing diabetes may not result in significant morbidity within the observation period in interventional trials of 3 to 5 years duration. Induction of diabetes is a negative characteristic of older drugs that may only generate significant consequences, leading to major cardiovascular and renal morbidity in studies with longer follow-ups. Another aspect is the incidence of side effects that promote drug withdrawal and low compliance. The prevalence of side effects could contribute to explain the low percentage of well controlled hypertensives in the Western world, that oscillates between 6% and 27%.8,47–49 A paucity of side-effects induced by some medications could result in better long-term control of BP and better outcomes.50,51

Post-hoc analysis of secondary end points in available studies has shown some differences, albeit not very robust ones, among different therapies. In the Medical Research Council (MRC) trial in the elderly, \(\beta\)-blockers did not protect from coronary artery disease, whereas diuretics did.52 However, there was a large crossover between groups, and a large withdrawal rate. In the Nordic Diltiazem study (NORDIL),17 there was less stroke with diltiazem than with conventional treatment. In STOP-213 there was less myocardial infarction and heart failure with ACEI than with CCB. In ALLHAT,53 more heart failure was found with doxazosin than conventional therapy.

TABLE 3. Incidence of New Cases of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAPP</th>
<th>HOPE</th>
<th>INSIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=10985)</td>
<td>(n=9297)</td>
<td>(n=6321)</td>
<td></td>
</tr>
<tr>
<td>Mean follow-up, y</td>
<td>6.1</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>new cases with old drug*</td>
<td>380 (6.9%)</td>
<td>155 (5.4%)</td>
<td>176 (5.6%)</td>
</tr>
<tr>
<td>new cases with new drugs</td>
<td>337 (6.1%)</td>
<td>102 (3.6%)</td>
<td>136 (4.3%)</td>
</tr>
<tr>
<td>Risk ratio for new drugs</td>
<td>0.86 (P=0.039)</td>
<td>0.66 (P=0.001)</td>
<td>0.77 (P=0.02)</td>
</tr>
</tbody>
</table>

*Or placebo.21,30,31

**Conclusion**

The issue of whether some drugs are better than others in prevention of events remains unresolved because of the small numbers of events in each group in trials performed so far comparing different classes of agents,24 as well as other limitations that have been mentioned in this review, some of which are summarized in Table 1. However, there is good reason to believe on the basis of the mechanism of action of some agents, particularly blockers of the renin-angiotensin system and some of the calcium channel antagonists, through their cardioprotective, vasculoprotective and renoprotective effects, in part mediated through reduction in oxidative stress, decreased interstitial fibrosis, cell migration and growth, and prevention of endothelial dysfunction, that indeed some antihypertensive agents may produce drug-specific benefits beyond BP lowering. However, so far, multicenter clinical trials have demonstrated the safety of most antihypertensive agents, but have been unable to detect moderate cause-specific benefits. Large trials such as ALLHAT,59 or, probably better, the final meta-analysis of the Trialist’s Collaboration,5 will have the numbers to answer the question. Until then, we have to lower BP to levels recommended by current guidelines, perhaps further, in as many hypertensive patients as possible. This often means 2 to 3 drugs, preferably those with fewest side-effects, and attempting to avoid precipitating the development of diabetes, that is such an major risk factor for cardiovascular and renal morbidity.

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**References**

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