Editorial Commentary

Treatment of Hypertension

Remaining Issues After the Anglo-Scandinavian Cardiac Outcomes Trial

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At least in hypertension, there has never been a perfect clinical trial. By its nature, hypertension poses several barriers to the performance and interpretation of even the most carefully planned and conducted therapeutic trial. First and perhaps foremost, blood pressure is a constantly moving target so that both the initial recognition of hypertension and its subsequent response to therapy are often difficult to validate. Certainly, the performance of only a few blood pressure measurements in an office setting usually provides blood pressure levels that are higher than multiple blood pressures taken out of the office.[1] Both automatic ambulatory measurements[2] and self-recorded home measurements[3] have been found to be more predictive of future morbidity and mortality than office readings, but until now, all clinical trials have used a few office readings for identification of hypertension and quantification of therapeutic benefits. The inclusion of even many thousands of patients in a given trial does not erase the potential errors of the inherent variability in blood pressure that is often accentuated by the alerting reaction to office measurements. Moreover, even carefully selected meta-analyses may not cover the faults of incorrect data.[4]

A second barrier to the interpretation of trials that last 3 to 5 years, as most do, is the usual long duration of hypertension before overt target organ damage develops. It is obvious that the results of trials of limited duration may not provide a valid indication of the effects of therapy over the longer duration of the disease. Moreover, only mortality is a certain end point; morbidities may be difficult to prove, and surrogate end points such as reduction of proteinuria are not adequate to document therapeutic benefit. In hopes of demonstrating a statistically adequate number of end points in the necessarily short duration of trials, selection has increasingly been directed to high-risk patients, providing evidence that may not apply to the majority of hypertensive patients.

Many other problems often confound therapeutic trials, including the inability to achieve similar reductions in blood pressure with the different therapies being compared; the combining of diverse end points that have different relationships to hypertension, eg, coronary disease and stroke; the implication that statistical significance equates to clinical significance; the post-hoc extrapolation of predetermined end points to multiple subgroups; the biases introduced by either too lax or too stringent exclusion criteria; and the high rates of drop-outs and crossovers from the therapy initially selected.

Beyond all of these potential barriers, the increasing need to use commercial funding for large and long trials introduces another element of concern. Fortunately, only a few large trials have suffered from the consequences of commercial interference.[5]

With all of these considerations in mind, I will examine a number of specific issues that remain unanswered after the publications of trials through October 1, 2005.

Can Hypertension Be Prevented?

All currently published trials have examined only hypertensive patients and many of the more recent ones have studied only hypertensive patients at high risk. Treatment as intensive as practical has reduced cardiovascular risks only partially (stroke more than coronary disease), but neither to the risk level seen in nonhypertensive people.[6] Beyond the inability of currently available therapy to remove risk, the inability of maintaining lifelong drug therapy is obvious. Therefore, a shotgun approach has been recommended by some wherein virtually all adults, regardless of blood pressure, should be given a Polypill that includes multiple antihypertensive agents, thereby potentially reducing cardiovascular disease by 80%.[7]

The more traditional approach to the primary prevention of hypertension has been modification of adverse lifestyles.[8] As effective as they may be, most people do not follow these modifications. Therefore, the use of an antihypertensive drug to prevent progression in those who are at the higher levels of normotension is being tested.[9] If the results prove the principle of prevention, larger and longer trials should follow.

Can Out-of-Office Measurements Be Used?

Beyond the problems of the white-coat effect and the more recent recognition that some have only out-of-the-office (masked) hypertension, there is clearly a need for more accurate ascertainment of the usual level of blood pressure, both before and after therapy. Repeated 24-hour automatic ambulatory recordings would be most accurate and predictive, particularly if the level achieved during the night is of critical importance, as suggested by the substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial.[10]

At least in the United States, ambulatory monitoring is not readily available, and, even if it were, the multiple number of recordings needed to monitor a large trial would make it impractical. Therefore, self-taken home readings are the logical solution. Other than for the inability to measure nighttime levels,

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home readings would provide a complete picture of the blood pressure range.[3] In particular, the morning surge of pressure could easily be identified and targeted since it may be the most critical target of therapy.[11]

Yet another reason for use of home monitoring is the ability to recognize over-treatment. Many of the side effects of therapy, including dizziness, vertigo, lethargy, fatigue, peripheral coldness, and erectile dysfunction,[12] could be secondary to blood pressure that is too low, a level that could easily be masked by the white-coat effect seen during office measurements.

What Is the Appropriate Endpoint of Therapy?

Most recent trials have used coronary disease as the primary end point of therapy. However, the causes of coronary disease are more multifactorial than are those for stroke. The analysis of the role of blood pressure and other variables in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) documents this fact.[13] The authors note:

"Our findings show that differences in serum HDL cholesterol had the biggest effect on differences in the rates of coronary events, but for stroke event rate differences only measures of blood pressure materially affected risk. Hence, in multivariate analyses, inclusion of all the biochemical variables, heart rate, and bodyweight added only slightly to the effect of adjusting for blood pressure alone with respect to risk of stroke, but for coronary events a greater additional effect was apparent."

Because stroke is more closely related to blood pressure, because it is reduced more than coronary disease by therapy, and because it is often easier to document than coronary disease, it seems logical that it be used as one of the primary end points of therapeutic trials.

How Urgent Is the Reduction in Pressure?

The greater protection against coronary disease and stroke that was seen in patients assigned to amlodipine than in those assigned to valsartan in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was attributed to the greater reduction in blood pressure during the first 3 months that was seen in the calcium channel blocker (CCB)–treated group.[14] As a consequence, a more rapid reduction in blood pressure has been called for. However, as in most recent trials, the patients enrolled in the VALUE trial were all high-risk hypertensives. For patients at less immediate risk, a more gentle, gradual reduction seems preferable, particularly from the often high levels of systolic pressure seen in the elderly, whose autoregulatory mechanisms may be impaired and who are most prone to orthostatic and postprandial hypotension.

What Is the Appropriate Goal of Therapy?

Most expert committee guidelines recommend that the goal of antihypertensive therapy be a blood pressure of 140/90 for most patients and 130/80 for those with diabetes or chronic renal disease. Recently, support for an even lower goal for hypertensive patients with overt coronary heart disease has been provided.[15] In the CAMELOT study, hypertensive patients with coronary heart disease whose initial blood pressure on multiple drugs was 129/78 were given either an angiotensin-converting enzyme inhibitor (ACEI) or a CCB, with a subsequent 5/2 mm Hg further fall in blood pressure with both agents. Although only those on the CCB had a reduction in coronary events, this greater benefit at lower blood pressure could be interpreted as a need to reduce pressure even below those levels recommended in current guidelines.

On the other hand, an analysis of the impact of achieved blood pressure on cardiovascular outcomes in 1590 hypertensive diabetics with nephropathy found that the incidence of myocardial infarction significantly increased when diastolic levels were lowered to 85 mm Hg or below.[16] Because this study included patients with diabetes and nephropathy, the 2 conditions wherein the lower diastolic goal of 80 mm Hg is generally recommended, caution seems well advised in bringing diastolic levels to below 85 mm Hg. There was no increased risk with reduction of systolic levels to 120 mm Hg, further documenting the apparent safety of lower goals for systolic pressure.

What Is the Impact of Diabetes?

The coexistence of diabetes markedly increases cardiovascular risk among hypertensive patients. Fortunately, as shown in data from 27 randomized trials, therapy with various antihypertensive agents provided broadly comparable protection from major cardiovascular events for both diabetic and nondiabetic patients.[17] No special advantage was seen for drugs that inhibit the renin–angiotensin system, ACEIs, or angiotensin II type 1 receptor blockers (ARBs) in comparison to other agents although renal outcomes were not examined in this analysis.

On the other hand, a lower incidence of new-onset diabetes has been repeatedly seen in hypertensive patients given renin–angiotensin inhibitors as compared with other agents.[18] Jandeleit-Dahm et al[18] describe both previously demonstrated and novel mechanisms to explain the ability of renin–angiotensin inhibiting agents to reduce the incidence of new-onset diabetes.

As expected, concerns have risen over the potential of added harm from diabetes that appears during treatment, concerns directed mainly toward β-blockers[19] and diuretics.[20] Whereas the high doses of diuretics used in the past (50 mg per day or more of hydrochlorothiazide or its equivalent) have clearly been shown to reduce insulin sensitivity,[21] the degree of interference with glucose metabolism seen with the smaller doses (12.5 to 25 mg per day) used in most recent clinical trials is less severe.[18]

In 2 trials wherein such smaller doses of diuretics were used, no obvious adverse effects were seen in those with new-onset diabetes. In the 5- to 7-year follow-up of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), there was no evidence of superiority for treatment with a CCB or an ACEI compared with the diuretic chlorthalidone as initial therapy.[22] During a mean follow-up of 14.3 years for patients enrolled in the Systolic Hypertension in the Elderly Program (SHEP), pa-

tients given chlorthalidone who developed new-onset diabetes had no increase in cardiovascular or total mortality rates, whereas there was an increased morbidity and mortality in those who developed diabetes while on placebo.[23] The SHEP data may reflect a more benign course for diabetes induced by a diuretic than for diabetes that develops spontaneously.

On the other hand, an association between new-onset diabetes associated with diuretic therapy and subsequent cardiovascular disease has been reported in a nonrandomized, uncontrolled cohort study of 795 hypertensive patients followed for a median of 3.1 years.[20] Although this study has been assumed to document a similar risk in new-onset diabetes associated with diuretic therapy as with pre-existing diabetes,[24] the study has many shortcomings that make its conclusions suspect. These include a small number of patients who developed diabetes, the presence of higher initial blood glucose and more severe hypertension among these few patients, the administration of multiple drugs so that only a handful of subjects were taking only a relatively low dose of a diuretic, and the multiple potential faults of a nonrandomized protocol.

For now, prudence seems appropriate in the use of β-blockers and higher doses of diuretics in diabetic hypertensive patients, but they should not be denied the treatments if they are indicated for concomitant compelling indications or to adequately control the hypertension.

Is There an Age Limit for Therapy?

As the population ages, more and more very elderly patients over age 80 with hypertension are being seen, most with isolated systolic hypertension. Unfortunately, there is scant evidence on the impact of antihypertensive therapy on them. The little that is available suggests that therapy reduces the incidence of stroke but increases non-stroke mortality.[25] Until the results of ongoing trials in the very elderly become available, only gentle and gradual treatment should be provided, perhaps down to no less than a systolic level of 160 mm Hg.

Is One Drug Better than Another?

All antihypertensive drugs are better than placebo. When compared with one another, they provide similar overall benefits if they provide equal degrees of antihypertensive effect.[17] Differences between individual drugs have been shown but there are multiple explanations for such putative differences, including failure to achieve the same level of blood pressures,[12,17] admixture of multiple other drugs to the initial selection to achieve the desired goal of therapy, and the common use of inherently inferior comparative drugs, perhaps most frequently with once-a-day atenolol.[26]

There may very well be differences: ACEIs and ARBs appear to protect better against heart failure, particularly in diabetic hypertensives[17]; CCBs seem to protect better against stroke[27]; and ACEIs and ARBs may be more renoprotective.[16] However, the overriding need is to effectively lower blood pressure while avoiding adverse effects and, at the same time, correcting as many of the other risk factors for cardiovascular diseases as possible.

As noted by others,[28] it is time to move on: to more careful assessment of blood pressure, to more intensive treatment of hypertension, to correction of coexisting risk factors, and, hopefully, to the prevention of hypertension.

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