Editorial

More Confusing Messages From the Hypertension Treatment Trials

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Editor in Chief

Over the past 5 years, numerous hypertension treatment trials have been completed and reported.[1–8] A majority of these trials were initiated to distinguish one therapy from another in reducing cardiovascular (CV) events. Some were blinded and appropriately randomized prospective trials; others were unblinded or prospective cohort studies. Various populations have been studied, and results have differed. Statistical manipulations have often been carried out to prove a point if trial results were different than the investigators had anticipated.

An ongoing question remains: "What really matters in determining therapy?" Is it the lowering of blood pressure (BP) that reduces CV events, or does the use of specific medications account for differing results? A meta-analysis of the clinical trials has determined that it is the degree of BP lowering that makes the major difference in outcome, and not specific medical therapy.[9]

Many individual trials appear to confirm this conclusion. For example, the Verapamil in Hypertension Atherosclerosis Study (VHAS)[10] reported no difference in outcome between a diuretic and verapamil. The Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE)[8] study reported no differences between a verapamil-based treatment and usual care, i.e., a diuretic plus a β blocker and other drugs, and the United Kingdom Prospective Diabetes Study (UKPDS)[11] in type 2 diabetics reported no difference in outcome between a β-blocker-based and an angiotensin-converting enzyme inhibitor (ACEI)-based treatment program if BPs were lowered to an equivalent degree. In the latter study, which included an 8.5-year follow-up of more than 1100 patients, a difference of only 10/5 mm Hg accounted for a significant decrease in macrovascular and microvascular CV events in diabetics in the group of patients who achieved the lower levels of BP.[11]

In the Swedish Trial in Old Patients with Hypertension (STOP-2) study,[12] both systolic and diastolic BPs were reduced to an equivalent degree with calcium channel blockers (CCBs) and ACEIs compared with diuretics and β blockers. There was also no significant difference in overall outcomes. In this study, however, patients on ACEIs had fewer myocardial infarctions (MIs) and less congestive heart failure than patients receiving a CCB. This finding had also been noted in several other smaller studies when a CCB-based regimen was compared with an ACEI-based treatment program.[13,14] In the Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis, however, these differences were not noted,[9] and more recent studies have reported that CCB-based therapy appears to result in CV outcomes similar to those with ACEI- or angiotensin receptor blocker (ARB)-based regimens. It appears, therefore, that abundant data confirm that BP lowering accounts for most of the benefit noted in the clinical trials.

In some high-risk patients, however, results have been somewhat different. In the Heart Outcomes Prevention Evaluation (HOPE),[7] the Irbesartan Diabetic Nephropathy Trial (IDNT),[15] the Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients (IRMA) study,[16] the Reduction in Endpoints in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL),[6] and the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE)[5] studies, the use of an

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ACEI or angiotensin receptor blocker (ARB), usually given with a diuretic, reduced CV events to a greater degree than a regimen that did not include these medications. In these studies, it appeared that specific medications made a difference in CV event outcome, especially in patients with diabetes and renal disease. Thus, while most trial results confirm the conclusions of the meta-analyses, others indicate that there are instances where specific medications may be more effective than others.

THE MORE RECENT CLINICAL TRIALS: ALLHAT, ASNBP-2, VALUE, LIFE, AND ASCOT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[1] a randomized, double-blind, multicenter, non–industry-sponsored clinical trial, reported that >60% of hypertensive patients with a mean age of 67 years could be controlled with BPs lower than 140/90 mm Hg if goal BPs were vigorously pursued.[17] Primary outcomes (fatal and nonfatal coronary heart disease) showed no difference when a diuretic (chlorthalidone)-based treatment regimen was compared with an ACEI (lisinopril) or a CCB (amlodipine)-based program. When further analyses were done, however, diuretic-treated patients had fewer strokes than ACEI subjects and fewer episodes of heart failure compared with either ACEI- or CCB-treated patients.

Some investigators were quick to note that black patients and patients over 65 years of age experienced a greater BP decrease on the diuretic than with other medications, especially when the ACEI was compared with the diuretic. A 4-mm Hg systolic BP difference was noted in black subjects; a 3-mm Hg systolic BP difference was noted in the over-65 group. This may have accounted for at least some of the significant differences in stroke outcome. Specific actions of one medication may, therefore, not have accounted for differences in benefit between groups. In this trial, as in all the others, multiple medications were necessary to achieve goal BPs in a majority of patients. The ALLHAT investigators concluded that a diuretic should be the first-choice drug in most patients but also concluded that a majority of hypertensive patients required more than one drug to achieve goal BPs.

The Second Australian National Blood Pressure study (ANBP-2),[2] which was not blinded, compared an ACEI-based to a diuretic-based regimen in elderly patients over 5 years. The ACEI-treated patients experienced a marginally better long-term outcome; the benefit, however, was noted only in male patients. Some physicians concluded that the ASNBP-2 results, which were different from ALLHAT, should be the ones to guide therapy—that an ACEI-based treatment program was more beneficial in reducing CV events than a diuretic-based regimen. In the Valsartan Antihypertension Long-Term Evaluation (VALUE),[3] BPs were lowered, especially during the first 6 months, to a greater degree with amlodipine than an ARB (valsartan). The occurrence of MIs was lower in the CCB group. Statistical calculations were done to demonstrate that in people with the same achieved BP there was no difference in outcome, but the question of whether it was the achieved BP or a specific treatment that made the difference was not settled. VALUE, like ALLHAT and ASNBP-2, was a trial of multiple-drug therapy and did not completely settle the question of one medication's superiority over another in reducing CV events.

The LIFE study,[5] which compared the results of an ARB (losartan)- to a β-blocker (atenolol)-based program in hypertensives with left ventricular hypertrophy, demonstrated that strokes were significantly reduced in the ARB group despite essentially similar BPs in both groups at the end of the trial. This trial suggested that specific therapy did make a difference in outcome, at least in some patient subgroups. It was not surprising that outcome was better with therapy other than a β blocker; this had been demonstrated many years ago in the Medical Research Council trial[18] in the elderly. When a diuretic was compared with a β blocker and a placebo, the use of a diuretic resulted in a significantly greater decrease in coronary heart disease events compared with the β blocker, but in this trial BP was reduced to a greater degree and in more patients with the diuretic.

Other studies, such as RENAAL[6] and HOPE,[7] suggest that there is some difference in outcome with certain agents compared with other medications with equivalent decreases in BP. But in some of these trials, especially the HOPE trial, there is still a question of whether or not it was BP lowering or medication that made the difference in outcome.

Finally, the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) trial,[4] which included 77% males and more than 90% Caucasians, concluded that a CCB-based (plus an ACEI) regimen reduced mortality and strokes more than a β-blocker-based (plus a diuretic) program. But, as in the ALLHAT trial, the primary outcome (MI) was similar with both therapies.[4,19] Basically, ASCOT compared a CCB titrated upward to a β blocker titrated upward regimen within the first few months of the study. There

was a difference of 5.9/2 mm Hg in BP control in the first few months; this may conceivably have resulted in the better outcome with the CCB. The ASCOT investigators concluded that, based on secondary end points, national guidelines should be changed and that so-called "contemporary" therapy (i.e., CCBs and ACEIs) was superior to older therapy (β blockers and diuretics). The results regarding the use of β blockers as initial therapy may be applicable to elderly Caucasian males but, based on ASCOT, cannot be applied to other gender and ethnic groups. It is also inappropriate, based on the results of ALLHAT and other trials in which diuretics were used as initial therapy, to suggest that the current recommendations for use of these agents be changed. The ASCOT results should not influence guidelines such as those of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[20] that suggested diuretics as initial therapy in most patients and suggested as early as 1998 in JNC VI[21] that β blocker monotherapy was not preferred initial therapy in the elderly. ASCOT has confirmed, however, what other trials had reported—multiple medications are necessary to reduce BP.

Thus, there are meta-analyses that indicate that it is the BP level that makes the difference in outcome, but also some confusion from several of the trials that suggest specific benefits of various medications over and above the effects of BP lowering. When the data are carefully considered, two conclusions, which may actually *not* be confusing, can be reached[22]: 1) the "my drug is better than your drug" argument may be moot—multiple medications are necessary to achieve goal BPs in most cases—and none of the recent trials which have been so highly promoted were trials of monotherapy; and 2) most of the benefit achieved in the treatment trials results from more effective BP control, with exceptions in the cases of patients with diabetes or renal disease.

THE PROBLEM OF NEW-ONSET DIABETES (NOD)

An additional confusing message relates to the occurrence of NOD as a result of treatment in some hypertensive patients. This has recently been reviewed.[23,24] It is well known that diabetes is more common in hypertensives than in normotensives.[25] There is, however, a <1% increase in NOD with diuretics and β blockers in placebo-controlled hypertensive treatment trials. In chart reviews, no difference has been found in NOD among diuretics, ACEIs, and CCBs, but an increase has been noted with β blockers.[25,26]

In comparative trials, a 1%–3.5% absolute increase in NOD has been reported with a diuretic-based compared with an ACEI-based treatment program and about a 1% increase when compared with CCBs.[27] The clinical significance of this finding has been questioned; further studies are needed to decide whether or not CV outcome is affected. Data are conflicting. One study with a small number of events suggests that NOD has a similar prognosis as pretreatment diabetes; another does not.[28,29] Both studies report that, while there appears to be a relationship between NOD and the use of diuretic-based treatments, there does not appear to be an independent relationship to CV outcome.

At present, the data do not indicate that the findings of NOD should lead to a change in the JNC 7 recommendation for diuretics as initial therapy for most patients. The results of some of the recent trials and the NOD data do suggest, however, that the use of β blockers (without vasodilator or α-blocking actions) may not be preferred as initial antihypertensive therapy, especially in obese patients or subjects with findings of the metabolic syndrome. These medications are indicated, however, in patients with angina, heart failure, and post-MI. They should also continue to be used in combination with a diuretic, if necessary, to reduce BP to goal levels.[27]

CONCLUSION

Despite all of the expense and effort expended to convince physicians that one therapy is superior to another, the bottom line remains: reduce the BP to as low as possible without interfering with the enjoyment of life, and CV outcome will improve. The choice of medication, with the exception of certain subgroups of patients, appears to be less important than achieving goal BP; medications with differing actions will be necessary in most patients to achieve goal BPs.

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