Editorial

ALLHAT and Beyond

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The publication of the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) results in the Journal of the American Medical Association, heralded by a carefully orchestrated press conference, television appearances, and national newspaper coverage, may have been an appropriate reflection of the ambition and magnitude of the enterprise. No prior trial of antihypertensive therapy approached the size and commitment of resources of ALLHAT. It is a record unlikely to be surpassed in the foreseeable future. Conceived a decade ago, the study addressed the much debated, but unresolved question of whether newer antihypertensive agents were superior to that of diuretics in providing protection against coronary artery disease events. A subtext was whether it really mattered how pressure was reduced, or was it blood pressure (BP) reduction per se, regardless of its methods, that made the difference.

The primary end points were fatal and nonfatal coronary events. Some 42,000 older, mildly hypertensive subjects, at higher than average risk of cardiovascular events, were randomized to blinded therapy with either an α-blocker, doxazosin, a calcium channel blocker, amlodipine, or an angiotensin converting enzyme (ACE) inhibitor, lisinopril, and a diuretic, chlorthalidone. The three newer agents were individually compared to the diuretic, and not to each other. The doxazosin arm had been terminated prematurely, primarily because of significantly less favorable protection against the secondary outcome of cardiovascular events, driven largely by a doubling in the rate of congestive heart failure. It was also adjudged unlikely that a significant benefit in regard to the primary end point could have been achieved had the study been carried through to its expected end.

Thus, the December 2003 publication dealt with the comparisons of amlodipine and lisinopril to chlorthalidone. Blood pressure control (<140/90 mm Hg) was achieved by nearly two-thirds of patients, but there were modest differences in BP, most notably a 2 mm Hg greater decrease in systolic pressure among patients randomized to chlorthalidone compared to lisinopril. Some 3000 coronary events, nearly 5000 deaths, and more than 1500 strokes were recorded. There was no significant difference in the primary end point, and, as the article reported, neither agent proved superior to the diuretic in any of the secondary end points. Moreover, chlorthalidone proved superior to amlodipine in prevention of heart failure, and to lisinopril in regard to both heart failure and stroke. As a result, patients randomized to chlorthalidone, compared to lisinopril, enjoyed greater protection against total cardiovascular disease (CVD). This variation in outcomes provides an affirmative answer to the question of whether it matters how BP is reduced.

In general, ALLHAT findings were similar across groups, including diabetics, with two important exceptions. The difference in stroke between chlorthalidone and lisinopril subjects was almost entirely due to the experience of African American participants, and the heart failure difference was also greater among African Americans than whites. This was associated with a 4 mm Hg greater systolic pressure in African American patients allocated to lisinopril compared to those allocated to chlorthalidone.

These robust findings should, nevertheless, be viewed in light of several contextual issues. First of all is the difference in BP to the disadvantage of subjects, particularly African Americans, randomized to lisinopril. Overall, the average of about 2 mm Hg difference in systolic pressure actually appeared somewhat greater during the first years of the study. Although a strong case is made for the BP difference not explaining the results, it is reasonable to assume that it contributed, particularly among African Americans where the difference was twice as great. In absence of the African American participants there was no difference in stroke between the two agents.

Why did this difference in pressure occur? The protocol directed that all patients reach the same target BP, and physicians were encouraged to increase doses and add second and third agents to achieve that goal. Between 72% and 82% of patients remained on their blinded drug throughout the study, and nearly half received at least a second agent. The shortfall in BP control among the lisinopril group may reflect the actual selection of the second agents. Although a choice of agents was recommended and provided by ALLHAT, the most recognized and gen-

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erally used was the β-blocker atenolol. Thus, in practice, the most common combinations were chlorthalidone plus atenolol versus lisinopril plus atenolol. That clearly produced an imbalance. As Dr. John Laragh has so elegantly demonstrated, all BP is maintained through the interplay of volume and vasoconstriction. In different subjects, volume or vasoconstriction may dominate or be most responsive to intervention. Thus, for example, patients whose renin system is relatively inactive, may sustain their hypertension through volume expansion. Such patients are not likely to respond to lisinopril, a vasodilating agent. The appropriate next step in such a patient would be the addition (or substitution) of a diuretic to tackle the otherwise unaddressed volume component of the system. However, in ALLHAT, the protocol led to the selection of atenolol (and discouraged crossing over to a diuretic) with the result that patients unresponsive to the first vasodilating drug were provided with a similarly acting second drug. Little wonder that a BP difference emerged. Whether and to what extent these differences in treatment, and their BP consequences, contributed to the observed outcomes can only be a matter of speculation.

The Australian Study

Any discussion of ALLHAT must also now take into account the seemingly conflicting results of the Australian National Antihypertensive Trial (ANBP-2). The Australian study directly compared the ACE inhibitor enalapril to a diuretic. Some 6000 subjects were randomized to an open label treatment, although outcome assessment was blinded, and the primary outcome was all (and not just first) cardiovascular events, both fatal and nonfatal. During 4 years, there were 1431 cardiovascular events or deaths. Subjects randomized to initiation of therapy with an ACE inhibitor were significantly less likely than the diuretic group to experience a CVD event or death (56.1 v 59.8/1000 patient-years, hazard risk = 0.89 (confidence interval 71–97, P = .05)). However, after stratification by gender, a significant advantage for the ACE inhibitor group was only realized by men. Moreover, when the outcome was time to first event, the end point measure used by ALLHAT, there was no significant difference between the diuretic and ACE inhibitor groups. Of interest, fatal strokes were significantly more common among patients randomized to the ACE inhibitor, and nonfatal myocardial events were more common among the diuretic group. In short, the results in this relatively small clinical trial were inconsistent across groups, fragile, and confidence intervals for all outcomes generally included the point estimates identified in ALLHAT.

Although there were many differences between ANBP-2 and ALLHAT, the important one involves study architecture. The critical facts are not only that the chlorthalidone to lisinopril comparison in ALLHAT involved more than twice as many subjects, a longer follow-up, and 10 times as many coronary event outcomes (3956 v 368) as ANBP-2. The critical issue is that ANBP-2 was not a blinded trial. Physicians and patients were aware of the drug to which they were randomized, and free to alter therapy. Of particular note is that although only about 60% of subjects remained on their assigned treatment, a slightly larger fraction (66%) were on monotherapy. The enviable BP decreases of about 26/12 mm Hg in both study arms strongly suggests that physicians wisely altered therapy to achieve optimal BP response. What may well have happened is that those who were volume dependent, and received a “volume” drug, or who were vasoconstriction dependent and received a vasodilator, both did very well. Moreover, those, in both arms, who failed to respond, were next treated with the alternate strategy. In other words, selection bias was introduced so that volume patients got a diuretic, vasoconstriction patients either an ACE inhibitor or a β-blocker, and a middle group probably got both. In this way, the barrier against bias provided by randomization was breached. Instead, treatment by indication was introduced. That flaw, inherent in open label design studies, renders this strategy inappropriate for the comparison of therapeutic interventions.

Under these circumstances, much as one might like to believe that therapy with an ACE inhibitor provides cardioprotection superior to a diuretic, neither ALLHAT nor ANBP-2 provide evidence to support that contention.

A Research Agenda

What then do these studies suggest for the future of antihypertensive therapeutic research. Because the mechanisms by which BP is maintained and vascular disease progresses differ, studies comparing therapies in subjects selected only according to a physical sign that may reflect multiple mechanisms, might not provide complete guidance for individual patient care. The ALLHAT and ANBP-2 approaches are, in part, analogous to comparing methotrexate, penicillin, and cephalosporin in patients selected for fever, but who have cancer, pneumonia, and urinary tract infections causing the fevers. If pneumococcal pneumonia were the most common condition, it is likely that in a randomized trial, penicillin might come out with an edge in efficacy. But that would not mean that penicillin would be superior in all cases of fever. While BP reduction in itself is vastly more valuable than fever control, antihypertensive treatment without consideration of mechanisms is, at best, incomplete technology. The need is for a better understanding of mechanisms, and the ability to evaluate treatments within homogeneous groups. For example, treatments could be evaluated in patients who had been classified according to activity of the renin/angiotensin system, according to their response to specific therapies, or as the tools become available, according to a particular genetic profile.
And for Physicians and Patients

Where does that leave the patient and physician? A variety of mechanisms must be at work, both to raise the pressure, and, in some, to advance vascular disease. More than fever, however, elevated pressure, per se, has adverse consequences and its reduction is beneficial. Drugs that lower BP, while producing benefit in the aggregate, albeit to a modest fraction of all those treated, may also produce unrecognized harm to others. On the basis of consistent results in many large, undifferentiated placebo-controlled clinical trials, it is better to lower the pressure than not. But, in addition, the wise patient and physician will only decide to treat when the overall CVD risk is substantial, and the potential for benefit meaningful.

Thus, the first objective is to lower BP. As for the specific choice of antihypertensive therapy, nothing has been proven superior to a diuretic and, all other things being equal, remains the first choice. Vasodilators, such as ACE inhibitors (or other vasodilators including angiotensin II receptor blockers and β-blockers) are the appropriate complementary agents. Those with an exclusively volume form of the condition will be successfully treated with a diuretic. The polar opposite patients, or purely vasoconstricted, are likely to respond well to a vasodilator alone, which might be sufficient. When volume and vasoconstriction are both at play, a combination of these two types of drugs will do best.

These are very general guidelines. The good physician will apply them with careful attention to each clinical situation, the environment in which it occurs, and the needs and desires of the patient.

References