Quite simply, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is one of the most important trials of antihypertensive therapy. For decades, experts have passionately debated which class of drugs should be initial therapy for hypertension. Resolution of this issue, which has enormous clinical, public health, and economic implications, comes at a time of intense pressure to reduce health care costs while improving clinical outcomes. In this setting, the ALLHAT results, reported in this issue of THE JOURNAL, are particularly noteworthy, because there is no cost-quality tradeoff; the most effective therapy was also the least expensive.¹

The magnitude of the hypertension epidemic is enormous. For individuals aged 55 to 65 years, the lifetime probability of developing hypertension is 90%.² Across the United States, more than 40 million adults aged 25 years and older have hypertension.² Of these, 21.9 million are treated with medication. Each year, an estimated 2 million persons develop hypertension.⁴ The ALLHAT results are of direct relevance to these patients with newly diagnosed hypertension and to medication-treated patients not receiving a thiazide diuretic.

Previous trials of antihypertensive therapy have consistently documented that diuretic-based drug regimens substantially reduce the risk of stroke.⁵ However, the benefits of diuretic therapy on coronary heart disease, although evident in quantitative overviews, were less than expected.⁵,⁶ Hypertension specialists postulated that diuretic-induced metabolic effects (ie, hypokalemia, dyslipidemia, and insulin resistance) might have mitigated the otherwise beneficial effects of blood pressure (BP) reduction. Such speculation led in part to a progressive shift from thiazide diuretic therapy to nondiuretic therapies, particularly angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs).⁷ Because these nondiuretic therapies reduce BP without apparently adverse metabolic consequences, many specialists concluded that such drugs would likely be superior to diuretics as a means to prevent coronary heart disease. Virtually no one thought that such therapies might be harmful.

Several years ago, the case-control study by Psaty et al⁸ stunned the hypertension community by providing strong, albeit nondefinitive, evidence that certain CCBs when used as drug therapy for hypertension were associated with an increased risk of myocardial infarction. This provocative report spawned numerous trials that tested the effects of newer antihypertensive therapies on clinical cardiovascular outcomes. However, none of these trials tested more than one alternate therapy, and several had design limitations including inadequate power. ALLHAT, which had been initiated prior to the publication of this case-control study,⁹ gained in importance because it simultaneously compared 3 classes of antihypertensive drug therapies with conventional thiazide therapy. Clinical researchers and practicing physicians have eagerly awaited the results of this trial.

ALLHAT compared 3 distinct medications: amlodipine (representing dihydropyridine CCBs [DHP-CCBs]), lisinopril (representing ACE inhibitors), and doxazosin (representing ß-blockers) with chlorthalidone (representing conventional thiazide therapy). In contrast to hundreds of trials with surrogate outcomes, the major outcomes in ALLHAT were clinically relevant cardiovascular events. The primary outcome was fatal coronary heart disease or nonfatal myocardial infarction. Secondary outcomes were all-cause mortality, fatal and nonfatal stroke, combined coronary heart disease, and combined cardiovascular disease. The planned follow-up was long (4-8 years). A previous report from ALLHAT documented that chlorthalidone was superior to doxazosin in preventing cardiovascular events, especially heart failure.⁵

Each of the medications substantially reduced BP, although the extent of BP reduction was not equivalent. Blood pressure reductions from chlorthalidone were somewhat greater than corresponding reductions from lisinopril. Amlodipine reduced diastolic BP to a slightly greater extent and systolic BP to a slightly lesser extent than chlorthalidone. By the fifth year of follow-up, control of hypertension (defined as a systolic BP <140 mm Hg and diastolic BP <90 mm Hg) was achieved in approximately two thirds of participants (61% lisinopril, 66% amlodipine, and 68% chlorthalidone); these hypertension control rates greatly exceed corresponding rates in the general population (approximately 44%).² Follow-up was excellent and the
number of dropins and dropouts from the assigned groups was relatively small. Hence, the trial has high internal validity.

The major finding of ALLHAT was a striking and unequivocal null result, namely, that the occurrence of coronary heart disease death and nonfatal myocardial infarction was virtually identical in the amlodipine, lisinopril, and chlorthalidone groups. The data effectively rule out a 10% or more difference between chlorthalidone and each of the other therapies. However, for certain secondary outcomes, there were apparent differences, some of which were anticipated. Chlorthalidone was superior to amlodipine in preventing heart failure. This finding is consistent with trends observed in other trials. In contrast with the study of Psaty et al, there was no excess of coronary heart disease in the amlodipine group.

Less expected were the results of the lisinopril group. Among the many researchers who tried to predict the results of ALLHAT, many had anticipated that lisinopril would be similar in efficacy, if not superior to chlorthalidone. Previous trials documented that ACE inhibitors were beneficial in heart failure, type 1 diabetic kidney disease, and nondiabetic kidney disease. Furthermore, there was a strong biological basis to anticipate a beneficial effect of an ACE inhibitor, which blocks the renin-angiotensin system, compared with diuretic therapy, which stimulates the renin-angiotensin system. Despite these considerations, chlorthalidone was superior to lisinopril as a means to lower BP and prevent stroke, combined cardiovascular disease, and perhaps heart failure. The increased risk of heart failure (statistically significant for total heart failure but nonsignificant for the more restrictive outcome of hospitalized for or death from heart failure) is surprising and difficult to reconcile in view of the well-documented benefits of ACE inhibitors in the treatment of heart failure. This phenomenon (i.e., an interaction in which ACE inhibitors might increase the risk of developing heart failure, yet improve health outcomes in persons with prevalent heart failure) is uncommon.

Even the best designed and executed trials raise critical interpretive issues. First and foremost is whether differences in achieved BP between groups might account for the observed differences in clinical outcomes. Not so for amlodipine. The BP differences between amlodipine and chlorthalidone were small (<1 mm Hg) and balanced (lower systolic BP in chlorthalidone but lower diastolic BP for amlodipine). Hence, the increased risk of heart failure associated with amlodipine most certainly represents a drug-specific effect rather than a difference in achieved BP. Findings are less clear for lisinopril, in which absolute BP levels were higher, hypertension control rates lower, and use of add-on drug therapy more common. Even though differences in clinical outcomes between lisinopril and chlorthalidone persisted after adjustment for follow-up BP, the possibility that the increased risk of stroke and cardiovascular disease resulted primarily from less BP reduction cannot be ruled out.

A second issue is the type of medication used as add-on therapy in ALLHAT. In contrast with the drug treatment algorithm used in ALLHAT, physicians commonly add a thiazide diuretic if BP reduction from an ACE inhibitor alone is unsatisfactory. Occasionally, physicians begin treatment with an ACE inhibitor/diuretic combination agent, particularly in black patients. Still, in light of ALLHAT results, it is unclear why physicians should implement an ACE inhibitor–based strategy that commonly leads to use of 2 drugs (ACE inhibitor and diuretic) when monotherapy with a thiazide diuretic can effectively reduce BP and prevent BP-related cardiovascular outcomes.

A third issue commonly raised by trials of drug therapies is whether results can be extrapolated from the specific drug tested to other drugs of the same class. For ACE inhibitors, there is no compelling reason to believe that any one ACE inhibitor is superior. Hence, physicians might be willing to extrapolate the results of ALLHAT to other ACE inhibitors. In contrast, differences in structure and function of the CCBs lead most physicians to consider DHP-CCBs as distinct from non–DHP-CCBs. Hence, it seems reasonable to extrapolate ALLHAT results to other DHP-CCBs but not to non–DHP-CCBs. As for the “winner,” chlorthalidone is a thiazide diuretic commonly used in large trials but infrequently used in clinical practice in the United States. Although thiazide-type diuretics are reasonably similar and ALLHAT results might be extrapolated to hydrochlorothiazide, purists might argue that chlorthalidone should be used in view of its well-documented efficacy in trials.

The metabolic effects and adverse effect profile of the drugs were anticipated. Instances of angioedema were rare but still occurred more frequently in the lisinopril group compared with the other groups. Hypokalemia, hypercholesterolemia, and evidence of insulin resistance were more evident among those assigned to chlorthalidone. Specifically, levels of fasting blood glucose were increased in the chlorthalidone group, and patients without diabetes had an increased risk of developing a fasting glucose of more than 125
mg/dL (>7 mmol/L). Despite these trends, it is important to emphasize that there was no excess of cardiovascular events or mortality from chlorthalidone in the entire population or among patients with diabetes. Such findings reaffirm the importance of relying on hard clinical outcomes rather than surrogate markers for clinical decision making.

The results of ALLHAT are robust, unambiguous, and generalizable, especially to the broad population of patients with stage 1 or 2 hypertension. Approximately 50% of participants were women and 35% were black. To enhance statistical power, the trial focused on high-risk patients with hypertension, defined by the presence of another risk factor for cardiovascular disease. Still, there is little reason to believe that the results should differ qualitatively in lower risk patients. The authors report no apparent differences in subgroups for the comparison of amlodipine and chlorthalidone. The only notable subgroup differences were an increased risk of stroke and combined cardiovascular disease in the ACE inhibitor group in black but not in nonblack patients. These findings may have resulted from the fact that among black patients, follow-up BP was substantially higher in the ACE inhibitor group than in the chlorthalidone group. Otherwise, among prespecified subgroups of interest defined by age, sex, race, and diabetes, results were remarkably consistent. Short of another large trial of similar design, the demographic heterogeneity of study participants and the consistency of subgroup findings suggest that ALLHAT results are generalizable.

The ALLHAT results provide compelling evidence that thiazide diuretics should be the initial drug of choice for patients with hypertension, especially compared with those agents that were directly tested in this trial. Although ß-blocker therapy was not one of the first-line therapies studied in ALLHAT, available data indicate that ß-blocker therapy is certainly no more effective and quite possibly may be less effective than thiazide-diuretic therapy. In this setting, an appropriate next question is what type of medication should be second-line therapy? In ALLHAT, the average number of medications used to control BP progressively increased from approximately 1.5 in first year of follow-up to 2.0 in the fifth year. While physicians may be tempted to use an on-patent CCB or ACE inhibitor, there is an impressive armamentarium of low-cost, off-patent drugs that can be used as add-on therapy after diuretics. These medications include a CCB (verapamil), 3 ACE inhibitors (captopril, enalapril, and lisinopril), several ß-blockers, low-dose reserpine, and a direct vasodilator (hydralazine). A logical strategy that incorporates these low-cost agents may differ from those that are more popular, but contemporary strategies may be somewhat artificial because of the heavy influence of marketing that preferentially leads to use of expensive medications. In short, physicians have the means to effectively control BP with inexpensive medications, even among patients who require multiple drugs.

While the challenges of designing and implementing ALLHAT were daunting, the subsequent tasks of disseminating results and changing physician prescription habits may be an even greater challenge. An important next step is to update policy documents to emphasize the unambiguous role of thiazide diuretics as initial therapy. Concomitantly, a concerted effort should be made to educate physicians, medical residents, and other health care professionals, as well as those who develop guidelines for provider networks and health maintenance organizations. Leading this effort will be the National High Blood Pressure Education Program and the ALLHAT investigators themselves. Is a massive shift in aggregate prescription patterns likely? The results of ALLHAT, if disseminated and implemented, will likely have their greatest impact on patients with newly diagnosed hypertension. Hence, a large immediate shift in aggregate prescription patterns is unlikely.

Finally, it is important to emphasize that treatment of hypertension is just one component of an overall strategy to prevent BP-related cardiovascular disease. Results from ALLHAT provide definitive data on one important aspect of hypertension management—selecting the best initial therapy. Attention must now return to other critical issues, specifically, controlling BP among patients with hypertension and preventing hypertension in the first place.
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