Guidelines for Antihypertensive Treatment: An Update after the ALLHAT Study

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Abstract. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Study, the largest double-blind, randomized trial in hypertensive patients, confirmed and strengthened the clinical relevance of thiazide diuretics in the treatment of hypertension but did not prove the superiority of these drugs. Its claim of the superiority of chlorthalidone was based on some secondary outcomes, principally represented by (*1*) an increased incidence of stroke in the doxazosin and lisinopril arms, an effect that might be explained by differences in systolic BP; (*2*) greater morbidity but not mortality for congestive heart failure (CHF) in the doxazosin, amlodipine, and lisinopril arms, a finding that might reflect poor accuracy in the diagnosis and/or especially the switching from diuretic treatment in 90% of patients. Moreover, the ALLHAT study has other limitations, and its conclusions are in contrast with data from overall controlled clinical trials indicating that given the same BP reduction, the benefit of different drug classes is similar. As to whether the ALLHAT study will influence ongoing guidelines concerning the choice of antihypertensive drugs, the answer is "yes" if interpretation of its data in favor of diuretics and cost of drugs become the preponderant considerations, as it was in recent JNC VII guidelines. However, the more liberal approach based on the choice of all available drug classes seems still to be valid, as is in the ESH-ESC guidelines, if the preponderant consideration is that the real benefit of antihypertensive therapy is due to efficient BP control and not to a particular benefit of a single drug class.

Data from controlled clinical trials and above all their interpretations have strongly influenced guidelines on antihypertensive drug therapy, as shown by divergent recommendations on the choice of antihypertensive drugs in the two most widespread guidelines, those of JNC VI (1) and World Health Organization–International Society of Hypertension (WHO-ISH) (2).

JNC VI guidelines recommend conventional therapy (diuretics and β-blockers) as first drug choices, claiming that these are the drugs used in clinical trials that showed the benefit of antihypertensive therapy (1). In contrast, WHO-ISH guidelines recommend all available antihypertensive drug classes as first choices, motivating these recommendations with the fact that BP reduction *per se* and not particular drug classes have accounted for this benefit (2). Since these guidelines were drawn up, several controlled clinical trials have been performed to evaluate whether new antihypertensive drugs, such as calcium-antagonists (3–5), angiotensin-converting enzyme (ACE) inhibitors (3,6) and AT_1-receptor antagonists (7,8), offer similar or additional benefits in preventing cardiovascular events as compared with conventional therapy.

However, recent data and interpretations of data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Study (9), the largest ever randomized trial of antihypertensive drugs, have intensified the debate on choice of antihypertensive drug therapy and are expected to influence strongly new guidelines. This trial randomized 42,418 patients, aged 55 yr or older, with mild to moderate hypertension and at least one additional cardiovascular risk factor, to double-blind therapy based on chlorthalidone 12.5 to 25 mg/d (n = 15,255), amlodipine 2 to 5 to 10 mg/d (n = 9048), lisinopril 10 to 40 mg/d (n = 9054), and doxazosin 1 to 8 mg/d (n = 9081), with possible addition of open-label drugs, such as atenolol, clonidine, and reserpine (second step) or hydralazine (third step), to obtain goal BP $<$140 to 90 mmHg.

The primary hypothesis of ALLHAT was that fatal coronary heart disease (CHD) and nonfatal myocardial infarction would be lower in patients who were randomized to new drugs as compared with those who were receiving diuretic treatment and investigator prespecified several secondary end points, including all-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (CVD), and renal disease (10). The doxazosin arm was stopped prematurely after a 3.3-yr median follow-up (11), whereas patients of the other three arms were followed up for a mean of 4.9 yr (9).

The primary outcome did not differ when comparing the reference drug, chlorthalidone, with doxazosin (relative risk [RR] 1.03; 95% confidence interval [CI] 0.90 to 1.17), amlodipine (RR 0.98; 95% CI 0.90 to 1.07), and lisinopril (RR 0.99; 95% CI 0.91 to 1.08). As far as secondary end points are concerned, patients in the doxazosin arm showed an increase in stroke (RR 1.15; 95% CI 1.01 to 1.40) and combined CHD (RR 1.10; 95% CI 1.00 to 1.12), owing to an increase in angina (RR

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1.16; 95% CI 1.05 to 1.27) and coronary revascularizations (RR 1.15; 95% CI 1.17 to 1.33). They also presented an increase in combined CVD (RR 1.25; 95% CI 1.17 to 1.33), owing to the greater frequency of the above-mentioned events and above all of congestive heart failure (CHF; RR 2.04; 95% CI 1.79 to 2.32). In the amlodipine arm, only one component of secondary end points, CHF, was significantly increased (RR 1.38; 95% CI 1.25 to 1.52), whereas the lisinopril arm was associated with higher rates of stroke (RR 1.15; 95% CI 1.02 to 1.30) and of combined CVD (RR 1.10; 95% CI 1.05 to 1.16), the latter as a result of the increase in stroke, angina (RR 1.11; 95% CI 1.03 to 1.20), coronary revascularizations (RR 1.10; 95% CI 1.00 to 1.21), and CHF (RR 1.19; 95% CI 1.07 to 1.31).

On the basis of these data, the authors concluded that thiazide-type diuretics are superior to newer drugs in preventing one or more major forms of CVD, are less expensive, and should be preferred for first step antihypertensive therapy (9). These data and conclusions and the way they may influence new guidelines on antihypertensive treatment will be discussed according to the following lines of reasoning.

ALLHAT Study: Strengths

The strengths of the ALLHAT Study include its large size with adequate representations of subgroups of special interest in the treatment of hypertension. The extensive representation of subgroups made it possible to analyze treatment effects in the elderly and the young, men and women, black and nonblack, and diabetic and nondiabetic patients. This analysis showed that primary and secondary outcome results in the amlodipine *versus* the chlorthalidone groups were consistent for all subgroups of participants. Comparison of the lisinopril *versus* the chlorthalidone arms gave results that were generally consistent by age, gender, and diabetes status but with greater difference in black *versus* nonblack patients for combined CVD and stroke, along with a similar trend for CHF. Thus, the ALLHAT results can be generalized to most of the patients with hypertension.

The second important finding to emerge from the ALLHAT study is that across a large number of comparisons for both primary and secondary outcomes *versus* a calcium antagonist, an ACE inhibitor, and an α-blocker, a diuretic was equally effective in primary outcomes or, in some instances, superior in comparison with secondary end points. Consequently, these results strengthen the prominent role of a diuretic as initial drug therapy in hypertensive patients.

Another important result of this study is the safety of calcium antagonists, because amlodipine was equally as effective as chlorthalidone in preventing CHD mortality and morbidity, did not increase the risk of cancer and gastrointestinal bleeding, and even reduced mortality from noncardiovascular causes when compared with chlorthalidone. Therefore, previous concerns about the safety of calcium antagonists can now be put to rest (12).

ALLHAT Study: Limitations

Choice of First Drug Therapy

The strong statement that diuretics ought to be the first-line treatment in all hypertensive patients should be reviewed considering the following limitations. Patients who were enrolled in the ALLHAT Study were high-risk patients and therefore were not representative of the population of mild hypertension without high-risk profile (13). Ninety percent of enrolled patients were already treated (but there was no information on what kind of treatment was given), and these patients were immediately randomized in the four arms.

Therefore, the ALLHAT Study seems to have investigated mainly the effect of switching of treatment. BP values at baseline were 146/84 mmHg in overall patients, 145/84 to 83 mmHg in treated patients, and 157 to 156/90 to 89 mmHg in untreated patients. These BP values indicate that BP control in already treated patients was similar to that achieved in the majority of other controlled clinical trials (14) and that the minority of untreated patients had mild prevalent systolic hypertension.

Another intriguing aspect of the ALLHAT Study was the event validation, which was performed in a random 10% subset of CHD and stroke events with a concordance of 90% for CHD and 84% for stroke. Moreover, there was an *a posteriori* validation of a small sample of hospitalized fatal and nonfatal CHF events ($n = 50$), with 22% of cases having incomplete data and 85% confirmation of CHF in cases with complete data. These results indicate that the diagnosis of CHF was validated only in 66% of overall examined cases (15). Because validation of all events by the Critical Event Committee seems to be crucial for the quality of a clinical trial (16), one wonders whether incomplete validation of all outcomes might have biased or randomly influenced final results.

Primary outcomes did not differ among the four arms, a finding that did not confirm the primary hypothesis of a superiority of new drugs in preventing coronary events. These data are in agreement with other controlled studies showing no superiority of new drugs *versus* conventional therapy on primary outcomes (3–5), with the exception of two recent trials, in which treatment with an ACE inhibitor (6) or an AT1-receptor antagonist (7) gave more successful results than conventional therapy.

The superiority of diuretics was based principally on two outcomes, stroke, which was a prespecified secondary end point, and CHF, which was a component of combined CVD, another secondary end point. Stroke incidence was increased in doxazosin- and lisinopril-treated patients, in whom systolic BP was reduced to a lesser extent when compared with chlorthalidone (doxazosin +3 mmHg at 1 yr and +2 mmHg at the end of follow-up; lisinopril +2 mmHg in overall patients, +3 mmHg in elderly patients, and +4 mmHg in black patients). Although the authors of the ALLHAT Study concluded that differences in systolic BP can only partially account for the observed stroke difference, such differences cannot be so simply dismissed, because there is a strong correlation between systolic BP and stroke (17) and the incidence of stroke in the

lisinopril group could be accounted for by the 40% greater incidence in black patients. This hypothesis is in agreement with results of a prospectively designed overview of a previous randomized study performed by the Blood Pressure Lowering Treatment Trialists' Collaboration (3) and of a recent controlled study in elderly patients (6). The results in question showed that given the same BP reduction, the incidence of stroke was not increased in patients who were treated with an ACE inhibitor as compared with those who received conventional therapy. Moreover, stroke incidence tended to be lower (RR 0.93; 95% CI 0.82 to 1.06) in the amlodipine as compared with the diuretic arm, despite that 5-yr systolic BP was 0.8 mmHg (although diastolic BP was −0.8 mmHg). This finding did not confirm but also did not exclude a possible advantage of calcium antagonists *versus* conventional therapy in reducing stroke risk (3). However, this possibility was not confirmed by two recent trials comparing non-DHP calcium antagonist–based *versus* conventional therapy in high-risk patients (4) or in those with documented CHD (5), who showed a similar incidence of stroke.

The greater incidence of CHF in the doxazosin, amlodipine, and lisinopril arms as compared with chlorthalidone was due to differences that occurred early after randomization and without an increase in mortality from CHF. These results can be explained by two nonmutually exclusive hypotheses. The first is that this remarkable finding of increased incidence of morbidity but not mortality from CHF might, as already mentioned, reflect poor accuracy in the diagnosis of CHF. Diagnosis is difficult to perform in patients who are receiving diuretic treatment, which can mask symptoms of fluid retention, and it needs to be validated by the Critical Event Committee. Second, it is conceivable that withdrawal of diuretic therapy, which is assumed to be administered to the majority of patients who enter the study, may have unmasked CHF symptoms in patients with left ventricular dysfunction rather than CHF being attributable to some other treatment. Moreover, the increase in CHF outcome in the lisinopril group is an unexpected finding, because data from previous trials (3) and recent data from the ANBP-2 Study (6) showed a tendency to a lower CHF event rate with ACE inhibitor–based therapy as compared with conventional therapy. Finally, the ALLHAT Study did not investigate the effect of AT1-receptor antagonists, a class of drugs that has been shown to reduce stroke when compared with conventional therapy in elderly hypertensive patients (7,8).

Combination Therapy

Combination therapy is often needed to obtain BP control. In the ALLHAT study, approximately 60% of patients received additional drugs. However, owing to the trial design, only atenolol, clonidine, and reserpine and eventually hydralazine were allowed to be used as second-step drugs, *i.e.*, as a drug that can be rationally combined with chlorthalidone and amlodipine but not with lisinopril and even more as far as clonidine and reserpine are concerned, with doxazosin. Thus, these combination therapies, while at least partially explaining why BP was less reduced in the lisinopril and doxazosin arms, did not allow evaluation of more rational combinations and in particular the rational addition of a diuretic, as the authors of the ALLHAT Study claimed in their conclusions.

Drug Selection in Selected Patients

As already stated, in the ALLHAT study, comparisons of end points observed with the diuretic *versus* the other drugs showed that there were no major differences in event rates between diabetic and nondiabetic patients. Although these data suggest that a thiazide diuretic could be a logical monotherapy in patients with diabetes, more detailed information on data in patients with diabetes is needed. In particular, data on BP control are required, because even small BP differences can influence CV outcomes in patients with diabetes, and renal function outcome, especially considering the well-established renoprotective action of ACE inhibitors and AT1-antagonists in these patients (18). Another aspect to be considered is that blood glucose and new-onset diabetes rose in the chlorthalidone group, a finding that suggests that thiazide-like diuretics alone or combined with a β-blocker should be avoided in patients at risk of developing diabetes (18).

ALLHAT data on renal function outcome showed that there were no significant differences in end-stage renal failure in the three arms. The slopes of the reciprocal of serum creatinine, as well as estimated creatinine clearance, were virtually identical in the chlorthalidone and lisinopril groups, whereas the decline in the slope of the reciprocal of serum creatinine was less marked and estimated creatinine clearance was better preserved in the amlodipine arm. These results, which differ from available evidence on the renoprotective action of ACE inhibitors, can be tentatively explained by good BP control (final BP values at approximately 135 to 75 mmHg), lower systolic BP control with the ACE inhibitor, especially in black patients and the relatively short-term treatment in patients with nephrosclerosis (19). However, more detailed information on the outcome of renal function is needed, above all as regards the presence of diabetic nephropathy, the amount of proteinuria, and the possible crossover to an ACE inhibitor in patients with diminished renal function.

Cost-Benefit Analysis

ALLHAT's strong conclusions in favor of thiazide-type diuretics as first-choice antihypertensive therapy were also based on cost of drugs, which could have a major impact on a nation's health care expenditure. The authors calculated that if diuretic prescription in the United States had not declined from 1982 to 1992, then the health care system would have saved $3.1 billion in estimated cost of antihypertensive drugs. However, cost is not the sole consideration, and a further cost-benefit analysis is awaited. We believe that this analysis should also take into account the adverse metabolic effects of chlorthalidone, consisting of an increase in cholesterol levels, blood glucose, new-onset diabetes, and hypokalemia. Although these metabolic effects did not translate into a greater frequency of CV events in the relatively short-term follow-up of the study, they could have a major impact on cost-benefit, because in the long term, they can reduce the benefit of

treatment and increase the cost owing to the need for other pharmacologic therapies designed to treat these metabolic abnormalities.

Conclusions

The ALLHAT Study confirmed and strengthened the clinical relevance of thiazide diuretics in the treatment of hypertension but did not prove the superiority of these drugs. As to whether this study will influence ongoing guidelines concerning the choice of antihypertensive drugs, the answer is "yes" if the interpretation of its data in favor of diuretics and cost of drugs become the preponderant consideration, as it was the case in the JNC VII Guidelines (20). However, the more liberal approach based on the choice of all available drug classes seems still to be valid, as stated in the recent European Society of Hypertension–European Society of Cardiology (ESH–ESC) guidelines (21) if the preponderant consideration is that the real benefit of antihypertensive therapy is due to efficient BP control and that, given the same BP reduction, there is no evident superiority of any particular drug class (22). Finally, because an efficient BP control often can be reached with the combination of two or more drugs, particular attention should be paid to use of rational drug combinations, which often need the inclusion of diuretics.

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