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.
cerns about the safety of calcium antagonists can now be put to
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 thia-
zone-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 non-
black, 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 \( \alpha \)-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 cal-
cium antagonists, because amlodipine was equally as effective
as chlorthalidone in preventing CHD mortality and morbidity,
did not increase the risk of cancer and gastrointestinal bleed-
ing, and even reduced mortality from noncardiovascular causes
when compared with chlorthalidone. Therefore, previous con-
cerns 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 con-
sidering 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 pa-
tients 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 \( a \) \textit{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 supe-
riority 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 pri-
mary 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 con-
ventional 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 chlortha-
idone (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 sim-
ply 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 unexplained 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.

References

5. INVEST trial. Presented at the 52nd Annual Meeting of the Cardiology Meeting, Chicago, IL, March 2003