Editorial Commentary

Amlodipine Better Than Lisinopril?
How One Randomized Clinical Trial Ended Fallacies From Observational Studies

Franz H. Messerli, Jan A. Staessen

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) compared in >30 000 high-risk hypertensive patients the effects on coronary heart disease of 3 treatment strategies: (1) based on the diuretic chlorthalidone, (2) the calcium-channel blocker (CCB) amlodipine, and (3) the angiotensin converting-enzyme (ACE) inhibitor lisinopril, respectively.1 Sponsored by the National Heart, Lung, and Blood Institute, ALLHAT stands out because no differences occurred in the incidence of the primary end point that consisted of the combination of fatal coronary heart disease and acute myocardial infarction.1 Not surprisingly, the attention of the ALLHAT consortium shifted to secondary end points, such as stroke, or to loosely defined components of secondary end points, such as heart failure. At the end of the line, the ALLHAT investigators based their main conclusions on events occurring during the on-treatment blood pressure despite vigorous attempts to titrate and combine the study medications to achieve a blood pressure of <140 mm Hg systolic and 90 mm Hg diastolic.1 These salient features of ALLHAT should be kept in mind whenever one attempts to interpret the findings of this landmark trial.

In this issue of Hypertension, Leenen et al2 published a post hoc analysis, in which they made a direct comparison of cardiovascular and other outcomes among the 18 102 ALLHAT participants randomly assigned to amlodipine or lisinopril. In line with previous reports,2 the incidence of the primary coronary end point and total cardiovascular mortality were similar in both groups. However, the patients randomly assigned to lisinopril experienced higher risks of stroke, combined cardiovascular disease, gastrointestinal bleeding, and angioedema, whereas the risk of heart failure was higher in the amlodipine group.4 The excess cardiovascular risk was particularly apparent in women and black patients. Leenen et al4 concluded that “considering the totality of outcome measures in ALLHAT, amlodipine appeared to have advantages over lisinopril.” This is a provocative statement that is in line with the published literature (Table) and that is prone to at least dent, if not shatter, the halo surrounding the ACE inhibitors. The conclusions of Leenen et al4 underscore the difficulty in bridging the gap between scientifically attractive pathogenetic concepts based on experimental models5 and the clinical reality that matters to patients, that is, event-free survival.

The ALLHAT investigators attributed at least part of the better cardiovascular outcome on amlodipine compared with lisinopril to the more pronounced blood pressure reduction on the CCB, particularly in women and black patients.4 The Heart Outcomes Prevention Evaluation study (HOPE)6 and the Losartan Intervention For Endpoint reduction in hypertension study (LIFE)7 launched the notion of benefit beyond blood pressure lowering, although in both trials the baseline-adjusted systolic blood pressure at the last visit was significantly lower in the patients randomly assigned to the ACE inhibitor (3.0 mm Hg; P<0.001) or the angiotensin II receptor blocker (1.3 mm Hg; P=0.017) than in those allocated placebo or atenolol,7 respectively. Stroke is the complication of hypertension that is most directly linked to the blood pressure level.8 Not surprisingly, metaregression analyses published by us9,10 and other researchers11 demonstrated that, in keeping with large-scale prospective observational studies12 and also in randomized clinical trials, small gradients in the achieved systolic blood pressure explain most of the differences in the cardiovascular outcomes. An updated metaregression analysis13 accounted not only for the differences in the achieved systolic blood pressure between groups randomly assigned in clinical trials but also for drug class, the interaction between on-treatment systolic pressure and drug class, age at randomization, year of publication, and duration of follow-up. The updated results corroborated that blood pressure reduction was by far the most important determinant of cardiovascular outcome.13 In keeping with the current ALLHAT findings, CCBs compared with ACE inhibitors provided a small blood pressure–independent benefit (=14%; P=0.042) in the prevention of stroke, and the same was true for ACE inhibitors compared with CCBs in relation to coronary heart disease (=10%; P=0.028).13 The observation that the incidence of the primary end point was similar in the 2 treatment groups in the study of Leenen et al4 might be interpreted as indirect evidence suggesting that lisinopril-based therapy conferred greater cardiac benefit than treatment initiated with amlodipine.

In 2003, the Blood Pressure Lowering Trialists’ Collaboration noticed that for every outcome other than heart failure, the differences between randomized groups in cardiovascular
outcomes were directly related to the achieved systolic blood pressure.\textsuperscript{11} However, the lack of association among 34 reviewed trials was mainly because of the noise of 4 that compared CCBs to placebo. The summary statistic breaking the relationship included results from a primary prevention trial in older patients and from 3 secondary prevention studies in diabetic patients with renal dysfunction or in high-risk patients with coronary heart disease.\textsuperscript{11} Substantial differences in the pathogenetic mechanisms causing left ventricular failure in such heterogeneous conditions cast doubt on the proposed conclusion of no association between the prevention of heart failure and the level of achieved systolic blood pressure.\textsuperscript{11} However, the lack of association among 34

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
Comparator & Trial & \(N\) & \(OR\ (95\% CI)\) & \(P\) \\
\hline
Versus placebo & PREVENT & 825 & 0.69 (0.49 to 0.97) & 0.031 \\
 & CAMELOT & 1318 & 0.60 (0.36 to 0.98) & 0.038 \\
 & IDNT & 1136 & 0.60 (0.36 to 0.98) & 0.038 \\
\hline
Versus diuretics/\(\beta\)-blockers & ALLHAT & 24309 & 0.96 (0.89 to 1.03) & 0.26 \\
 & ASCOT & 19257 & 0.96 (0.89 to 1.03) & 0.26 \\
 & IDNT & 1136 & 0.96 (0.89 to 1.03) & 0.26 \\
\hline
Versus ACE inhibitors & ALLHAT & 18102 & 0.86 (0.78 to 0.95) & 0.002 \\
 & CAMELOT & 1336 & 0.82 (0.71 to 0.94) & 0.004 \\
 & IDNT & 1146 & 0.82 (0.71 to 0.94) & 0.004 \\
\hline
Versus angiotensin II receptor blockers & VALUE & 15245 & 0.84 (0.72 to 0.99) & 0.032 \\
\hline
\end{tabular}
\caption{Amlodipine Versus Other Reference Treatment in the Prevention of Myocardial Infarction or Stroke}
\end{table}

\(N\) indicates the number of patients included from each trial; OR, odds ratio. Pooled ORs with 95\% CIs were computed from the number of events (amlodipine/reference) and the number of patients per group randomly assigned in each trial by use of stratified 2\(\times\)2 contingency tables. Coronary heart disease included coronary mortality and acute myocardial infarction in ALLHAT and ASCOT; fatal and nonfatal myocardial infarction in CAMELOT, IDNT, PREVENT, and VALUE; and nonfatal myocardial infarction in CAMELOT. The trial acronyms are given in Reference.\textsuperscript{10} Most clinicians regard ACE inhibitors as being well-tolerated antihypertensive drugs. Unexpectedly, in the current ALLHAT report, adherence to randomized treatment was significantly lower in the lisinopril than in the amloidipine arm (at 5 years, 72.6\% versus 80.4\%). Persistence was lowest in women and blacks. The reason for this difference is unclear but is likely to be because of adverse effects, frequently dry cough on ACE inhibitors and ankle edema on CCBs. For drugs that are used by hypertensive patients over decades, long-term safety is of paramount concern. Angioedema is a well-documented but rare adverse event in patients taking ACE inhibitors. It can appear unexpectedly, in the current ALLHAT trial acronyms are given in Reference.\textsuperscript{10}

Finally, how should clinicians translate the new ALLHAT findings in their day-to-day practice? Foremost, they should be aware that high blood pressure is a reversible risk factor with lower levels leading to fewer strokes and heart attacks. Furthermore, several landmark trials, over and above those listed in the Table (for review, see Reference 10), proved in no uncertain terms that CCBs are powerful, efficacious, and safe antihypertensive drugs and that they can be prescribed to high-risk patients as first-line drugs for indications that were until now dominated by inhibitors of the renin–angiotensin system.
system. Finally, observational studies, which are prone to observer bias, should never be taken at face value, even if they make headlines in the medical and lay media and even if, in some instances, they might be hypothesis generating. The analysis of Leenen et al. puts a definite end to what was called the CCB controversy, which flourished for more than a decade. Only randomized trials provide evidence strong enough to be useful in the management of hypertensive patients, which currently already represent 20% to 30% of the world’s population, a proportion likely to steadily increase over the next decades.

Disclosures

F.H.M. and J.A.S. are ad-hoc consultants for pharmaceutical companies with commercial interests in CCBs and ACE inhibitors and have received funding for studies, seminars, and travel from such companies.

References

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In a *Hypertension* editorial commentary by Messerli and Staessen (Messerli FH, Staessen JA. Amlodipine better than lisinopril? How one randomized clinical trial ended fallacies from observational studies. *Hypertension*. 2006;48:359–361), the statement “considering the totality of outcome measures in ALLHAT, amlodipine appeared to have advantages over lisinopril” was based upon an earlier version of the paper by Leenen et al. (Leenen FHH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, Alderman MH, Atlas SA, Basile JN, Cuyjet AB, Dart R, Felicetta JV, Grimm RH, Haywood LJ, Jafri SZA, Proschon MA, Thadani U, Whelton PK, Wright JT; for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Collaborative Research Group. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Hypertension*. 2006;48:374–384.). However, this statement was not included in the accepted version of the paper Leenan et al.