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.

Sponsored by the National Heart, Lung, and Blood Institute, ALLHAT stands out because, at the initiation of the trial, they regarded as “soft data that consisted of the combination of fatal coronary heart disease and acute myocardial infarction.” 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 in women and black patients. Leenen et al. demonstrated that, in keeping with large-scale prospective observational studies 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 analysis 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.

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 small. However, the incidence of the primary end point was similar in the 2 treatment groups in the study of Leenen et al. The observation that the incidence of the primary end point was similar in the 2 treatment groups in the study of Leenen et al. 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 small. However, the incidence of the primary end point was similar in the 2 treatment groups in the study of Leenen et al. The observation that the incidence of the primary end point was similar in the 2 treatment groups in the study of Leenen et al. might be interpreted as indirect evidence suggesting that lisinopril-based therapy conferred greater cardiac benefit than treatment initiated with amlodipine.
outcomes were directly related to the achieved systolic blood pressure. 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.

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. In the Antihypertensive Long-term Use Evaluation trial (VALUE), as well as in the Valsartan in Myocardial Infarction (V-MI) trial and the ASCOT-BPLA, the rates were 0.72% in blacks and 0.26% in nonblacks. Although fatalities of angioedema are exceedingly rare, one should consider that as worldwide 30 to 40 million 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 from a few hours to 8 years after an ACE inhibitor is first taken. Unfortunately, a median of 10 months may elapse before onset of angioedema and withdrawal of the ACE inhibitor. This potentially fatal adverse event was observed in 38 patients in the lisinopril group but only in 3 randomly assigned to amlodipine. In the lisinopril arm, the rates were 0.72% in blacks and 0.26% in nonblacks. Although fatalities of angioedema are exceedingly rare, one should consider that as worldwide 30 to 40 million patients are exposed to ACE inhibitors, this drug class might account for several hundred fatalities per year.

Remarkably, in ALLHAT, as well as in the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE), heart failure, against the blood pressure gradient, occurred more frequently on amlodipine than on lisinopril or valsartan. This could either indicate that, for a given fall in blood pressure, blockers of the renin–angiotensin system are more powerful in preventing heart failure than are CCBs or that blood pressure is a less important predictor of congestive heart failure than of heart attack and stroke. However, in both trials, the Kaplan–Meier estimates for heart failure only started to diverge after 2 to 3 years, when, compared with the amlodipine arm, a greater proportion of patients randomly assigned to the ACE inhibitor stopped the alternative first-line treatment, had crossed over, and/or were receiving combination therapy, including second-line antihypertensive medications.

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 arm than the amlodipine 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 from a few hours to 8 years after an ACE inhibitor is first taken. Unfortunately, a median of 10 months may elapse before onset of angioedema and withdrawal of the ACE inhibitor. This potentially fatal adverse event was observed in 38 patients in the lisinopril group but only in 3 randomly assigned to amlodipine. In the lisinopril arm, the rates were 0.72% in blacks and 0.26% in nonblacks. Although fatalities of angioedema are exceedingly rare, one should consider that as worldwide 30 to 40 million patients are exposed to ACE inhibitors, this drug class might account for several hundred fatalities per year. That these are not just hypothetical numbers is underscored by instances of fatal angioedema in both ALLHAT and HOPE6 and also by a recent report from a single coroner’s office describing 7 cases of asphyxiation associated with ACE inhibitors within a mere 3-year period of time.

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 pathway.

Amlodipine Versus Other Reference Treatment in the Prevention of Myocardial Infarction or Stroke

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Trial</th>
<th>N</th>
<th>Coronary Heart Disease</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Versus placebo</td>
<td>PREVENT</td>
<td>825</td>
<td>0.69 (0.49 to 0.97)</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>CAMELOT</td>
<td>1318</td>
<td>0.96 (0.89 to 1.03)</td>
<td>0.26</td>
</tr>
<tr>
<td>Versus diuretics/β-blockers</td>
<td>ALLHAT</td>
<td>24309</td>
<td>1.01 (0.91 to 1.12)</td>
<td>0.89</td>
</tr>
<tr>
<td>Versus ACE inhibitors</td>
<td>ALLHAT</td>
<td>18102</td>
<td>0.96 (0.89 to 1.03)</td>
<td>0.86 (0.78 to 0.95)</td>
</tr>
<tr>
<td>Versus angiotensin II receptor blockers</td>
<td>VALUE</td>
<td>15245</td>
<td>0.82 (0.71 to 0.96)</td>
<td>0.009</td>
</tr>
</tbody>
</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 2×2 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.
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\textsuperscript{4} 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, Proschan 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.