Do Treatment Choices for Hypertension Affect Risk for Developing Heart Failure?

Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation 2006;113:2201–10.

Study Overview

Objective. To examine initial drug choices for treating hypertension and the risk for developing heart failure (HF).

Design. Analysis of a secondary outcome of a large multisite, double-blind, randomized controlled trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [1].

Setting and participants. 33,357 patients with hypertension aged ≥ 55 years with at least 1 additional risk factor for coronary heart disease. Participants were randomly assigned to initial treatment with chlorthalidone (12.5–25 mg/day), amlodipine (10 mg/day), or lisinopril (10–40 mg/day). Open-label second-line drugs, such as atenolol, reserpine, or clonidine, could be added when goal blood pressure was not met.

Main outcome measures. HF incidence (defined as the first occurrence of hospitalization or death due to HF) by treatment group and over time as well as post-HF mortality overall and by treatment group. Additional analyses examined the potential roles of antihypertensive medication use prior to trial entry and differences in blood pressure during treatment and in explaining differences in HF outcomes.

Main results. HF requiring hospitalization/fatal HF was more common in the amlodipine-treated patients (relative risk [RR], 1.35 [95% confidence interval {CI}, 1.21–1.50]) and tended to be more common in lisinopril-treated patients (RR, 1.11 [95% CI, 0.99–1.24]) compared with chlorthalidone-treated patients. Differences in HF occurrence per group varied with time. In the first year, HF was more common in the amlodipine (RR, 2.22 [95% CI, 1.69–2.91]) and lisinopril groups (RR, 2.08 [95% CI, 1.58–2.74]) than the chlorthalidone group. After year 1, the risk for HF was still increased for the amlodipine group (RR, 1.22 [95% CI, 1.08–1.38]) but was not increased for the lisinopril group (RR, 0.96 [95% CI, 0.85–1.10]). Adjustment for the small differences in blood pressure during the trial had little effect on these relationships. Subgroup analysis of HF cases did not show a significant interaction between the type of prior antihypertensive drug used and treatment group in the first year. Mortality after a hospitalization for HF was high (25% at 2.5 years for patients with HF compared with 5% for patients without HF) and did not vary by treatment group.

Conclusion. In the first year, chlorthalidone reduced the risk of HF compared with amlodipine or lisinopril. After the first year, however, there was a persistent reduction in HF incidence with chlorthalidone compared with amlodipine but not with lisinopril.

Commentary

Davis et al's results improve our understanding of the unequal HF rates described in the original ALLHAT report [1]. The authors' use of the more clinically important endpoint of hospitalized or fatal HF (rather than any treated HF) and the high mortality rates following hospitalization tell us that it is unlikely that misattribution of HF diagnosis due to amlodipine-induced benign lower extremity edema is likely the cause of the HF excess in this group.

The additional analyses should be considered preliminary findings (ALLHAT was not formally designed to address them), and some results appear to be inconsistent. The differences between treatments were most pronounced during the first year, and for the lisinopril-chlorthalidone comparison there was no discernable difference in HF incidence after the first year. This suggests that the diuretic may have been more effective than the other 2 drugs at controlling HF symptoms in patients who already had subclinical HF at trial entry. If this were the case, patients using a diuretic at baseline who then were switched to amlodipine or lisinopril would be expected to be more likely to develop HF early during the study. However, the authors reported that group differences in early HF were not easily explained by prior antihypertensive treatment. Because data regarding prior treatment were not given (but will be presented in a forthcoming report), firm conclusions cannot be made.

The impact of long-term treatment with amlodipine, lisinopril, or chlorthalidone on incident HF is still uncertain. Even a large 5-year trial like ALLHAT cannot address

whether these drugs would yield comparable results in younger, newly diagnosed or lower-risk hypertensive population treated for 10 years or more. Small differences in blood glucose or other metabolic parameters that tended to be worse in chlorthalidone-treated patients may have had an inconsequential impact on cardiovascular events and HF incidence over a 5-year period but could potentially play a more important role over decades.

Applications for Clinical Practice

In middle-aged and older adults with hypertension and cardiovascular risk factors, thiazide-type diuretics can be chosen over calcium channel blockers for the prevention of HF. The initial effect of angiotensin-converting enzyme inhibitors on HF risk reduction is probably less than thiazides but greater than calcium channel blockers but becomesvery similar to thiazides after 1 year. Becauseno differences were seen in major coronary heart disease events and mortality among the 3 treatment groups in ALLHAT and because multiple drugs are often required for treatment of hypertension, efficacy in blood pressure control, tolerability, and affordability should factor heavily into prescribing choices.

—Review by Stephen D. Persell, MD, MPH

Reference

1. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published errata appear in JAMA 2003;289:178 and 2004;291:2196]. JAMA 2002;288:2981–97.