Diuretics were superior to calcium-channel blockers and short-term ACE inhibitors for reducing heart failure in hypertension

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.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆

QUESTIONS

In high-risk patients with hypertension, what effect do chlorthalidone, amlodipine, and lisinopril have on hospitalized or fatal heart failure (HF)? Does the effect differ across time and prespecified subgroups?

METHODS

Design: Randomized controlled trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]).

Allocation: {Concealed}†.*

Blinding: Blinded {patients, clinicians, data collectors, outcome assessors, and investigators}‡.*

Follow-up period: Mean 4.9 years.

Setting: {623 centers in the United States, Canada, Puerto Rico, and the U.S. Virgin Islands.}†

Patients: 33 357 patients who were ≥ 55 years of age (mean age 67 y, 53% men) and had stage 1 or 2 hypertension plus an additional risk factor for coronary artery disease. Exclusion criteria were history of hospitalized or symptomatic HF or known left ventricular ejection fraction < 35%.

Intervention: Chlorthalidone, 12.5 to 25 mg/d {*n* = 15 255}†; amlodipine, 2.5 to 10 mg/d {*n* = 9048}†; or lisinopril, 10 to 40 mg/d {*n* = 9054}†. Target blood pressure was < 140/90 mm Hg, which was achieved by step 1 drugs (randomly assigned treatment) with the addition of open-label drugs (atenolol, reserpine, and clonidine [step 2] and hydralazine [step 3]) when necessary.

Outcomes: Hospitalized or fatal HF.

Patient follow-up: {97%. All patients were included in the intention-to-treat analysis.}†

MAIN RESULTS

The hazard ratios (relative risks [RRs]) were not constant over time, so results are presented according to time periods (Table). The effects were consistent across prespecified subgroups (men vs women, < 65 y vs ≥ 65 y of age, black vs nonblack patients, and patients with diabetes vs those without) with no significant interactions among subgroups.

CONCLUSIONS

In high-risk patients with hypertension, the risk for hospitalized or fatal heart failure was higher with lisinopril or amlodipine than with chlorthalidone during year 1. The risk remained higher with amlodipine than with chlorthalidone after year 1 (although the difference in risk was smaller), and the difference with lisinopril was no longer significant. The effects were consistent across prespecified subgroups.

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For correspondence: Dr. B.R. Davis, University of Texas School of Public Health, Houston, TX, USA. E-mail barry.r.davis@uth.tmc.edu. ■

*See Glossary.

†**ALLHAT.** JAMA. 2002;288:2981-97. 12479763

‡Information provided by author.

Effect of chlorthalidone, amlodipine, or lisinopril on hospitalized or fatal heart failure in high-risk patients with hypertension§

Comparisons	Follow-up	RRI (95% CI)
Amlodipine vs chlorthalidone	≤ 1 y	122% (69 to 191)
	> 1 y	22% (8 to 38)
Lisinopril vs chlorthalidone	≤ 1 y	108% (58 to 174)
Amlodipine vs lisinopril	≤ 1 y	7% (–18 to 38)‖
	> 1 y	27% (10 to 46)
		RRR (CI)
Lisinopril vs chlorthalidone	> 1 y	4% (–10 to 15)‖

§Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.
‖Not significant.

COMMENTARY

The main ALLHAT trial focused on combined fatal coronary heart disease (CHD) or nonfatal myocardial infarction as the primary endpoint. The report by Davis and colleagues explores an important secondary outcome—the differential effect of treatment type on HF incidence. HF remains a common and serious cardiovascular complication despite obvious advances in antihypertensive treatment and control. Of significance, the cohort started with 36% with diabetes, 25% with previously documented CHD, and 53% men.

The observed association of the dihydropyridine calcium-channel blocker (CCB) amlodipine with increased rates of HF is hardly surprising, given its tendency to cause fluid retention. The weaker (not statistically significant) association with lisinopril use seems counterintuitive, since angiotensin-converting enzyme (ACE) inhibitors usually reduce afterload and have decreased HF rates in other studies. Potential explanations include chance, less effective blood pressure reduction, delayed effect compared with diuretics, and confounding cotherapies after year 1 of the trial.

Davis and colleagues provide more support for the thesis that diuretic therapy is as good as (if not better than) alternative antihypertensive therapies, both for blood pressure control and for complication prevention. The current reality for most hypertensive patients is combination therapy with ≥ 2 medications, most often using diuretics with ACE inhibitors, diuretics with CCBs, or diuretics with β-blockers (1). ACE inhibitors or angiotensin-receptor blockers as monotherapy to prevent HF episodes are less effective than diuretics but more effective than CCBs. The results apply equally to patients with diabetes (2) and those with renal insufficiency (3), as reported by other ALLHAT investigators searching for risk reduction. Finally, the results reinforce the guidelines for managing patients at high risk for HF (4).

Peter Rudd, MD
Stanford University School of Medicine
Stanford, California, USA

References

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