Amlodipine or lisinopril was not better than chlorthalidone in reducing renal outcomes in hypertension and impaired renal function

Rahman M, Pressel S, Davis BR, et al. **Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).** Arch Intern Med. 2005;165:936-46.

Clinical impact ratings: GIM/FP/GP ★★★★★★★ Hospitalists ★★★★★★☆ Cardiology ★★★★★★☆ Endocrinology ★★★★★★☆ Nephrology ★★★★★☆☆

QUESTION

What is the effect of first-line therapy with a calcium-channel blocker (amlodipine) or an angiotensin-converting enzyme (ACE) inhibitor (lisinopril) compared with a diuretic (chlorthalidone) on renal disease outcomes in patients with hypertension and impaired renal function?

METHODS

Design: Subgroup analysis of a randomized placebo-controlled trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]).

Allocation: {Concealed}†.*

Blinding: {Blinded (clinicians, patients, data collectors, outcome assessors, and steering committee)}†.*

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 ≥ 55 years of age (mean age 67 y, 53% men) who had stage 1 or stage 2 hypertension and ≥ 1 additional risk factor for coronary heart disease. Exclusion criteria were symptomatic heart failure, left ventricular ejection fraction < 35%, or serum creatinine level > 176.8 μmol/L (2 mg/dL).

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). Patients were stratified by baseline glomerular filtration rate (GFR) (≥ 90, 60 to 89, and < 60 mL/min per 1.73 m^2) and by presence or absence of diabetes mellitus (36% of patients had diabetes).

Outcomes: End-stage renal disease (ESRD) (kidney transplantation, start of dialysis, or death caused by kidney disease).

Patient follow-up: Baseline GFR data were available for 31 897 patients (96%) (intention-to-treat analysis).

MAIN RESULTS

ESRD developed in 448 patients. Overall, rates of ESRD did not differ between patients who received chlorthalidone (1.8/100 patients) and either those who received amlodipine (2.1/100 patients) (relative risk [RR] 1.1, 95% CI 0.9 to 1.4) or those who received lisinopril (2.0/100 patients) (RR 1.1, CI 0.9 to 1.4). These results were similar across the 3 strata of baseline GFR (Table).

CONCLUSION

In patients with hypertension, amlodipine or lisinopril was not superior to chlorthalidone in reducing end-stage renal disease, even among those who started with reduced renal function.

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

*See Glossary.

†**Psaty BM.** ACP J Club. 2003 Jul-Aug;139:7.

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Outcome	GFR strata (mL/min per 1.73 m^2)	Relative risk (95% CI)	
		Amlodipine vs chlorthalidone	Lisinopril vs chlorthalidone
End-stage renal disease	≥ 90	1.3 (0.5 to 3.2)	1.1 (0.4 to 2.8)
	60 to 89	1.5 (0.97 to 2.2)	1.3 (0.9 to 2.1)
	30 to 59§	0.9 (0.7 to 1.2)	0.98 (0.7 to 1.3)

‡GFR = glomerular filtration rate. CI defined in Glossary. All comparisons are not significant.

§0.6% of patients had GFR ≤ 29 mL/min per 1.73 m^2.

COMMENTARY

Previously published results from ALLHAT (1) indicate that thiazide diuretics are an excellent first-line therapy for hypertension, especially in patients at higher cardiovascular risk. The subgroup analysis by Rahman and colleagues found no evidence that the ACE inhibitor lisinopril reduced risk for ESRD in hypertensive patients at high risk for cardiovascular events more than other classes of antihypertensive agents. Lisinopril did not seem beneficial even in patients with estimated GFR < 60 mL/min per 1.73 m^2 or those with diabetes mellitus.

Based on evidence from overlapping randomized trials, ACE inhibitors and angiotensin-receptor blockers (ARBs) are recommended for first-line management of hypertension in patients with proteinuric kidney disease (urine protein–creatinine ratio > 200 mg/g [> 22.6 mg/mmol]) or diabetic nephropathy (2). The results of ALLHAT may differ from those of previous trials because of differences in patient characteristics and co-interventions. Among the higher-risk subgroups in the ALLHAT analysis, only 11% to 12% of patients developed the composite renal outcome, compared with 22% to 27% in the AASK and IDNT trials (3, 4). In contrast to common clinical practice, the design of ALLHAT precluded the concomitant use of ACE inhibitors and diuretics. Also, the lack of data on proteinuria makes it unclear which ALLHAT participants would have been recommended for ACE inhibitors or ARBs according to existing guidelines. Finally, as noted by the authors, the 95% CIs do not exclude a clinically relevant benefit of ACE inhibitors. Thus, this subgroup analysis by itself does not justify changes to existing recommendations that an ACE inhibitor or ARB be used for first line-therapy of hypertension in proteinuric or diabetic kidney disease.

Marcello Tonelli, MD, SM, FRCPC
University of Alberta
Edmonton, Alberta, Canada

Phil McFarlane, MD, PhD
University of Toronto
Toronto, Ontario, Canada

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