

The ALLHAT Study

Reviewed by David C. Goff Jr., MD, PhD

STUDY

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: 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). *JAMA* 288:2981–2997, 2002

SUMMARY

Design. A randomized, double-blind, active-controlled clinical trial conducted from February 1994 through March 2002. Participants with hypertension were randomly assigned to receive chlorthalidone, 12.5–25 mg/day ($n = 15,255$); amlodipine, 2.5–10 mg/day ($n = 9,048$); or lisinopril, 10–40 mg/day ($n = 9,054$) for planned follow-up of ~4–8 years.

Participants. A total of 33,357 participants aged ≥ 55 years with hypertension and at least one other coronary heart disease (CHD) risk factor from 623 North American centers; 12,063 participants had diabetes.

Primary hypothesis. The primary outcome was combined fatal CHD or non-fatal myocardial infarction (MI), analyzed by intent-to-treat.

Secondary hypotheses. Secondary outcomes were total mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined cardiovascular disease (CVD) (combined CHD, stroke,

treated angina without hospitalization, heart failure [HF], and peripheral arterial disease).

Results. Mean follow-up was 4.9 years. The primary outcome occurred in 2,956 participants, with no difference between treatments. Compared with chlorthalidone, the relative risks (RRs) were 0.98 (95% CI, 0.90–1.07) for amlodipine and 0.99 (95% CI, 0.91–1.08) for lisinopril. Likewise, all-cause mortality did not differ between groups. For amlodipine versus chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2 vs. 7.7%; RR, 1.38; 95% CI, 1.25–1.52). For lisinopril versus chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3 vs. 30.9%; RR, 1.10; 95% CI, 1.05–1.16), stroke (6.3 vs. 5.6%; RR, 1.15; 95% CI, 1.02–1.30), and HF (8.7 vs. 7.7%; RR, 1.19; 95% CI, 1.07–1.31). Treatment group comparisons were similar in the subgroup of 12,063 participants with diabetes.

Conclusion. Thiazide-type diuretics are superior to angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers in preventing one or more major forms of CVD in high-risk patients with hypertension and in patients with hypertension and diabetes.

COMMENTARY

Because of its frequency and medical impact, hypertension is an extremely important comorbidity for patients with diabetes. More than 60% of middle-aged and older patients with diabetes also have hypertension.¹ High blood pressure

doubles the already elevated risk of CVD in patients with diabetes.²

Treatment of hypertension is especially effective in patients with diabetes. In studies achieving mean systolic blood pressures (SBP) of ~140 mmHg (range 132–153 mmHg), compared with groups achieving mean SBP of ~150 mmHg (range 138–162 mmHg), reductions of 30–60% in the risk of CVD events have been documented.^{3–8}

Debate has centered on the most appropriate initial agent for blood pressure control and the appropriate level of control in people with diabetes. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was designed to address the first question for patients with hypertension in general and provides strong evidence pertinent to all patients with hypertension, including those with diabetes.

Before ALLHAT, several other studies addressed this question. In the patients in the intensive control group of the U.K. Prospective Diabetes Study, the ACE inhibitor captopril and the β -blocker atenolol were equally effective in reducing the incidence of diabetic macrovascular and microvascular complications.⁶ In the Captopril Prevention Project (CAPPP), there were no significant differences in CVD mortality or MI for captopril versus conventional treatment with diuretics and/or β -blockers in the nearly 11,000 hypertensive patients (although strokes were 25% more frequent with captopril). However, in a post hoc subgroup analysis in the 572 patients with diabetes, the risk reduction for the primary CVD endpoint was 41% ($P = 0.019$) with

captopril versus conventional treatment.⁹ In the second Swedish Trial in Old Patients with Hypertension (STOP-2), there was no difference for the primary outcome (cardiovascular mortality) between patients randomized to diuretics and/or β -blockers versus ACE inhibitors versus calcium antagonists, both overall and in the 719 patients with diabetes.¹⁰ The diabetic hypertensive participants in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial had a sevenfold higher incidence of fatal and nonfatal MIs with the dihydropyridine calcium-channel blocker nisoldipine than with the ACE inhibitor enalapril through 5 years of follow-up,⁸ although microvascular outcomes were not different between the two drugs.¹¹ In the Fosinopril Amlodipine Cardiovascular Events Trial (FACET), diabetic hypertensive patients experienced a 51% lower incidence of the combination of acute MI, hospitalized angina, and stroke with fosinopril compared with amlodipine ($P = 0.03$) over 2.8 years of follow-up.¹² These and other reports focusing on renal outcomes have been interpreted as supporting the use of ACE inhibitors as first-line therapy for hypertension in patients with diabetes.

The results of ALLHAT from a much larger population of patients with diabetes provide much greater insight into this issue. In early 2000, the doxazosin arm of ALLHAT was stopped because of a significantly higher incidence of cardiovascular events in the group assigned to the α -blocker doxazosin versus the chlorthalidone group.¹³ In the diabetic subgroup, the rates of CVD and coronary HF were significantly higher in participants randomized to doxazosin versus chlorthalidone (RR, 1.24 [$P < 0.0001$] and 2.14 [$P < 0.0001$], respectively). The remaining three treatment arms continued until the planned end of the study, with results as described above.

Longstanding concerns regarding the glucose-raising and potassium-depleting effects of thiazide-type diuretics were

shown to be relatively minor considerations in ALLHAT. Despite the rationales of improved physiological parameters, including insulin sensitivity and lipoprotein metabolism, attributed to ACE inhibitors, calcium-channel blockers, and α -blockers, patient outcomes were superior with thiazide therapy in patients with and without diabetes. This finding was especially true for heart failure, an outcome of major importance for patients with both diabetes and hypertension.

Since ALLHAT, results of an open-label, randomized trial conducted in Australia have been reported.¹⁴ This trial, conducted in an older but otherwise lower-risk population of patients with hypertension, reported ~10% lower rates of cardiovascular disease and total mortality among participants randomized to the ACE inhibitor group than among those randomized to the diuretic group. Only 7% of study participants had diabetes, and no subgroup analysis was reported.

ALLHAT was a masked trial and had a larger and more ethnically diverse population of participants with a greater prevalence of CVD risk factors. Given these design differences, it is difficult to compare the results of these studies directly. However, ALLHAT had greater power and was unlikely to miss detecting effects of similar magnitude to those observed in the Australian trial.

Discussions of the ALLHAT results have focused on two important questions for clinicians. First, should thiazide-type diuretics replace ACE inhibitors as the first-line therapy for patients with diabetes and hypertension? For now, the answer is yes, given the superior efficacy of thiazide diuretics demonstrated in ALLHAT and their lower cost.

Second, what about the subset of patients with microalbuminuria? Microalbuminuria was not assessed in ALLHAT. Patients with microalbuminuria were not excluded from ALLHAT and might be expected to have been highly represented among this group of older patients with both diabetes and hypertension. Hence, the results of ALLHAT seem very likely to apply to

patients with diabetes, hypertension, and microalbuminuria.

Given the proven superiority of thiazides for hypertension and the proven efficacy (relative to placebo) of ACE inhibitors for microalbuminuria, a prudent course might be to add an ACE inhibitor to initial thiazide therapy whenever possible when hypertension and microalbuminuria coexist in patients with diabetes.

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David C. Goff Jr., MD, PhD, is a professor of public health sciences and internal medicine at Wake Forest University School of Medicine in Winston-Salem, N.C.