Should hypertension be treated with angiotensin-converting-enzyme inhibitors, calcium-channel blockers or diuretics?

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) [erratum appears in *JAMA* 2003; 289(2):178]. *JAMA* 2002;288(23): 2981-97.

Background: Over the past decade, newer and more expensive antihypertensive drugs, such as calcium-channel blockers and angiotensin-converting-enzyme (ACE) inhibitors, have become common first-line therapy for hypertension. Although newer antihypertensive medications have proven benefit in lowering both blood pressure and the rate of cardiovascular events, few large clinical trials have compared them with diuretics.

Question: Does antihypertensive therapy with calcium-channel blockers or ACE inhibitors lower the incidence of cardiovascular disease more than treatment with a diuretic?

Design: This very large randomized trial recruited 33 357 participants aged 55 years or more with hypertension at 623 centres in the United States and Canada. In addition to hypertension, all participants had at least 1 additional risk factor for or history of coronary artery disease (CAD). Exclusion criteria included a history of clinical heart failure or a left ventricular ejection fraction below 35%. Participants were randomly assigned in a ratio of 1.7:1:1 to receive 1 of 3 "step 1" medications, a diuretic (chlorthalidone, n = 15 255), a dihydropyridine calcium-channel blocker (amlodipine, n = 9048) or an ACE inhibitor (lisinopril, n = 9054). A fourth step 1 medication, doxazosin, was compared with chlorthalidone, but this arm of the trial was stopped prematurely because of an excess of congestive heart failure in the doxazosin group.

Step 1 medications were prepared as identical capsules. After randomization, participants stopped taking other antihypertensive drugs and started the study drug. If the blood pressure goal (< 140/90 mm Hg) was not achieved at the initial dose of the step 1 medication, the dose was increased until the maximum dose was reached. If control remained inadequate, designated steps 2 and 3 medication (reserpine, atenolol, clonidine or hydralazine) were added. Open-label use of step 1 medications was permitted if clinically indicated.

The primary outcome was fatal and nonfatal CAD combined. The 4 secondary outcomes were death from all causes, stroke (fatal and nonfatal), combined CAD (primary outcome, coronary revascularization and admission to hospital with angina) and combined cardiovascular disease (combined CAD, stroke, treated angina with no admission to hospital, heart failure and peripheral arterial disease). Intention-to-treat analysis was used.

Results: Over half of the participants were over the age of 65, and over half were either black (35%) or Hispanic (19%). Mean blood pressure at randomization was 146/84 mm Hg, and 90% of participants were taking antihypertensive medication before randomization. Diabetes mellitus was common (36%), as was pre-existing atherosclerotic vascular disease (52%). Baseline characteristics were similar in all 3 groups.

Mean follow-up time was 4.9 years. Vital status data were missing in 2.7% (chlorthalidone) to 3.0% (lisinopril) of participants at the end of the trial. Follow-up visits were completed by 92% of participants in year 1, and this declined with time to 84%–87% at year 5 in all 3 treatment groups.

At the end of the first year, more patients in the lisinopril group were taking a step 2 or step 3 medication (32.6%) compared with the other 2 groups (chlorthalidone 26.7%, amlodipine 25.9%). Because open-label step 1 medication was permitted at the clinician's discretion, some participants were taking 2 step 1 medications. In the chlorthalidone group, 67.5% of participants took only one step 1 drug, as did 63.8% in the amlodipine group and 56.9% in the lisinopril group.

At year 5, significantly fewer participants were taking the drug that they were randomly assigned in the lisinopril group than in the other 2 groups (61.2% v. 71.2% in the chlorthalidone group and 72.1% in the amlodipine group).

Mean systolic blood pressure was lower in the chlorthalidone group than in the other 2 groups from year 1 through year 5, and diastolic blood pressure was lower in the amlodipine group. More participants in the chlorthalidone group achieved the blood pressure goal of < 140/90 mm Hg at year 5 than participants in the other 2 groups (chlorthalidone 68.2%, amlodipine 66.3%, lisinopril 61.2%; $p < 0.001$). By the end of the trial, participants were taking an average of about 2 antihypertensive medications.

There was no significant difference among the 3 groups regarding the primary outcome. When comparing amlodipine and chlorthalidone, there were no overall differences in the secondary outcomes. The secondary outcomes of combined cardiovascular disease and stroke occurred more often in the lisinopril group than in the chlorthalidone group, with a 15% increased risk of stroke and a 10% increased risk of combined cardiovascular disease. Stroke was more common only in the black participants (relative risk 1.4). Congestive heart failure occurred more frequently in both the amlodipine and lisinopril groups (increased risk 38%

amlodipine v. chlorthalidone, $p < 0.001$; lisinopril v. chlorthalidone 19%, $p < 0.001$). Development of diabetes (glucose > 7.0 mmol/L) occurred more frequently in participants who took chlorthalidone (11.6%) than in those who took amlodipine (9.8%) or lisinopril (8.1%).

Commentary: This study is the first large trial to compare a thiazide diuretic with newer antihypertensive medications for the treatment of hypertension. The results show no significant cardiovascular benefit of the newer medications over diuretics as a first choice for the treatment of hypertension. Although there were differences in secondary outcomes in the lisinopril group, this can be attributed in part to the fact that equivalent blood pressure lowering was not achieved in this group. The investigators state that the increased incidence of newly diagnosed diabetes in the diuretic group was not associated with an increase in primary or secondary outcomes, but it is likely that it was too early in the course of diabetes to detect such an effect. The lower incidence of new diabetes in the ACE inhibitor group is consistent with findings in previous studies.[1,2]

Practice implications: Twenty-two percent of Canadians have hypertension, and the costs of treatment are substantial.[3] This study showed that diuretics are at least equivalent to either amlodipine or lisinopril in lowering blood pressure and preventing CAD. Given their demonstrated effectiveness, and their lower cost, they should be considered as the first choice for most patients who require medication for hypertension. The results of ALLHAT cannot be generalized to other agents, such as angiotensin-receptor blockers, or to nondihydropyridine calcium-channel blockers. Physicians should use caution when prescribing diuretics to patients at high risk of developing diabetes.

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