Clinical Update

Hypertension and α-adrenergic blockers: preliminary ALLHAT results

The ALLHAT officers and coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;283:1967-75.

Background

Hypertension increases the risk of morbidity and mortality from cardiovascular disease.[1] Canadian guidelines recommend the use of diuretics, β-adrenergic blockers or angiotensin-converting-enzyme (ACE) inhibitors as first-line therapies.[2] The role of other antihypertensive drugs as first-line therapy is less clear.

Question

Does the treatment of hypertension with an α-adrenergic blocker (doxazosin) reduce the risk of cardiovascular events as effectively as a thiazide diuretic (chlorthalidone)?

Design

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a randomized, double-blind trial involving 625 centres in the United States and Canada.[1] Between 1994 and 1998, 42 448 hypertensive patients were randomly assigned to receive 1 of 4 antihypertensive drugs as first-line therapy: a calcium antagonist, an ACE inhibitor, an α-adrenergic blocker and a thiazide diuretic. The α-adrenergic blocker arm was discontinued early following interim data analysis. Results from the 24 335 patients randomly assigned to receive either the α-adrenergic blocker (doxazosin, 2–8 mg/d) or the thiazide diuretic (chlorthalidone, 12.5–25 mg/d) were published in this initial report.[1]

All subjects were 55 years of age or older with hypertension and had at least one cardiac risk factor, such as previous myocardial infarction (MI) or stroke, left ventricular hypertrophy, type 2 diabetes mellitus, low level of high-density-lipoprotein cholesterol and current cigarette smoking. The treatment goal was a blood pressure of 140/90 mm Hg or less. If the treatment goal was not achieved despite maximum doses of the study drug, antihypertensive therapy was intensified according to a predetermined protocol involving additional drugs (atenolol, reserpine, clonidine or hydralazine). The primary end point was the composite of fatal coronary artery disease (CAD) and nonfatal MI. Secondary end points included all-cause mortality, CAD-related death, nonfatal MI, revascularization procedures, angina, congestive heart failure, stroke and peripheral vascular disease.

Results

The subjects' mean age was 67 years; similar numbers of men and women participated. Diabetes was an additional risk factor in 36% of subjects, and 22% were current cigarette smokers. The mean blood pressure was 145/83 mm Hg at the time of enrolment, with 90% of subjects already receiving an antihypertensive drug. The median length of follow-up was 3.3 years.

At 4 years' follow-up the mean blood pressure was 137/76 mm Hg among the patients receiving the α-adrenergic blocker, with 58% of these subjects reaching the treatment goal of a blood pressure below 140/90 mm Hg; the mean blood pressure of subjects receiving the diuretic was 135/76 mm Hg, with 64% reaching the treatment goal. No significant difference was observed between the 2 groups for the primary outcome (fatal CAD and nonfatal MI), for all-cause mortality, or for peripheral vascular disease. However, the group receiving the α-adrenergic blocker had a significantly higher relative risk (RR) for coronary revascularization (RR 1.15; 95% confidence interval [CI] 1.00–1.32; $p = 0.05$), stroke (RR 1.19; 95% CI 1.01–1.40; $p = 0.04$), angina (RR 1.16; 95% CI 1.05–1.27; $p < 0.001$) and congestive heart failure (RR 2.04; 95% CI 1.79–2.32; $p < 0.001$).

Commentary

ALLHAT is the largest trial yet comparing the effectiveness of several classes of antihypertensive drug with a thiazide diuretic as first-line therapy. These preliminary results show increased relative risk for a number of cardiovascular end points, including a doubling of the risk of congestive heart failure, in patients treated with an α-adrenergic blocker. That one-third of the subjects in both groups failed to reach the target blood pressure of less than 140/90 mm Hg is disappointing.

Practice implications

α-Adrenergic blockers should not be used in the first-line treatment of hypertension. The relative effectiveness of calcium antagonists and ACE inhibitors in comparison with thiazide diuretics will not be determined until the conclusion of ALLHAT in 2002. In the meantime, better attainment of blood pressure goals can reduce cardiovascular morbidity further. — *Benjamin H. Chen*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

Reference

1. The ALLHAT officers and coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;283:1967-75.
2. Feldman RD, Campbell N, Larochelle P, Bolli P, Burgess ED, Carruthers SG, et al. 1999 Canadian recommendations for the management of hypertension. *CMAJ* 1999;161(Suppl 12):S1-17. Available: www.cma.ca/cmaj/vol-161/issue-12/hypertension/hyper-e.htm