

Statement on the Use of Alpha-Adrenergic Blockers as Monotherapy in the Management of Patients with Hypertension

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a long-term study designed to evaluate whether the composite endpoint of fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI) differed between treatment with 4 agents (chlorthalidone, amlodipine, lisinopril, or doxazosin) in high-risk hypertensive patients. Results of ALLHAT, comparing doxazosin with chlorthalidone in the treatment of patients with hypertension (HTN) and at least one other CHD risk factor, were published in 2000.¹ The doxazosin treatment arm of the study was discontinued by the National Heart, Lung, and Blood Institute based on comparisons with chlorthalidone. The secondary outcome of stroke risk was significantly higher (RR 1.19; 95% CI 1.01-1.40, P=0.04) with doxazosin, as were the combined cardiovascular disease (CVD) events (4 year rates 25.45% vs. 21.76%, RR 1.25; 95% CI 1.17-1.33, P<0.001; NNH=27), compared to chlorthalidone. The secondary outcome measure of all cause mortality was not significantly different between the two treatment groups. When evaluated separately, the risk for congestive heart failure (CHF) was doubled (4 year rates 8.13% vs. 4.45%, RR 2.04; 95% CI 1.79-2.32, P<0.001; NNH=27) in patients treated with doxazosin compared with chlorthalidone. The primary outcome of risk of CHD death or nonfatal MI did not differ between the treatment groups. Mean blood pressure of the two treatments was not significantly different at 4 years (135/76 mm Hg in the chlorthalidone group compared to 137/76 mm Hg in the doxazosin group), although the authors suggest that this may partially account for the difference in results. At 4 years, 64% of patients in the chlorthalidone group were at or below blood pressure goal (< 140/90 mm Hg) compared to 58% of patients in the doxazosin group. Adherence at 4 years was 86% in the chlorthalidone group compared to 75% in the doxazosin group.

In response to discontinuation of the doxazosin treatment arm in the ALLHAT trial, the American College of Cardiology (ACC) released a statement that physicians should reassess the use of the alpha-adrenergic blocker (e.g., doxazosin) for the treatment of HTN.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)² and the VHA/DoD Clinical Practice Guideline for Diagnosis and Management of Hypertension in the Clinical Practice Setting, recommend a thiazide-type diuretic as preferred therapy for treating patients with uncomplicated HTN. Antihypertensive therapy should also be selected according to compelling indications based on outcomes of randomized controlled-trials or favorable effects on comorbid conditions. An alpha-adrenergic blocker may be used as adjunct therapy for patients with HTN and symptomatic benign prostatic hyperplasia (BPH), or if HTN is not controlled by other therapies.

Results of ALLHAT raise concerns about the safety of using doxazosin as initial therapy for HTN, compared to patients treated with chlorthalidone who experienced significantly better outcomes. This trial did not evaluate whether or not treatment with doxazosin had a detrimental effect in patients with HTN since there was not a placebo group. It is also unclear how the ALLHAT results apply to patients on doxazosin as adjunct treatment for HTN. At the end of 4 years of the trial, 47% of patients in the doxazosin group were receiving a Step 2 (atenolol 25-100mg/d, reserpine 0.05-0.2mg/d, or clonidine 0.1-0.3mg twice daily) or Step 3 (hydralazine 25-100mg twice daily) agent compared to 40% of patients in the chlorthalidone group. In addition, it is unknown how the ALLHAT results translate into recommendations for patients who are being treated with an alpha-adrenergic blocker for the management of BPH. However, patients receiving monotherapy with an alpha-adrenergic blocker for the treatment of BPH and HTN should have their therapy reevaluated for potential modifications. Whether or not the results with doxazosin can be extrapolated to other available alpha-adrenergic blockers (i.e., prazosin or terazosin) has yet to be determined, but it is prudent to consider this as a possible class effect until information to the contrary becomes available.

In summary:

- Patients treated with an alpha-adrenergic blocker (e.g., doxazosin, prazosin, terazosin) as monotherapy for HTN should be reevaluated to determine the most appropriate antihypertensive therapy in light of the ALLHAT results that patients on a thiazide diuretic had better outcomes than patients receiving an alpha-adrenergic blocker as initial therapy for HTN. Therapy should include an agent that has been shown to reduce hypertension-related morbidity and mortality.

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 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL et al. for the National High blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC 7 Report. JAMA. 2003;289(19):2560-2572.