

Doxazosin was associated with more stroke and cardiovascular disease events than chlorthalidone in high risk hypertension

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 Apr 19;283:1967-75.

QUESTION: In high risk hypertensive patients, is doxazosin (an α -adrenergic blocker) or chlorthalidone (a diuretic) more effective in reducing cardiovascular disease (CVD) events?

Design

Randomised (allocation concealed*), blinded (clinicians and patients)*, controlled trial with median 3.3 year follow up.

Setting

625 centres in the US and Canada.

Patients

24 335 patients who were ≥ 55 years of age (mean age 67 y, 53% men, 49% white non-Hispanic), had systolic blood pressure (BP) ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg, took medication for hypertension, and had ≥ 1 other risk factor for coronary heart disease (CHD). [Exclusion criteria included myocardial infarction (MI), stroke, or angina pectoris in the past 6 months; congestive heart failure (CHF) or ejection fraction $< 35\%$; or serum creatinine concentration ≥ 177 $\mu\text{mol/l}$.]† 97% of patients were included in the analysis.

Intervention

Patients were allocated to doxazosin, 2 to 8 mg/day (n=9067), or chlorthalidone, 12.5 to 25 mg/day (n=15 268).

Main outcome measures

The primary outcome was a composite end point of fatal CHD and non-fatal MI. Secondary outcomes were all cause mortality, combined CHD events (CHD death, non-fatal MI, revascularisation, and angina requiring admission to hospital), stroke, or combined CVD events (CHD death, non-fatal MI, stroke, revascularisation, angina, CHF, and peripheral arterial disease).

Main results

Treatment with doxazosin was discontinued early. Analysis was by intention to treat. A proportional hazards model was used. At the stopping point, the groups did not differ for the primary outcome (relative risk [RR] 1.03, 95% CI 0.09 to 1.17; $p=0.71$). However, for secondary outcomes, the doxazosin group had an increased risk for stroke (RR 1.19, 95% CI 1.01 to 1.40; $p=0.04$) and combined CVD events (RR 1.25, CI 1.17 to 1.33; $p<0.001$), which included an increase in CHF (RR 2.04, CI 1.79 to 2.32; $p<0.001$) and angina (RR 1.16, CI 1.05 to 1.27; $p<0.001$).

Conclusion

In high risk hypertensive patients, doxazosin was associated with a higher incidence of stroke and

cardiovascular disease events, especially congestive heart failure, than was chlorthalidone.

*See glossary.

†Davis BR, Cutler JA, Gordon DJ, *et al.* *Am J Hypertens* 1996;9:342-60.

COMMENTARY

ALLHAT is a study of astonishing methodological beauty. A practice based trial, ALLHAT used both concealed allocation and double blinding in 625 centres; participants were randomised to one of several first line agents, doxazosin or chlorthalidone in this report; and the outcomes included all the major disease end points associated with uncontrolled hypertension. This study thus provides essential information about the optimal treatment strategy for patients with high BP.

Although chlorthalidone and doxazosin have a similar effect on BP lowering, they have different effects on the risks for stroke, angina, and CHF. In retrospect, it may seem obvious that drugs with such different mechanisms of action might well have different effects on various outcomes. The US Food and Drug Administration and other regulatory bodies, however, approve antihypertensive drugs on the basis of how well they lower BP.¹ In light of the ALLHAT results, the assumption that the effect an antihypertensive agent has on BP lowering is a valid and adequate surrogate for the effect of the agent on the occurrence of major disease end points is no longer tenable. The criteria for antihypertensive drug approval ought to change.

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended diuretics as first line agents but also included a section titled "May have favorable effects on comorbid conditions," which advocates the use of α -blockers in patients with dyslipidemia or prostatism.² Although heavily promoted, these "surrogate" arguments for favoring unproven antihypertensive treatments are not good evidence-based medicine.³ Despite beneficial effects on lipid concentrations, doxazosin was associated with an increased risk for CVD events. This study reinforces a key question for clinicians: if your patient with drug treated hypertension is not on a low dose diuretic, why not?

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1 Psaty BM, Weiss NS, Furberg CD, *et al.* *JAMA* 1999;282:786-90.

2 *Arch Intern Med* 1997;157:2413-46.

3 Psaty BM, Furberg CD. *BMJ* 1999;319:589-90.

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