Clinical Outcomes with 2-Drug Antihypertensive Regimens

Boger-Megiddo I, Heckbert SR, Weiss NS, et al. Myocardial infarction and stroke associated with diuretic based two drug antihypertensive regimens: population based case-control study. BMJ 2010;340:c103. doi: 10.1136/bmj.c103.

Study Overview

Objective. To examine the association of myocardial infarction (MI) and stroke incidence with 3 common 2-drug antihypertensive treatment regimens.

Design. Retrospective, population-based case-control study.

Setting and participants: Patients were enrolled in a large health maintenance organization in western Washington State. Cases (n = 353) had pharmacologically treated hypertension and were diagnosed with a first fatal or nonfatal MI or stroke between 1989 and 2005. Age- and gender-matched controls (n = 952) were a random sample of patients who were pharmacologically treated for hypertension but without history of MI or stroke. Individuals with heart failure, coronary artery disease, or chronic kidney disease were excluded.

Main outcome measures. Incidence of fatal or nonfatal MI or stroke.

Main results. Baseline characteristics of cases and controls were generally similar. However, the rates of most recent systolic blood pressure measured below 140 mm Hg were highest in controls and lowest in cases treated with diuretics and calcium channel blockers. Patients treated with diuretics plus calcium channel blockers had significantly increased risk of MI (adjusted odds ratio [OR], 1.98 [95% confidence interval {CI}, 1.37–2.87]) compared with patients treated with diuretics plus beta blockers. The risk of stroke was not significantly different (OR, 1.02 [95% CI, 0.63–1.64]). The risks of MI or stroke were not significantly lower in patients treated with diuretics plus ACE inhibitor or angiotension receptor blockers than in patients treated with diuretics plus beta blockers (MI: OR, 0.76 [95% CI, 0.52–1.11]; stroke: OR, 0.71, [95% CI, 0.46–1.10]).

Conclusion. In hypertensive patients with low risk for cardiovascular disease, combination therapy with diuretic plus calcium channel blocker is associated with higher risk of MI compared with other common 2-drug regimens.

Commentary

Nearly 1 in 6 people around the world will develop hypertension. Heavily influenced by the results of ALLHAT [1], the Seventh Report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends using thiazide-type diuretics as initial monotherapy in uncomplicated hypertension. But a large proportion of patients will require a second antihypertensive to achieve control of blood pressure, and there is little guidance or consensus as to the most effective combination. Recent statements issued by the American Heart Society and European Society of Hypertension/European Society of Cardiology reiterate that the major determinant of cardiovascular risk reduction is the absolute blood pressure reduction rather than the type of drug used for treatment. The present study contributes to accumulating evidence that challenges this notion and suggests there may be specific class effects that govern other mechanisms of cardiovascular risk reduction.

This study identified patients enrolled in a large HMO who had pharmacologically treated hypertension and suffered a first time MI or stroke over a 16-year period. The authors included only patients who were treated with 1 of 3 common 2-drug combinations: diuretics plus beta blockers; diuretics plus ACE inhibitors/ARB; and diuretics plus calcium channel blockers. The authors compared the outcomes of these patients with a control group who had similar characteristics but without a history of MI or stroke. Using basic risk adjustment, the authors found that patients treated with diuretics plus calcium channel blockers had a significant increased risk of MI. There were no significant differences in the risk of stroke between the 6 groups.

There are several design and methodologic flaws in this study that severely restrict the conclusions that can be drawn. This study identified "cases" at the time of their first cardiovascular incident (prevalent antihypertensive medication users) instead of identifying patients at the start of their antihypertensive therapy (new users). This prevalent-user design can introduce a selection bias by underestimating early deaths or complications from medical therapy [2].

Furthermore, this was not a randomized study, and addressing confounders and baseline differences is critical to obtaining unbiased data. Their risk adjustment model only included 5 variables and did not include other important factors such as frequency of aspirin use, obesity, peripheral

vascular disease, or family history of coronary artery disease. Though the authors contend they used a population-based approach, one wonders if 353 cases and 952 controls is really enough. Also while the authors conclude that there are specific class effects, they failed to control for variations in blood pressure control between the 3 types of cases, which may account for the difference in cardiovascular risk. For instance, patients treated with diuretics plus calcium channel blockers may have the highest risk of MI, but this group had the highest average blood pressures on follow-up and the lowest percentage of patients with systolic blood pressure < 130 mm Hg.

Applications for Clinical Practice

This study attempts to address an important clinical question regarding the optimal management of low-risk patients with hypertension. For a large proportion of patients, multidrug therapy is a necessity to adequately treat hypertension and prevent cardiovascular complications. Unfortunately this study provides insufficient evidence to truly change clinical practice at this time. In the interim, clinicians should continue to follow national guidelines in choosing initial and adjunctive antihypertensive therapy. As the authors conclude, a large-scale randomized trial should be conducted to understand the most effective combination of diurectics and second-line medication.

—Review by Henry Tran, MD, NYU School of Medicine, New York, NY, and Nirav R. Shah, MD, MPH

Reference

1. 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 2002;288:2981–97.
2. Ray WA. Evaluating medication effects outside of clinical trials: New-user design. Amer J Epidemiol 2003:158:915–20.