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The benazepril-amlodipine combination is superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events *(the ACCOMPLISH study)*

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The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study was a multicenter, double-blind clinical trial, designed to test the hypothesis that treatment with an ACE inhibitor combined with amlodipine would result in better cardiovascular outcomes than treatment with the same ACE inhibitor combined with a thiazide diuretic.

The primary end point was the composite of death from cardiovascular causes, and cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization

Secondary end points were a composite of cardiovascular events, defined as the primary end point, excluding fatal events, and a composite of death from cardiovascular causes, non fatal stroke and nonfatal myocardial infarction.

Between October 2003 and May 2005, 11506 patients with hypertension who were at high risk for cardiovascular events were randomly assigned to a study group – 5744 to the benazepril-amlodipine group and 5762 to the benazepril-hydrochlorothiazide group. There were no significant differences in baseline characteristics between the patients in the two treatment groups. The mean follow-up was 35.7 months for the benazepril–amlodipine group and 35.6 months for the benazepril–hydrochlorothiazide group. The baseline blood pressures were similar between the two groups, and the reduction in blood pressure from baseline was similar over the course of the trial.

Patients began treatment with either a combination of 20 mg of benazepril and 5 mg of amlodipine or a combination of 20 mg of benazepril and 12.5 mg of hydrochlorothiazide, once daily. As dictated by the protocol, the benazepril component in both groups was increased to 40 mg daily 1 month after randomization. Thereafter, investigators could increase the amlodipine dose to 10 mg daily and increase the hydrochlorothiazide dose to 25 mg

daily, if necessary, to attain a target blood pressure of less than 140/90 mm Hg (or a recommended target of 130/80 mm Hg for patients with diabetes or kidney disease). The addition of other antihypertensive agents was permitted (excluding any calcium-channel blockers, any ACE inhibitors, any angiotensin II– receptor blockers, and any thiazide diuretics).

In October 2007, after a mean of 30 months of treatment exposure and with data on 979 patients with primary adjudicated end points (59.6% of the originally projected primary end points), the data and safety monitoring committee observed a difference between the two treatment groups that exceeded the boundary of the prespecified stopping rule and recommended early termination of the study. The trial was terminated early after a mean follow-up of 36 months.

The primary-outcome event occurred in 552 patients (9.6%) in the benazepril–amlodipine group as compared with 679 patients (11.8%) in the benazepril–hydrochlorothiazide group, representing an absolute risk reduction of 2.2 percentage points and a relative risk reduction of 19.6% (hazard ratio, 0.80; P<0.001). For the secondary end point of death from cardiovascular causes plus nonfatal myocardial infarction and nonfatal stroke, there were 288 events (5.0%) in the benazepril–amlodipine group as compared with 364 (6.3%) in the benazepril–hydrochlorothiazide group, representing an absolute risk reduction of 1.3 percentage points and a relative risk reduction of 21.2% (hazard ratio, 0.79; P = 0.002). For the secondary end point of cardiovascular events, there were 494 events (8.6%) in the benazepril–amlodipine group and 592 events (10.3%) in the benazepril–hydrochlorothiazide group, representing an absolute risk reduction of 1.7 percentage points and a relative risk reduction of 17.4% (hazard ratio, 0.83; P = 0.002).

The authors discuss that their observation that amlodipine was superior to hydrochlorothiazide in preventing cardiovascular events among patients receiving an ACE inhibitor might appear surprising in light of the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In ALLHAT, amlodipine-based and chlorthalidone-based therapy had similar effects on mortality and on the rates of stroke and myocardial infarction. A possible explanation for the difference between the outcomes of ACCOMPLISH trial and those of ALLHAT is that chlorthalidone may differ from hydrochlorothiazide in its effect on outcomes independently of its effect on blood pressure. Another explanation, however, is that the combination of amlodipine with a drug that inhibits the renin–angiotensin system, as compared with amlodipine monotherapy, may provide unique beneficial effects.

The authors' conclusion is that the trial shows that combination therapy with benazepril and amlodipine results not only in excellent blood-pressure control but also in a clear benefit with respect to cardiovascular outcomes. ❑

Comment on the paper:
Jamerson K, Weber MA, et al – Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. *N Engl J Med* 2008; 359:2417-2428