

## Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

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### ABSTRACT

#### BACKGROUND

The optimal combination drug therapy for hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic. We hypothesized that treatment with the combination of an angiotensin-converting-enzyme (ACE) inhibitor and a dihydropyridine calcium-channel blocker would be more effective in reducing the rate of cardiovascular events than treatment with an ACE inhibitor plus a thiazide diuretic.

#### METHODS

In a randomized, double-blind trial, we assigned 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.

#### RESULTS

The baseline characteristics of the two groups were similar. The trial was terminated early after a mean follow-up of 36 months, when the boundary of the prespecified stopping rule was exceeded. Mean blood pressures after dose adjustment were 131.6/73.3 mm Hg in the benazepril-amlodipine group and 132.5/74.4 mm Hg in the benazepril-hydrochlorothiazide group. There were 552 primary-outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-hydrochlorothiazide group (11.8%), representing an absolute risk reduction with benazepril-amlodipine therapy of 2.2% and a relative risk reduction of 19.6% (hazard ratio, 0.80, 95% confidence interval [CI], 0.72 to 0.90;  $P < 0.001$ ). For the secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, the hazard ratio was 0.79 (95% CI, 0.67 to 0.92;  $P = 0.002$ ). Rates of adverse events were consistent with those observed from clinical experience with the study drugs.

#### CONCLUSIONS

The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events. (ClinicalTrials.gov number, NCT00170950.)

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**T**HERE IS INCOMPLETE EVIDENCE THAT the cardiovascular benefits of specific classes of antihypertensive drugs extend beyond lowering blood pressure.<sup>1</sup> A review of clinical trials involving patients with hypertension who were at high risk for cardiovascular events showed that treatment with multiple antihypertensive medications was often necessary to attain blood-pressure goals recommended by guidelines.<sup>2,3</sup> In previous trials designed to test single agents, other drugs were often added for blood-pressure control, thus confounding the interpretation of the effects of the initial drug on the study end points.

Initial therapy for hypertension with a combination of drugs is recommended by both the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and European guidelines for patients whose blood pressures are 20/10 mm Hg or more above their treatment goals.<sup>1,4</sup> JNC 7 guidelines recommend that thiazide diuretics be included in combination regimens. However, combinations that do not include thiazide diuretics should be considered. Experimental work has shown that the calcium-channel blocker amlodipine effectively increases the availability of vascular endothelial nitric oxide,<sup>5</sup> whereas other studies have shown that the combined effects of amlodipine and an angiotensin-converting-enzyme (ACE) inhibitor on nitric oxide are greater than the effect with either drug alone.<sup>6-9</sup> This combination, as compared with other therapies, has also been shown to slow the progression of atherosclerotic lesions in laboratory animals.<sup>7-9</sup> Similarly, in humans, the combination of amlodipine and benazepril has additive effects in reducing left ventricular hypertrophy and arterial stiffness.<sup>10</sup> Thus, the combination of benazepril, an ACE inhibitor, and amlodipine, a calcium-channel blocker, may confer protection of target organs independently of the drugs' blood-pressure-lowering effects.

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial was 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.

## METHODS

Two of the academic authors initiated the clinical trial. Members of the executive committee designed the study, which was funded by Novartis. An independent data and safety monitoring committee and the institutional review board or ethics committee at each participating site approved the protocol. An operations committee composed of representative members of the executive committee and the sponsor (Novartis) met regularly and oversaw all aspects of coordination and data gathering. Analyses were performed by the sponsor in coordination with the executive committee. Investigators at the clinical sites entered data directly into an electronic database maintained by Novartis. Data analysis was performed according to a statistical plan devised by the executive committee and carried out by the Clinical Information Sciences statistical group at Novartis.

All prespecified end points<sup>11</sup> were adjudicated by independent clinical end-point committees at Brigham and Women's Hospital, Boston, and the Duke Clinical Research Institute, Durham, NC. The end-point database was maintained at the Duke Clinical Research Institute. The members of the executive committee vouch for the accuracy and completeness of the reported data.

The ACCOMPLISH study was a multicenter, double-blind clinical trial that compared the rates of morbidity and mortality from cardiovascular causes when two different combination therapies were used as the initial trial intervention in patients with hypertension who were at high risk for a cardiovascular event. The outcomes for the group receiving a combination of benazepril and amlodipine were compared with the outcomes for the group receiving benazepril and hydrochlorothiazide. Both groups took the study medications in a single-capsule formulation. The study design and rationale have been reported in detail previously.<sup>11,12</sup>

## PATIENTS

Participants from five countries (the United States, Sweden, Norway, Denmark, and Finland), representing 548 centers, were included in the trial. All enrolled patients had hypertension and were at high risk for cardiovascular events; patients were included who had a history of coronary

events, myocardial infarction, revascularization, or stroke; impaired renal function; peripheral arterial disease; left ventricular hypertrophy; or diabetes mellitus. Detailed eligibility criteria have been described previously.<sup>11</sup> All participants provided written informed consent.

#### PROCEDURES

The first patient was assigned to a study group on October 29, 2003. Immediately on entering the study (without a washout period), patients were randomly assigned in a global one-to-one ratio to either of the two treatment groups, with assignments made centrally by telephone. 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 but including beta-blockers, alpha-blockers, clonidine, and spironolactone). Loop diuretics taken once daily were permitted for volume management. After the initial 3-month dose-adjustment period, patients returned at 6 months and then at 6-month intervals until the end of the trial. Blood pressures were recorded as the average of three readings taken at 2-minute intervals after the patient had remained in a seated position for 5 minutes. Follow-up of patients for the evaluation of end points continued until the trial's end, even if the study medication had been permanently discontinued.

#### END POINTS

The primary end point was measured as the time to the first event (which was defined as the composite of a cardiovascular event and death from cardiovascular causes). Death from cardiovascular causes was defined as a death attributed to

sudden death from cardiac causes, myocardial infarction, stroke, coronary intervention, congestive heart failure, or other cardiovascular causes. A cardiovascular event was defined as a nonfatal myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or resuscitation after sudden cardiac arrest. Only the first event in an individual patient was counted in the analysis of the primary end point. However, in subsequent prespecified analyses of the individual components of the primary and secondary end points, the event count was performed without censoring for previous end points. 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, nonfatal stroke, and nonfatal myocardial infarction. Other reported end points included the individual components of the primary and secondary end points, hospitalization for heart failure, and death from any cause. Prespecified subgroup analyses based on age, sex, and presence or absence of diabetes were also performed.

#### STATISTICAL ANALYSIS

##### *Power and Sample Size*

We calculated that with a total of 1642 patients with primary events, the study would have 90% power to detect a 15% reduction in risk for the benazepril-amlodipine group, assuming an annual event rate of 3.5% for the benazepril-hydrochlorothiazide group. An O'Brien-Fleming spending function was used to attain an overall two-sided significance level of 0.05 (type I error rate, 5%). On October 2, 2007, an amendment to reduce the study's power to 80% was accepted. Accordingly, the targeted final number of patients with primary events was reduced to 1199.

##### *Analysis of End Points*

All prespecified study outcomes (as reported previously)<sup>11</sup> were adjudicated according to standard criteria by a central committee whose members were unaware of study-group assignments.

An independent data and safety monitoring committee met twice yearly. For each formal interim analysis of efficacy, a spending function was used to determine significance criteria or stopping rules.<sup>13</sup> Interim analyses performed between January 2006 (6 months after study recruit-

ment ended) and October 2007, the results of which prompted the data and safety monitoring committee to recommend termination, were based on 326, 541, 720, 850, and 979 events, and the associated normal-distribution z-value criteria were determined to be 4.90, 3.73, 3.20, 2.95, and 2.74, respectively. (For the last analysis, despite the pending decision to shorten the trial, the bound-

**Table 1. Demographic and Baseline Characteristics of the Study Patients.\***

Characteristic	Benazepril–Amlodipine Group (N = 5744)	Benazepril–Hydrochlorothiazide Group (N = 5762)
Sex — no. (%)		
Male	3448 (60.0)	3515 (61.0)
Female	2296 (40.0)	2246 (39.0)
Age — yr	68.4±6.86	68.3±6.86
≥65 yr — no. (%)	3813 (66.4)	3827 (66.4)
≥70 yr — no. (%)	2363 (41.1)	2340 (40.6)
Race or ethnic group — no. (%)†		
Black	697 (12.1)	719 (12.5)
White	4817 (83.9)	4795 (83.2)
Hispanic	300 (5.2)	323 (5.6)
Other	230 (4.0)	247 (4.3)
Region — no. (%)		
United States	4067 (70.8)	4086 (70.9)
Nordic countries	1677 (29.2)	1676 (29.1)
Weight — kg	88.7±19.0	88.5±18.9
Waist circumference — cm	103.9±15.2	103.8±15.4
Body-mass index‡	31.0±6.2	31.0±6.2
Blood pressure — mm Hg		
Systolic	145.3±18.4	145.4±18.1
Diastolic	80.1±10.8	80.0±10.7
Pulse — beats/min	70.5±10.9	70.3±11.1
Estimated glomerular filtration rate — ml/min/1.73 m <sup>2</sup> of body-surface area§	78.9±21.2	79.0±21.5
Serum values¶		
Creatinine — mg/dl	1.0±0.3	1.0±0.3
Glucose — mg/dl	127.9±47.4	127.0±45.8
Potassium — mmol/liter	4.3±0.4	4.3±0.4
Total cholesterol — mg/dl	184.9±40.5	184.1±39.3
High-density lipoprotein cholesterol — mg/dl	49.6±14.1	49.5±14.1
Previous antihypertensive treatment — no. (%)		
No. of agents		
0	169 (2.9)	153 (2.7)
1	1312 (22.8)	1279 (22.2)
2	2116 (36.8)	2047 (35.5)
≥3	2147 (37.4)	2283 (39.6)
Lipid-lowering agents	3851 (67.0)	3971 (68.9)
Beta-blockers	2675 (46.6)	2807 (48.7)
Antiplatelets agents	3710 (64.6)	3735 (64.8)

**Table 1. (Continued.)**

Characteristic	Benazepril–Amlodipine Group (N=5744)	Benazepril–Hydrochlorothiazide Group (N=5762)
Risk factors — no. (%)		
Previous myocardial infarction	1337 (23.3)	1372 (23.8)
Previous stroke	762 (13.3)	736 (12.8)
Previous hospitalization for unstable angina	653 (11.4)	671 (11.6)
Diabetes mellitus	3478 (60.6)	3468 (60.2)
Renal disease <sup>  </sup>	352 (6.1)	353 (6.1)
Estimated glomerular filtration rate <60	1047 (18.2)	1030 (17.9)
Previous coronary revascularization	2044 (35.6)	2073 (36.0)
Coronary-artery bypass grafting	1248 (21.7)	1197 (20.8)
Percutaneous coronary intervention	1055 (18.4)	1123 (19.5)
Left ventricular hypertrophy <sup>**</sup>	763 (13.3)	758 (13.2)
Other		
Current smoking	641 (11.2)	658 (11.4)
Dyslipidemia	4221 (73.5)	4319 (75.0)
Atrial fibrillation	376 (6.5)	403 (7.0)

\* Plus-minus values are means  $\pm$ SD.

† Race or ethnic group was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The estimated glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease (MDRD) Study equation.

¶ To convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for glucose to millimoles per liter, multiply by 0.05551; to convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

|| Renal disease was determined by the investigator on the basis of either a serum creatinine level of more than 1.5 mg per deciliter (133  $\mu$ mol per liter) in women or greater than 1.7 mg per deciliter (150  $\mu$ mol per liter) in men or the presence of macroalbuminuria, confirmed on two separate occasions at least 48 hours apart.

\*\* Left ventricular hypertrophy was determined on the basis of electrocardiographic findings (central reading).

ary value was determined according to the original trial design, since this was a more cautious approach with regard to potential stopping.)

The analysis of the primary end point included all patients, according to the intention-to-treat principle. Kaplan–Meier methods were used to construct cumulative time-to-event curves for the two groups, and the primary comparison was based on a log-rank test. Univariate Cox regression (which included only treatment in the model) was performed for the time to the first primary event in order to obtain the point estimate and confidence interval for the hazard ratio between the two treatment groups. We concluded that the benazepril–amlodipine combination had superior efficacy if the log-rank test was significant and the hazard ratio favored this combination. Separate analyses were also performed for each component of the primary end point, without censoring for previous primary events, and each was

presented as a sensitivity analysis of the primary outcome.

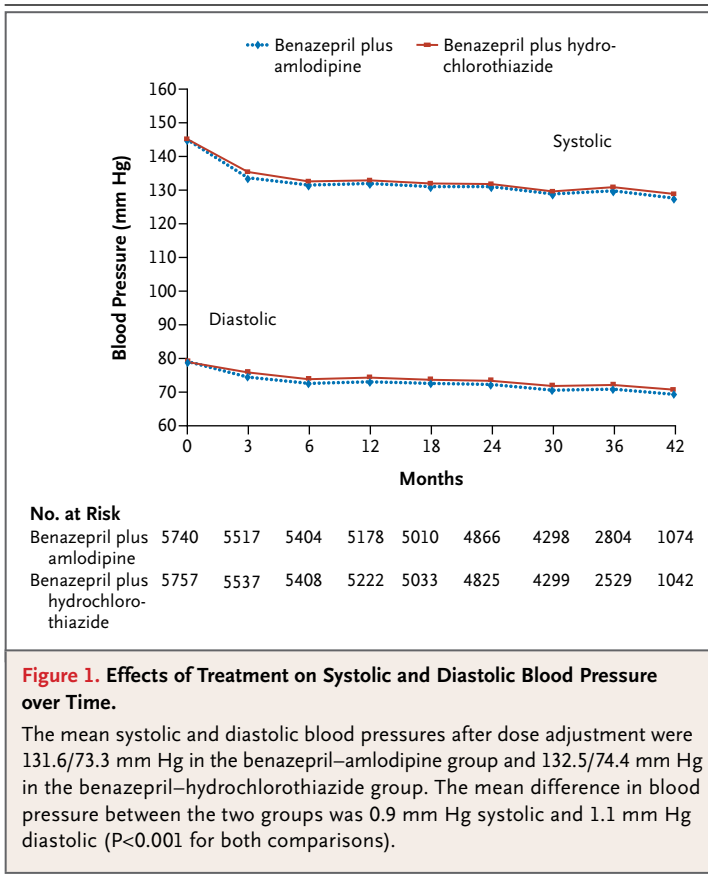
Secondary and other efficacy end points were analyzed with the use of a similar log-rank test and univariate Cox regression analyses.

## RESULTS

### PATIENTS

Between October 2003 and May 2005, a total of 13,782 patients were screened, and 11,506 were assigned to a study group — 5744 patients to the benazepril–amlodipine group and 5762 to the benazepril–hydrochlorothiazide group.

Table 1 lists the baseline characteristics of the patients randomly assigned to the two groups, including key risk factors and previous cardiovascular and renal events. There were no significant differences in baseline characteristics between the patients in the two treatment groups.



**Figure 1. Effects of Treatment on Systolic and Diastolic Blood Pressure over Time.**

The mean systolic and diastolic blood pressures after dose adjustment were 131.6/73.3 mm Hg in the benazepril–amlodipine group and 132.5/74.4 mm Hg in the benazepril–hydrochlorothiazide group. The mean difference in blood pressure between the two groups was 0.9 mm Hg systolic and 1.1 mm Hg diastolic ( $P < 0.001$  for both comparisons).

The mean age of the patients in this trial was 68.4 years, and 39.5% of the patients were women. Approximately half of the study population (49.6%) had a body-mass index (the weight in kilograms divided by the square of the height in meters) greater than 30, and the mean body-mass index was 31. Of note, 60.4% of the patients had a diagnosis of diabetes.

The study medication was administered in all but nine patients (seven in the benazepril–amlodipine group and two in the benazepril–hydrochlorothiazide group). The mean follow-up was 35.7 months for the benazepril–amlodipine group and 35.6 months for the benazepril–hydrochlorothiazide group. The mean duration of treatment exposure was 30.0 months and 29.3 months for the patients in the two groups, respectively. For the patients in the benazepril–amlodipine group, the mean daily dose was 36.3 mg of benazepril and 7.7 mg of amlodipine, and the median daily dose was 39.4 mg and 8.9 mg, respectively; for patients in the benazepril–hydrochlorothiazide group, the mean daily dose was 36.1 mg of benazepril and 19.3 mg of hydrochlorothiazide, and the median

daily dose was 39.4 mg and 22.1 mg, respectively. By the end of the 6-month dose-adjustment period, 60.9% of the patients in the benazepril–amlodipine group were receiving the maximum dose of 40 mg of benazepril and 10 mg of amlodipine, and 60.3% of the patients in the benazepril–hydrochlorothiazide group received the maximum dose of 40 mg of benazepril and 25 mg of hydrochlorothiazide. In each group, 32.3% of the patients received approved antihypertensive agents in addition to the highest dose of study medication after 1 year in the study. At the completion of the trial, 143 participants did not provide information about vital status. Of these, 5 withdrew their consent and 21 were from sites that were closed before the end of the trial (10 from sites affected by Hurricane Katrina), leaving 117 subjects (1.0%) who were lost to follow-up.

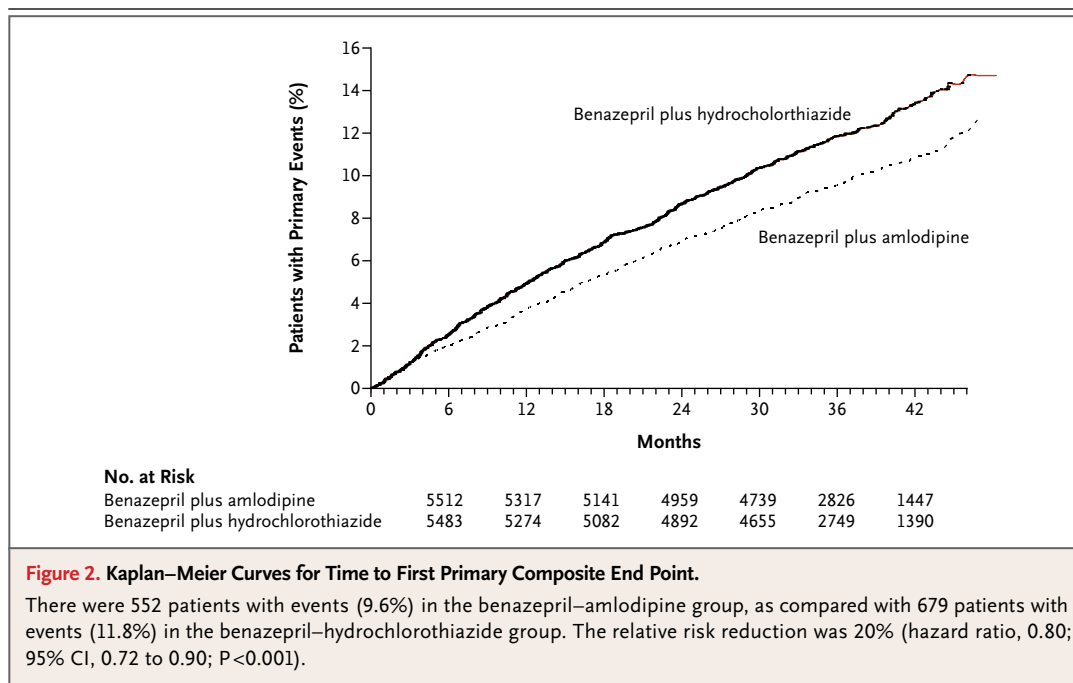
#### BLOOD PRESSURE

At the time of enrollment in the trial, most patients (97.2%) were being treated for hypertension, and 74.7% were taking two or more classes of antihypertensive medications, though only 37.3% had blood pressure below 140/90 mm Hg at baseline (Table 1).

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 (Fig. 1). Mean blood pressure after dose adjustment was 131.6/73.3 mm Hg in the benazepril–amlodipine group (5463 patients) and 132.5/74.4 mm Hg in the benazepril–hydrochlorothiazide group (5474 patients). The mean difference in blood pressure between the two groups was 0.9 mm Hg systolic and 1.1 mm Hg diastolic ( $P < 0.001$  for both systolic and diastolic pressures). Blood pressure control, which was defined as a blood pressure of less than 140/90 mm Hg, was attained in an average of 75.4% of patients in the benazepril–amlodipine group and 72.4% in the benazepril–hydrochlorothiazide group.

#### PRIMARY AND PRESPECIFIED SECONDARY STUDY END POINTS

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



**Figure 2. Kaplan–Meier Curves for Time to First Primary Composite End Point.**

There were 552 patients with events (9.6%) in the benazepril–amlodipine group, as compared with 679 patients with events (11.8%) in the benazepril–hydrochlorothiazide group. The relative risk reduction was 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90;  $P < 0.001$ ).

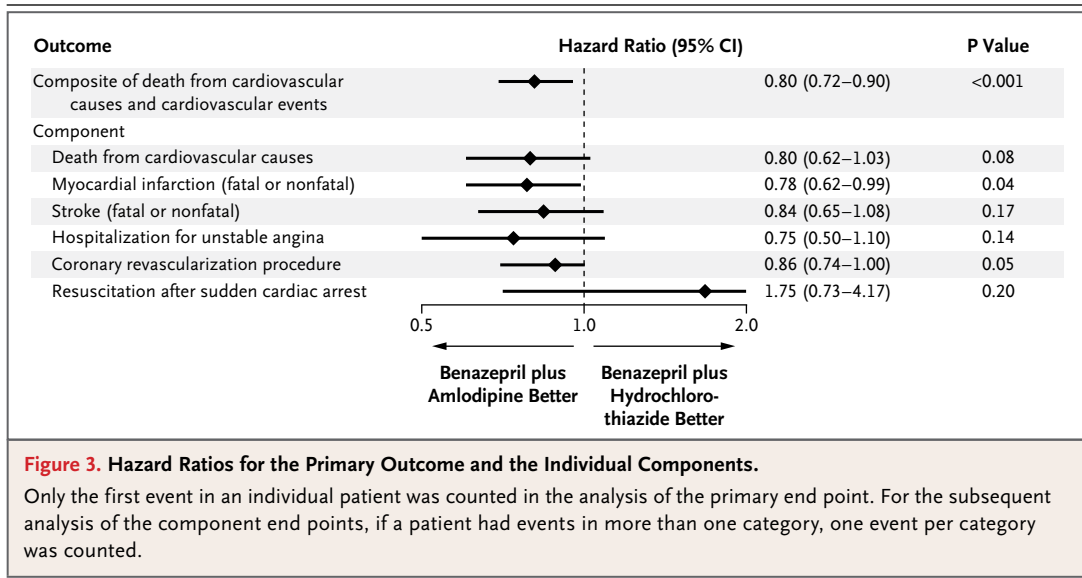
the study. For the analysis used by the data and safety monitoring committee, the boundary value for the z-score interim analysis was 2.74, corresponding to a nominal alpha level of approximately 0.0062 and a cumulative level (based on the alpha-spending function) of 0.0074. The z score for the October 2007 interim analysis was 2.92. Accordingly, the executive committee terminated the trial. However, by January 2008, when all patients had been called back for a final visit within 3 months of the data and safety monitoring committee's recommendation, 1231 patients had reached a primary end point, representing 75.0% of the projected number of patients with primary end points.

The time to the first primary end point in each of the two treatment groups is shown in Figure 2. The results of the sensitivity analysis of the primary end point are shown in Figure 3. 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;  $P < 0.001$ ). The primary event rates per 1000 patient-years were 32.3 in the benazepril–amlodipine group and 39.7 in the benazepril–hydrochlorothiazide group. For the secondary end point of death from cardiovascular causes plus nonfatal myocar-

dial 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 (Table 2), representing an absolute risk reduction of 1.7 percentage points and a relative risk reduction of 17.4% (hazard ratio, 0.83;  $P = 0.002$ ).

#### OTHER PRESPECIFIED END POINTS

There were fewer fatal and nonfatal myocardial infarctions in the benazepril–amlodipine group than in the benazepril–hydrochlorothiazide group (absolute risk reduction, 0.6 percentage points; relative risk reduction, 21.5%;  $P = 0.04$ ) and fewer coronary revascularization procedures (absolute risk reduction, 0.9 percentage points; relative risk reduction, 13.9%;  $P = 0.04$ ). The rates of adjudicated hospitalization for congestive heart failure did not differ between the two study groups (1.7% in both groups; hazard ratio for the benazepril–amlodipine group, 1.04;  $P = 0.77$ ) (Table 2). Moreover, when heart failure events that required hospitalization were added to the primary composite end point, the event rate was 10.7% in the benazepril–amlo-



dipine group versus 12.8% in the benazepril–hydrochlorothiazide group, representing an absolute risk reduction of 2.1 percentage points and a relative risk reduction of 17.2% (hazard ratio, 0.83,  $P<0.001$ ). Resuscitation after sudden cardiac arrest occurred in only 22 patients — 0.2% of the patients in the benazepril–amlodipine group and 0.1% of the patients in the benazepril–hydrochlorothiazide group (hazard ratio for the benazepril–amlodipine group, 1.75;  $P=0.20$ ). Table 2 shows the consistency of the primary outcome for prespecified subgroups (according to age, sex, and presence or absence of diabetes).

#### SAFETY AND ADVERSE EVENTS

The incidence of prespecified adverse events, serious adverse events, and drug-related serious adverse events is shown in Table 3. The cumulative rate of discontinuation of a study drug, excluding discontinuation due to death, was similar in the two groups (28.8% and 31.2% in the benazepril–amlodipine group and the benazepril–hydrochlorothiazide group, respectively). Within the first 90 days of treatment, 8.8% of all patients discontinued treatment (8.5% in the benazepril–amlodipine group and 9.1% in the benazepril–hydrochlorothiazide group). The most common reasons for discontinuation of the study medication were an adverse event or laboratory-test abnormality; 17.6% of the patients in the benazepril–amlodipine group and 18.4% of those in the benazepril–hydrochlorothiazide group discontinued the study medication for these reasons, with 13.4% and 14.3%

of patients, respectively, discontinuing treatment owing to adverse events alone. The number of patients who permanently withdrew from the study was also similar in the two groups (15.1% in the benazepril–amlodipine group and 15.4% in the benazepril–hydrochlorothiazide group). Withdrawal of consent by the patient was the principal reason for premature withdrawal from the study (8.6% in the benazepril–amlodipine group and 8.6% in the benazepril–hydrochlorothiazide group).

#### DISCUSSION

This trial shows that combination treatment with benazepril plus amlodipine is superior to treatment with benazepril plus hydrochlorothiazide in reducing the risk of cardiovascular events and of death among high-risk patients with hypertension. The use of combination therapy as the initial trial intervention provides evidence that has implications for clinical management of hypertension.

The high rate of blood-pressure control with both combination strategies is a compelling feature of this trial. The difference in systolic blood pressure between the two groups was less than 1 mm Hg over the course of the trial.

When combination therapies are needed, often for high-risk patients, JNC 7 guidelines indicate a strong preference for a thiazide diuretic. The superiority of the amlodipine-based therapy with respect to the clinical outcomes in this trial suggests that approaches that do not include thia-



**Table 2. Hazard Ratios for Primary, Secondary, and Other Prespecified End Points, and Results of the Subgroup Analysis.**

End Point	Benazepril–Amlodipine Group (N=5744)	Benazepril–Hydrochlorothiazide Group (N=5762)	Hazard Ratio (95% CI)*	P Value†
<b>Primary</b>				
Composite of cardiovascular events and death from cardiovascular causes — no. (%)	552 (9.6)	679 (11.8)	0.80 (0.72–0.90)	<0.001
Individual component — no (%)				
Death from cardiovascular causes	107 (1.9)	134 (2.3)	0.80 (0.62–1.03)	0.08
Fatal and nonfatal myocardial infarction	125 (2.2)	159 (2.8)	0.78 (0.62–0.99)	0.04
Fatal and nonfatal stroke	112 (1.9)	133 (2.3)	0.84 (0.65–1.08)	0.17
Hospitalization for unstable angina	44 (0.8)	59 (1.0)	0.75 (0.50–1.10)	0.14
Coronary revascularization procedure	334 (5.8)	386 (6.7)	0.86 (0.74–1.00)	0.04
Resuscitation after sudden cardiac arrest	14 (0.2)	8 (0.1)	1.75 (0.73–4.17)	0.20
Subgroup — no. with primary end point/total no. (%)				
Sex				
Male	365/3448 (10.6)	461/3515 (13.1)	0.80 (0.69–0.91)	0.001
Female	187/2296 (8.1)	218/2246 (9.7)	0.83 (0.68–1.01)	0.06
Age				
≥65 yr	386/3813 (10.1)	474/3827 (12.4)	0.81 (0.71–0.92)	0.002
≥70 yr	260/2363 (11.0)	323/2340 (13.8)	0.79 (0.67–0.93)	0.004
Presence of diabetes				
Yes	307/3478 (8.8)	383/3468 (11.0)	0.79 (0.68–0.92)	0.003
No	245/2266 (10.8)	296/2294 (12.9)	0.82 (0.69–0.97)	0.02
<b>Secondary and other</b>				
Composite of cardiovascular events — no. (%)	494 (8.6)	592 (10.3)	0.83 (0.73–0.93)	0.002
Composite of death from cardiovascular events, nonfatal myocardial infarction, and nonfatal stroke — no. (%)	288 (5.0)	364 (6.3)	0.79 (0.67–0.92)	0.002
Death from any cause — no. (%)	236 (4.1)	262 (4.5)	0.90 (0.76–1.07)	0.24
Hospitalization for congestive heart failure — no. (%)	100 (1.7)	96 (1.7)	1.04 (0.79–1.38)	0.77
Primary end point plus hospitalization for congestive heart failure — no. (%)	617 (10.7)	738 (12.8)	0.83 (0.74–0.92)	0.0005

\* Hazard ratios are for the benazepril–amlodipine group.

† The P values are derived from a log-rank test.

zides may be better for some populations. Nevertheless, these results should not cast doubt on the efficacy of diuretics in reducing the risk of cardiovascular events. In the recent Hypertension in the Very Elderly Trial (HYVET) (ClinicalTrials.gov number, NCT00122811), mortality was reduced with therapy that combined a diuretic with an ACE inhibitor as compared with placebo.<sup>14</sup> Certainly, thiazide-like diuretics have been shown to be effective in preventing cardiovascular events in meta-analyses of clinical trials involving patients with hypertension.<sup>15,16</sup>

Our 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) (NCT00000542).<sup>17</sup> 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 this trial and those of ALLHAT is that chlorthali-

**Table 3. Results of Prespecified Safety Analysis.\***

Adverse Event	Any		Serious		Drug-Related Serious	
	Benazepril– Amlodipine Group (N=5744)	Benazepril– Hydrochlorothiazide Group (N=5762)	Benazepril– Amlodipine Group (N=5744)	Benazepril– Hydrochlorothiazide Group (N=5762)	Benazepril– Amlodipine Group (N=5744)	Benazepril– Hydrochlorothiazide Group (N=5762)
	<i>number (percent)</i>					
Dizziness	1189 (20.7)	1461 (25.4)	18 (0.3)	31 (0.5)	2 (<0.1)	5 (0.1)
Peripheral edema	1792 (31.2)	772 (13.4)	10 (0.2)	8 (0.1)	4 (0.1)	2 (<0.1)
Dry cough	1177 (20.5)	1220 (21.2)	7 (0.1)	7 (0.1)	3 (0.1)	3 (0.1)
Angioedema	53 (0.9)	34 (0.6)	7 (0.1)	13 (0.2)	2 (<0.1)	5 (0.1)
Hyperkalemia	34 (0.6)	33 (0.6)	10 (0.2)	11 (0.2)	6 (0.1)	6 (0.1)
Hypokalemia	3 (0.1)	17 (0.3)	2 (<0.1)	12 (0.2)	1 (<0.1)	0
Hypotension	142 (2.5)	208 (3.6)	22 (0.4)	30 (0.5)	6 (0.1)	9 (0.2)

\* Safety data were ascertained on the basis of reports by participants or investigators, discovered on physical examination or report by the central laboratory.

done (which was used in ALLHAT) may differ from hydrochlorothiazide (which was used in the ACCOMPLISH trial) 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.

Although one might argue that 25 mg of hydrochlorothiazide, a dose that reflects broad clinical practice, was not sufficient to provide an optimal cardiovascular benefit, since the systolic blood-pressure levels in the two treatment groups over the course of our trial differed by less than 1 mm Hg, the dose of hydrochlorothiazide was clinically adequate. Although clinical trial data have not established outcome benefits of diuretics beyond their blood-pressure-lowering effects, recent studies involving animals suggest that diuretics have limited, if any, nonhemodynamic vascular benefits.<sup>18</sup>

The composite primary end point in our trial was intentionally broad in order to enhance the study's power to test our hypothesis. The end point included coronary revascularization procedures and hospitalization for unstable angina, the necessity for which may depend, at least in part, on subjective judgments by clinicians and investigators. Therefore, we also analyzed the composite end point (excluding these components) of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke. Judged by this end

point, the combination of benazepril and amlodipine resulted in a highly significant 21.2% reduction in risk ( $P=0.002$ ). Although fatal heart-failure events were part of the primary end point, hospitalization for heart failure was not. However, when hospitalization for heart-failure events is factored into the primary end point, the overall study results remain highly significant in favor of benazepril–amlodipine. Of note, the overall primary end point was not driven by any one outcome (Fig. 3).

Many participants in our trial had previous coronary disease and diabetes and thus are not fully representative of the broad population of patients with hypertension. Furthermore, the diuretic-based combination may not have been the optimal treatment for patients with diabetes. However, the ALLHAT study showed that diuretic-based therapy had the same relative benefits in patients with diabetes as in patients without diabetes.<sup>19</sup> These limitations temper the conclusions of the ACCOMPLISH trial.

Our 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. Thus, our findings may increase the options for combination treatment to reduce the risk of cardiovascular events among patients with hypertension.

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#### APPENDIX

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