Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension

TO THE EDITOR: In their report on the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, Jamerson et al. (Dec. 4 issue) challenge current treatment recommendations for hypertension. In the study, they reported that the use of combined therapy with an angiotensin-converting–enzyme (ACE) inhibitor, benazepril, plus a calcium-channel blocker, amlodipine, was superior to that of benazepril plus a thiazide diuretic, hydrochlorothiazide, in reducing cardiovascular events. However, an analysis that is based on potassium levels or the presence of hypokalemia may explain differences between the two study groups. In the Systolic Hypertension in the Elderly Program (SHEP) trial, participants receiving the diuretic chlorthalidone who had hypokalemia had a risk of cardiovascular events that was similar to the risk among those receiving placebo.

The choice of hydrochlorothiazide in the ACCOMPLISH trial may have had an effect on the results. In the Multiple Risk Factor Intervention Trial (MRFIT), the hypertension protocol was amended to recommend the use of chlorthalidone rather than hydrochlorothiazide as the initial diuretic for the intervention group, based in part on an unfavorable trend in mortality in clinics using predominantly hydrochlorothiazide. Switching to chlorthalidone at these clinics was associated with a trend toward improved outcomes.

Finally, we believe there is a need to better define the population that was tested in studies such as the ACCOMPLISH trial. For example, it is apparent that the response of a patient with hypertension to therapy may differ on the basis of renin levels. Perhaps improving the phenotypic characterization during the screening and randomization of patients with the use of additional markers would yield more refined results.

David Parra, Pharm.D.
Robert Rosenstein, M.D.
Veterans Affairs Medical Center West Palm Beach
West Palm Beach, FL 33410-6400
david.parra@va.gov

3. Bartsch GE, Broste SK, Grandits GA, Grimm RH, Neaton JD, Swendsen KH. Hydrochlorothiazide, chlorthalidone and mortal-
TO THE EDITOR: Rates of coronary-artery revascularization\(^1\) and angina\(^2\) are reduced with the use of calcium-channel blockers. In the ACCOMPLISH trial, revascularization procedures accounted for more than half the primary end points, with a relative risk reduction of 19.6% in the group of patients receiving benazepril plus amlodipine, as compared with those receiving benazepril plus hydrochlorothiazide. Almost half the patients had had a previous coronary-artery event.\(^3\) Furthermore, the withdrawal of calcium-channel blockers in the 36% of patients who were receiving such drugs at baseline, the lack of a washout phase,\(^3\) and the apparent exclusion of the use of calcium-channel blockers for symptomatic angina all might have played a part in the apparent efficacy of amlodipine.

The clinical implications of the ACCOMPLISH trial should be evaluated in the context of concomitant therapies. We would ask the authors to clarify whether the 47% of patients who were taking a beta-blocker at randomization continued to receive the drug, since in clinical practice that treatment is not recommended in high-risk patients. Furthermore, volume overload is a major contributor to hypertension,\(^4\) and the use of loop diuretics was permitted but was not reported. Were loop diuretics prescribed to more patients receiving amlodipine than those receiving hydrochlorothiazide? If so, the trial confirms the necessity of a diuretic in combination therapy.

Martin H. Strauss, M.D.
Jordan Weinstein, M.D.
Saint Michael’s Hospital
Toronto, ON M5B 1W8, Canada

Gary E. Newton, M.D.
Mount Sinai Hospital
Toronto, ON M5G 1X5, Canada


TO THE EDITOR: The results of the ACCOMPLISH trial appear to be inconsistent with those of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)\(^5\) (Table 1). Although the amlodipine dose in the ACCOMPLISH trial was similar to that associated with favorable outcomes in other trials,\(^1-3\) the hydrochlorothiazide dose was lower than the 25 to 50 mg per day (or equivalents such as 12.5 to 25 mg of chlorothalidone per day) used in trials demonstrating the beneficial effects of thiazides on cardiovascular disease.\(^1-3\) A significant though small difference in blood pressure measured in the clinic favored the benazepril–amlodipine group; 24-hour ambulatory pressures from the ACCOMPLISH trial are not yet available. Also, the authors do not provide data on the types and doses of additional antihypertensive agents that were prescribed during the study. Recommended supplementary drugs were beta-blockers and alpha-blockers, which have inferior effects on clinical outcomes.\(^3,4\) The results of the ACCOMPLISH trial may suggest that doses of thiazide-type diuretics that are equivalent to 25 mg or less of hydrochlorothiazide per day are less effective for the prevention of cardiovascular events than full doses of amlodipine or doses of diuretics used in previous trials.

Barry R. Davis, M.D., Ph.D.
University of Texas School of Public Health
Houston, TX 77030

Paul K. Whelton, M.D., M.Sc.
Loyola University Medical Center
Maywood, IL 60153

for the ALLHAT Collaborative Research Group

Dr. Davis reports having served as a consultant to BioMarin, GlaxoSmithKline, Procter and Gamble, and Takeda and reports holding equity interest in Amgen. No other potential conflict of interest relevant to this letter was reported.

1. 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
Correspondence


The Authors Reply: The ACCOMPLISH trial demonstrated the efficacy of benazepril plus amlodipine over benazepril plus hydrochlorothiazide in reducing cardiovascular outcomes in patients with hypertension. Parra and Rosenstein raise the possibility that hypokalemia might attenuate the benefits of the diuretic combination. However, we found no significant interaction between hypokalemia and cardiovascular events. On the basis of the choice of chlorthalidone over hydrochlorothiazide in MRFIT, they argue that our study should have considered chlorthalidone as the diuretic agent. The data in MRFIT were not definitive, and contemporary expert opinion continues to recommend “thiazide-like” diuretics. Hydrochlorothiazide is used by the vast majority of clinicians globally. Lastly, Parra and Rosenstein suggest the use of renin profiling. This test would not have provided guidance in a study comparing combination regimens, each of which contained agents that addressed both the renin and volume components of hypertension.

Table 1. A Comparison of Outcomes in the ACCOMPLISH Trial and the ALLHAT Trial.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ACCOMPLISH</th>
<th>ALLHAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide, 12.5-25 mg, plus Benazepril, 40 mg (N = 5762)</td>
<td>Amlodipine, 5-10 mg, plus Benazepril, 40 mg (N = 5744)</td>
<td>Chlorthalidone, 12.5-25 mg (N = 15,255)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>no. (%)</td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, stroke, hospitalization for angina, and cardiac revascularization</td>
<td>679 (11.8)</td>
<td>552 (9.6)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, and stroke</td>
<td>364 (6.3)</td>
<td>288 (5.0)</td>
</tr>
<tr>
<td>Hospitalization for fatal heart failure</td>
<td>96 (1.7)</td>
<td>100 (1.7)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, stroke, and hospitalization for heart failure</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, stroke, hospitalization for angina, cardiac revascularization, and hospitalization for heart failure</td>
<td>738 (12.8)</td>
<td>617 (10.7)</td>
</tr>
<tr>
<td>Fatal and nonfatal myocardial infarction</td>
<td>159 (2.8)</td>
<td>125 (2.2)</td>
</tr>
</tbody>
</table>

* The follow-up periods were 3 years in the ACCOMPLISH trial and 4.9 years in the ALLHAT trial. NA denotes not available.
† In the ACCOMPLISH trial, this category included resuscitation after sudden cardiac arrest.
‡ In the ALLHAT study, this category included silent myocardial infarction.
§ This category was also an end point of the Blood Pressure Lowering Treatment Trialists’ Collaboration.

Specifically, beta-blockers were continued in all patients for whom these drugs were indicated. Patients who were known to require either calcium-channel blockers or diuretics were excluded from the study. The use of furosemide in our trial was infrequent but was slightly lower in the hydrochlorothiazide group (5%) than in the amlopidine group (8%).

Davis and Whelton assert that the findings of our study are inconsistent with those of ALLHAT.2 The two trials were fundamentally different. ALLHAT was primarily a comparison of monotherapies, whereas our trial was a comparison of treatment combinations. Table 1 accompanying their letter indicates a strong difference in outcomes between the studies, with event rates in our trial only about half those in ALLHAT, despite the higher baseline risk profile of the patients in our study. This difference might reflect the overall lower achieved blood pressures in our trial, as well as the potential superiority of well-chosen combination therapies in optimizing cardiovascular protection. With respect to the query about the adequacy of the dose of hydrochlorothiazide in our study, we report levels of achieved blood pressure at the end of the dosing interval; by this measure, the hydrochlorothiazide group had lower systolic blood pressure over the entire a 24-hour period. However, we agree with Davis and Whelton that the 24-hour blood-pressure data from our trial will be definitive in determining the adequacy of the dose of hydrochlorothiazide.

We confirm our original conclusion that our trial indicates the benefit of combining amlodipine with a blocker of the renin-angiotensin system in high-risk patients with hypertension.

Kenneth A. Jamerson, M.D.
University of Michigan School of Medicine
Ann Arbor, MI 48106
emarshal@umich.edu

Michael A. Weber, M.D.
SUNY Downstate Medical College
Brooklyn, NY 11203


TO THE EDITOR: Merritt et al. (Dec. 18 issue)1 report finding a relation between prognosis and the expression of Dicer and Drosha in women with ovarian carcinoma of unstated histologic subtype. The histologically defined subtypes of ovarian carcinoma (high-grade serous, clear cell, endometrioid, mucinous, and low-grade serous) are distinct diseases that can be reproducibly diagnosed2 and that vary with respect to characteristics of the precursor lesions, the genetic events during oncogenesis,3 outcome,2,4 and response to chemotherapy.4 These subtypes have distinct biomarker-expression profiles.5 In cohorts of patients with ovarian carcinoma consisting of a mixture of subtypes, biomarkers preferentially expressed by specific subtypes often have prognostic or other clinical associations for the entire cohort that are not significant after correction for subtype. We therefore ask whether Dicer and Drosha expression levels correlate with histologic subtype and whether their prognostic significance and association with tumor stage and optimal type of cytoreduction hold true within each subtype.

Martin Köbel, M.D.
University of British Columbia
Vancouver, BC V5Z 1M9, Canada
C. Blake Gilks, M.D.
Vancouver General Hospital
Vancouver, BC V5Z 1M9, Canada
David G. Huntsman, M.D.
British Columbia Cancer Agency
Vancouver, BC V5Z 4E6, Canada
dhuntsma@bccancer.bc.ca