Comparative Effectiveness in Hypertension: What Can We ACCOMPLISH?

Jamerson K, Weber MA, Bakris GL, et al; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417–28.

Study Overview

Objective. To compare combination therapy with an angiotensin-converting enzyme (ACE) inhibitor/dihydropyridine calcium channel blocker (CCB; benazepril/amlodipine) or an ACE inhibitor/thiazide diuretic (benazepril/hydrochlorothiazide) for reducing cardiovascular outcomes in high-risk hypertensive patients.

Design. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a multicenter, randomized, double-blind trial.

Setting and participants. 11,506 patients in 5 countries (Norway, Sweden, Denmark, Finland, U.S.) aged ≥ 55 years with hypertension (mean systolic blood pressure, 145 mm Hg) and at high risk for cardiovascular events (documented history of coronary events, stroke, renal disease, or target organ damage) were randomized to either 20 mg benazepril/5 mg amlodipine (n = 5744) or 20 mg benazepril/12.5 mg hydrochlorothiazide (n = 5762) once daily. One month after randomization, the dose of benazepril was increased to 40 mg in both groups, and amlodipine and hydrochlorothiazide could be increased to 10 mg and 25 mg, respectively, if necessary to achieve target blood pressure.

Main outcome measures. The primary endpoint was the composite of cardiovascular events (defined as nonfatal myocardial infarction [MI], nonfatal stroke, hospitalization for unstable angina, resuscitation after sudden cardiac arrest, or coronary revascularization) and death from cardiovascular causes. Secondary endpoints were a composite of cardiovascular events (the primary endpoint excluding fatal events) and a composite of death from cardiovascular causes, nonfatal MI, and nonfatal stroke.

Main results. Baseline characteristics between the benazepril/amlodipine and benazepril/hydrochlorothiazide groups were similar. The data and safety monitoring committee ended the trial early after a mean of 30 months of treatment based on an observed difference in the primary endpoints between the 2 groups. Primary endpoints were obtained for 1231 patients, representing 75% of the projected number. There were 552 events (9.6%) in the benazepril/amlodipine group versus 679 events (11.8%) in the benazepril/hydrochlorothiazide group, indicating a relative risk reduction (RR) of 19.6% (hazard ratio [HR], 0.80 [95% confidence interval, 0.72–0.90]; $P < 0.001$). For secondary endpoints including death from cardiovascular causes plus nonfatal MI or stroke, there was a relative RR of 21.2% (HR, 0.79; P = 0.002), with 288 events (5%) in the benazepril/amlodipine group compared with 364 events (6.3%) in the benazepril/hydrochlorothiazide group. Incidence of cardiovascular events (secondary endpoint) was 494 events (8.6%) in the benazepril/amlodipine group compared with 592 events (10.3%) in the benazepril/hydrochlorothiazide group (relative RR, 17.4%; HR, 0.83; P = 0.002). Both groups had similar baseline blood pressures and reductions in blood pressure with treatment. After dose adjustment, the mean difference

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in blood pressure between the groups was 0.9 mm Hg systolic and 1.1 mm Hg diastolic ($P < 0.001$ for both systolic and diastolic pressures).

Conclusion. In high-risk hypertensive patients, benazepril/amlodipine is superior to benazepril/hydrochlorothiazide for reducing cardiovascular events.

Commentary

Current treatment guidelines for hypertension defined by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [1] and the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology [2] recommend a combination of 2 or more drugs as first-line therapy, especially for high-risk patients such as those with diabetes or chronic kidney disease. A growing body of evidence supports fixed-dose combination therapy as optimal treatment for hypertension; however, evidence on the comparative effectiveness of various treatment combinations is lacking. Given this uncertainty, studies that directly compare treatment combinations are the best indicators of efficacy.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial (ALLHAT) is a landmark hypertension comparative effectiveness study. In ALLHAT, the majority of participants (60%) required a combination of 2 or more drugs to control blood pressure to less than 140/90 mm Hg as compared with 30% of participants who achieved blood pressure control with monotherapy. However, no difference was found between each of 3 monotherapies (ie, chlorthalidone, lisinopril, and amlodipine) in preventing the primary outcome of combined nonfatal MI and coronary heart disease death. A second hypertension comparative effectiveness study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), found no significant differences in fatal coronary heart disease and nonfatal MI between patients receiving a combination of amlodipine and perindopril versus a combination of atenolol and bendroflumethiazide [3]. The ACCOMPLISH trial was the first to compare an ACE inhibitor with either a CCB or diuretic in high-risk hypertensive patients for reducing cardiovascular events. Although previous studies demonstrated the success of combination therapy in lowering blood pressure, the ACCOMPLISH trial yielded significant differences in primary cardiovascular events.

Data from randomized trials such as ACCOMPLISH and ALLHAT are invaluable, but unfortunately such head-to-head studies are few and far between. Furthermore, research is limited by the sample sizes required to find clinically and statistically significant differences between treatment regimens, the duration of follow-up required (ACCOMPLISH, 3 years; ALLHAT, 8 years), and the cost and complexity of actually completing such a trial. Hence, these studies tend to avoid many subgroups, long-term outcomes, or hard-to-measure events such as adverse effects. In this void, well-designed observational studies have the potential to fill evidence gaps, which might be especially helpful in the case of antihypertensive medications, as there are many possible treatment combinations. Even though observational studies present a greater possibility for bias, statistical models including propensity scores, marginal structural models, and instrumental variable models have been developed to bolster causal inference. Planned and in-progress observational studies will be useful in hypertension comparative effectiveness research; several large-scale studies sponsored by the Agency for Healthcare Research and Quality are underway [4]. Evidence from both randomized and observational studies will ultimately contribute to a broader clinical understanding of hypertensive treatments.

Applications for Clinical Practice

Although JNC7 first recommends a thiazide diuretic in combination with another class of antihypertensive medication to achieve blood pressure control, multiple clinical trials have shown that combination therapy with a renin-angiotensin-aldosterone-system inhibitor plus CCB in particular is associated with significant blood pressure lowering and control [5]. The ACCOMPLISH trial provides definitive evidence that allows for greater flexibility when choosing initial drugs, increasing options for combination treatment to reduce important cardiovascular events. Although side effects, comorbidities, and other clinical factors should be considered in every clinical decision regarding antihypertensive therapy, look for a larger role for renin-angiotensin-aldosterone-system inhibitor plus CCB combination therapy as well as updates to clinical guidelines in the near future.

—Review by Jennifer L. Quon (New York University, New York, NY) and Nirav R. Shah, MD, MPH

References

1. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.
2. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007;28:1462–536.
3. Chobanian AV. Does it matter how hypertension is controlled

[editorial]? N Engl J Med 2008;359:2485–8.
4. Addressing knowledge gaps in the treatment of hypertension using ACE/ARB therapies. Available at http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=71. Accessed 9 Jan 2009.
5. Kjeldsen SE, Weber M, Oparil S, Jamerson KA. Combining RAAS and calcium channel blockade: ACCOMPLISH in perspective. Blood Press 2008;17:260–9.

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