SJHG Heartbeat

**Number 126** **May 2008**

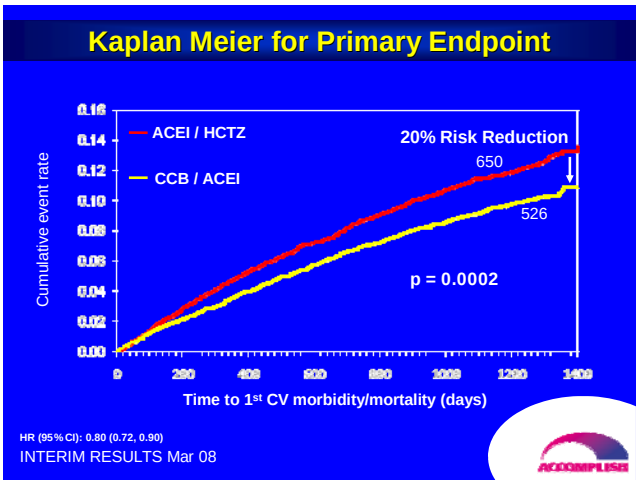
# Principal Disease State Leading to Number One Cause of Death

Hypertension, which affects approximately 50 million people in the United States and an estimated 1 billion people worldwide with a direct causal relation to coronary artery disease (CAD)—the principal disease state leading to the number one cause of death—is a very important topic. Since May is National High Blood Pressure Month, this *Heartbeat* will present some new and exciting data on hypertension and review recent guideline recommendations emphasizing the difficult job ahead of us.

## Clear Data with a Clear Message — Lotrel is good for HBP

New data from the **ACCOMPLISH** trial (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) presented at the **American College of Cardiology (ACC) 2008 Scientific Sessions**, raised quite a stir. This major morbidity and mortality trial showed that a single-tablet dual-mechanism therapy initiated in high-risk hypertensive patients significantly reduced the risk of morbidity and mortality by 20% compared with conventional therapy. (Figure 1.)[1] The trial, which was stopped prematurely at 3 years, compared the effects of two forms of antihypertensive combination therapies on major fatal and nonfatal cardiovascular (CVD) events. Treatment with the angiotensin-converting enzyme (ACE) inhibitor **benazepril** plus the calcium-channel blocker **amlodipine (Lotrel)** was more effective than the ACE inhibitor plus diuretic.

**Figure 1. Morbidity, Mortality Benefits in ACCOMPLISH.**




**ACCOMPLISH** compared the effects of two forms of antihypertensive combination therapies in 11,400 men and women aged 55 years or older who had systolic BP ≥ 160 mm Hg or were currently on antihypertensive therapy and who had evidence of CVD, renal disease or target-organ damage. Patients enrolled in the trial were obese, 60% had diabetes mellitus, and nearly all had been treated previously for hypertension. More than 70% had been treated with two or more hypertensive agents and just 37.5% of patients had their BP controlled to < 140/90 mm Hg at baseline, the currently recommended target of the **Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure** seventh report (JNC 7). All patients stopped their medication and, without a washout period, were randomized to combination

treatment with benazepril + hydrochlorothiazide or amlodipine + benazepril.

At 36 months, BP levels were significantly improved, with almost 80% of patients in both treatment arms having BP levels < 140/90 mm Hg. Investigators report that combination treatment with benazepril plus amlodipine reduced CV morbidity and mortality [defined as CV death, fatal/nonfatal myocardial infarction (MI), fatal/nonfatal stroke, hospitalization for unstable angina, and coronary revascularization] by 20%, compared with those treated with benazepril plus a diuretic.

The average age of patients in the study was 68 and the oldest patient was 98 years old. Although hypotension might be a concern and can result in falls and fractures in elderly and/or frail patients, these problems weren't noted in ACCOMPLISH.

Based on the present guidelines, combination treatment for hypertension would normally include a diuretic as one of the two agents. Most experts believe that this data will alter the guidelines and favor amlodipine.

## You're never too old to Start Treatment for Hypertension

Findings from The Hypertension in the Very Elderly Trial (**HYVET**) randomized trial suggest that antihypertensive therapy lowers risk not only for stroke but also for death from any cause in adults aged 80 years or older.[2]

Controversy surrounds the role of antihypertensive therapy in the elderly. This study was designed to determine the relative benefits and risks of antihypertensive treatment in persons aged 80 years or older. Investigators randomized 3845 participants with systolic hypertension (>160 mm Hg) aged 80 years or older to receive indapamide (sustained release, 1.5 mg) or placebo, titrating with perindopril (2 mg or 4 mg) or placebo as necessary to achieve a target BP of 150/80 mm Hg.

At baseline, participants' mean age was about 84 years, their mean BP was 173/91 mm Hg, and few (12%) had a history of CVD. At a mean follow-up of 2.1 years, BP was lower in the active-treatment group than in the placebo group by 15.0/6.1 mm Hg. This difference was associated with a 30% reduction in fatal or nonfatal stroke (the primary outcome), a 39% reduction in the rate of death from stroke, a 21% reduction in all-cause mortality, a 23% reduction in CV mortality, and a 64% reduction in heart failure. Of note, fewer adverse events were reported in the active-treatment group than in the placebo group ($P$=0.001). The trial was halted early because of ethical concerns.

## Broaden lower BP targets for high-risk and established-CAD patients

A recent AHA scientific statement specifies BP targets in men and women with established coronary artery disease (CAD) or who are at high risk of developing CAD should be 130/80 mm Hg, lower than the 140/90 mm Hg specified in the JNC 7.[3] This is the first time the AHA has specifically tackled the topic of BP targets in the CAD population, despite the fact that the two conditions are pathophysiologically linked and constitute an "enormous public-health issue."

**Target BP.** The lower target of 130/80 mm Hg being used in patients with diabetes or chronic kidney disease (CKD), as presently recommended per JNC 7, should be broadened to all those with CAD or high CAD risk. The statement deals both with primary-prevention high CAD risk patients as well as patients with preexisting CAD in different forms: stable angina, unstable angina/non-ST-elevation MI, ST-elevation MI, and heart failure secondary to CAD. Patients in the high-risk category are defined as patients who also have diabetes, CKD, known CAD, a CAD-risk equivalent (carotid disease, peripheral artery disease, or abdominal aortic aneurysm), or a 10-year Framingham risk score ≥10% which would include all metabolic syndrome patients. These patients should all have their BP lowered to

<130/80 mm Hg, as should patients with preexisting CAD. In patients with heart failure, physicians should consider an even lower target of <120/80 mm Hg, although BP lowering should done cautiously.

**Lifestyle Modification.** Therapeutic lifestyle changes (TLC) including smoking cessation, weight loss, reduced sodium intake, moderation of alcohol consumption, exercise, and an overall healthy dietary pattern are appropriate for reducing the burden of hypertension in the population as a whole. These modalities aren't proven because of associated drug treatment issues, but a recent impressive diet study concluded that adherence to a DASH-style diet (a diet high in fruits and vegetables, including plant proteins, fiber, whole grains, nuts and low-fat dairy, red and processed meats, sweetened beverages, and sodium) is associated with a lower risk for CHD and stroke among 88,517 middle-aged women during 24 years of follow-up.[4] This study is evidence that **DASH-style diet is associated not only with reductions in BP, but also translates into reductions in CV events.**

**Drug Recommendations.** In contrast with recent European guidelines beta blockers (BBs) are no longer recommended for BP control in the primary-prevention group. There are lots of comparative clinical trails to show that for preventing both stroke and CAD complications, BBs are inferior to newer classes of drugs like ACE inhibitors, angiotensin receptor blockers (ARBs), or calcium-channel blockers (CCBs), so BBs were dropped out of the picture for prevention. But once there is established CAD, with symptoms like angina or acute MI, then BBs come right back to center stage.

Although drug treatment for primary prevention remains controversial, the authors found general consensus that the amount of BP reduction, rather than the choice of antihypertensive drug, is the major determinant of reducing CV risk — not being believers of effects of ACEs or ARBs *above and beyond* BP lowering. They concluded that there is sufficient evidence from comparative clinical trials to support the use of an ACE inhibitor or ARB, a CCB, or thiazide-type diuretic as first-line therapy, supplemented by a second drug if blood pressure control is not achieved with monotherapy. **The guidelines stress that most patients will require ≥ 2 drugs to reach goal and that when the BP is > 20/10 mm Hg above goal, physicians should think of using 2 drug combinations from the outset.**

## New guidelines aim to help in the identification and control of resistant hypertension

New guidelines from the American Heart Association (AHA) were released to help doctors and patients identify and control resistant hypertension—*a problem that effects 30% of the hypertensive population*. Individuals who are taking three or more drugs and still have high BP, as well as those who must take four or more drugs before they can get their BP controlled, suffer from resistant hypertension.

Successful treatment of resistant hypertension requires consideration of modifiable lifestyle factors (obesity, dietary salt intake, and alcohol use) that contribute to the problem, diagnosing and treating secondary causes, and using combination therapy, according to the guidelines, which were published online in *Hypertension* in April and will be in the June 2008 issue.

A number of noncardiac drugs raise BP and "should be avoided or withdrawn." They include selective cyclooxygenase-2 (COX-2) inhibitors and traditional nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin; amphetamines; oral contraceptives; erythropoietin; and even natural licorice and some herbal medications such as ephedra.

"Diuretics are often underused in people with resistant hypertension." The committee also said that "some patients may benefit from adding mineralocorticoid receptor antagonists (MRAs)

to their treatment regimens." These drugs "treat primary aldosteronism, which is found in about 20 percent of people with resistant hypertension." And for unknown reasons MRAs such as the very inexpensive generic spironolactone, benefit a significant number of resistant hypertensive patients, who don't have aldosteronism.

## Summary/ conclusions:

When people walk into your offices with systolic pressures between 130 and 140, most primary-care doctors and many cardiologists would believe that patient had normal BP and wouldn't require additional treatment. New data shows that, in fact, there is a great deal to be gained by treating those patients to lower levels (< 130/80). Some feel this goal should be lower.[5]

The *lower is better* mantra for LDL-C is now being applied to BP. Just 10 mm Hg—doesn't sound like a lot, but in terms of the number of patients who are going to now require treatment, it is huge. Many more people will require antihypertensive medication, and others already on antihypertensive medication will need more intensive treatment. But it will translate into better outcomes—fewer heart attacks, strokes and fewer patients going into kidney failure.

The exciting new **ACCOMPLISH** *guideline altering* data provides compelling evidence that most patients should be on the Lotrel combination of amlodipine/ benazepril as first line therapy for HBP with the addition of thiazide diuretic as the 3rd drug. Interestingly, only the lower dose combinations (5/10 & 5/20) are generic. Hopefully the 10/20 and 10/40 will follow shortly. If your patients are intolerant to ACE inhibitors, I believe an amlodipine/ARB combination like Exforge (amlodipine/valsartan) or Azor (amlodipine/olmesartan) with similar efficacy (20mmHg lowering) would be appropriate, based on non-inferiority trials of ARBs compared to ACE inhibitors. We obviously lean toward the generic first because of the cost benefits.

It is reasonable to attempt to achieve a target blood pressure of 150/80 mm Hg in patients older than 80 based on **HYVET.** Further BP lowering in stable elderly patients would probably be safe and even more beneficial.

## Perspective:

The attainment of 80% compliance to goal BP of < 140/90 in ACCOMPLISH would probably calculate to about 40% if the goal BP was <130/80. A lot of our patients will be classified as resistant hypertension—requiring intense aggressive BP lowering. The job ahead of us is huge and the amount of drugs necessary for us to get our patients to these goals is even more immense. But the benefits of that additional lowering should be dramatic.

Happy BP lowering!

Mario L Maiese DO, FACC, FACOI
Clinical Associate Professor of Medicine, UMDNJSOM
Email: maiese1@comcast.net

*Heartbeats* online: www.sjhg.org

***Heartbeat* is a South Jersey Heart Group publication.**

---

[1] Jamerson KA, on behalf of the ACCOMPLISH investigators. Avoiding cardiovascular events in combination therapy in patients living with systolic hypertension. American College of Cardiology Scientific Sessions; March 31, 2008; Chicago, Illinois. **[Slide lecture is on website. Physic ed. PowerPoint]**

[2] Beckett NS et al. for the HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008 May 1; 358. (http://dx.doi.org/10.1056/NEJMoa801369)

[3] Rosendorff C, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: A scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention.

*Circulation* June 2007; 115:2761-2788.

[4] Fung TT, et al. Adherence to a DASH-Style Diet and Risk of Coronary Heart Disease and Stroke in Women.
*Arch Intern Med* April 2008; 168:713-720.

[5] Sipahi I, et al. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. *J Am Coll Cardiol* 2006; 48:833-838.