Best of the ASH Scientific Sessions 2008

Highlights From the American Society of Hypertension 2008 Scientific Sessions, May 14-17, 2008, New Orleans, LA

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At this year's meeting of the American Society of Hypertension, researchers presented important new data regarding the treatment of hypertension. Here we discuss 4 studies of particular interest to cardiologists.

A New Dual-Acting Receptor Antagonist

The agent PS433540 (Pharmacopeia, Princeton, NJ), a dual-acting receptor antagonist (DARA), blocks the angiotensin and endothelin receptors. Both angiotensin and endothelin are potent vasoconstrictors, and therefore blocking these systems may provide enhanced blood pressure (BP) control. In the first-in-human clinical trial of this DARA compound, 93 patients were randomized to treatment with 200 mg of PS433540, 500 mg of PS433540, or placebo.[1] Inclusion criteria were developed to exclude patients with "white coat hypertension." Subjects met 2 different BP criteria: (1) baseline seated office BP of 150 mm Hg to 179 mm Hg for systolic and below 110 mm Hg for diastolic, and (2) ambulatory BP criteria for hypertension.

After 4 weeks, treatment with both 200 mg and 500 mg of the DARA reduced systolic and diastolic BP, as measured by mean 24-hour ambulatory recording and traditional methods taken in the doctor's office (Table 1). The investigators reported that the drug was safe and well tolerated, with a side effect profile no different from placebo. We await further clinical studies of this very interesting antihypertensive compound.

ONTARGET Substudy

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) magnetic resonance imaging (MRI) substudy tested how well left ventricular hypertrophy (LVH) in high-risk hypertensive patients can be reversed by the angiotensin receptor blocker (ARB) telmisartan, the angiotensin-converting enzyme inhibitor ramipril, or these 2 drugs combined (Figure 1).[2] The development of LVH is a marker of cardiovascular risk. Regression of LVH with treatment of hypertension is associated with improved outcomes.

The initial results showed no difference in the ability of any of these treatments to induce regression of LVH (Table 2). On further analysis of data from all treatment groups, it was shown that ventricular mass decreased 8% in the largest hearts but did not change in the smaller hearts.

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Table 1
Blood Pressure Reduction With a DARA Compound

Blood Pressure Measurement, mm Hg (mean change)	Placebo (n = 25)	PS433540 200 mg (n = 35)	PS433540 500 mg (n = 33)
Systolic 24-hour ABP	−4.0	−12.20*	−14.80*
Diastolic 24-hour ABP	0.3	−9.3*	−10.1*
Seated office systolic BP	−4.2	−16.9*	−17.3*
Seated office diastolic BP	1.6	−10.5*	−9.8*

*$P < .001$ vs placebo.
DARA, dual-acting receptor antagonist; ABP, ambulatory blood pressure; BP, blood pressure.
Reprinted with permission from Neutel JM.[1]

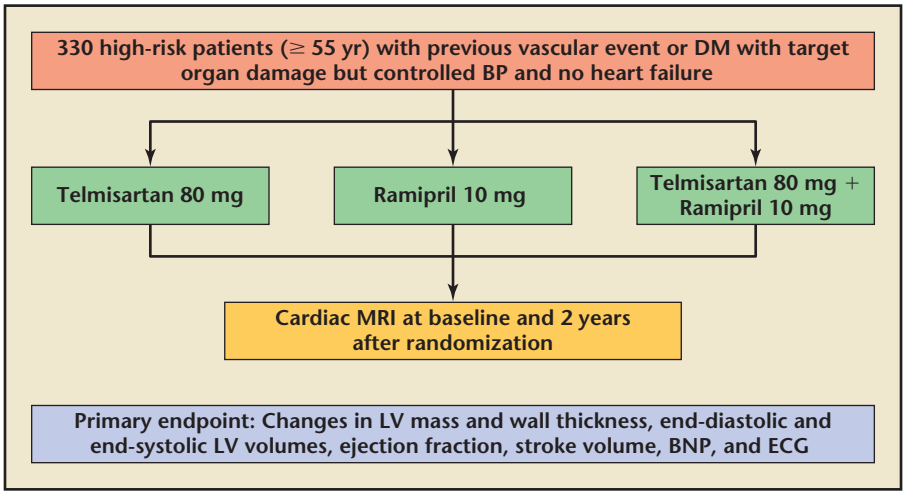

Figure 1. *The study design of the ONTARGET MRI substudy. ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; MRI, magnetic resonance imaging; DM, diabetes mellitus; BP, blood pressure; LV, left ventricular; BNP, brain natriuretic peptide; ECG, electrocardiogram. Reprinted with permission from Cowan B.*[2]

The key determinants of left ventricular mass reduction were baseline left ventricular mass measurement, history of hypertension, and extent of blood-pressure lowering. Although no treatment approach was shown to be superior, it is comforting to know that an angiotensin-converting enzyme (ACE) inhibitor or an ARB can prevent progression of LVH as measured by MRI.

The results of the previously published ONTARGET trial showed that telmisartan monotherapy was as effective as ramipril monotherapy in reducing the primary outcome of cardiovascular death, stroke, heart attack, or hospitalization for heart failure—as well as each component of this composite outcome—in patients with high-risk vascular disease or diabetes.

The PROMPT Study

The Randomized, Double-Blind Study to Compare a Valsartan-Based Versus an Amlodipine-Based Treatment Algorithm in Achieving Blood Pressure Control (PROMPT) study compared the efficacy of the ARB valsartan and the calcium channel blocker (CCB) amlodipine titrated to their highest recommended doses, and with and without hydrochlorothiazide (HCTZ) (Figure 2).[3] Patients were separated into 2 groups: (1) those with stage 1 hypertension that had never been treated, and (2) those with stage 2 hypertension that had never been treated or had not been controlled by monotherapy. Patients were excluded if they were being treated with a CCB or had severe hypertension or diabetes.

An ARB-based therapeutic approach seemed superior to a CCB-based approach in the ability to normalize BP (Figure 3). The incidence of adverse effects was similar between

Table 2
Results of the ONTARGET Cardiac MRI Substudy

Treatment	Baseline Left Ventricular Mass (g)	2-Year Left Ventricular Mass (g)	Change in Left Ventricular Mass (%)	*P* Value
Ramipril	37.5	35.7	−4.8	NS
Telmisartan	35.3	34.2	−3.3	NS
Combination	36.8	34.7	−5.8	NS

ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; MRI, magnetic resonance imaging; NS, not significant.
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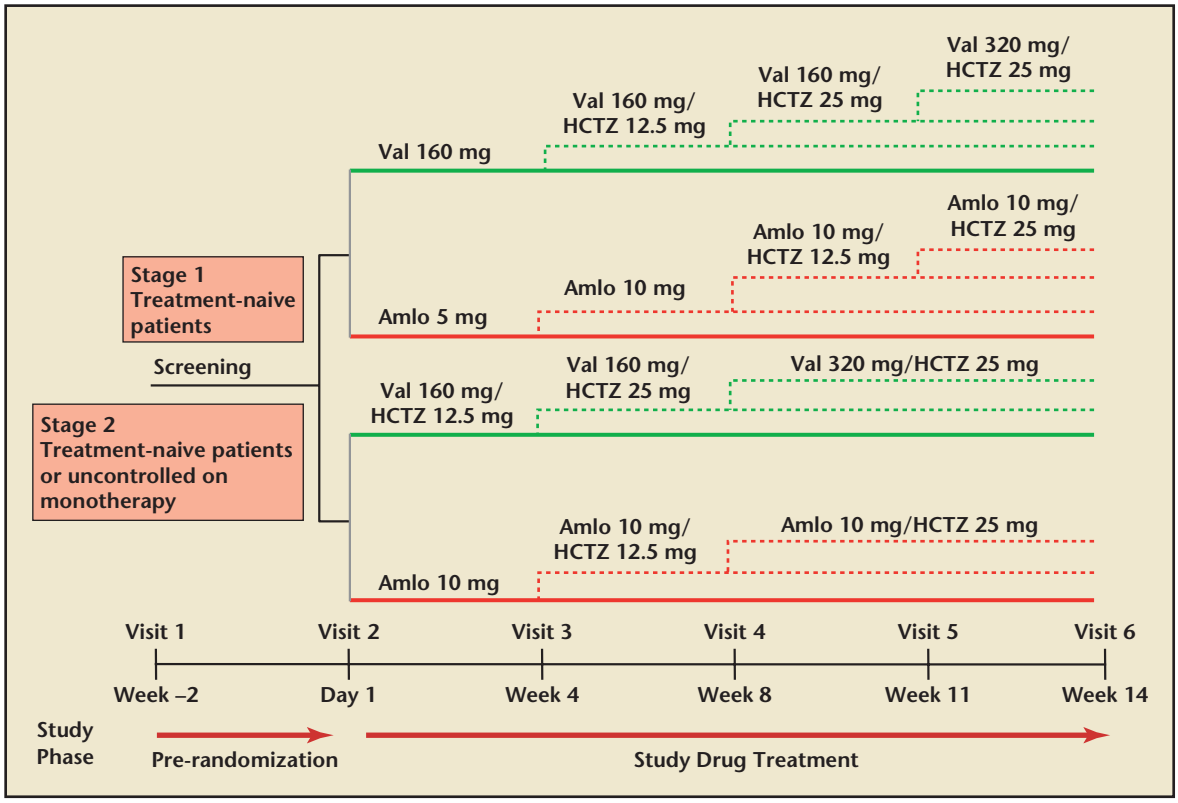


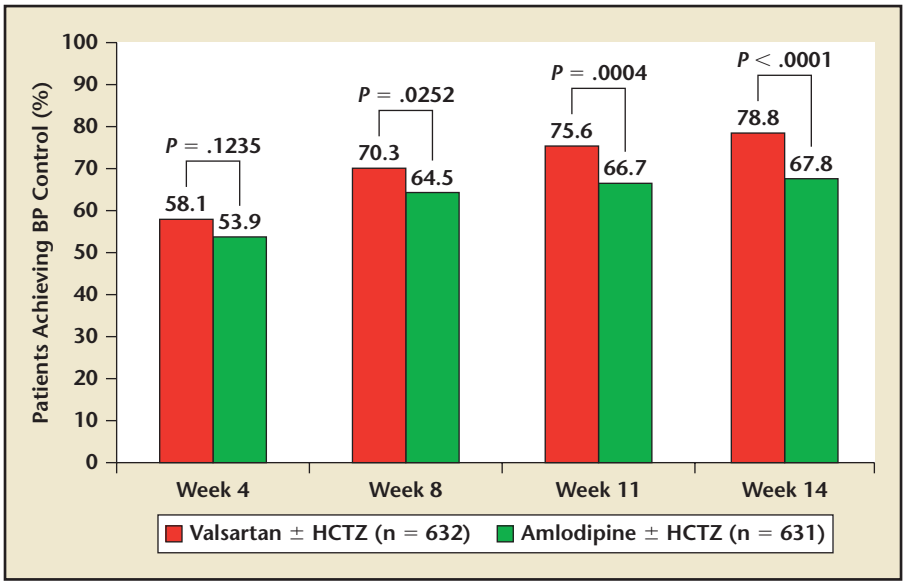
Figure 2. *Design of the PROMPT study. PROMPT, Randomized, Double-Blind Study to Compare a Valsartan-Based Versus an Amlodipine-Based Treatment Algorithm in Achieving Blood Pressure Control; Val, valsartan; Amlo, amlodipine; HCTZ, hydrochlorothiazide. Reprinted with permission from Zappe DH.*[3]

the 2 experimental groups, except for the increased incidence of edema in the CCB patients (22.4% vs 2.2%). This result supports the use of an ARB-based therapy to normalize BP in patients with mild-to-moderate hypertension. One criticism of this trial was that more patients in the ARB group received additional HCTZ than in the CCB group.

AASK: 15-Year Follow-Up Cohort Study

Analysis of data from more than 15 years of follow-up in the African American Study of Kidney Disease (AASK) shows that despite the benefits of therapy that blocks the renin-angiotensin system on the progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD),

Figure 3. *Patients achieving BP control (< 140/90 mm Hg) in the PROMPT trial. PROMPT, Randomized, Double-Blind Study to Compare a Valsartan-Based Versus an Amlodipine-Based Treatment Algorithm in Achieving Blood Pressure Control; HCTZ, hydrochlorothiazide; BP, blood pressure. Reprinted with permission from Zappe DH.*[3]



most African Americans with hypertensive-nondiabetic CKD who are treated with currently recommended antihypertensive therapy continue to progress over the long-term.[4]

The original AASK study compared the effects of 2 levels of BP control and 3 antihypertensive drug classes on glomerular filtration rate (GFR) decline in hypertension. A total of 1094 African American patients ages 18 to 70 years with hypertensive CKD (GFR 20 mL/min/1.73 m^2 to 65 mL/min/1.73 m^2) were followed for 3.0 to 6.4 years. Participants were randomly assigned to a mean arterial pressure goal of either 102 mm Hg to 107 mm Hg (usual) or a more aggressive goal of at or below 92 mm Hg, and to initial treatment with either a beta-blocker (metoprolol 50 mg/d to 200 mg/d), an ACE inhibitor (ramipril 2.5 mg/d to 10 mg/d), or a dihydropyridine CCB (amlodipine 5 mg/d to 10 mg/d).

The primary endpoint of the original AASK trial was a composite of the following clinical events: reduction in GFR by at least 50% or at least 25 mL/min/1.73 m^2 from baseline, development of ESRD (GFR < 30 mL/min/1.73 m^2), or death. The results of the trial showed that ACE inhibitors appeared to be more effective than beta-blockers or CCBs in slowing GFR decline, with the largest difference seen in patients with a baseline urinary protein to creatinine ratio greater than 0.22. There was no difference in clinical endpoints in patients randomized to aggressive BP goals compared with the usual BP goals.

AASK trial participants who had not reached ESRD were then asked to enroll in the AASK Cohort Study so that researchers could evaluate the long-term use of a renin-angiotensin-system inhibitor—either an ACE inhibitor or an angiotensin receptor blocker—to treat BP to a target of less than 130/80 mm Hg. At the start of the cohort phase, participants were switched from randomized therapy to an ACE inhibitor (ramipril 10 mg/d as first-line treatment) or an ARB if the ACE inhibitor was not tolerated. The AASK Cohort Study showed no benefit in treating to a lower BP target for most patients who have hypertension and renal disease. A subgroup analysis showed that patients with significant proteinuria did benefit from a lower target BP goal. ■

References

1. Neutel JM. A double blind, placebo controlled study to evaluate the safety and efficacy of a novel new dual acting receptor antagonist (DARA compound) in human subjects with hypertension. Paper presented at: American Society of Hypertension 23rd Annual Scientific Meeting and Exposition; May 14-17, 2008; New Orleans, LA.
2. Cowan B. Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). Paper presented at: American Society of Hypertension 23rd Annual Scientific Meeting and Exposition; May 14-17, 2008; New Orleans, LA.
3. Zappe DH. The PROMPT study: a randomized, double-blind study to compare a valsartan-based versus an amlodipine-based treatment algorithm in achieving blood pressure control. Paper presented at: American Society of Hypertension 23rd Annual Scientific Meeting and Exposition; May 14-17, 2008; New Orleans, LA.
4. Wright JT Jr. Progression of hypertensive kidney disease in the AASK and AASK Cohort Study. Paper presented at: American Society of Hypertension 23rd Annual Scientific Meeting and Exposition; May 14-17, 2008; New Orleans, LA.

Main Points

- Four weeks of treatment with a dual-acting receptor antagonist reduced systolic and diastolic blood pressure as compared with placebo.
- In a study testing whether left ventricular hypertrophy in high-risk hypertensive patients can be reversed by the angiotensin receptor blocker telmisartan, the angiotensin-converting enzyme inhibitor ramipril, or these 2 drugs combined, all treatment approaches achieved similar results.
- Results from a new study supported the use of an angiotensin receptor blocker–based therapy to normalize blood pressure in patients with mild-to-moderate hypertension.
- Most patients with hypertension and renal disease did not benefit from treatment to a lower blood pressure target (< 130/80 mm Hg) in a cohort study. Patients with significant proteinuria did benefit from the lower target blood pressure goal.