

Valsartan Reduces Inflammatory Marker Associated with Hypertensive and Comorbid Risk; Effect Neutralized by Thiazide Diuretic

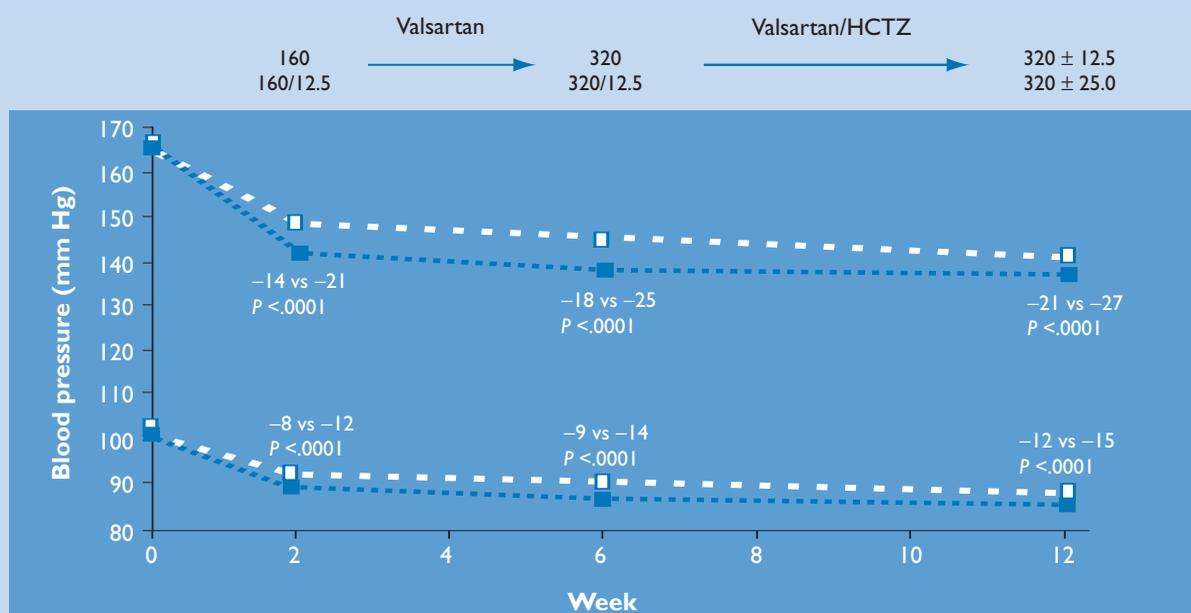
The angiotensin receptor blocker valsartan is associated with a reduction in levels of high-sensitivity C-reactive protein (hs-CRP), a known indicator of future risk for hypertension in normotensive persons. In addition, hs-CRP has been shown to modify the impact of blood pressure on stroke, myocardial infarction, and cardiovascular-associated death. These hs-CRP-associated effects are independent of the reduction in blood pressure pro-

duced by valsartan, said Paul M. Ridker, MD, MPH, at the 21st Annual Scientific Meeting and Exposition of the American Society of Hypertension.

“Inflammation is crucial to the development of hypertension,” noted Dr Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Women’s Hospital in Boston, Massachusetts. Until now, statins were among only a few medications shown to reduce hs-CRP. The effect of valsartan on hs-CRP was neutralized by adding hydrochlorothiazide, he said.

In the Valsartan-Managing blood pressure Aggressively and Evaluating Reductions in hs-CRP (Val-MARC) trial, the effect of valsartan alone and in combination with hydrochlorothiazide on levels of hs-CRP was studied in 1668 patients with stage 2 hypertension (ASH 2006. Abstract P121). Patients were randomized to valsartan 160 mg/day or valsartan plus hydrochlorothiazide 12.5 mg/day. The valsartan dosage was then titrated to 320 mg/day at week 2.

Figure. Systolic and Diastolic Blood Pressure: Response to Therapy



HCTZ indicates hydrochlorothiazide.

The primary blood pressure/hs-CRP end point was measured at week 6. Patients in the valsartan monotherapy group had hydrochlorothiazide 12.5 mg/day added to their regimen, whereas those in the combination arm had the hydrochlorothiazide dosage increased to 25 mg/day. Blood pressure and hs-CRP measurements were then repeated at week 12.

Six-week changes in systolic blood pressure were statistically superior ($P < .001$) in the combination arm compared with valsartan monotherapy (median changes, 25 vs 18 mm Hg). More patients receiving combination versus monotherapy achieved blood pressure 140/90 mm Hg (48% vs 32%; $P < .0001$) (Figure). The median hs-CRP level decreased from 2.17 mg/L at baseline to 1.98 mg/L at 6 weeks in the group assigned to valsartan monotherapy, a decline of 8.9%, whereas hs-CRP increased from 2.09 to 2.15 mg/L in the group assigned to valsartan/hydrochlorothiazide, an increase of 4.4%. Therefore, the net difference between groups in the median percentage change in hs-CRP was 13.3% ($P < .001$).

The difference between the effect of valsartan and valsartan/hydrochlorothiazide on hs-CRP was evident in all subgroups studied, despite a greater blood pressure reduction in the group receiving combination therapy, said Dr Ridker. “In the study group as a whole and within each

study arm, we observed minimal evidence of correlation between change in blood pressure and change in hs-CRP,” he noted. The same effect of valsartan on hs-CRP was observed in statin and aspirin users and nonusers.

No published data have confirmed an effect of other antihypertensive agents on hs-CRP, according to Dr Ridker. “As far as we know, angiotensin-converting enzyme inhibitors don’t have this effect,” he said. “I generally believe in class effect, but we’ve been proved wrong so many times...it is incumbent to prove [this effect] with other drugs.”

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Although there is no evidence that lowering hs-CRP decreases cardiovascular risk, most evidence has proved that interventions in cardiovascular medicine, such as weight loss, aspirin, smoking cessation, and use of statins, lower hs-CRP. “But that doesn’t prove causality,” Dr Ridker noted. To detect clinical differences between antihypertensive drugs, future trials may have to focus on higher-risk patients, such as those with elevated hs-CRP, he added.