

Valsartan Lowers Serum C-Reactive Protein Levels

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — Monotherapy with valsartan has been shown for the first time to lower serum levels of C-reactive protein, raising the possibility that valsartan—and possibly other antihypertensive agents—might have a beneficial effect on cardiovascular events that goes beyond blood pressure reduction.

Results from Val-MARC (Valsartan-Managing Blood Pressure Aggressively and Evaluating Reductions in hs-CRP) also showed that valsartan's effect on CRP was



Some antihypertensive regimens may have a beneficial CV effect that goes beyond blood pressure reduction.

DR. RIDKER

independent of BP reduction, suggesting that a pleiotropic, anti-inflammatory effect by this angiotensin II receptor blocker (ARB) might have produced the result.

And in the study, with more than 1,600 patients, concurrent treatment with the popular diuretic hydrochlorothiazide (HCTZ) plus valsartan appeared to somehow blunt the CRP reduction, raising questions about possible adverse, pleiotropic effects of HCTZ.

"The current data raise the hypothesis that some antihypertensive regimens may have additional anti-inflammatory properties," Dr. Paul M. Ridker reported at the annual meeting of the American Society of Hypertension. "Whether this translates to a net clinical advantage will require well-designed, prospective trials of hypertension treatment that specifically target" patients with elevated CRP levels, said Dr. Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston.

The open-label study enrolled patients with stage 2 hypertension at 384 centers in the United States during January 2004–June 2005. Of the 1,668 patients, 836 were randomized to treatment with 320 mg valsartan daily, and 832 were assigned to receive 320 mg valsartan and 12.5 mg HCTZ daily. The study's primary end point was

blood pressure reduction and changes in serum levels of CRP measured after 6 weeks of treatment.

The study was sponsored by Novartis, which markets valsartan (Diovan). Dr. Ridker has received research support from Novartis and is co-owner of a patent for a high-sensitivity CRP test.

After 6 weeks, valsartan monotherapy cut systolic pressure by an average of 18 mm Hg, compared with an average drop of 25 mm Hg in patients on the combined

regimen. The percentage of patients who reached the goal pressure target of 140/90 mm Hg or less was 32% in the monotherapy group and 48% in the valsartan plus HCTZ group. These results were published online simultaneously with Dr. Ridker's report (Hypertension 2006 [doi: 10.1161/01.HYP.0000226046.58883.32]).

CRP measurements showed that patients treated with only valsartan had a median reduction of 0.12 mg/L, a reduction of 8.9% from baseline. In contrast,

among patients treated with valsartan plus HCTZ, the median change in CRP was an increase of 0.05 mg/L, a median rise of 4.4%, a statistically significant difference.

"We saw no relationship whatsoever between the extent of blood pressure reduction and the extent of CRP reduction," said Dr. Ridker, who is also the Eugene Braunwald Professor of Medicine at Harvard Medical School in Boston. "The data lead to the hypothesis that valsartan reduces inflammation in a way that's in-

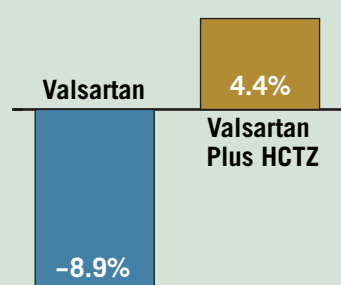
ADVERTISEMENT

INTRA-ABDOMINAL ADIPOSITY (IAA)* ... A MAJOR CARDIOMETABOLIC RISK FACTOR

Adipose tissue is an active endocrine organ, secreting proteins with local and systemic effects.

*As measured by increased waist circumference.

Median Change From Baseline in CRP Levels



Note: Based on a study of 1,668 patients.

Source: Dr. Ridker

dependent of blood pressure reduction.”

The effect of valsartan alone and of valsartan plus HCTZ on CRP levels was “remarkably consistent” across every patient subgroup examined, including patients who were also treated with statins and those who were not, he said. This last observation suggests that the ability of valsartan alone to lower CRP levels is independent of the action of statins, and so the two effects might be additive.

Although Dr. Ridker acknowledged that CRP-lowering may be a class effect for all ARBs, he stressed that so far the effect has been proved only for valsartan: “We’ve been [wrong] about class effects

for statins; it may not be as simple as we once thought.” ARBs were hypothesized to have an effect on CRP because of angiotensin II’s proinflammatory effects. (ARBs block the angiotensin II receptor.)

It’s unclear what effect HCTZ might have on inflammatory processes. The drug is known to boost insulin resistance, the incidence of diabetes, and serum levels of plasminogen activator inhibitor-1. All of these activities track with elevated CRP levels, but it’s too soon to say whether this explains the study’s results, he said.

Even if HCTZ is eventually shown to block a beneficial reduction in CRP levels, and despite the drug’s other adverse

effects, physicians will probably find it hard to avoid using the drug in patients with refractory hypertension.

“In many patients with hypertension, it’s extremely hard to get them to their goal pressure without a diuretic,” commented Dr. Joel M. Neutel, medical director of clinical pharmacology at the Orange County Research Center in Tustin, Calif.

“If a patient is on two vasodilator drugs, such as an ARB and a calcium channel blocker, the third drug almost has to be a diuretic. We need diuretics to treat hypertension. You use other drugs to balance their negative effects,” Dr. Neutel said. ■

Aldosterone May Worsen Sleep Apnea

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — A link between aldosterone, hypertension, and obstructive sleep apnea was made in a study with 71 patients.

“We found an extraordinarily high prevalence of obstructive sleep apnea in patients with [treatment-] resistant hypertension,” and serum aldosterone levels were significantly related to the severity of sleep apnea,” Dr. David A. Calhoun said at the annual meeting of the American Society of Hypertension. “We went in thinking that obstructive sleep apnea was driving aldosterone release, but now we think that a high serum level of aldosterone somehow contributes to worsening sleep apnea,” said Dr. Calhoun, a hypertension specialist at the University of Alabama, Birmingham.

The link may be mediated by increased salt and water retention or perhaps by a change in flow resistance.

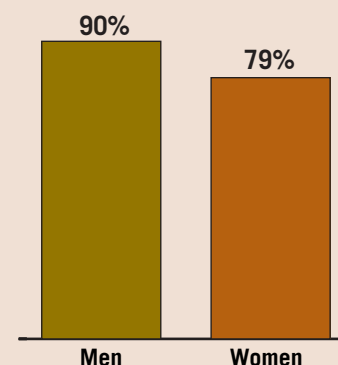
Dr. Calhoun and his associates have begun a study to explore the implications of their findings for patient management. They are withholding continuous positive air pressure, a standard treatment for obstructive sleep apnea, from patients with the disorder and are instead treating them with spironolactone, an aldosterone antagonist. The goal is to see whether spironolactone alone is effective at relieving sleep apnea.

The current study involved a consecutive series of 41 men and 30 women who were referred to the hypertension clinic at UAB because of treatment-resistant hypertension. Their mean blood pressure was 156/88 mm Hg despite treatment with an average of four antihypertensive drugs.

The patients were assessed for obstructive sleep apnea by diagnostic polysomnography. The overall prevalence of obstructive sleep apnea was 85%, with a prevalence of 90% in the men and 79% in the women. The average apnea-hypopnea index for all patients was 24 apnea events per hour.

The patients with sleep apnea also had high serum and urine levels of aldosterone. Those with the most severe sleep apnea had the highest levels, Dr. Calhoun said. ■

Obstructive Sleep Apnea In Hypertensive Patients



Note: Based on a study of 71 patients with treatment-resistant hypertension.
Source: Dr. Calhoun

Brought to you by **sanofi aventis**

INCREASED ACTIVITY OF THE ENDOCANNABINOID SYSTEM (ECS) IS ASSOCIATED WITH INCREASED WAIST CIRCUMFERENCE^{1,2}

INCREASED WAIST CIRCUMFERENCE, A MARKER FOR IAA, IS AN ESTABLISHED CARDIOMETABOLIC RISK FACTOR³

- Significantly increases the risk of myocardial infarction, death from cardiovascular disease, and all-cause mortality⁴
- Has been found to be an independent predictor of type 2 diabetes⁵

ADIPOSE TISSUE IS A HIGHLY ACTIVE ENDOCRINE ORGAN⁶

- Fat cells (adipocytes) produce adiponectin⁶
 - In type 2 diabetes and obesity, adiponectin levels are reduced⁶

TARGETING THE ECS MAY PLAY A POTENTIAL ROLE IN THE CONTROL OF MAJOR CARDIOMETABOLIC RISK FACTORS SUCH AS IAA*

IF YOU ARE INTERESTED IN LEARNING MORE ABOUT THE ECS,
PLEASE CALL 1-800-815-0298 TO RECEIVE A MONOGRAPH.

References

1. DiMarzo V, Matias I. Endocannabinoid control of food intake and energy balance. *Nat Neurosci*. 2005;8:585-589.
2. Cota D, Marsicano G, Tschöp M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest*. 2003;112:423-431.
3. National Heart, Lung, and Blood Institute. National Cholesterol Education Program. *ATP III Guidelines At-A-Glance: Quick Desk Reference*. Bethesda, Md: National Institutes of Health; May 2001.
4. Dagenais GR, Yi Q, Mann JFE, et al. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J*. 2005;149:54-60.
5. Carey VJ, Walters EE, Colditz GA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: the Nurses' Health Study. *Am J Epidemiol*. 1997;145:614-619.
6. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89:2548-2556.