Angiotensin, Inflammation, and Vascular Injury

Valsartan, Blood Pressure Reduction, and C-Reactive Protein
Primary Report of the Val-MARC Trial

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Abstract—Increased levels of high-sensitivity C-reactive protein (hsCRP) are associated with incident hypertension as well as cardiovascular events, and angiotensin II is a potent proinflammatory mediator. However, whether angiotensin receptor blockade lowers hsCRP is uncertain. We performed a randomized trial in which 1668 patients with stage 2 hypertension were treated with 160 mg valsartan or 160/12.5 mg valsartan/hydrochlorothiazide (HCTZ) once daily for 2 weeks with forced titration to 320 mg valsartan or 320/12.5 mg valsartan/HCTZ for an additional 4 weeks. After 6 weeks, systolic blood pressure (−25 versus −18 mm Hg; \(P<0.001\)) and diastolic blood pressure (−14 versus −9 mm Hg; \(P<0.001\)) were reduced to a greater degree among those allocated to valsartan/HCTZ than to valsartan monotherapy. The median change in hsCRP was −0.12 mg/L among those allocated to valsartan compared with +0.05 mg/L among those allocated to valsartan/HCTZ, a 13.3% difference \(P<0.001\); this difference between valsartan and valsartan/HCTZ was present in all subgroups evaluated despite the fact that blood pressure reduction was greater in the combined therapy group. No relationship was observed between hsCRP reduction and blood pressure; in all analyses, the proportion of variation in change in hsCRP with valsartan monotherapy explained by change in blood pressure was <2%. Thus, in this prospective trial, valsartan reduced hsCRP levels in a manner independent of degree of blood pressure reduction. These data raise the hypothesis that angiotensin receptor blockade may have anti-inflammatory effects in addition to blood pressure–lowering effects. (Hypertension. 2006;48:73-79.)

Key Words: clinical trials  ■  antihypertensive therapy  ■  angiotensin antagonist

Despite the availability of multiple antihypertensive medications, hypertension control rates remain low, and the incidence of hypertension-associated cardiovascular events continues to increase. Recognizing this issue, recent guidelines from the Seventh Report of the Joint National Committee (JNC-7) offer multiple strategies for improved treatment of hypertension, including emphasis on lifestyle and dietary modification and a recommendation to use thiazide diuretics of hypertension, including emphasis on lifestyle and dietary modification and a recommendation to use thiazide diuretics.

These observations have potential clinical relevance because elevated levels of high-sensitivity CRP (hsCRP) are commonly found among individuals at high risk for myocardial infarction, stroke, and cardiovascular death. Further, in previous work, we and others have demonstrated that hsCRP and blood pressure interact to determine risk of future vascular events, particularly among those with stage 2 hypertension, and that hsCRP levels predict incident hypertension among currently normotensive individuals. Nonetheless, it remains controversial as to whether blood pressure reduction per se lowers CRP levels, and thus it is unknown whether any postulated effects of ARBs on hsCRP are independent of blood pressure reduction or reflect a lowering of systemic intravascular pressures.

To directly address these issues, we randomly allocated 1668 patients with stage 2 hypertension to either valsartan...
alone (320 mg) or to valsartan/hydrochlorothiazide (HCTZ; 320 mg/12.5 mg) for a period of 6 weeks. In addition to the primary inflammation and blood pressure end points ascertained at the 6-week time point, all participants were followed for an additional 6-week period during which optional treatment with 12.5 mg HCTZ was allowed in both study arms to better achieve JNC-7 blood pressure target levels.

Methods
The Valsartan-Managing blood pressure Aggressively and evaluating Reductions in hsCRP (Val-MARC) trial was prospectively designed to compare the efficacy of valsartan alone versus valsartan plus HCTZ as initial therapy for patients with stage 2 hypertension to evaluate any effect of these 2 regimens on change in plasma levels of hsCRP and to determine whether any treatment effects on hsCRP were dependent or independent of blood pressure reduction.

In brief, Val-MARC was a multicenter, open-label, randomized trial conducted in the United States between January 2004 and June 2005 that included men and women between 18 and 75 years of age with stage 2 hypertension. For purposes of the trial, stage 2 hypertension was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg based on the mean of 3 consecutive seated blood pressure readings using a standardized electronic automated blood pressure monitor (Omron Healthcare Inc). All study personnel were formally trained in the use of this device before study initiation.

Because of safety concerns, screened patients found to have systolic blood pressure >185 mm Hg or diastolic blood pressure >109 mm Hg were not eligible for the study but were instead referred for immediate therapy. Patients were further ineligible for Val-MARC if they had received angiotensin-converting enzyme inhibitors, ARBs, or aldosterone receptor antagonists during the 3 months before randomization or thiazide diuretics during the month before randomization. Because of known effects of statin therapy on hsCRP, lipid-lowering medications were not allowed to be initiated or modified during the study period. Documentation of serum creatinine ≤2 mg/dL, serum potassium ≥3.5 and ≤5.5 mEq/L, hemoglobin A1C (HbA1C) ≤11.0%, and serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2× the upper limit of normal was required of all potential participants before randomization. Pregnant or lactating women as well as those with a history of secondary hypertension or history of myocardial infarction, stroke, cardiac revascularization, unstable angina, or onset of congestive heart failure within the last 6 months were excluded from the study. Subjects with chronic inflammatory conditions such as rheumatoid arthritis, osteoarthritis, lupus, or inflammatory bowel disease were ineligible, as were those with a need for chronic anti-inflammatory therapies such as prednisone and other related steroid agents.

In total, 2390 patients were screened for the Val-MARC trial, of whom 1668 were deemed eligible, provided a baseline blood sample for hsCRP evaluation, and were then randomly allocated to either 160 mg valsartan once daily or to 160/12.5 mg valsartan/HCTZ once daily for an initial 2-week period (Figure 1); randomization was blocked by clinical site. After 2 weeks, participants returned to the outpatient clinics, at which time those who remained asymptomatic received a force-titrated dose of either 320 mg valsartan or 320/12.5 mg valsartan/HCTZ, according to their initial randomization. Participants then remained on this dose of study medication and returned at 6 weeks to provide a second blood sample for hsCRP evaluation (primary inflammation end point) and undergo repeat standardized blood pressure evaluation (primary blood pressure end point). If blood pressure was uncontrolled at week 6, investigators were allowed at their discretion to use 12.5 mg HCTZ as add-on therapy in both study groups until the end of trial at week 12, when hsCRP and blood pressure levels were again ascertained.

All plasma samples were processed centrally in a core laboratory (Center for Cardiovascular Disease Prevention, Brigham and Wom-
Results

Table 1 presents baseline clinical characteristics of the 2 study groups according to randomized treatment assignment. The study groups were well matched with regard to age, gender, ethnicity, smoking status, obesity, initial blood pressure, and baseline hsCRP levels, although diabetes was more prevalent in the valsartan monotherapy group (11.3%) than in the combination therapy group (8.3%).

**Primary Blood Pressure End Point**

Among participants initially treated with valsartan alone, the median change in systolic blood pressure at 6 weeks was −18 mm Hg (interquartile range [IQR] −28, −7), whereas the median change in diastolic blood pressure was −9 mm Hg (IQR −17, −2). As anticipated, among participants initially treated with combined valsartan/HCTZ, significantly larger reductions in both systolic and diastolic blood pressure were observed (−25 [IQR −37, −13] and −14 [IQR −21, −7] mm Hg, respectively; both between group P values <0.001; Figure 2). The greater efficacy of combination treatment was observed as early as 2 weeks for both systolic (−14 versus −21 mm Hg; P<0.001) and diastolic (−8 versus −12 mm Hg; P<0.001) blood pressure. At 6 weeks, the proportions of study participants reaching blood pressure goals of <140/90 mm Hg were 32% and 48% in the valsartan and valsartan/HCTZ groups, respectively (P<0.001). Differences in efficacy between the 2 randomized blood pressure regimens were similar in men and women and present across all ethnic groups. At 12 weeks, after the optional use of an additional 12.5 mg of HCTZ in both study arms, the proportions of study participants reaching JNC-7 goals was 42% and 52%, respectively.

**Primary Inflammation End Point**

Table 2 summarizes results from the primary inflammation end point change in hsCRP after 6 weeks of therapy. Among participants treated with valsartan monotherapy, the median change in hsCRP was −0.12 mg/L compared with +0.05 mg/L among those treated with valsartan plus HCTZ (Figure 3). Reductions in hsCRP were also significantly greater in women (−0.18 mg/L) than in men (−0.05 mg/L; P<0.01).

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**Table 1. Baseline Characteristics of the Study Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Valsartan (n=836)</th>
<th>Valsartan/HCTZ (n=832)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years†</td>
<td>50 (43–58)</td>
<td>50 (43–59)</td>
<td>0.45</td>
</tr>
<tr>
<td>Female, %</td>
<td>44.6</td>
<td>46.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Ethnic group, %</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>67.8</td>
<td>67.5</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>22.7</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>6.9</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.6 (27.2–36.4)</td>
<td>31.4 (27.2–36.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>164 (156–172)</td>
<td>165 (157–173)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diastolic</td>
<td>101 (95–105)</td>
<td>101 (95–105)</td>
<td>0.24</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>26.8</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>19.0</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54.2</td>
<td>52.9</td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.6</td>
<td>8.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Concomitant therapy, %</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>11.5</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>15.0</td>
<td>16.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Hormone replacement†</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives‡</td>
<td>2.1</td>
<td>2.3</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*P values are based on a Wilcoxon rank sum test for continuous variables and a χ² test for categorical variables.†Median (IQR); ‡rates are for women only.

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Figure 2. Primary blood pressure end point. Median change in blood pressure (mm Hg) from randomization to 6-week follow-up. P<0.01 for all comparisons.
mg/L among those allocated to valsartan/HCTZ, a net difference between treatment groups of 13.3% (P<0.001). The difference between valsartan alone and valsartan/HCTZ in terms of hsCRP reduction was highly significant (P<0.001) despite the fact that blood pressure reduction was substantially greater in the combined therapy group.

Table 3 demonstrates the consistency of these effects across all major subgroups evaluated. As shown, random allocation to valsartan alone resulted in lower hsCRP levels in analyses stratified by age, gender, ethnicity, smoking status, body mass index, diabetes, and use or nonuse of concomitant medications. The median change in hsCRP attributable to valsartan among participants taking statin therapy was at least as large as that seen in the cohort as a whole. In contrast, no consistent pattern in terms of increase or decrease in median hsCRP levels was observed among those randomly allocated to combination therapy with valsartan/HCTZ.

The observation in these data that valsartan monotherapy resulted in decreased hsCRP levels but that combined valsartan/HCTZ did not lower hsCRP levels suggests that the observed effects are unlikely to be attributable to blood pressure reduction per se. To further address this issue, we computed Spearman correlation coefficients between the change in hsCRP and the change in blood pressure, both at 6 and 12 weeks in the total cohort and separately according to randomized treatment allocation. As shown in Table 4, the proportion of variation in change in hsCRP explained by change in blood pressure was <1% regardless of group evaluated. As shown in Table 3, median hsCRP levels were reduced among those allocated to valsartan in the subgroups who achieved blood pressure reductions >20 mm Hg or <20 mm Hg (the overall study median), whereas no reduction was observed in these subgroups among those allocated to valsartan/HCTZ.

**Twelve-Week Follow-Up Analyses**

According to the study design, patients randomly assigned to the valsartan-alone arm were allowed for ethical reasons to receive 12.5 mg HCTZ as add-on therapy at the investigators’ discretion if blood pressure remained uncontrolled after 6 weeks of treatment. Thus, direct comparisons of the change in hsCRP between valsartan and valsartan/HCTZ cannot be made past the primary inflammation end point of 6 weeks. However, to determine whether the effect of valsartan alone on hsCRP could be maintained over time, an exploratory analysis was performed in the cohort of 224 patients who did not receive add-on HCTZ and who provided a blood sample for analysis at week 12. In this group, plasma hsCRP levels at

### TABLE 3. Primary Inflammation End Point, Subgroup Analyses: Median Change (IQR) in hsCRP From Randomization to 6-Week Follow-Up

<table>
<thead>
<tr>
<th>Measure of Change</th>
<th>Valsartan</th>
<th>Valsartan/HCTZ</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.11</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>1.90</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.17</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>1.98</td>
<td>2.15</td>
<td></td>
</tr>
<tr>
<td>Median change, mg/L</td>
<td>-0.12</td>
<td>+0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median change, %</td>
<td>-0.8</td>
<td>+4.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**HRT** indicates hormone replacement therapy.
12 weeks remained below those observed at baseline and were similar to those observed at 6 weeks, suggesting that the effect of valsartan monotherapy on hsCRP can be maintained over extended periods of treatment. Interestingly, among those initially allocated to valsartan alone who did receive add-on HCTZ after 6 weeks (n=385), the reduction in hsCRP observed from baseline to 6 weeks was no longer present at 12 weeks.

**Side Effect Profile**

Adverse event rates during the study period were low and are provided by treatment arm in Table 5. As anticipated with a more aggressive blood pressure–reducing regimen, those allocated to valsartan/HCTZ had higher rates of reported dizziness compared with those allocated valsartan alone (P=0.002). No other significant differences were observed.

**Discussion**

In this randomized trial of valsartan monotherapy compared with valsartan/HCTZ as initial treatment for stage 2 hypertension, we observed that valsartan alone significantly reduced hsCRP levels at 6 weeks and that this effect could be maintained over an extended follow-up period. In contrast, combining HCTZ with valsartan appeared to neutralize this effect, an intriguing observation because this group achieved significantly greater blood pressure reduction than those allocated to valsartan alone; these effects were consistent across all prespecified subgroup analyses. 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 hsCRP. Thus, these randomized data raise the hypothesis that valsartan monotherapy may lower inflammation in a manner independent of the degree of blood pressure reduction.

The observation in these data that valsartan lowers hsCRP levels is consistent with previous evidence from a number of small studies suggesting that angiotensin receptor blockade may have clinically relevant anti-inflammatory effects.\(^{11-17}\) The fact that this reduction in hsCRP is not related to change in blood pressure is also concordant with work suggesting that vascular inflammation is regulated in part by the renin-angiotensin system in a pressure-independent manner and that antagonism of angiotensin II may modulate the atherosclerotic process.\(^{27}\) We also believe it is of clinical interest that the reduction in hsCRP associated with valsartan was present not only in the total cohort but also among those taking statin agents, a class of drugs shown previously to significantly reduce hsCRP levels.\(^{26,28}\)

Given the observation that valsartan monotherapy reduces hsCRP, the lack of hsCRP reduction among those treated with valsartan/HCTZ raises the possibility that HCTZ might neutralize this effect. On literature review, we were unable to find adequately powered studies evaluating the effect of HCTZ on inflammatory biomarkers, although in one evaluation, no reduction in soluble vascular cell adhesion molecule-1 nor macrophage chemotactic protein-1 was observed among patients randomly allocated to HCTZ, whereas significant reductions in these inflammatory markers were observed among those allocated to ARB therapy.\(^{14}\) Whereas thiazide diuretics have proven to be highly effective blood pressure agents,\(^{29}\) HCTZ is known to increase insulin resistance and, in certain settings, can lead to adverse metabolic changes as well as increases in plasminogen activator inhibitor-1,\(^{30,31}\) effects known to correlate with increased hsCRP levels. In contrast, ARBs have been shown to have beneficial effects on multiple components of the metabolic syndrome,\(^{32}\) an observation consistent with primary links between angiotensin II and insulin resistance.\(^{33}\) Similarly, HCTZ has been reported to reduce the antiatherosclerotic effects ascribed to inhibition of the renin-angiotensin system, at least in hypercholesterolemic rabbit models.\(^{34}\) Whether or not HCTZ alone adversely impacts on vascular inflammation will need evaluation in future clinical trials.

Limitations of our study design merit consideration. Because we evaluated patients with stage 2 hypertension, we believed it unethical to have a placebo treatment arm in our trial. However, hsCRP levels are documented in multiple previous placebo-controlled trials to be stable in the absence of intervention.\(^{26}\) Also, because we limited our study to those with stage 2 hypertension, these data should not be generalized to other populations in which ARB is commonly used. Nonetheless, in the Val-HEFT study of patients with congestive heart failure, randomized treatment with valsartan lowered hsCRP levels, whereas placebo did not.\(^{35}\)

As detailed in the JNC-7 report, individuals with stage 2 hypertension are unlikely to reach treatment goals with single agent regimens, even when combined with lifestyle and dietary modification, and on this basis, multidiuretics have proven to be highly effective blood pressure agents,\(^{29}\) HCTZ is known to increase insulin resistance, and, at least in hypercholesterolemic rabbit models.\(^{34}\) Whether or not HCTZ alone adversely impacts on vascular inflammation will need evaluation in future clinical trials.

The current trial data provide important confirmation of this recommendation; in this community-based study of 1668 stage 2 hypertensive patients randomly allocated to valsartan monotherapy or valsartan/HCTZ, significantly larger reductions in systolic and diastolic blood pressure were achieved in the combination therapy group as early as 2 weeks after randomization and persisted throughout the study period. Moreover, the proportion of patients reaching JNC-7 target goals for blood pressure reduction in this high-risk group was substantially greater among those initially allocated to combined rather than monotherapy. Thus, in addition to raising hypotheses with regard to blood pressure–independent effects of valsartan therapy on hsCRP, these data also provide clinical evidence that men and women with stage 2 hyper-

**TABLE 5. Adverse Effects of Study Medication (%)**

<table>
<thead>
<tr>
<th>Reported Side Effect</th>
<th>Valsartan</th>
<th>Valsartan/HCTZ</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>4.7</td>
<td>8.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Headache</td>
<td>3.8</td>
<td>4.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.2</td>
<td>4.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.9</td>
<td>2.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2.4</td>
<td>1.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.0</td>
<td>1.9</td>
<td>0.87</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6</td>
<td>2.4</td>
<td>0.21</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.4</td>
<td>1.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.4</td>
<td>2.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1.9</td>
<td>1.3</td>
<td>0.34</td>
</tr>
</tbody>
</table>
tension obtain substantially improved reductions in blood pressure when combined therapy is used as the initial treatment plan.

Multiple large-scale prospective studies demonstrate that hsCRP levels predict incident myocardial infarction and stroke,19–22 and evaluation of hsCRP has been advocated by the Centers for Disease Control and Prevention and the American Heart Association as an adjunct to global risk prediction among those at intermediate risk.36 Although not a relevant issue for risk detection, it is nonetheless important to recognize that no hard evidence yet exists demonstrating that hsCRP reduction per se lowers risk of heart attack, stroke, or incident hypertension. However, observational studies consistently indicate that the most important interventions known to lower vascular event rates, including diet, exercise, smoking cessation, and lipid-lowering with statins, also result in hsCRP reduction. Further, at least in the setting of statin therapy, patients who achieve lower levels of hsCRP appear to have improved clinical outcomes27 and less atherosclerotic progression.37 To date, no end point trial of hypertension therapy has stratified participants on the basis of underlying inflammatory profile. Thus, although the current data raise the hypothesis that some antihypertensive regimens may have additional anti-inflammatory properties, whether this translates to a net clinical advantage will require well-designed prospective trials of hypertension treatment that specifically target those with an enhanced innate immune response.

Perspectives

In addition to increasing the risk for myocardial infarction and stroke, elevated levels of CRP are associated with increased risk of developing hypertension. At the same time, laboratory studies have raised the hypothesis that angiotensin receptor blockade may have anti-inflammatory effects. In the Val-MARC randomized trial of patients with stage 2 hypertension, valsartan monotherapy was found to significantly reduce plasma levels of the inflammatory biomarker hsCRP. However, this effect was not related to the degree of blood pressure reduction and was not observed among those allocated to combined therapy with valsartan/HCTZ. As such, future studies will be required to address whether or not thiazide diuretics given alone may have adverse effects on hsCRP. Although the current data raise the hypothesis that some antihypertensive regimens may have additional anti-inflammatory properties, whether this will translate to a net clinical advantage will require well-designed prospective trials of hypertension treatment that specifically target those with an enhanced innate immune response. Because hsCRP levels are known to predict incident hypertension, these data also have implications for future trials of hypertension prevention, particularly because ARB therapy was shown to lower hsCRP in all patient subgroups evaluated.

Acknowledgments

The authors wish to thank Dr Ricardo Rocha for his assistance in study design and the 1668 Val-MARC participants who volunteered to take part in this study.

Sources of Funding

The Val-MARC trial was funded by Novartis, Inc. P.M.R. has received research support from Novartis, Astra-Zeneca, Aventis, and Dade-Behring. R.J.G. has received research support from Novartis and Astra-Zeneca.

Disclosures

P.M.R. is listed as a coinventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. R.J.G. is a statistician at the Brigham and Women’s Hospital and the Harvard Medical School and performed an independent statistical analysis of the raw data set. That analysis comprises all results reported in this article. Employees of the sponsor assisted in the development of the Val-MARC protocol and in the collection of the data. The sponsor played no role in the drafting of this manuscript. The remaining authors report no conflicts.

References


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Hypertension. 2006;48:73-79; originally published online May 19, 2006;
doi: 10.1161/01.HYP.0000226046.58883.32
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
http://hyper.ahajournals.org/content/48/1/73

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