Heart Failure

C-Reactive Protein in Heart Failure
Prognostic Value and the Effect of Valsartan

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Background—The role of C-reactive protein (CRP) in heart failure is not well studied. We assessed the prognostic value of CRP in patients randomized in Val-HeFT (Valsartan Heart Failure Trial) and studied changes in CRP that were associated with valsartan.

Methods and Results—Characteristics of patients with baseline CRP levels above and below the median value were compared. Univariable and multivariable Cox proportional hazards regression models were used to examine the relationship of CRP to mortality and morbidity. Interactions were tested to determine whether differences in CRP changes from baseline to 4 and 12 months between groups randomly assigned to valsartan or placebo depended on baseline ACE inhibitor use. Median plasma CRP was 3.23 mg/L (interquartile range 1.42 to 7.56 mg/L), which is higher than in the general population. Patients with CRP above the median had features of more severe heart failure than those with CRP levels below the median. The cumulative likelihood of death and first morbid event increased with increasing quartile of CRP. Relative to the lowest CRP quartile, the risk of mortality (hazard ratio 1.51, 95% CI 1.2 to 1.9) and first morbid event (hazard ratio 1.53, 95% CI 1.28 to 1.84) was increased in the highest CRP quartile in multivariable models. CRP added incremental prognostic information to that provided by brain natriuretic peptide alone. CRP did not change significantly over time in the placebo group; however, after 12 months, valsartan was associated with a decrease in CRP in patients not receiving ACE inhibitors but not in those receiving ACE inhibitors at 12 months.

Conclusions—CRP is increased in heart failure. Higher levels are associated with features of more severe heart failure and are independently associated with mortality and morbidity. The ability of treatments to reduce CRP levels and the prognostic importance of reducing CRP require further study. (Circulation. 2005;112:1428-1434.)

Key Words: heart failure ■ C-reactive protein ■ prognosis ■ angiotensin receptor blockers ■ inflammation

Inflammation plays an important role in the progression of atherosclerosis.1 High-sensitivity C-reactive protein (CRP) has emerged as an important risk factor for systemic atherosclerosis and is related to its clinical complications.2–5 Activation of the immune system may also play a role in the pathogenesis of heart failure (HF).6,7 Small studies have shown that plasma CRP is elevated in patients with HF.8–10 In several community studies, plasma CRP predicted the development of HF and other adverse events.4,5,11 However, clinical data on the prognostic value of CRP in patients with established HF are limited, inconsistent, and obtained in modest sample sizes.8,9,12 Moreover, there are no data in HF patients to show that agents that may have antinflammatory activity, such as angiotensin receptor blockers, affect plasma CRP.

In this study, we performed a retrospective analysis of the predictive value of baseline CRP for long-term outcomes in patients with moderate to severe HF randomized to valsartan or placebo in the Valsartan Heart Failure Trial (Val-HeFT); we also report the effect of valsartan on plasma CRP.

Methods

Study Design and Patients
Val-HeFT evaluated the efficacy of the angiotensin receptor blocker valsartan versus placebo in 5010 patients with New York Heart Association (NYHA) class II, III, or IV HF.13 The study had 2 primary end points: mortality and the first morbid event (morbidity), which was defined as death, sudden death with resuscitation, hospitalization for HF, or administration of an intravenous inotropic or vasodilator drug for 4 hours or more without hospitalization.

CRP and Biochemical Measurements.
Plasma CRP (mg/L) was measured by a nephelometric analyzer (Dade Behring) in core laboratories at baseline (n=4202) and at
months 4 (n = 3639) and 12 (n = 3165) during follow-up. At the same
time points, neurohormones (brain natriuretic peptide [BNP], nor-
epinephrine, and aldosterone), total protein, albumin, serum creati-
ine, and blood urea nitrogen were also measured. Glomerular
filtration rate was calculated with the Modification of Diet in Renal
Disease Study (MRDS) equation.14

### Statistical Analysis

A \( t \) test, rank sum test, or \( \chi^2 \) test was used, as appropriate for the level of measurement and variable distribution, to compare demographic and clinical characteristics of groups defined by the median CRP value. Four- and 12-month changes in CRP from baseline values were analyzed within the groups randomly assigned to placebo or valsartan with the signed ranks test. The rank sum test was used to compare changes in CRP between groups. In addition, a multivari-
able regression model with change in CRP over 4 or 12 months was
used to test for interaction between the effects of valsartan/placebo
and baseline ACE inhibitor (ACEI)/no ACEI. Spearman rank corre-
ation coefficients were calculated to examine relationships between
variables. A 2-tailed probability value of \( <0.05 \) was considered
statistically significant.

Cox proportional-hazards regression models15 were used to assess
the association between baseline variables and time to death or first
morbidity event. CRP was grouped into quartiles for analysis because
of skewed distribution and undefined relationship to the dependent
variables. Indicator (“dummy”) variables that coded baseline CRP
quartile membership were used to assess the effects of CRP in
multivariable Cox proportional regression models. Thus, adjusted
hazard ratios (HRs) for mortality and first morbid event were calculated for patients in each of the 3 highest CRP quartiles relative to patients in the lowest CRP quartile (reference quartile). SPSS statistical software (version 12.0) was used for all analyses.

**Results**

**Baseline Patient Demographics**

The median value of plasma CRP at baseline in 4202 patients was 3.23 mg/L (interquartile range 1.42 to 7.56), which is higher than that reported in the general population. Baseline characteristics of patients with plasma CRP above and below the median are compared in Table 1. Patients with plasma CRP above the median had features of more severe HF with lower left ventricular ejection fraction; higher heart rate; higher prevalence of atrial fibrillation, third heart sound, and NYHA classes III or IV; poorer quality of life; higher neutrophil counts; and worse neurohormonal profile than those with plasma CRP below the median. Patients with higher CRP were also more likely to be female and to take diuretics and digoxin and were less likely to be taking a β-blocker, statin, or aspirin. Importantly, however, the percentages of patients with ischemic or nonischemic etiology did not differ.

**Association of Baseline Plasma CRP With Mortality and First Morbid Event**

A quartile-dependent increase in the risk of mortality and first morbid event was seen with increasing plasma CRP (Figure 1; Table 2). The fully adjusted relative risks for the second-lowest (Q2), second-highest (Q3), and highest (Q4) quartiles of CRP compared with the lowest quartile (Q1, reference group) were 1.21 \((P=0.10)\), 1.24 \((P=0.07)\), and 1.51 \((P<0.001)\) for mortality and 1.38 \((P=0.01)\), 1.33 \((P=0.003)\), and 1.53 \((P<0.001)\) for the first morbid event (Table 3). The trend for increasing risk of mortality and first morbid event with increasing CRP quartile in Table 3 was highly significant \((P<0.0001)\).

**Interaction Between CRP and BNP**

As shown in Table 3, CRP and BNP were independently related to mortality and morbidity. The interaction between CRP and BNP was analyzed to determine whether the relationship between CRP and mortality and morbidity risk varied with levels of BNP. For this, analyses were conducted with median baseline values of BNP (96 pg/mL) and CRP (3.23 mg/L) for subgroups of patients (Figure 2; Table 4). Cox proportional hazards models were used to adjust for all variables shown in Table 3. When BNP was below the median, the increased risk associated with an above-median CRP level was not significant compared with CRP below the median \((HR 1.15, 95\% CI 0.88 to 1.51, P=0.31)\). When BNP was above the median, the increased risk associated with a CRP above the median was significant compared with CRP below the median \((HR 1.21, 95\% CI 1.01 to 1.46, P=0.04)\). However, the interaction between CRP and BNP was not statistically significant \((P=0.63)\), which indicates that the increased relative risk associated with CRP above the median was not significantly different for those who had a BNP above or below the median value \((HR of 1.15 versus 1.21)\). Because having a BNP or a CRP above median values was independently associated with increased relative risk, having high levels of both was indicative of a particularly high relative risk compared with those with levels below the median values \((HR 2.08, 95\% CI 1.64 to 2.63, P<0.001)\).

**Changes in Plasma CRP in Valsartan and Placebo Groups**

Only 7% of patients in Val-HeFT were not taking ACEIs at baseline. CRP in the group without an ACEI (median

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**Table 2. Relative Risk and 95% CI by Quartiles of Baseline Plasma CRP for Subsequent Mortality and First Morbid Event in All Randomized Patients Unadjusted for Covariates \((n=4202)\)**

<table>
<thead>
<tr>
<th>Baseline Quartiles</th>
<th>Plasma CRP, mg/L</th>
<th>Mortality, %</th>
<th>Relative Risk vs Reference Group</th>
<th>95% CI</th>
<th>(P)</th>
<th>First Morbid Event, %</th>
<th>Relative Risk vs Reference Group</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1, (n=1045)</td>
<td>&lt;1.42</td>
<td>13.1</td>
<td>1.0</td>
<td>Reference group</td>
<td>20.8</td>
<td>1.0</td>
<td>Reference group</td>
<td>20.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Q2, (n=1050)</td>
<td>1.42 to &lt;3.23</td>
<td>17.8</td>
<td>1.36</td>
<td>1.09–1.70</td>
<td>0.006</td>
<td>27.8</td>
<td>1.38</td>
<td>1.15–1.64</td>
<td>0.0004</td>
</tr>
<tr>
<td>Q3, (n=1056)</td>
<td>3.23 to &lt;7.32</td>
<td>19.9</td>
<td>1.56</td>
<td>1.25–1.93</td>
<td>0.0001</td>
<td>32.2</td>
<td>1.66</td>
<td>1.40–1.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q4, (n=1051)</td>
<td>≥7.32</td>
<td>25.3</td>
<td>2.06</td>
<td>1.67–2.5</td>
<td>&lt;0.0001</td>
<td>38.6</td>
<td>2.11</td>
<td>1.79–2.49</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(Q\) indicates quartile.
3.84 mg/L, interquartile range 1.53 to 7.9, n=297) was somewhat higher but not significantly different from CRP in patients taking an ACEI (3.21 mg/L, interquartile range 1.42 to 7.51, n=3905, P=0.16). The interaction between valsartan/placebo and baseline ACEI/no ACEI in a multivariable regression analysis of changes in CRP levels over 12 months was nearly significant (P=0.059), which suggests that valsartan might have a different effect on CRP depending on use of an ACEI at baseline. The changes in CRP in the valsartan and placebo patients subgrouped by baseline ACEI use are shown in Figure 3. In the group with no ACEI use, CRP remained unchanged at 4 and 12 months in placebo patients. CRP deceased in the valsartan group at 4 (P=0.04) and 12 (P=0.02) months. However, the changes in CRP between the small placebo and valsartan subgroups without an ACEI at baseline were not significantly different. The changes in CRP in the valsartan and placebo patients subgrouped by baseline ACEI use are shown in Figure 3.

### Table 3. Cox Multiple Regression Results for Mortality and First Morbid Event, Including Baseline Plasma CRP Quartile Groupings and Other Baseline Prognostic Factors That Were Significant in a Univariable Analysis, Sorted by Decreasing Order of Significance for Mortality (n=3792)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mortality</th>
<th>First Morbid Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>BNP, pg/mL†</td>
<td>1.010 1.007 1.012</td>
<td>1.009 1.007 1.011</td>
</tr>
<tr>
<td>LVIdd/BSA, cm/m²</td>
<td>1.60 1.39 1.84</td>
<td>1.52 1.36 1.70</td>
</tr>
<tr>
<td>Nonischemic/ischemic</td>
<td>0.71 0.60 0.85</td>
<td>0.81 0.71 0.93</td>
</tr>
<tr>
<td>NYHA class I-II-III-IV</td>
<td>1.34 1.15 1.57</td>
<td>1.52 1.34 1.72</td>
</tr>
<tr>
<td>CRP quartile 4 vs quartile 1</td>
<td>1.51 1.20 1.90</td>
<td>1.53 1.28 1.84</td>
</tr>
<tr>
<td>β-Blocker use, yes/no</td>
<td>0.76 0.64 0.90</td>
<td>0.79 0.69 0.90</td>
</tr>
<tr>
<td>Male/female</td>
<td>1.46 1.16 1.84</td>
<td>1.17 0.99 1.39</td>
</tr>
<tr>
<td>Uric acid, μmol/L‡</td>
<td>1.02 1.01 1.03</td>
<td>1.02 1.01 1.03</td>
</tr>
<tr>
<td>GFR, mL/min⁻¹.73 m⁻²</td>
<td>0.991 0.984 0.997</td>
<td>0.99 0.986 0.996</td>
</tr>
<tr>
<td>CRP quartile 3 vs quartile 1</td>
<td>1.24 0.99 1.57</td>
<td>1.33 1.10 1.59</td>
</tr>
<tr>
<td>LVEF, %*</td>
<td>0.95 0.90 1.01</td>
<td>0.95 0.914 0.997</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>0.95 0.90 1.01</td>
<td>0.96 0.92 1.001</td>
</tr>
<tr>
<td>CRP quartile 2 vs quartile 1</td>
<td>1.21 0.96 1.53</td>
<td>1.28 1.06 1.54</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL⁻¹·h⁻¹†</td>
<td>1.02 0.99 1.05</td>
<td>1.02 0.99 1.04</td>
</tr>
<tr>
<td>Aldosterone, pg/mL†</td>
<td>1.004 0.999 1.009</td>
<td>1.003 0.999 1.007</td>
</tr>
<tr>
<td>Statin use, yes/no</td>
<td>0.89 0.75 1.05</td>
<td>0.97 0.85 1.11</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.006 0.996 1.014</td>
<td>1.003 0.996 1.009</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL‡</td>
<td>1.002 0.992 1.009</td>
<td>1.001 0.997 1.005</td>
</tr>
<tr>
<td>Aspirin use, yes/no</td>
<td>0.98 0.84 1.14</td>
<td>0.94 0.83 1.06</td>
</tr>
<tr>
<td>Treatment, valsartan vs placebo</td>
<td>0.98 0.85 1.14</td>
<td>0.85 0.76 0.96</td>
</tr>
</tbody>
</table>

LVIDd/BSA indicates left ventricular internal diastolic diameter/body surface area; GFR, glomerular filtration rate; and LVEF, left ventricular ejection fraction.

*For every 5-unit increase; †for every 10-unit increase; ‡for every 20-unit increase.
different at 4 \((P=0.47)\) or 12 \((P=0.14)\) months. In patients taking an ACEI at baseline, no meaningful change in CRP was seen for either placebo or valsartan at 4 or 12 months.

**Discussion**

It has long been recognized that patients with HF may manifest some of the clinical features observed in chronic inflammatory conditions.\(^\text{17}\) The findings that several proinflammatory cytokines may be involved in the pathogenesis of ventricular dysfunction\(^6,18\) and may contribute to the cachexia of severe HF\(^19\) have led to a resurgence of interest in the role of inflammation and its markers, such as CRP, in HF. The results of the present study show that CRP is increased in HF, patients with higher CRP have features of more severe HF, and plasma CRP is independently related to subsequent mortality and morbidity. The present study also found a signal to suggest that valsartan may cause a modest decrease in plasma CRP in patients not receiving ACEI at baseline.

CRP is a product of inflammation whose synthesis by the liver is stimulated by cytokines in response to an inflammatory stimulus.\(^20\) CRP activates the classic complement pathway and participates in the opsonization of ligands for phagocytosis.\(^21\) Previous investigators have shown that an increase in plasma CRP increases the risk of myocardial infarction and subsequent mortality.\(^2,3,5,22,23\) The results of the present study extend these observations and show that CRP may also have important pathophysiological and prognostic implications in patients with HF. However, CRP levels were almost identical in patients with ischemic and nonischemic HF etiology (6.4\(\times\)9.5 versus 6.5\(\times\)10.7 mg/L, \(P=0.76\)), and high CRP was associated with increased mortality independent of ischemic/nonischemic etiology. CRP was related to mortality and morbid events even when other known risk factors were in the analysis, which suggests there might be a unique link between CRP and risk. These data therefore suggest that the role of CRP in HF may be independent of atherosclerosis. However, the diagnosis of HF etiology was clinical and not based on coronary angiographic findings.

The mechanism by which CRP is increased in patients with HF is unknown. Interleukin-6 is the primary determinant of the hepatic production of CRP\(^24\) and is produced in monocytes/macrophages, endothelial cells, vascular smooth muscle cells, fibroblasts, and cardiac myocytes under hypoxic stress.\(^10,24,25\) Left ventricular dysfunction, hepatic or renal organ damage induced by low cardiac output, hypoperfusion, hypoxia, and venous congestion may all be sources of increased interleukin-6 and hence CRP production.\(^18\) Vasan and colleagues found that serum interleukin-6 is related to CRP.\(^7\) Our data show that of all the variables measured in Val-HeFT, absolute neutrophil count, another marker of

| Subgroups | n | CRP, mg/L, Median (IQR) | BNP, pg/mL, Median (IQR) | % Events | HR | 95% CI | P | % Events | HR | 95% CI | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CRP \(\leq 3.23\) mg/L | 2017 | 1.43 (0.8–2.3) | \(\ldots\) | 15.5 | Reference group | 24.3 | Reference group |
| CRP \(>3.23\) mg/L | 2036 | 7.6 (5.0–12.6) | \(\ldots\) | 22.6 | 1.23 | 1.05–1.44 | 0.009 | 35.5 | 1.29 | 1.14–1.46 | \(<0.001\) |
| BNP \(\leq 96\) pg/mL | 1998 | \(\ldots\) | 40 (20–64) | 12 | Reference group | 19.3 | Reference group |
| BNP \(>96\) pg/mL | 2055 | \(\ldots\) | 237 (147–389) | 26.5 | 1.74 | 1.46–2.07 | \(<0.0001\) | 41.3 | 1.93 | 1.69–2.21 | \(<0.0001\) |
| BNP \(=\) median, 96 pg/mL | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) |

Table 4. All-Cause Mortality and First Morbid Event in Groups According to CRP and BNP Median Levels

HR and 95% CIs have been calculated against the reference group with a Cox multiple regression model that included all baseline prognostic factors shown in Table 3 except for BNP and CRP. All \(P\) values are against the reference group.

Figure 3. Effect of valsartan vs placebo on median changes in plasma CRP from baseline to 4 and 12 months in patients subgrouped by baseline use of ACEI. The number of patients in each treatment arm at 4 and 12 months is shown in the Figure.
systemic inflammation, had the highest correlation with CRP ($p=0.36, P<0.0001$), whereas lymphocytes and monocytes were less correlated with CRP ($p=-0.05, P<0.001$ and $p=-0.10, P<0.01$ respectively).

It is unclear whether CRP is merely a marker of inflammation or directly modulates the disease process. Plasma CRP may increase as a response to the pathophysiological processes that drive progressive ventricular remodeling. It is also possible that the association between plasma CRP and the syndrome of HF is a causal one. CRP may activate the complement system and stimulate cytokine production and thereby cause myocyte loss and promote left ventricular remodeling and dysfunction. CRP was shown to attenuate nitric oxide production and has a direct proinflammatory effect on human endothelial cells. Thus, CRP could worsen HF through multiple mechanisms.

CRP was associated with a quartile-dependent increase in mortality and morbidity even after adjustment for other significant predictors of HF mortality and morbidity, including BNP (Table 3). Compared with patients in the lowest quartile of CRP, the adjusted risk of mortality and first morbidity event were increased by 1.5 in the highest CRP quartile (Table 3). The correlation between baseline CRP and BNP was small ($p=0.12, P<0.01$), and the relationship between CRP and risk did not depend on BNP. In this population, BNP and changes in BNP were found to be powerful predictors of events. Here, we show that in the same sample, patients who had both CRP and BNP levels above the median values had twice the risk of those with levels of both markers below the median. Thus, CRP can be utilized to complement other markers used to identify high-risk patients with HF.

Several studies have assessed the effects of pharmacological and other therapies on plasma CRP in patients with coronary heart disease. Although therapeutic lifestyle modifications and exercise training have been shown to reduce CRP, statins and aspirin remain the major treatment option available to the clinician pursuing therapy for elevated CRP. Blockade of the renin-angiotensin system with ACE inhibitors has recently been shown to have antiinflammatory effects. Despite existing knowledge concerning the role of inflammation in the progression of HF, no clinical data are currently available on the role of inhibiting inflammatory activity in this condition. In our post hoc analysis, we found that valsartan was associated with a significant within-treatment decrease in CRP in the small number of patients who were not taking an ACEI but no meaningful change in those who were taking an ACEI. These findings suggest that the effect of valsartan on CRP, if any, may be diminished in patients already receiving blockade of the renin-angiotensin system with an ACEI. A larger sample of patients who are not taking an ACEI is needed to confirm the suggestion that valsartan can reduce CRP levels.

The present analysis has several limitations. It was a post hoc analysis of the Val-HeFT database, which was not designed to address the present findings. The difference in the effect of valsartan on CRP levels between the ACEI/non-ACEI subgroups based on a test for a valsartan-by-ACEI interaction was of borderline significance ($P=0.059$). Moreover, the effect of improvement versus worsening of HF on CRP, independent of any drug effect, is difficult to assess. The present findings are therefore hypothesis generating rather than conclusive statements about the role of CRP in HF and the ability of valsartan to reduce CRP levels. Furthermore, because we did not attempt to find the best-fitting multivariable model of time to death or first morbidity event, model misspecification and overfitting might limit generalization of the results.

In summary, the results of the present study show a direct relationship between elevated plasma CRP and the progression of HF. Higher plasma CRP is associated with a worse hemodynamic and neurohormonal profile and a poorer quality of life. CRP is a predictor of adverse clinical outcomes, independent of ischemic/nonischemic etiology and other predictors of adverse outcomes. The relationship between CRP and risk was independent of value of BNP. Thus, measurement of CRP may provide additional prognostic information as an adjunct for global risk assessment in patients with HF. These data raise important questions about the role of inflammation in the progression of HF. Further studies designed to investigate the role of inflammation in HF are needed to guide tests of therapies aimed at inhibiting it.

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Disclosure
Drs Glazer and Hester are employees of Novartis Pharmaceuticals Corp.

References


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