Prognostic Significance of the Centers for Disease Control/American Heart Association High-Sensitivity C-Reactive Protein Cut Points for Cardiovascular and Other Outcomes in Patients With Stable Coronary Artery Disease

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Background—Data supporting the prognostic significance of high-sensitivity C-reactive protein (hs-CRP) are derived largely from individuals with no overt coronary artery disease or from patients with acute coronary syndromes. In contrast, the ability of hs-CRP to predict outcomes in patients with stable coronary artery disease and the prognostic significance of the Centers for Disease Control/American Heart Association hs-CRP cut points in such a population remain relatively unexplored.

Methods and Results—We measured hs-CRP in 3771 patients with stable coronary artery disease from the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial, a randomized placebo-controlled trial of the angiotensin-converting enzyme inhibitor trandolapril. Patients were followed up for a median of 4.8 years for cardiovascular death, myocardial infarction, or stroke, as well as new heart failure and diabetes. After adjustment for baseline characteristics and treatments, higher hs-CRP levels, even >1 mg/L, were associated with a significantly greater risk of cardiovascular death, myocardial infarction, or stroke (hs-CRP 1 to 3 mg/L: adjusted hazard ratio, 1.39; 95% CI, 1.06 to 1.81; \( P = 0.016 \); hs-CRP >3 mg/L: adjusted hazard ratio, 1.52; 95% CI, 1.15 to 2.02; \( P = 0.003 \)). Similarly, elevated hs-CRP levels were an independent predictor of new heart failure (adjusted \( P < 0.001 \) for trend) and new diabetes (adjusted \( P < 0.001 \) for trend). There were no significant interactions between hs-CRP levels and the effects of trandolapril on any of the above outcomes.

Conclusions—In stable coronary artery disease, an elevated hs-CRP level, even >1 mg/L, is a significant predictor of adverse cardiovascular events independently of baseline characteristics and treatments. An elevated hs-CRP does not appear to identify patients with stable coronary artery disease and preserved ejection fraction who derive particular benefit from angiotensin-converting enzyme inhibition. (Circulation. 2007;115:1528-1536.)

Key Words: coronary disease \( \bullet \) C-reactive protein \( \bullet \) inflammation \( \bullet \) risk factors

The contribution of inflammation to the pathobiology of atherosclerosis is well characterized. In that regard, elevated levels of C-reactive protein (CRP), a biomarker of inflammation, have been shown to predict vascular events. However, the data supporting the prognostic significance of CRP are derived largely from populations at 2 extremes: individuals with no overt coronary artery disease (CAD)\(^1-4\) or patients with acute coronary syndromes.\(^5-8\) In contrast, there is a paucity of data that address the prognostic significance of CRP in patients with established, stable CAD, a population estimated to be >13 million in the United States alone.

Clinical Perspective p 1536

The data that do exist were generated largely before statin use was common.\(^9,10\) Two studies that recorded statin use reported that CRP was not a significant predictor of clinical events in patients on statin therapy.\(^11,12\) Moreover, these older studies used quantile analysis; thus, each study used different CRP concentrations to define patients at high risk. More
recently, however, the Centers for Disease Control (CDC) and the American Heart Association (AHA) have issued a joint statement that recommends categorizing patients using predefined CRP cut points of <1, 1 to 3, and >3 mg/L into low-, average-, and high-risk categories, respectively.13

Our goal was to determine the independent prognostic significance of the CDC/AHA high-sensitivity (hs)-CRP risk categories in a large, contemporary cohort of patients with established but stable CAD who were receiving modern medical therapy. In addition, we wanted to explore the ability of hs-CRP to predict not only traditional cardiovascular events such as cardiovascular death, myocardial infarction (MI), and stroke but also other clinical outcomes with a potential inflammatory component, including new-onset heart failure and diabetes mellitus. We also sought to determine whether baseline hs-CRP levels affected the magnitude of effect of the angiotensin-converting enzyme (ACE) inhibitor trandolapril on cardiovascular and other clinical outcomes. To accomplish these goals, we measured hs-CRP in 3771 patients with stable CAD enrolled in the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial, a randomized placebo-controlled trial of the ACE inhibitor trandolapril.

### Methods

#### Patient Population

The design and primary results of the PEACE trial have been published.14,15 In brief, 8290 patients with documented stable CAD (defined as an MI at least 3 months before enrollment, coronary revascularization at least 3 months before enrollment, or obstruction of ≥50% of the luminal diameter of at least 1 native vessel on coronary angiography) and preserved left ventricular systolic function were assigned randomly to trandolapril or placebo. Median follow-up was 4.8 years. Cardiovascular death, MI, and stroke were adjudicated in a blinded fashion by an independent morbidity and mortality review committee using medical records. New-onset heart failure was recorded if it was a documented fatal or hospitalized event. Diabetes mellitus was based on patient report of having been diagnosed by a physician.

#### Biomarker Analyses

As part of the study protocol, a sample of blood was obtained at the time of enrollment in 3778 subjects and at a follow-up visit (range, 6 months to 6 years from randomization; median, 3 years) in 2777 subjects. Samples were obtained at both baseline and a follow-up visit in 1961 subjects. Plasma was frozen and shipped to a central laboratory, where samples were stored at −70°C or colder until thawed for determination of biomarkers.

Aliquots were shipped frozen on dry ice to the Thrombolysis in Myocardial Infarction Biomarker Laboratory (Boston, Mass) for hs-CRP testing using the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken, Tokyo, Japan). This assay has a minimal detectable concentration of 0.03 mg/L and a total imprecision of 5.1% and 2.5% at concentrations of 0.2 and 1.9 mg/L, respectively.16 All testing was performed by personnel blinded to clinical outcomes and treatment allocation.

#### Statistical Analyses

Patients were divided into 3 groups on the basis of the CDC/AHA-recommended hs-CRP cut points (<1, 1 to 3, and >3 mg/L). In terms of baseline characteristics, differences between continuous variables were assessed with ANOVA and between categorical variables with χ² tests. Cumulative event rate curves were calculated with the Kaplan-Meier method. Cox proportional hazards models were used to calculate hazard ratios (HRs) adjusted only for randomized treatment arm and then also adjusted for components of the Framingham coronary disease risk prediction score, including age, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, history of diabetes, and current smoking, as well as body mass index, history of hypertension, history of MI, estimated glomerular filtration rate, and use of aspirin, β-blockers, and lipid-lowering therapy. Schoenfeld residuals and the log survivor function were used to verify that the proportional-hazards assumption was not violated. Residual analysis was used to assess model fit. The linearity index was used to check for linear combinations among covariates. For models predicting heart failure, left ventricular ejection fraction also was included. Analyses for incident diabetes were restricted to patients who did not report a history of diabetes at baseline (n = 3151). Interaction between hs-CRP and treatment assignment was tested by incorporation of formal interaction terms in the models.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

Baseline hs-CRP measurements were available in 3771 patients. There were no clinically relevant differences in the baseline characteristics or outcomes of patients who did and did not participate in the biomarker study (data not shown). Per the protocol, all patients had stable CAD. Fifty-six percent of patients had a prior MI, and 73% had undergone coronary revascularization (either percutaneous coronary intervention or coronary artery bypass graft surgery), both at a minimum of 3 months before enrollment. The median concentration of hs-CRP was 1.71 mg/L; the 25th and 75th percentiles were 0.83 and 3.50 mg/L, respectively. Using the CDC/AHA-recommended CRP cut points showed that 1168 patients (31%) had a baseline hs-CRP <1 mg/L, 1494 (40%) had an hs-CRP of 1 to 3 mg/L, and 1109 (29%) had an hs-CRP >3 mg/L.

Follow-up hs-CRP levels were measured after a median of 3 years (range, 6 months to 6 years) and did not differ significantly from baseline levels in either the placebo (median difference, 0 mg/L; interquartile range, −0.9 to 0.6 mg/L) or trandolapril (−0.1 mg/L; interquartile range, −0.8 to 0.6 mg/L) arm.

Characteristics at enrollment of patients divided into the 3 hs-CRP categories are shown in Table 1. Higher baseline hs-CRP levels were significantly associated with female sex and traditional cardiovascular risk factors such as hypertension, diabetes, smoking, hypercholesterolemia, and higher body mass index. Lower baseline hs-CRP levels were seen in patients taking lipid-lowering therapy.

#### Cardiovascular Death, MI, and Stroke

Higher baseline hs-CRP levels were associated with a significantly greater risk of the composite of cardiovascular death, MI, or stroke during an average of 4.8 years of follow-up (P < 0.001; Figure 1). The absolute event rate of cardiovascular death, MI, or stroke over the course of follow-up was 7.4% in those with an hs-CRP <1 mg/L, 11.3% in those with an hs-CRP of 1 to 3 mg/L, and 12.8% in those with an hs-CRP >3 mg/L. In a Cox proportional hazards model, compared with those with an hs-CRP <1 mg/L, patients with an hs-CRP of 1 to 3 mg/L were at a 57% increased risk of suffering cardiovascular death, MI, or stroke (HR, 1.57; 95%
CI, 1.21 to 2.03; \( P < 0.001 \)), and those with an hs-CRP >3 mg/L were at an 78% increased risk of suffering such adverse outcomes (HR, 1.78; 95% CI, 1.37 to 2.33; \( P < 0.001 \)). There was directional consistency for all 3 components of the composite end point (data not shown). Of note, compared with hs-CRP <1 mg/L, those with very high hs-CRP levels (>10 mg/L) were at especially high risk (HR, 2.27; 95% CI, 1.47 to 3.49; \( P < 0.001 \)). Higher levels of hs-CRP also predicted all-cause mortality (hs-CRP 1 to 3 mg/L: HR, 1.49; 95% CI, 1.10 to 2.01; \( P = 0.009 \); hs-CRP >3 mg/L: HR, 1.78; 95% CI, 1.31 to 2.42; \( P < 0.001 \)).

The association between hs-CRP and cardiovascular death, MI, or stroke was apparent both in patients randomized to trandolapril and in those randomized to placebo with no significant heterogeneity (Figure 2). Similarly, the effect of trandolapril on the incidence of cardiovascular death, MI, or stroke was similar in magnitude and not statistically significant in all 3 hs-CRP groups, with no evidence of heterogeneity.

The association between an elevated hs-CRP and cardiovascular death, MI, or stroke was consistent across multiple clinically important subgroups. Specifically, regardless of the patient’s sex, coronary revascularization status, and use of lipid-lowering therapy, an elevated baseline hs-CRP was associated with an increased risk of cardiovascular death, MI, or stroke (Figure 3).

After adjustment for elements from the Framingham risk model, including age, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, history of diabetes, and smoking, as well as body mass index, history of hypertension, history of MI, estimated glomerular filtration rate, and use of aspirin, \( \beta \)-blocker, and lipid-lowering therapy, hs-CRP remained a significant predictor of cardiovascular death, MI, or stroke (\( P = 0.004 \) for trend; Figure 4). Compared with those with an hs-CRP <1 mg/L, patients with an hs-CRP 1 to 3 mg/L had an adjusted HR of 1.39 (95% CI, 1.06 to 1.81; \( P = 0.016 \)) and patients with an hs-CRP >3 mg/L had an adjusted HR of 1.52 (95% CI, 1.15 to 2.02, \( P = 0.003 \)) for cardiovascular death, MI, or stroke. The adjusted associations with individual components of the composite end point are shown in Table 2.

### New-Onset Heart Failure
Higher baseline hs-CRP levels also were associated with a significantly greater risk of new heart failure (106 cases) (\( P < 0.001 \); Figure 5). The association between hs-CRP and heart failure was apparent both in patients randomized to trandolapril and in those randomized to placebo with no significant heterogeneity. Analogously, there was no statisti-
cally significant difference in the magnitude of the effect of trandolapril on the incidence of heart failure (25% reduction in the overall PEACE trial) across the CRP categories. Nonetheless, given the higher absolute event rates, only 35 patients with stable CAD and an hs-CRP >3 mg/L needed to be treated with trandolapril for a median of 4.8 years to have prevented the development of 1 new case of heart failure. After adjustment for all of the previously mentioned covariates plus left ventricular ejection fraction, hs-CRP remained a significant predictor of heart failure ($P<0.001$ for trend).

Compared with those with an hs-CRP <1 mg/L, patients with an hs-CRP of 1 to 3 mg/L had an adjusted HR of 1.55 (95% CI, 0.83 to 2.92; $P=0.17$) and patients with an hs-CRP >3 mg/L had an adjusted HR of 2.83 (95% CI, 1.54 to 5.22; $P<0.001$) for heart failure. In sensitivity analyses in which MI during the follow-up period was added as a time-varying covariate and in which patients who developed an interim MI were censored, an elevated hs-CRP remained a significant predictor of new heart failure ($P<0.001$ for trend for both fully adjusted models).

**New-Onset Diabetes Mellitus**

Higher baseline hs-CRP levels also were associated with a significantly greater risk of new-onset diabetes mellitus among the 3151 patients without diabetes at enrollment (339 cases) ($P<0.001$; Figure 6). The association between hs-CRP and diabetes was apparent both in patients randomized to trandolapril and in those randomized to placebo with no significant heterogeneity. Similarly, the effect of trandolapril on the incidence of diabetes (17% reduction in the overall PEACE trial) was of comparable magnitude across the CRP categories.

After adjustment for all of the previously mentioned covariates, hs-CRP remained a significant predictor of diabetes ($P<0.001$ for trend). Compared with those with an hs-CRP <1 mg/L, patients with an hs-CRP of 1 to 3 mg/L had an adjusted HR of 1.80 (95% CI, 1.34 to 2.42; $P<0.001$) and patients with an hs-CRP >3 mg/L had an adjusted HR of 1.96 (95% CI, 1.43 to 2.68; $P<0.001$) for diabetes.

**Discussion**

We found that in patients with stable CAD, an elevated hs-CRP was a strong predictor of cardiovascular death, MI, or stroke, even after adjusting for baseline characteristics and treatments. Increased risk was apparent even in patients with what is considered an average hs-CRP of 1 to 3 mg/L. Moreover, an elevated hs-CRP was associated with a significantly increased risk of new heart failure and new diabetes.

![Figure 1. Cumulative incidence curves for cardiovascular death, MI, or stroke by hs-CRP group.](image1)

**Table 1.**

<table>
<thead>
<tr>
<th>CRP Group</th>
<th>Number at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mg/L</td>
<td>1168</td>
<td>1139</td>
</tr>
<tr>
<td>1-3 mg/L</td>
<td>1494</td>
<td>1443</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>1109</td>
<td>1077</td>
</tr>
</tbody>
</table>

![Figure 2. Rate of cardiovascular death, MI, or stroke by hs-CRP group and treatment group. Solid bars indicate patients randomized to placebo; striped bars, patients randomized to trandolapril.](image2)
Interestingly, the magnitude of the relative benefit of ACE inhibition with trandolapril on the incidence of diabetes and heart failure was not affected by baseline hs-CRP concentration.

The pathophysiological basis for the association between CRP and cardiovascular events remains a topic of intense study. It is well recognized that inflammation plays a critical role in the development and progression of atherosclerosis. CRP may be a marker of a proinflammatory milieu and, among the inflammatory biomarkers, may show the most robust association with clinical events because of its biological stability and ability to measure levels with a high degree of precision. CRP, however, also may be a direct risk factor.17 This supposition is supported by several lines of evidence, including the ability of CRP to activate complement and the colocalization of CRP and complement in ruptured atherosclerotic plaques,18 to bind to leukocytes and endothelial cells and to cause both upregulation of adhesion molecules and decreased production of nitric oxide,19 and to induce atherosclerosis, thrombosis, and increase infarct size in transgenic animal models.20

In analogous fashion, the link between CRP and heart failure may stem both from the cardiotoxic effects of associated proinflammatory cytokines such as tumor necrosis factor-α and from direct effects of CRP on secretion of endothelin-1 and upregulation of angiotensin type-1 receptors.21 With regard to the development of diabetes, activation of the innate immune system may contribute directly to the pathogenesis of type II diabetes mellitus.22 Associated proinflammatory cytokines such as tumor necrosis factor-α inhibit the tyrosine kinase activity of the insulin receptor.23 Additionally, CRP-induced endothelial dysfunction at the arteriolar and capillary levels may further contribute to insulin resistance.24

Figure 3. Association of hs-CRP with the risk of cardiovascular death, MI, or stroke in various subgroups. Subgroup analyses are based on available data for each characteristic. The association in the overall study population is represented by the diamonds, the left and right borders of which indicate the 95% CI. The squares indicate the adjusted HRs, and the size of each box is proportional to the number of patients in the individual analysis. The horizontal lines represent the 95% CIs.

Figure 4. Multivariable adjustment for the association of hs-CRP with the risk of cardiovascular death, MI, or stroke. Adjusted (adj) HRs (squares) and 95% CIs (vertical bars) are shown. See Methods for a list of covariates in the model.
Although the underlying pathobiology remains under study, the overall epidemiological data supporting the association between CRP and adverse cardiovascular outcomes are clear. To that end, the CDC and the AHA have now recognized the prognostic utility of hs-CRP in a joint statement. Yet, as hs-CRP makes the transition from a tool used by researchers to one used by clinicians, several issues need to be resolved. In particular, the most appropriate cut points to use and the prognostic implications of CRP levels above those cut points in different populations remain incompletely defined.

With regard to specific previous studies, the European Concerted Action on Thrombosis investigators examined the prognostic utility of CRP in patients with angina. A highsensitivity assay was not used, however, so CRP levels were undetectable in 30% of patients, and the association was of borderline statistical significance. A subsequent analysis specifically used a high-sensitivity assay and found an association between higher CRP levels and coronary events. In this population, however, which included both patients with stable and patients with unstable angina, there were only 75 coronary events during the 2 years of follow-up, and excess risk was demonstrated only when hs-CRP levels were in the top quintile (>3.6 mg/L), with no evidence for a gradient of risk across the lower quintiles. Moreover, the association between CRP levels and coronary events was greatly attenuated and no longer significant in patients randomized to statin therapy. An association between hs-CRP and cardiovascular outcomes has been seen in 2 cohorts of patients with angiographically proven coronary artery disease. However, both studies included a mix of patients with stable and unstable angina, and the latter group is known to have acutely elevated levels of CRP and a worse prognosis. Moreover in one of the studies, only CRP in the top quartile (>12.7 mg/L) was a significant predictor of cardiovascular events, and this association was no longer apparent in patients taking a statin.

In contrast, using a large cohort of patients with stable CAD, we have been able to significantly widen our understanding of the prognostic impact of particular hs-CRP levels. Specifically, we were able to prospectively apply the CDC/AHA hs-CRP cut points and demonstrate that an elevated level of hs-CRP, even >1 mg/L, was associated with an increased risk of cardiovascular death, MI, or stroke. The risk was consistent across all the elements of the composite end point and remained significant even after adjustment for elements of the Framingham Risk Score and other clinical and laboratory parameters. These data suggest that among patients with CAD, hs-CRP levels can be used to gain fundamental insight into which patients are, despite being asymptomatic at a given time and hence deemed clinically stable, in fact pathobiologically unstable and at higher risk for adverse cardiovascular events. However, an elevated hs-CRP does not appear to identify patients with stable CAD and preserved ejection fraction who derive particular benefit from ACE inhibition.
With regard to hs-CRP and new-onset heart failure and diabetes, there have been previous reports of associations, primarily in healthy individuals with few numbers of events and typically at much higher CRP levels. We build on these observations by demonstrating that elevated levels of hs-CRP predict the development of new-onset heart failure and new-onset diabetes in patients with established CAD, even after adjustment for other relevant clinical and laboratory parameters. In the PEACE trial, treatment with an ACE inhibitor resulted in reductions in the development of both heart failure and diabetes. Previous investigators have postulated that the antiinflammatory properties of ACE inhibitors may have contributed to this effect. Yet we found no evidence for an interaction between hs-CRP, a global barometer of systemic inflammation, and the relative efficacy of trandolapril in reducing either heart failure or diabetes. Thus, our data suggest that the mechanisms by which ACE inhibition reduces the likelihood of these events are distinct from inflammation, at least as measured systemically by hs-CRP. To that end, we found no effect of ACE inhibition on hs-CRP levels, a finding that is supported by data from small, short-term studies of hs-CRP levels after initiation of ACE inhibition and is of interest given other data indicating that angiotensin receptor blockade therapy reduces hs-CRP.

Potential limitations of the present study merit consideration. The study population was derived from a clinical trial, not a population cohort. Because PEACE excluded patients with heart failure, a left ventricular ejection fraction $\leq 40\%$, or a serum creatinine $>2.0$ mg/dL, we cannot comment on the utility of hs-CRP in patients with those characteristics. In general, though, the characteristics of patients in the present study are typical of patients with stable CAD. The cardiovascular event rates in PEACE were lower than seen in previous cohorts with stable CAD, possibly reflecting more modern and aggressive medical therapy and coronary revascularization. However, the relative health of this cohort should not alter the validity of our results. Only 19% of the patients were women. Although there was no statistically significant heterogeneity in terms of the predictive ability of hs-CRP in men versus in women, the small size of the latter subgroup created wide CIs that limit our ability to comment on optimal thresholds. Blood samples were obtained from only a subgroup of the participants in the overall PEACE trial. There were no clinically relevant differences between patients who did and did not participate in the biomarker substudy, however. Only a single baseline CRP measurement was used to categorize patients. As per the CDC/AHA guidelines, measurement ideally should be done twice (averaging results), and very high levels should prompt an investigation for sources of infection or inflammation. Fasting blood samples were not mandated, which prevented us from measuring fasting glucose, insulin, or lipid fractions. Heart failure and diabetes were not adjudicated by a clinical events committee. However, any misclassification should be random with respect to CRP status and thus should only bias toward the null hypothesis.

**Conclusions**

In patients with stable CAD and a preserved ejection fraction, the majority of whom were men and had only mild or no renal dysfunction, an elevated level of hs-CRP, even in the average range of 1 to 3 mg/L, is a strong predictor of cardiovascular death, MI, and stroke, new heart failure, and new diabetes, independent of baseline characteristics and treatments. Although CRP offers prognostic value, there is currently no mandate to measure CRP in all patients with CAD because therapies such as statins that display a gradient of benefit based on baseline CRP levels are already routinely prescribed. Although use of ACE inhibitors is controversial and not universal in this patient population, our data suggest that hs-CRP levels do not identify patients who derive particular benefit from ACE inhibition. Data from studies of statin therapy suggest that patients with CAD who have a persistently elevated hs-CRP level remain at increased risk of adverse cardiovascular events and that lower levels of hs-CRP are achieved with more intensive statin therapy. However, we await the results of prospective trials that target therapy based on CRP levels. Depending on the data that emerge, CRP may then join the other classic risk factors that we routinely measure and treat.

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References

CLINICAL PERSPECTIVE

There is a paucity of data that address the prognostic significance of C-reactive protein (CRP) in patients with established, stable coronary artery disease, a population estimated to be >13 million in the United States alone. We measured high-sensitivity (hs)-CRP in 3771 patients with stable coronary artery disease enrolled in the Prevention of Events With Angiotensin-Converting Enzyme Inhibition trial, a randomized placebo-controlled trial of the angiotensin-converting enzyme inhibitor trandolapril. We found that elevated hs-CRP was a strong predictor of cardiovascular death, myocardial infarction, or stroke, even after adjustment for baseline characteristics and treatments. Increased risk was apparent even in patients with what is considered an average hs-CRP of 1 to 3 mg/L. Moreover, an elevated hs-CRP was associated with a significantly increased risk of new-onset heart failure and new-onset diabetes. These data suggest that among patients with coronary artery disease, hs-CRP levels can be used to gain fundamental insight into which patients are, despite being asymptomatic at a given time, at higher risk for adverse cardiovascular events. Interestingly, however, an elevated hs-CRP did not appear to identify patients who derived particular benefit from angiotensin-converting enzyme inhibition. Although CRP offers prognostic value, there is currently no mandate to measure CRP in all patients with coronary artery disease because therapies such as statins that display a gradient of benefit based on baseline CRP levels are already routinely prescribed. Ongoing trials will clarify whether targeting therapy based on CRP levels and even targeting CRP itself will be of benefit to patients.
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