Clinical Relevance of C-Reactive Protein During Follow-Up of Patients With Acute Coronary Syndromes in the Aggrastat-to-Zocor Trial

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Background—Elevated levels of high-sensitivity C-reactive protein (hsCRP) are associated with higher risk of adverse outcomes in patients at risk for or with established coronary artery disease. Retrospective analyses suggest that this risk may be modified with statin therapy. However, a role for hsCRP in monitoring the success of therapy remains uncertain.

Methods and Results—We measured the serum concentration of hsCRP at 30 days (n=3813) and 4 months in patients with non–ST-elevation or ST-elevation acute coronary syndrome randomly assigned to an early intensive versus delayed conservative simvastatin strategy in the Aggrastat-to-Zocor Trial. Patients with hsCRP >3 mg/L at 30 days had significantly higher 2-year mortality rates than those with hsCRP 1 to 3 mg/L or hsCRP <1 mg/L (6.1% versus 3.7% versus 1.6%, P <0.0001). Results were similar with hsCRP measured at 4 months. After adjusting for age, gender, diabetes, smoking, cardiovascular history, index event, lipid levels, and randomly assigned treatment, patients with hsCRP >3 mg/L were at more than 3-fold higher risk of death (HR, 3.7; 95% CI, 1.9 to 7.2) compared with those with hsCRP <1 mg/L. “Average” levels of hsCRP (1 to 3 mg/L) were also associated with increased risk compared with those with hsCRP <1 mg/L (HR, 2.3; 95% CI, 1.2 to 4.6). Patients allocated to early intensive statin therapy were more likely to achieve hsCRP levels <1 mg/L at 30 days (P=0.028) and 4 months (P <0.0001).

Conclusions—Achieved levels of hsCRP at 30 days and 4 months after acute coronary syndrome are independently associated with long-term survival. Patients treated with more aggressive statin therapy are more likely to achieve lower levels of hsCRP. (Circulation. 2006;114:281-288.)

Key Words: coronary disease • prognosis • myocardial infarction • inflammation • C-reactive protein

Inflammation is established as an important contributor to atherogenesis and acute atherothrombosis.1–2 Researchers and clinicians have thus turned to biochemical markers of inflammation as possible noninvasive indicators of underlying atherosclerosis, the risk of first or recurrent cardiovascular events, and the success of therapeutic and preventive interventions.3 High-sensitivity measurement of C-reactive protein (hsCRP) is the most extensively studied of these markers and is associated with the risk of adverse cardiovascular outcomes in apparently healthy individuals and in patients with established coronary artery disease.4 Treatment with HMG-CoA reductase inhibitors (statins) lowers the concentration of hsCRP in patients with atherosclerosis by 13% to 50% compared with placebo5–7 and in retrospective analyses has been shown to reduce the risk associated with elevated levels of this inflammatory marker.8–10 Recently, we demonstrated that a lower achieved level of hsCRP while on statin therapy is associated with a more favorable clinical outcome,11,12 suggesting a role for hsCRP in monitoring the response to statin therapy and other preventive interventions that influence inflammation.13 This intriguing finding from a single study warrants additional investigation.

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Therefore, we assessed the prognostic value of the achieved level of hsCRP during follow-up of patients with an acute coronary syndrome enrolled in the Aggrastat-to-Zocor (A-to-Z) Trial of an early intensive versus a delayed, less intensive statin regimen.14 In addition, by virtue of the initial placebo period, this trial enabled the investigation of the temporal course and clinical correlates of hsCRP concentration after an acute coronary syndrome in patients treated without a statin.
Methods

Study Population
The study design and primary results of the A-to-Z Trial have been published previously.\textsuperscript{14,15} The A-to-Z Trial was a multinational study of patients presenting with either non-ST elevation or ST-elevation acute coronary syndrome (ACS). Phase A compared enoxaparin with unfractionated heparin among patients with non-ST-elevation ACS. Phase Z was a double-blinded trial comparing early intensive statin treatment (simvastatin, 40 mg/d for 30 days followed by 80 mg/d) to a delayed conservative statin strategy (placebo for 4 months followed by 20 mg/d simvastatin) among patients with non-ST-elevation and ST-elevation ACS.

Inclusion criteria for patients with non–ST-elevation ACS included chest pain typical of myocardial ischemia at rest (≥10 minutes) associated with either ST-segment depression or transient elevation ≥0.05 mV, or with an elevated concentration of creatine kinase-MB or troponin. Before random assignment, patients were required to be stable for a minimum of 12 consecutive hours within 5 days after symptom onset. Patients with ST-elevation myocardial infarction (STEMI) were eligible if they were treated with a reperfusion strategy (fibrinolytic or primary percutaneous coronary revascularization) within 12 hours of symptom onset or without reperfusion for those with delayed presentations (>12 hours). All patients were required to have at least one of the following indicators of high risk: age >70 years, diabetes mellitus, prior documented coronary or peripheral arterial disease, prior stroke, elevated cardiac marker of necrosis, recurrent angina with ST-segment changes, positive predischarge stress test, or multivessel disease at coronary angiography. Exclusion criteria relevant to this analysis included history of statin therapy at the time of random assignment or for coronary artery bypass grafting at any time. All patients provided written informed consent, and the protocol was approved by the institutional review board of each participating center.

End Points
The primary end point for this analysis was death from any cause. Additional end points recorded were new or worsening heart failure and the primary end point of the A-to-Z Trial, which was a composite of major cardiovascular events, specifically cardiovascular death, myocardial infarction, readmission for ACS (requiring new electrocardiographic changes or elevated biomarker(s) of necrosis), or stroke. Cause of death, myocardial infarction, and readmission for ACS were adjudicated by an independent clinical end points committee, blinded to treatment assignment. The remaining end points were determined by the local investigator.

Statistical Methods
The serum concentration of CRP at each time point was described by the median (25th, 75th percentiles). The results of hsCRP testing were evaluated by using cut-points recommended by the American College of Cardiology and the American Heart Association.

CRP Testing
As part of the protocol, serum samples were obtained before random assignment into phase Z, at 30 days, and at the subsequent month 4 and month 8 visits. For this analysis, we focused on the observed concentration of hsCRP at day 30 follow-up after the residual influence of the qualifying ischemic event would have resolved and at month 4, the end of treatment with placebo in the delayed conservative treatment group. Serum was isolated and shipped refrigerated overnight in plastic tubes, at which time aliquots were prepared and stored at −80°C. Aliquots were later shipped frozen on dry ice to the TIMI Biomarker Laboratory (Boston, Mass), where they were thawed and analyzed in batches. High-sensitivity testing for CRP was performed by using the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken, Tokyo, Japan) on a Hitachi 911 immunoanalyzer (Roche Diagnostics, Indianapolis, Ind).\textsuperscript{16} 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 mg/L and 1.9 mg/L, respectively.\textsuperscript{17} All testing was performed by personnel blinded to clinical outcomes and treatment allocation.

Table 1. Patient Characteristics Stratified by hsCRP at 30 Days

<table>
<thead>
<tr>
<th>Demographics</th>
<th>hsCRP &lt;1 mg/L (n=765)</th>
<th>hsCRP 1–3 mg/L (n=1425)</th>
<th>hsCRP &gt;3 mg/L (n=1623)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59 (51, 68)</td>
<td>60 (52, 69)</td>
<td>62 (53, 69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>157 (20.5%)</td>
<td>326 (22.9%)</td>
<td>435 (28.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Female, not taking HRT</td>
<td>148 (19.3%)</td>
<td>294 (20.6%)</td>
<td>375 (23.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>258 (33.8%)</td>
<td>571 (40.1%)</td>
<td>725 (44.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>327 (42.8%)</td>
<td>693 (48.7%)</td>
<td>874 (53.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>108 (14.1%)</td>
<td>276 (19.4%)</td>
<td>385 (23.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 (68, 86)</td>
<td>80 (70, 90)</td>
<td>80 (70, 91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>110 (14.4%)</td>
<td>262 (18.4%)</td>
<td>365 (22.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>39 (5.1%)</td>
<td>70 (4.9%)</td>
<td>112 (6.9%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>27 (3.5%)</td>
<td>78 (5.5%)</td>
<td>117 (7.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Presenting characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qualifying event=STEMI</td>
<td>304 (39.7%)</td>
<td>560 (39.3%)</td>
<td>622 (38.3%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>76 (62, 92)</td>
<td>77 (61, 93)</td>
<td>76 (60, 95)</td>
<td>0.92</td>
</tr>
<tr>
<td>Concomitant therapies at hospital discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>739 (96.6%)</td>
<td>1388 (97.5%)</td>
<td>1560 (96.1%)</td>
<td>0.11</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>413 (54.0%)</td>
<td>792 (55.6%)</td>
<td>976 (60.1%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are shown as n (%) for dichotomous variables and median (25th, 75th percentiles) for continuous variables. HRT indicates hormonal replacement therapy; STEMI, ST-elevation myocardial infarction.
Heart Association/Centers for Disease Control (AHA/CDC) Scientific Statement. Baseline characteristics across hsCRP groups were compared by using the \( \chi^2 \) test for categorical variables and the Wilcoxon rank-sums test for continuous variables. The correlation between hsCRP and continuous parameters was described by using the Spearman correlation coefficient. Changes in the concentration of hsCRP between visits were evaluated by using a nonparametric approach to paired measures (signed-ranks test). Testing for an association between the concentration of hsCRP at 30 days and 4 months with subsequent outcome was performed by a time-to-event (landmark) analysis, beginning at the time of sampling and including all patients with an available hsCRP result from the relevant visit. Confirmatory analyses excluding patients with nonfatal ischemic events before the visit were also performed to eliminate possible confounding by recent cardiac events resulting in an increase in hsCRP at that visit.

Event rates for clinical outcomes were determined by using the Kaplan-Meier method and compared by using the log-rank test. Multivariable analyses of the association between hsCRP and outcomes were performed by using Cox regression to adjust for the effects of potential confounders associated with hsCRP (age, gender, diabetes mellitus, smoking, history of known cardiovascular disease, index event, achieved LDL, use of estrogen hormonal replacement therapy, treatment with ACE inhibitors, BNP, and the study treatment allocation). Body weight, creatinine clearance, and HDL were revealed not to be significant confounders (<10% change in hazard ratio) among those with available data (≈10% missing). Similarly, premature cessation of statin therapy was evaluated and found not to be a significant confounder. The association between clinical characteristics and the achieved level of hsCRP at 30 days was performed by using linear regression with log-transformed concentrations of CRP as the dependent covariate. All analyses were performed with the use of STATA v8.2 (STATA Corp, College Station, Tex). Probability values of <0.05 (2-tailed) were considered to indicate statistical significance. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

A total of 3813 patients had the serum level of hsCRP determined at 30 days after random assignment into phase Z. The median concentration of hsCRP at 30 days was 2.4 mg/L (25th to 75th percentiles, 1.2 to 5.5 mg/L). Consistent with our intent to measure hsCRP after the inflammatory influence of the qualifying ACS had resolved, the concentration of hsCRP did not differ between those enrolled with STEMI (2.3 mg/L, 1.2 to 5.3) versus non–ST-elevation ACS (2.5 mg/L, 1.2 to 5.5, \( P=0.36 \)). The patients’ clinical characteristics stratified by hsCRP concentration are presented in Table 1. Patients with an elevated concentration of hsCRP at 30 days were older, more likely to be female, and to have a history of smoking, hypertension, diabetes, and preexisting atherosclerotic vascular disease. The correlation between the level of LDL cholesterol and hsCRP at 30 days was minimal (\( r=0.05 \)).

**Relation Between CRP and Outcome**

There was a strong graded relation between the concentration of hsCRP at 1 month after presentation with ACS and the subsequent risk of cardiovascular death, as well as a significant association with nonfatal cardiovascular events during 2 years of follow-up (Table 2). Similarly, the cumulative incidence of death from any cause through 2 years was significantly higher in patients with elevated levels of hsCRP by using the cut-points established by the AHA/CDC expert panel (Figure 1). After adjusting for age, gender, diabetes mellitus, smoking, history of known cardiovascular disease, index event, achieved LDL, use of estrogen hormonal replacement therapy, treatment with ACE inhibitors, and the study treatment allocation, patients with a level of hsCRP >3 mg/L had a >3-fold-higher risk of death (adjusted HR, 3.7; 95% CI, 1.9 to 7.2) compared with patients with a level of hsCRP <1 mg/L. Notably, using the AHA/CDC cut-points, patients with “average” levels of hsCRP (1 to 3 mg/L) were at detectably higher risk of death compared with those with low levels of hsCRP (adjusted HR, 2.3; 95% CI, 1.2 to 4.6).

This relation was not altered in analyses excluding patients...
(n=122) with recurrent ischemic events during the first 30
days; hsCRP >3 mg/L: adjusted HR, 3.1; 95% CI, 1.5 to 6.3,
and hsCRP 1 to 3 mg/L: adjusted HR, 2.3; 95% CI, 1.1 to
4.8). In addition, the relation between hsCRP and survival
was independent (HR, 3.4; 95% CI, 1.8 to 6.6) of the
concentration of B-type natriuretic peptide, another signifi-
cant predictor of death in patients with recent ACS.18

When evaluated at 4 months, hsCRP again showed a
significant independent association with subsequent out-
comes (Figure 2). Moreover, when hsCRP was assessed by
using the same cut-point (2 mg/L) as applied in the
PROVE-IT TIMI 22 trial,11 we found strong consistency in
the risk relation by using hsCRP in these two separate
populations of patients with ACS (Figure 3).

**Influence of Statin Therapy**

Overall, reflecting the acute phase response associated with
the qualifying acute ischemic event, hsCRP declined signif-

![Figure 1. Cumulative probability of death from any cause stratified by the concentration of hsCRP at 30 days after presentation with an acute coronary syndrome.](image1)

**Figure 2.** Kaplan-Meier estimates of the probability of death from any cause or major cardiovascular events (composite of cardiovascular death, MI, rehospitalization for acute coronary syndrome, or stroke) from 4 months to 2 years of follow-up after an acute coronary syndrome stratified by hsCRP measured at 4 months (n=3546).
significantly between the baseline measurement before hospital discharge and measurement performed at 30 days (20.2 to 2.4 mg/L, \( P < 0.0001 \)). By 30 days, patients treated with 40 mg daily of simvastatin were modestly more likely to be shifted to lower levels of hsCRP than those treated with placebo (Table 3, \( P = 0.028 \)). This difference increased by 4 months, after treatment with 80 mg daily of simvastatin versus placebo for 90 days (Table 3, \( P < 0.001 \)). Specifically, statin-treated patients had a significant additional decline in hsCRP between 30 days and 4 months (2.4 to 1.7 mg/L, \( P < 0.0001 \)), whereas those treated with placebo had a reduction in hsCRP that was quantitatively modest, albeit statistically significant (2.5 to 2.3 mg/L, \( P < 0.0001 \)).

Notably, patients who achieved lower levels of hsCRP at 30 days were at lower risk of subsequent death and recurrent cardiovascular events irrespective of treatment allocation (\( P \) for interaction, 0.88). Similarly, when assessed at 4 months, the relation between hsCRP and the risk of subsequent recurrent events did not differ between treatment groups (\( P \) for interaction, 0.82). As such, patients with lower achieved levels of hsCRP while on placebo also had more favorable outcomes than those with evidence of persistent inflammation after ACS.

### Clinical Correlates of Achieved CRP

Given the strong independent relation between the achieved level of hsCRP and outcome in patients treated with placebo, we performed additional analyses to characterize further the clinical correlates of hsCRP at 30 days. Among patients allocated to the delayed statin arm, we found that age, gender, body weight, smoking, hypertension, hyperglycemia, preexisting coronary artery disease, HDL cholesterol, and use of estrogen hormonal replacement therapy were all significant independent correlates (each \( P \leq 0.01 \)) of the achieved concentration of hsCRP during recovery after ACS. Importantly, each of these characteristics was addressed in our multivariable assessment of the prognostic value of hsCRP.

### Achieved LDL

In this study, the relation between the achieved level of LDL cholesterol and subsequent outcome was less robust than that observed for hsCRP. Specifically, patients with LDL \( \leq 70 \) mg/dL (\( n = 1137 \)) at 30 days were at similar risk for death (4.0% versus 4.1%, \( P = 0.80 \)) and major cardiovascular events (10.4% versus 11.1% \( P = 0.99 \)) as those with LDL above this cut-point. Assessed at 4 months, the risk of subsequent major cardiovascular events tended to be lower in patients with LDL \( \leq 70 \) mg/dL (\( n = 1249, 6.3\% \) versus 8.2%, \( P = 0.18 \)). The difference was not significant after adjustment for clinical characteristics, hsCRP, and treatment group when analyzed either dichotomized at \( \leq 70 \) mg/dL (adjusted HR, 1.1; 95% CI, 0.8 to 1.6) or as a continuous variable (adjusted HR, 1.0; 95% CI, 0.99 to 1.0,

### Table 3. Distribution of hsCRP in Patients Treated With Simvastatin Versus Placebo

<table>
<thead>
<tr>
<th>hsCRP Concentration, mg/L</th>
<th>&lt;1.0</th>
<th>1.0–3.0</th>
<th>&gt;3.0</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessed at 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>343  (18.3)</td>
<td>707 (37.8)</td>
<td>821 (43.9)</td>
<td>0.028</td>
</tr>
<tr>
<td>Simvastatin 40 mg daily</td>
<td>422  (21.7)</td>
<td>718 (37.0)</td>
<td>802 (41.3)</td>
<td></td>
</tr>
<tr>
<td>Assessed at 4 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>375  (21.5)</td>
<td>691 (39.6)</td>
<td>681 (39.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Simvastatin 40 mg daily for 30 days followed by 80 mg daily</td>
<td>532 (29.6)</td>
<td>712 (39.6)</td>
<td>555 (30.9)</td>
<td></td>
</tr>
</tbody>
</table>

Data represent n (%) of patients in each group.
Stratification by the achieved level of hsCRP and LDL at 4 months revealed a pattern consistent with that observed in our prior study, with highest risk in those who failed to achieve either hsCRP <2 mg/dL or LDL <70 mg/dL, intermediate risk in those who achieve one but not both goals and lowest risk in those who achieved these potential dual goals of therapy (Figure 4).

Discussion
When measured at 1 and 4 months after presentation with an ACS, the achieved levels of hsCRP were independently associated with subsequent clinical outcome. Compared with placebo, treatment with simvastatin (40 mg daily) shifted patients to modestly lower levels of hsCRP at 1 month, with a larger difference evident by 4 months of follow-up, 3 months after initiation of high-dose simvastatin (80 mg daily). Importantly, patients with evidence of less inflammation during follow-up after ACS had favorable outcomes compared with those with elevated hsCRP, whether or not they had been treated initially with a statin.

Clinical Implications
These findings have several implications for hsCRP as a biochemical marker of inflammation in patients with established atherosclerotic vascular disease. First, our findings provide robust evidence that the achieved level of hsCRP during follow-up after ACS is a strong independent predictor of subsequent outcomes in patients treated initially with or without a statin. These data are consistent with our recent report of a relation between hsCRP and outcome in patients treated with an intensive versus moderate statin strategy (Figure 3) and support the hypothesis that hsCRP, as an indicator of the intensity of underlying inflammation, may be useful not only as a prognostic tool but also as a measure of the success of treatment and/or an indicator by which to direct preventive therapies that reduce inflammation. Second, as shown in this report and at 4 months in a prior trial of atorvastatin versus placebo, treatment with statins, particularly at high doses, achieves a reduction in hsCRP that is incremental to the natural decline after ACS.

Third, it is possible to identify clinical characteristics such as advanced age, female gender, ongoing tobacco use, hypertension, and diabetes that are associated with a higher likelihood of persistent inflammation after ACS. This finding extends observations made previously in patients at risk for coronary artery disease to the population of patients with ACS without the influence of statin therapy. Notably, many of these characteristics are modifiable, and aggressive treatment of some, such as obesity, have been shown to reduce levels of inflammatory markers. Our observation in patients treated with placebo in A-to-Z, along with similar findings in patients treated with intensive or moderate statin therapy in the PROVE-IT TIMI 22 trial, reinforces the importance of traditional risk factors and the incompletely explored potential to ameliorate inflammation, as reflected by hsCRP, through lifestyle modification and other preventive therapies. Moreover, the substantial risk of recurrent events in patients with elevated hsCRP despite administration of high-dose statins additionally supports interest in the investigation of other antiinflammatory agents and interventions for treatment of patients with recent ACS.

Fourth, these observations contribute to the epidemiological and experimental evidence that CRP itself may be a direct participant in atherothrombosis and can be modified by treatment. CRP has been consistently found within atherosclerotic lesions, and exposure to exogenous CRP has been shown to stimulate inflammatory changes in cells and animals. Together, these observations have raised the hypothesis that CRP is a causal agent in atherothrombosis rather than merely a marker of other underlying inflammatory processes. Nevertheless, recent insight into the limitations of rodent models of CRP and possible contaminants in exogenous CRP have highlighted the need for additional study. The consistent finding from both A-to-Z and PROVE-IT TIMI 22 that patients who achieve lower levels of CRP during preventive therapy have better long-term outcomes lends new support for the hypothesis that CRP is a modifiable risk factor in coronary heart disease.

Limitations
We acknowledge the limitations inherent in assessing the relation between a postrandomization variable and out-
come. We have addressed this limitation by adjustment for a comprehensive group of clinical characteristics known to be associated with levels of hsCRP from our present and prior work. Nevertheless, it is possible that there are as-yet unidentified confounders that may influence the relation between the achieved level of hsCRP and outcome. Prospective, randomized studies are necessary to support the conclusion that the risks associated with persistently elevated hsCRP should be reduced with intensive statin or other antiinflammatory therapies. Specifically, placebo-controlled trials of statin therapy in patients with below-average levels of LDL but identified as higher risk using hsCRP,26 as well as trials that randomly assign patients to either a standard preventive strategy or one guided by a goal of targeting lower levels of hsCRP, would substantially advance the evidence supporting such novel clinical applications of this marker.

Conclusions

Achieved levels of hsCRP at 30 days and 4 months after ACS are independently associated with long-term survival. Treatment with an intensive statin regimen augments the natural decline in markers of inflammatory activation after ACS and increases the proportion of patients achieving the lower categories of risk based on hsCRP. Measurement of hsCRP during follow-up after ACS may be useful in evaluating the success and guiding the intensity of treatment with statins and other preventive interventions that reduce inflammation.

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Disclosures

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References

CLINICAL PERSPECTIVE

Researchers and clinicians have turned to biochemical markers of inflammation as possible noninvasive indicators of atherosclerosis and the risk of future cardiovascular events. Elevated levels of high-sensitivity C-reactive protein (hsCRP) are associated with higher risk of adverse outcomes in patients at risk for or with established coronary artery disease. In a single prior study, lower levels of hsCRP achieved while on statin therapy were associated with better clinical outcomes. We studied 3813 patients after an acute coronary syndrome (ACS) who were randomly assigned to an early intensive versus delayed conservative simvastatin strategy in the A-to-Z Trial with hsCRP measured at 30 days and 4 months. We found that patients with hsCRP >3 mg/L were at more than 3-fold-higher risk of death compared with those with hsCRP <1 mg/L after adjusting for traditional risk indicators and that patients treated with intensive statin therapy were more likely to achieve lower levels of hsCRP. Our findings provide strong evidence that the achieved level of hsCRP after ACS is an independent predictor of subsequent outcomes. Treatment with statins, particularly at high doses, achieves a reduction in hsCRP that is incremental to the natural decline after ACS. Together, these observations suggest a role for hsCRP in monitoring the success of statin therapy as well as other preventive interventions that influence inflammation. In patients presenting for follow-up after ACS, an achieved level of hsCRP <1 mg/L along with an LDL below 70 mg/dL (established by prior studies) appear to be desirable goals for therapy.
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