Incremental Prognostic Value of Elevated Baseline C-Reactive Protein Among Established Markers of Risk in Percutaneous Coronary Intervention

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Background—Established methods of risk assessment in percutaneous coronary intervention have focused on clinical and anatomical lesion characteristics. Emerging evidence indicates the substantial contribution of inflammatory processes to short-term and long-term outcomes in coronary artery disease.

Methods and Results—Within a single-center registry of contemporary percutaneous coronary revascularization strategies with postprocedural creatine kinase and clinical events routinely recorded, we assessed the association of baseline C-reactive protein with death or myocardial infarction within the first 30 days. Predictive usefulness of baseline C-reactive protein within the context of established clinical and angiographic predictors of risk was also examined. Among 727 consecutive patients, elevated baseline C-reactive protein before percutaneous coronary intervention was associated with progressive increase in death or myocardial infarction at 30 days (lowest quartile, 3.9%, versus highest quartile, 14.2%; \( P = 0.002 \)). Among clinical and procedural characteristics, baseline C-reactive protein remained independently predictive of adverse events, with the highest quartile of C-reactive protein associated with an odds ratio for excess 30-day death or myocardial infarction of 3.68 (95% CI, 1.51 to 8.99; \( P = 0.004 \)). A predictive model that included baseline C-reactive protein quartiles, American College of Cardiology/American Heart Association lesion score, acute coronary syndrome presentation, and coronary stenting appears strongly predictive of 30-day death or myocardial infarction within this population (C-statistic, 0.735) and among individual patients (Brier score, 0.006).

Conclusions—Elevated baseline C-reactive protein portends heightened risk of 30-day death or myocardial infarction after coronary intervention. Coupled anatomic, clinical, and inflammatory risk stratification demonstrates strong predictive utility among patients undergoing percutaneous coronary intervention and may be useful for guiding future strategies. (Circulation. 2001;104:992-997.)

Key Words: angioplasty ■ stents ■ inflammation

Clinical risk stratification and angiographic lesion classification have served to identify high-risk patients undergoing percutaneous coronary intervention (PCI).\(^{1-3}\) More recently, the usefulness of inflammatory markers for prediction of ischemic events among patients with coronary artery disease has been recognized.\(^{4-8}\) Relatively small studies have identified a heightened and sustained inflammatory response after PCI to be a predictor of periprocedural events after coronary angioplasty and a marker of increased restenosis risk among patients undergoing coronary stenting.\(^{7-9}\) However, no studies have established the prognostic value of elevated baseline C-reactive protein (CRP) within the context of established clinical and angiographic risk predictors. Therefore, within a prospective single-center registry of patients undergoing PCI, we sought to determine the relative value of elevated baseline CRP for prediction of 30-day ischemic events within the context of current approaches to risk stratification.

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Methods

Study Population

Within an ongoing PCI registry at the Cleveland Clinic Foundation, clinical demographics, angiographic characteristics, and long-term follow-up are collected on the first 1000 consecutive patients undergoing routine PCI in each calendar year. Baseline data includes patient acuity, risk factor status, number of diseased vessels, LV function, and American College of Cardiology/American Heart Association (ACC/AHA) lesion classification.\(^{2-10}\) The present study consists of patients enrolled within this registry between January and July 2000. Baseline CRP routinely was obtained before each coronary intervention. Patients who presented with myocardial infarction (MI; either Q-wave or non–Q wave MI) were excluded because of the possible confounding effect of myocardial necrosis on baseline CRP.
CRP and Clinical End Points
Samples were assayed with a routine test for CRP and, if within the normal range, determination of CRP level was then repeated with high-sensitivity CRP assay. As previously defined, a CRP level $\geq 0.3$ mg/dL was considered elevated. Routine follow-up data during the first 30 days included vital status, MI, need for revascularization, and day-1 postprocedural ECG and were collected by chart review and telephone contact. Creatine kinase (CK) data were collected at 8 hours and the morning after PCI in all patients, regardless of clinical symptoms or ECG changes. Among patients with postprocedural CK elevations, repeat CK analysis was performed at 8-hour intervals until peak CK elevation was defined.

Death was defined as all-cause mortality within 30 days. MI was defined as periprocedural CK elevation by use of a prespecified level of greater than twice the upper limit of normal for the reference laboratory or development of new Q waves on postprocedural ECG associated with cardiac enzyme elevation consistent with myocardial necrosis within 30 days. End point of death or MI was assessed as time to first event, without double counting of clinical events within the same patient.

Statistics
Continuous variables are expressed as a mean $\pm$ SD or median and interquartile ranges for variables with nongaussian distributions. Discrete variables are expressed as counts and percentages of the study population. Groups were compared by $\chi^2$ analysis for discrete variables and $t$ test for continuous variables. A Kaplan-Meier survival analysis that compared normal and elevated CRP groups was performed.

By use of logistic regression, association of baseline CRP and outcome was analyzed. Baseline CRP was considered to be a continuous variable, with logarithmic, inverse logarithmic, and quadratic transformations, and by tertiles, quartiles, and quintiles. Hosmer-Lemeshow goodness-of-fit test, a measure of the statistical difference between observed and expected event rates, was used to assess each model. Assessment of CRP by quartiles demonstrated best fit. For each quartile of CRP, 30-day event rates were compared by $\chi^2$ analysis for trend. Association between quartiles of CRP and 30-day event rates among certain prespecified high-risk groups, including diabetics (physician diagnosed or treated with antidiabetic medications); increased lesion complexity (ACC/AHA lesion classification), and acute coronary syndrome patients (new-onset, crescendo, and rest angina) was also analyzed. Examination of this relationship among patients receiving glycoprotein IIb/IIIa inhibition was undertaken. Interaction between these clinical and procedural characteristics and baseline CRP quartiles was assessed with the Breslow-Day test. Logistic regression analyses incorporating the univariate predictor of elevated CRP and univariate predictors of 30-day death or MI were performed.

The incremental value of incorporating CRP among established risk predictors was examined. Logistic regression models for 30-day death or MI after PCI were compared with an Akaike weight analysis. Model discrimination also was assessed by the C-statistic. To examine the predictive utility of the best model within individual patients, a Brier score was calculated, for which 0.0 implies perfect calibration. The predictive value of the best model was assessed for patients without follow-up (0.4 versus 0.5 mg/dL, $P=0.94$). Table 1 presents clinical and procedural characteristics of the study population. Elevated CRP ($\geq 0.3$ mg/dL) was observed in 65% of this study population. Covariates of elevated baseline CRP included female sex, angiotensin-converting enzyme inhibitor therapy, body mass index $> 30$ kg/m$^2$, creatinine $> 2.0$ mg/dL, and ejection fraction $< 40\%$.

Thirty-Day Death or MI and CRP
Death or MI within 30 days was increased substantially among patients with elevated CRP levels (CRP $< 0.3$ mg/dL, 4.7%, versus CRP $\geq 0.3$ mg/dL, 12.1%; $P=0.001$; Figure 1). Elevated baseline CRP also was associated with excess of death alone (CRP $< 0.3$ mg/dL, 0%, versus CRP $\geq 0.3$ mg/dL, 1.7%; $P=0.037$). When examined in quartiles, a progressive increase in 30-day death or MI was observed, with increased levels of baseline CRP ($\chi^2$ for trend, $P=0.002$). Highest quartile of baseline CRP was associated with a 3.6-fold excess in death or MI ($P=0.011$; Figure 2A). When analysis was confined to patients receiving glycoprotein IIb/IIIa inhibition ($n=619$), the relationship between quartiles of CRP and death or MI mirrored the overall population (Figure 2B). Formal interaction analysis demonstrated no interaction between treatment with glycoprotein IIb/IIIa inhibition and outcome related to quartiles of CRP ($P=0.73$).

Increasing lesion complexity, defined by ACC/AHA lesion score, was associated with greater 30-day ischemic risk. Stratification by quartiles of CRP and ACC/AHA lesion score demonstrates a more prominent gradient of risk (Figure 3). Among diabetic patients ($n=251$), association between quartiles of CRP and adverse ischemic event rate was also more prominent. Highest quartile of CRP was associated with a striking excess in 30-day death or MI (1st quartile, 0%; 2nd, 2.9%; 3rd, 8.8%; 4th, 20.3%; $\chi^2$ for trend, $P<0.001$). Mortality was confined to the highest quartile. Relationship between quartiles of CRP and 30-day death or MI was more evident among patients presenting with acute coronary syndromes ($n=405$; 1st quartile, 4.6%; 2nd, 9.1%; 3rd, 15.7%; 4th, 19.1%; $\chi^2$ for trend, $P=0.001$). However, no significant interaction between ACC/AHA lesion score, diabetes or acute coronary syndrome presentation, and quartiles of CRP with respect to death or MI was found.

Multivariate Analysis
Number of diseased vessels, LV ejection fraction $< 40\%$, prior CABG, lesion complexity (ACC/AHA type B2 or C lesions), creatinine $> 2.0$ mg/dL, coronary stenting, and quartiles of baseline CRP were all predictive of 30-day death or MI. Within logistic regression analysis, odds ratio for excess 30-day death or MI progressively increased with higher quartiles of CRP (2nd quartile, 2.44 [95% CI, 0.99 to 6.04; $P=0.054$]; 3rd quartile, 2.83 [95% CI, 1.14 to 7.03; $P=0.025$]; 4th quartile, 3.68 [95% CI, 1.51 to 8.99; $P=0.004$]). ACC/AHA B2 or C lesion complexity (odds ratio, 3.75; 95% CI, 1.85 to 7.60; $P<0.001$), coronary stenting (odds ratio, 2.94; 95% CI, 1.22 to 7.05; $P=0.016$), and presentation with unstable angina (odds ratio, 2.01; 95% CI, 1.16 to 3.66; $P=0.012$) also were independently associated with death or MI at 30 days. These relationships
were reexamined by use of a CK-MB definition for postpro-
cedural MI of $>1\times$ and $>3\times$ upper limit of normal. At both
of these levels, relationship between quartiles of CRP and
30-day death or MI remained statistically significant within
univariate and multivariate analysis. (Odds ratio with CK-MB
$>3\times$ upper limit of normal definition, 2nd quartile, 2.6 [95% CI,
0.84 to 8.45], $P=0.107$; 3rd quartile, 3.6 [95% CI, 1.36 to
11.36], $P=0.027$; 4th quartile, 4.2 [95% CI, 1.36 to 13.15],
$P=0.013$).

**Predictive Modeling Analyses**

Among logistic regression models, the combination of base-
line CRP by quartiles, ACC/AHA lesion score, presentation
with unstable angina, and coronary stenting appeared be
strongly predictive of 30-day death or MI (Hosmer-
Lemeshow goodness-of-fit, 6.65 with 8 df, $P=0.575$;
receiver-operating curve, 0.74). To examine the value of
adding CRP by quartiles to established clinical and proce-
dural risk predictors, several models were compared. Addi-
tion of an assessment of CRP to each model improved the
likelihood that the model examined represented the best
model for predicting 30-day risk. The combination of base-
line CRP and the other independent covariates identified in
multivariate analysis demonstrated the greatest likelihood of
representing the best predictive model (Table 2, Figure 4). In
addition, Brier score analysis using this model demonstrated
a median value of 0.006 (interquartile range, 0.002 to 0.028),
which suggests a highly predictive capacity within individual
patients.

**Discussion**

Patient demographics and anatomical characteristics (lesion
complexity and number of diseased vessels) are currently
used to define individual risk among patients undergoing
PCI.\textsuperscript{1,2,14} Emerging evidence highlights the prognostic value
of inflammatory markers such as CRP among patients with
coronary artery disease.\textsuperscript{4,15} The present analysis documents

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**Table 1. Patient and Procedural Characteristics**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>CRP $&lt;0.3$ mg/dL (n=255)</th>
<th>CRP $\geq0.3$ mg/dL (n=472)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>64.9±11.4</td>
<td>66.4±10.6</td>
<td>0.086</td>
</tr>
<tr>
<td>Female, %</td>
<td>21.9</td>
<td>32.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>27.5</td>
<td>38.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>70.1</td>
<td>78.6</td>
<td>0.049</td>
</tr>
<tr>
<td>Acute coronary syndrome, %</td>
<td>50.6</td>
<td>58.5</td>
<td>0.041</td>
</tr>
<tr>
<td>Smoker within 1 y, %</td>
<td>62.8</td>
<td>67.2</td>
<td>0.232</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>26.6</td>
<td>33.2</td>
<td>0.080</td>
</tr>
<tr>
<td>NYHA class III or IV, %</td>
<td>0.4</td>
<td>3.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society class III or IV, %</td>
<td>53.3</td>
<td>60.8</td>
<td>0.051</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>82.3</td>
<td>74.8</td>
<td>0.022</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$ (mean±SD)</td>
<td>28.1±4.7</td>
<td>29.9±10.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior PCI, %</td>
<td>29.2</td>
<td>27.6</td>
<td>0.283</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>34.8</td>
<td>35.8</td>
<td>0.820</td>
</tr>
<tr>
<td>LV ejection fraction, % (mean±SD)</td>
<td>54.1±11.3</td>
<td>50.7±13.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine $&gt;2.0$ mg/dL, %</td>
<td>2.4</td>
<td>8.5</td>
<td>0.001</td>
</tr>
<tr>
<td>$\beta$-blocker, %</td>
<td>55.7</td>
<td>57.6</td>
<td>0.614</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor, %</td>
<td>19.6</td>
<td>30.7</td>
<td>0.001</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitor, %</td>
<td>50.6</td>
<td>44.7</td>
<td>0.129</td>
</tr>
<tr>
<td>ADP antagonist pretreatment, %</td>
<td>77.3</td>
<td>75.0</td>
<td>0.498</td>
</tr>
<tr>
<td>Urgent indication, %</td>
<td>1.2</td>
<td>1.1</td>
<td>0.885</td>
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<tr>
<td>ACC/AHA lesion B2 or C, %</td>
<td>62.4</td>
<td>60.8</td>
<td>0.683</td>
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<tr>
<td>Saphenous vein graft intervention, %</td>
<td>5.6</td>
<td>6.4</td>
<td>0.731</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa use, %</td>
<td>82.7</td>
<td>86.4</td>
<td>0.181</td>
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<tr>
<td>$\geq1$ stent, %</td>
<td>81.9</td>
<td>80.7</td>
<td>0.683</td>
</tr>
<tr>
<td>Rotational atherectomy, %</td>
<td>9.4</td>
<td>7.8</td>
<td>0.465</td>
</tr>
</tbody>
</table>

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**Figure 1.** Kaplan-Meier survival curves for 30-day death or MI stratified by baseline CRP.
the incremental prognostic significance of elevated CRP beyond that defined by traditional risk predictors in PCI. By quartile analysis, progressive excess in risk is evident, with the highest quartile of CRP independently conferring a 3.7-fold excess risk of death or MI at 30 days. Furthermore, a predictive model combining clinical presentation (presence of unstable angina), ACC/AHA lesion score (anatomical lesion complexity), stent use, and baseline CRP (assessment of the inflammatory status) appears to provide excellent prognostic usefulness for risk stratification of patients undergoing PCI.

PCI is known to induce an inflammatory response within the vascular wall, and the magnitude of this response correlates with degree of neointimal hyperplasia. Consequently, initial data has demonstrated a substantial increase in postprocedural CRP, peaking at 48 to 72 hours, among patients with unstable angina undergoing coronary angioplasty. Furthermore, clinical restenosis after coronary stenting also appears to be confined to patients with a persistent

**TABLE 2. Predictive Models of 30-d Death or MI With Akaike Information Scores and Weights**

<table>
<thead>
<tr>
<th>Model (variables)</th>
<th>AIC</th>
<th>Δ*</th>
<th>ω†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics‡</td>
<td>443.700</td>
<td>22.950</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedural characteristics§</td>
<td>433.246</td>
<td>12.496</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinical‡ and procedural§ characteristics</td>
<td>429.146</td>
<td>8.396</td>
<td>0.013</td>
</tr>
<tr>
<td>CRP quartiles and ACC/AHA lesion score</td>
<td>429.776</td>
<td>9.026</td>
<td>0.010</td>
</tr>
<tr>
<td>CRP quartiles, clinical‡ and procedural§</td>
<td>425.596</td>
<td>4.846</td>
<td>0.079</td>
</tr>
<tr>
<td>CRP quartiles, stent, acute coronary syndromes, and ACC/AHA lesion score</td>
<td>420.750</td>
<td>0</td>
<td>0.896</td>
</tr>
</tbody>
</table>

*Difference between the Akaike information criterion (AIC) of a given model i and the best model, ie, the model with the lowest AIC value. AIC is calculated as AIC = −2log likelihood + 2p (p indicates number of parameters in the model). A value of 0 implies the best model. A low value implies a better fit.
†Akaike weight, which is an estimate of the likelihood that a given model i is the best model of those studied. Hence, the value of 0.896 for the model combining quartile baseline CRP, ACC/AHA lesion score, stenting, and unstable angina represents an 89.6% probability that this is the best model. Very low values suggest that these models are unlikely to be the best model. Akaike weight is calculated as

\[
ω_i = \frac{\exp \left( -\frac{1}{2} \Delta_i \right)}{\sum_{j=1}^{n} \exp \left( -\frac{1}{2} \Delta_j \right)}
\]

‡Age, sex, diabetes, No. of diseased vessels, prior CABG, creatinine >2.0 mg/dL, and presentation with unstable angina.
§ACC/AHA lesion score, stenting, and LVEF<40%.
postprocedural increase in CRP. However, although these data support the role of postprocedural inflammatory response in long-term clinical events, data defining the association between baseline CRP elevation and early postprocedural outcome within the context of current practice is limited. This analysis highlights the association between baseline CRP and postprocedural ischemic events, particularly, events that occur in the first few days after PCI. This relationship suggests that CRP may predict the risk of distal embolization or may play a direct role in augmenting microvascular inflammatory response after ischemic insult. Although its precise role in ischemic injury requires further elucidation, a focus on baseline CRP may prove useful for identification of patients who may benefit from adjunctive pharmacological or mechanical therapies around the time of PCI.

Previous studies examining the relationship between baseline CRP and early ischemic events after PCI have been performed in the setting of coronary angioplasty. In a series of 121 angioplasty patients, preprocedural CRP >0.3 mg/dL was associated with greater early adverse outcome. A nonsignificant increase in periprocedural death or MI was observed at 72 hours among patients with elevated baseline CRP in the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, reaching statistical significance by 30 days and 6 months. Factors possibly contributing to this marginal early excess risk include the higher, arbitrarily defined, dichotomous definition of elevated CRP (1.0 mg/dL), the relatively small study population, and the lack of coronary stenting within the present study. Nevertheless, an increased rate of death was noted at 30 days. Including patients from a more contemporary “stenting era,” our large experience provides confirmatory evidence of the association between preprocedural CRP and 30-day events. This analysis defines the independent association between elevated baseline CRP and 30-day death or MI while showing a significant increase in death alone, corroborating the CAPTURE experience.

Among patients undergoing PCI, the contribution of lesion complexity to procedural risk is well established. The present study adds to this previous experience by documenting a profound increase in ischemic events associated with elevated CRP that is independent of, but additive to, the effect of increased ACC/AHA lesion score. A prognostic model coupling anatomic lesion characteristics with an assessment of the inflammatory state appears superior to risk assessment by lesion complexity alone. These factors combined with consideration of the clinical presentation and coronary stent use appears highly predictive of risk within this analysis. Furthermore, the Brier score analysis, an assessment of the predictive utility within each individual patient, confirms the high prognostic utility of this risk-stratification model.

Limitations
High-sensitivity testing was not uniformly used. Only those CRP samples within normal range of the standard assay were reanalyzed with the high-sensitivity test to defray some of the cost associated with performing the present study. Nevertheless, this is more likely to underestimate event rates in the high CRP group given that low-risk patients may be included within the high-risk group if their initial CRP sample was elevated falsely. Heightened risk observed among diabetics and acute coronary syndrome patients was observed within smaller population sizes, resulting in a limited capacity for multivariate logistic regression modeling. Therefore, although these associations are consistent with the known elevated risk associated with these subgroups, absolute magnitude of risk should be interpreted with caution. The high rate of glycoprotein IIb/IIIa inhibitor use limits analysis of the relative value of baseline CRP among patients receiving or not receiving glycoprotein IIb/IIIa inhibition. However, previous studies have not observed a differing benefit of abciximab among patients with normal and elevated baseline CRP.

Conclusions
Elevated baseline CRP is independently predictive of early adverse outcome after PCI. Risk assessment incorporating clinical presentation, lesion complexity, use of stenting, and inflammatory status provides an effective risk-stratification model of 30-day death or MI among patients undergoing percutaneous coronary revascularization and demonstrates high prognostic usefulness among individual patients. Baseline assessment of CRP may be useful in routine evaluation of patients undergoing coronary intervention, although its value in guiding management strategies requires prospective validation within the context of randomized trials.

References


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