High Sensitivity C-Reactive Protein and Outcomes Following Percutaneous Coronary Intervention in Contemporary Practice

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Background—High sensitivity C-reactive protein (hsCRP) has been identified as a predictor of adverse cardiovascular outcomes. Whether hsCRP is a useful biomarker for risk stratification in contemporary percutaneous coronary intervention remains unknown.

Methods and Results—We conducted a prospective study among 513 patients undergoing non-emergency percutaneous coronary intervention and examined the relationship between pre- and postprocedural hsCRP levels and outcomes. The patients were divided according to the median preprocedural hsCRP level (0.3 mg/dL). Patients with high hsCRP had significantly more adverse clinical characteristics. Preprocedural hsCRP level was an independent predictor of periprocedural myocardial infarction (odds ratio per doubling of hsCRP 1.15 [95% confidence interval, 1.01–1.31]; P=0.038). Unadjusted mortality (29.7% versus 9.9%; P=0.001) and the combined end point of death or myocardial infarction (36.5% versus 16.0%, P=0.001) during a follow-up of 5 years were markedly greater in patients with high preprocedural hsCRP. Similar relationships existed for postprocedural hsCRP. However, after multivariable adjustment, neither preprocedural hsCRP levels (hazard ratio per doubling 0.96 [0.92, 1.00]; P=0.066) nor postprocedural hsCRP levels (hazard ratio 0.98 [0.94, 1.02]; P=0.27) were significantly associated with mortality.

Conclusions—High sensitivity C-reactive protein (hsCRP) has been identified as a predictor of adverse cardiovascular outcomes. Whether hsCRP is a useful biomarker for risk stratification in contemporary percutaneous coronary intervention remains unknown. Our findings suggest that routine measurement of hsCRP in patients undergoing percutaneous coronary intervention in contemporary practice is unlikely to be beneficial. (Circ Cardiovasc Interv. 2012;5:00-00.)

Key Words: angioplasty ■ C-reactive protein ■ coronary disease ■ outcome

Inflammation has a central role in the pathogenesis of atherosclerosis as well as plaque instability. High sensitivity C-reactive protein (hsCRP) is one of the most extensively investigated markers of inflammation and has been used to predict the risk of major adverse cardiac events in patients with stable and unstable coronary artery disease after percutaneous coronary intervention (PCI). Importantly, PCI itself causes an acute vascular and systemic inflammatory response, which is diminished by potent preprocedural antiplatelet (glycoprotein IIb/IIIa inhibitors, clopidogrel, and other P2Y12 inhibitors) and statin therapy. Hence, periprocedural hsCRP monitoring could be of use in identifying high-risk patients and guiding adjunctive periprocedural therapy to improve PCI outcomes.

Much of the published data on the predictive value of hsCRP in patients undergoing PCI, however, suffers from limited follow-up and is derived from observations preceding therapeutic advances such as drug-eluting stents (DES), routine intense statin therapy, and frequent use of glycoprotein IIb/IIIa inhibitors. Moreover, the availability of contemporary troponin assays has facilitated more accurate assessment of preprocedural risk and periprocedural myocardial injury. Thus, it remains to be established whether hsCRP is a useful biomarker for risk stratification across a broad spectrum of patients in contemporary PCI practice. The aim of this study was to evaluate the relationship between periprocedural hsCRP levels and immediate and long-term clinical outcomes in patients undergoing PCI using predominantly DES and contemporary adjunctive medical therapies.

Methods

The current study included 513 patients who underwent non-emergency PCI between July 10, 2006 and June 25, 2007 and consented to provide blood samples for hsCRP. An additional cohort of 560 patients who underwent PCI over the same time frame but did not consent to hsCRP measurements was included to assess for enrollment bias. Exclusion criteria were severe acute noncardiac comorbid conditions and chronic inflammatory disease (autoimmune diseases, inflammatory bowel disease etc.) that may impact hsCRP levels. Emergency procedures were defined as those needed to be performed...
WHAT IS KNOWN

• Higher levels of high sensitivity C-reactive protein (hsCRP) before and after percutaneous coronary intervention are independently associated with a higher risk of major adverse cardiac events.
• Postprocedural elevation of hsCRP has been attributed to the inflammatory response to percutaneous coronary intervention and related complications and may also predict outcomes.

WHAT THE STUDY ADDS

• Higher preprocedural hsCRP levels relate to baseline patient characteristics and are independently predictive of periprocedural myocardial injury but not long-term outcome.
• Postprocedural increase in hsCRP also relates to baseline patient characteristics but, in general, is not secondary to periprocedural myocardial injury and does not predict long-term outcome.
• The prognostic yield of periprocedural hsCRP measurements argues against routine use in patients undergoing percutaneous coronary intervention in contemporary practice.

within hours of symptom onset such as those requiring primary PCI, rescue PCI, or PCI for severe ischemia. Patients were excluded if paired baseline and postprocedure hsCRP were unavailable. Hospital charts of each patient were reviewed to verify the data. Each patient was surveyed by telephone using a standardized questionnaire at 6 months, 1 year, and then annually after the procedure. All adverse events during follow-up were confirmed by reviewing the medical records of the patients followed at our institution and by contacting the patients’ physicians and reviewing the hospital records of patients treated elsewhere. The study was approved by the Institutional Review Board. A total of 513 patients (516 PCI) were included in this study. Eight hundred and eighty-three patients who had PCI during December 2012

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Statistical Analysis

Data are presented as the mean±SD for most continuous variables, median (25th, 75th percentiles) for skewed variables, or as a frequency (percentage) for discrete data. Kaplan-Meier methods were used to estimate survival curves. Follow-up began at discharge and excluded 2 patients who died in-hospital. Comparisons between groups are made using Student t test, Wilcoxon rank-sum test, Pearson χ² test, and the log-rank test, respectively. To assess independent associations with pre-PCI hsCRP, we fit a linear regression model for a log-transformation of that measure. Three degrees of freedom splines were used for age, BMI, and creatinine clearance to allow for nonlinear associations.

To assess the association between hsCRP and in-hospital and follow-up events, we first created 5 multiple imputation data sets to handle missing values. Most clinical, angiographic and procedural variables had fewer than 10 observations (<2%) with missing data. Information on multivessel disease was missing in 15%, on thrombus in 9%, and on American College of Cardiology /American Heart Association in 6%. Logistic regression models were used for in-hospital end points: Cox proportional hazards models were used for the follow-up end points. Models were fit to each of the 5 imputation data sets, and the parameter estimates were combined into a single set of estimates using Rubin’s rules. Covariates were chosen from a pool of variables, which were significantly associated with the end point at the 0.15 significance level. Backward selection was used to reduce the model to include only variables significant at the 0.05 significance level. After covariates were selected, hsCRP was added to the model as a continuous, log-transformed variable. S-Plus 6.0 software (Insightful, Seattle, WA) was used to create the 5 imputation data sets (using the aregImpute function from Frank Harrell’s Hmisc package). All other analyses presented here were performed using SAS version 9 software (SAS, Inc, Cary, NC).

Results

Baseline characteristics and hsCRP

The clinical characteristics of the 513 patients that were enrolled are summarized in Table 1. By study design, the entire cohort of enrolled patients was divided into 2 groups according to the median hsCRP value, which was 0.3 mg/dL. Patients with higher hsCRP had significantly more adverse clinical characteristics. They were more likely to be female; have congestive heart failure, MI within 7 days of PCI, diabetes mellitus, and impaired renal function. Table 2 summarizes the angiographic and procedural characteristics in the 2 groups. Consistent with a more frequent recent acute coronary and cardiac presentation, patients with higher preprocedural hsCRP had a greater likelihood of undergoing non-elective procedures and presenting with thrombotic lesions and impaired epicardial blood flow (thrombolysis in myocardial infarction grade <2). The correlation coefficient between pre- and post-PCI hsCRP level was 0.88 (P<0.001).

By multivariable analysis, variables independently associated with preprocedural hsCRP were female sex (39% increase versus men; P=0.028), body mass index (P=0.002), low creatinine clearance (P=0.007), MI within 24 hours pre-PCI (302% increase versus no MI history, P<0.001), MI within 1 to 7 days pre-PCI (260% increase versus no MI history, P<0.001), and presenting with congestive heart failure (74% increase, P=0.008). There was a positive relationship between the number of these characteristics and preprocedural hsCRP levels (Figure 1). Independent predictors of delta hsCRP were age (P=0.048), class ≥III angina (P=0.013), MI within prior 24 hours (P<0.001), and pre-PCI CRP (P=0.046).
Patients who refused hsCRP analysis did not differ in most clinical, angiographic, and procedural characteristics with the following exceptions. They less often had a history of MI (49% versus 56%, P<0.05) and were less often on aspirin (91% versus 97%, P<0.001) and clopidogrel (34% versus 42%, P<0.01), even though they had more frequently a history of peripheral arterial disease (15% versus 11%, P<0.05). They more frequently underwent an elective PCI (61% versus 51%, P<0.001) and less frequently had a successful procedure (92% versus 96%, P<0.05).
In-hospital events including periprocedural MI

In-hospital death (0.4% in both groups), Q-wave MI (0.8% versus 0%; \( P = 0.16 \)), and the composite end point of death/Q-wave MI/emergency coronary artery bypass surgery/stroke (1.2% versus 0.8%; \( P = 0.65 \)) were similar in those with preprocedural hsCRP below versus above the median value.

Periprocedural MI in patients with normal baseline cTnT (n=279) was more frequent in patients with elevated preprocedural hsCRP (24% versus 42%, \( P = 0.002 \)). By multivariable analysis, independent predictors of periprocedural MI were higher than preprocedural hsCRP level (odds ratio per doubling of hsCRP 1.15 [1.01:1.31]; \( P = 0.039 \)), angiographic presence of thrombus (2.38 [1.11:7.24]; \( P = 0.030 \)), unstable angina (2.39 [1.19:4.80]; \( P = 0.014 \)), glycoprotein IIb/IIIa inhibitor use (1.84 [1.07:3.16]; \( P = 0.027 \)), and DES use (0.39 [0.19:0.79]; \( P = 0.009 \)). There was a weak correlation between postprocedural cTnT and postprocedural hsCRP (\( r = 0.19 \), \( P < 0.001 \)), but there was no significant correlation with delta hsCRP (\( r = 0.09 \), \( P = 0.13 \)).

Long-term outcome

Unadjusted mortality and the combined end point of death or MI during a median follow-up of 60 months (25th, 75th percentile: 47, 63) were markedly greater in patients with higher preprocedural hsCRP (29.7% versus 9.9%, \( P < 0.001 \) and 36.5% versus 16.0%, \( P < 0.001 \), respectively, at 5 years, Figure 2A and 2B) and postprocedural hsCRP (27.1% versus 12.5%, \( P < 0.001 \) and 34.9% versus 17.5%, \( P < 0.001 \), at 5 years, respectively, Figure 3A and 3B). On the contrary, there was no significant association between PCI-related change (delta) in hsCRP levels and mortality without and with MI (Figures 4A and 4B).

In a model for mortality based on clinical characteristics, MI within 1 to 7 days of PCI (hazard ratio [HR] 1.33 [1.07, 1.66]; \( P = 0.010 \)) and heart failure at PCI (HR 1.36 [1.04, 1.77], \( P = 0.026 \)) were independent predictors of mortality during follow-up. Preprocedural hsCRP levels (HR per doubling 0.96 [0.92, 1.00]; \( P = 0.066 \)) and postprocedural hsCRP levels (HR 0.98 [0.94, 1.02]; \( P = 0.27 \)) were not significantly associated with follow-up mortality after clinical covariate adjustment. Delta hsCRP (HR 1.07 [0.98, 1.16]; \( P = 0.12 \)) was also not an independent predictor of mortality. No models demonstrated a significant association between hsCRP and the combined end point of death or MI.

Discussion

The major findings of our study, performed among patients requiring contemporary PCI, are as following: (1) higher preprocedural hsCRP is associated with adverse clinical and angiographic characteristics; (2) higher preprocedural hsCRP is an independent predictor of periprocedural MI; however, (3) hsCRP levels before or after PCI, and the relative change with the procedure, do not independently predict long-term mortality or the combined end point of death or MI.

Patients Characteristics and Inflammation

CRP is produced in the liver in response to circulating cytokines, the predominant source of which is inflamed and
adipose tissue. Hence, not surprisingly, CRP is elevated in patients with central obesity and the metabolic syndrome.19–24 Consistent with these prior reports, we observed BMI to be an independent predictor of elevated preprocedural hsCRP levels. In addition, decreased creatinine clearance was associated with higher hsCRP levels.25,26 Thus, obesity and renal failure seem to be potent risk factors for inflammation in patients requiring PCI, independent of other cardiovascular risk factor and noncardiac comorbid conditions.

With respect to cardiac characteristics, current but not past history of heart failure is an independent correlate. This finding is consistent with prior publications showing that hsCRP elevation seems to be related to overt heart failure presentation rather than left ventricular systolic function per se.27–30 Furthermore, a history of a recent acute MI was independently associated with elevated hsCRP, whereas coronary lesion characteristics (multivessel disease, presence of peripheral or cerebral vascular disease, and prior revascularization) were not. These data support the concept that preprocedural inflammation is associated to a large extent with the biological activity of coronary and cardiac disease processes rather than their anatomical severity.9,31–33 Importantly, the inflammatory response to PCI, measured as delta hsCRP, seemed to be primed by the baseline presentation rather than procedural factors. In particular, it did not correlate with postprocedural cTnT levels, and hence was not the consequence of periprocedural MI, which has been questioned before.34

Finally, female gender was an independent predictor of hsCRP elevation in our PCI cohort. This is in agreement with a prior study reporting a higher prevalence of female gender in patients with elevated preprocedural hsCRP levels (≥0.3 mg/dL), and the Dallas Heart Study, which demonstrated higher CRP levels in both black and white women compared with men, even after adjustment for risk factors and medication use.2,35 The mechanisms for these observations remain unexplained at present.

**Preprocedural Inflammation and Periprocedural MI**

Prior studies exploring the relationship between hsCRP and periprocedural MI have yielded conflicting results.2,36–40 However, these studies were conducted mostly in an era that used creatine kinase-MB as the predominant biomarker, predating contemporary cardiac troponin assays, or did not consider the 99th percentile cutoff for normal values. In the present study, we explored this issue by applying the universal definition of periprocedural MI (type 4a) using a contemporary.
cardiac troponin assay to detect myocardial injury. We did not include patients with elevated baseline cardiac troponin levels because it is a challenge to diagnose peri-procedural MI in these patients. Our results indicate that preprocedural hsCRP elevation was associated with a 2-fold higher risk of peri-procedural MI by univariate analysis. This remained true even after adjusting for confounding baseline characteristics in the multivariable analysis, ie, independent of the clinical, lesion, and procedural characteristics that are typically known to be associated with peri-procedural MI. However, the strength of the relationship was significantly decreased, and we cannot determine from our retrospective study whether inflammation is a risk factor or indicator for peri-procedural myocardial injury. A recent meta-analysis that found statin therapy to reduce periprocedural MI most prominently in patients with elevated preprocedural CRP levels is subject to the same conundrum. Although these observations may relate to the association of hsCRP levels with epicardial coronary atherosclerosis activity and vulnerability, inflammation may equally impair coronary microvascular function and hence reduce myocardial tolerance to ischemia.

**Periprocedural hsCRP and Outcomes**

Gaspardone et al were among the first to show that CRP elevation was virtually a universal phenomenon in the first 48 hours after PCI. In their study, all cardiovascular events over an 1-year follow-up period occurred in those patients whose CRP levels did not normalize at 72 hours after PCI. The appealing aspect of this and other studies reaching similar conclusions was the implication that inflammation per se may promote adverse outcomes after PCI. However, the introduction of DES, longer duration of dual antiplatelet therapy, and greater awareness of the risk of stent thrombosis have led to many changes in PCI practice, which may have impacted the putative relationship between inflammation and outcomes. Indeed, in the present study, there was no relationship between delta hsCRP and mortality and a weak univariate relationship with the combined end point of death and outcomes. This remained true even after adjusting for clinical covariates, however, no independent relationship with mortality was present for either preor post-PCI hsCRP levels. Importantly, this observation was not attributable to a low number of events. In fact, 5-year mortality rate was relatively high in this patient population (20% overall), which may be attributed to the burden of comorbidities. Another consideration is the low usage of lipid-lowering medications at the time of admission in this study cohort, which may have influenced the outcome data. In particular, statins have been shown to mitigate peri-procedural hsCRP levels and their impact on 1-year event rates (mortality and non-fatal MI), especially in those with highest preprocedural hsCRP levels.

In summary, our study suggests that the observed independent adverse relationship of hsCRP with mortality during follow-up reported in prior studies, including those conducted with DES, may have been attributed to incomplete adjustment for baseline risk related to unmeasured variables.

**Limitations**

One of the main limitations of our investigation is that this is a single-center study and hence the data may not be applicable to all patients. Furthermore, the sample size is small and in a larger population, a more modest effect of hsCRP might have been observed. An additional consideration is the fact that the study cohort includes only those individuals who consented to provide blood samples, introducing a potential for bias. However, the characteristics and outcomes of patients who did not consent to provide blood samples for hsCRP were relatively comparable overall. Finally, hsCRP was measured using immunoturbidimetric assay, the standard in our research laboratory at the time the samples were collected, and not the immunoassay used currently in clinical practice.

**Conclusions**

Our findings corroborate the view that, in general, it is the atherosclerotic burden and disease activity that determine long-term clinical outcomes after PCI rather than inflammation per se. Preprocedural hsCRP level seems to be a marker of baseline risk and is independently associated with the risk of peri-procedural MI. The inflammatory response to PCI (delta CRP) is also determined by baseline patient characteristics and, in general, is not secondary to peri-procedural myocardial injury. Thus, our findings do not support a role for routine measurement of hsCRP in the management of patients undergoing PCI in contemporary practice.

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**Disclosures**

None.

**References**


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