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Preoperative C-reactive Protein Predicts Long-term Mortality and Hospital Length of Stay after Primary, Nonemergent Coronary Artery Bypass Grafting

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ABSTRACT

Background: Preoperative C-reactive protein (CRP) levels more than 10 mg/l have been shown to be associated with increased morbidity and mortality after cardiac surgery. We examine the value of preoperative CRP levels less than 10 mg/l for predicting long-term, all-cause mortality and hospital length of stay in surgical patients undergoing primary, nonemergent coronary artery bypass graft-only surgery.

Methods: We examined the association between preoperative CRP levels stratified into four categories (< 1, 1–3, 3–10, and > 10 mg/l), and 7-yr all-cause mortality and hospital length of stay in 914 prospectively enrolled primary, nonemergent coronary artery bypass graft-only surgical patients using a proportional hazards regression model.

Results: Eighty-seven patients (9.5%) died during a mean follow-up period of 4.8 ± 1.5 yr. After proportional hazards adjustment, the 3–10 and > 10 mg/l preoperative CRP groups were associated with long-term, all-cause mortality (hazards ratios [95% CI]: 2.50 [1.22–5.16], $P = 0.01$ and 2.66 [1.21–5.80], $P = 0.02$, respectively) and extended hospital length of stay (1.32 [1.07–1.63], $P < 0.001$ and 1.27 [1.02–1.62], $P = 0.001$, respectively).

Conclusion: We demonstrate that preoperative CRP levels as low as 3 mg/l are associated with increased long-term mortality and extended hospital length of stay in relatively lower-acuity patients undergoing primary, nonemergent coronary artery bypass graft-only surgery. These important findings may allow for more objective risk stratification of patients who present for uncomplicated surgical coronary revascularization.

What We Already Know about This Topic

- Preoperative C reactive protein (CRP) concentrations more than 10 mg/L are predictive of mortality after cardiac surgery in patients with ongoing ischemia, but whether lower values predict mortality in stable patients is unclear

What This Article Tells Us That Is New

- In more than 900 patients without ongoing ischemia undergoing coronary artery bypass grafting only, CRP concentrations as low as 3 mg/l were associated with increased 5-yr mortality and increased hospital length of stay

C-REACTIVE protein (CRP) is a well-recognized marker and a possible mediator of systemic inflammation. Low (< 1 mg/l), moderate (1–3 mg/l), and high (> 3 mg/l) CRP risk categories are currently used to predict cardiovascular events in nonsurgical populations.[1] These validated CRP risk categories have been shown to predict future cardiovascular events in apparently healthy individuals, as well as recurrent myocardial infarction, and death in patients with acute coronary syndromes.[2–5] Previous studies in cardiac surgical patients suggest that increased preoperative CRP levels are associated with increased short- and long-term morbidity and mortality.[6–8] However, these studies have, for the most part, included higher-acuity cardiac surgical patients with profoundly increased preoperative CRP levels undergoing combined valve or coronary artery bypass graft (CABG) surgery. The significance of lower preoperative CRP values for predicting postoperative mortality and morbidity in a lower-acuity cardiac patient population has not been defined. Therefore, the aim of this study was to examine the value of preoperative CRP levels for predicting long-term, all-cause mortality and hospital length of stay (HLOS) in a relatively homogeneous patient sample population undergoing primary, nonemergent CABG-only surgery with cardiopulmonary bypass.

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Materials and Methods

Study Design and Patient Population

Between August 2001 and June 2007, 1,444 patients aged 20 to 89 yr scheduled for primary CABG-only surgery with cardiopulmonary bypass at the Brigham and Women's Hospital, Boston, Massachusetts, and the Texas Heart Institute, St Luke's Episcopal Hospital, Houston, Texas, were enrolled under the auspices of the parent study known as CABG Genomics.‖ CABG Genomics is an institutional review board-approved, prospective longitudinal study examining the association between genetic variation and adverse outcomes after CABG surgery. Exclusion criteria for enrollment into the parent study were preoperative hematocrit less than 25% and a history of leukocyte-rich blood product transfusion ≤ 30 days before surgery. After informed consent, preoperative demographic characteristics, environmental risk factors and comorbidities, operative surgical and anesthetic management, and in-hospital events were recorded for all patients. After hospital discharge, the annual incidence of all-cause death was discovered through mailed questionnaires or examination of the Social Security Index for those patients lost to follow-up.

To address the specific aim of this study, we further restricted our analysis to lower-acuity CABG-only patients by excluding patients with increased preoperative cardiac troponin I (cTnI) levels (> 0.03 μg/l, n = 421), evidence of a preoperative infection defined as fever, the need for preoperative antibiotics, or positive blood cultures 7 days before surgery (n = 40); patients having concomitant valve surgery (n = 41), emergent surgery (n = 1), off-pump surgery (n = 32), or reoperative cardiac surgery (n = 1); and patients with missing preoperative CRP values (n = 8).

CRP and cTnI levels were measured from whole blood samples drawn immediately before surgery and on postoperative days (PODs) 1–5. After collection of whole blood, aliquoted citrated plasma samples were stored in liquid-phase nitrogen. CRP and cTnI were calculated using a sandwich immunoassay on Triage® platform (Biosite, Inc., San Diego, CA) by a single blinded core facility. CRP concentrations were calculated using a set of spiked plasma samples as the calibration reference. The analytical sensitivity of the CRP assay was 0.33 mg/l, with a precision of more than 17% the measurable range of the assay (0.33–300 mg/l).

Patients were categorized into the following CRP categories: less than 1, 1–3, 3–10, and more than 10 mg/l based on preoperative CRP levels. The primary outcomes were all-cause mortality occurring up to 7 yr after surgery, and HLOS defined as the number of days spent in the hospital after the operation, with the operative day and last day of hospitalization counted as whole days.

‖ http://clinicaltrials.gov/show/NCT00281164. Accessed December 1, 2009.

Statistical Analysis

Separate Cox proportional hazards regression models were used to estimate adjusted hazards ratios (HR) for the association between preoperative CRP risk categories and all-cause mortality and HLOS. A separate list of clinical risk factors for all-cause postoperative mortality and HLOS was initially generated through a theory-driven selection from more than 1,500 data points used to phenotype patients enrolled in CABG Genomics. We subsequently built separate proportional hazards models using a data-driven stepwise regression approach by including variables with $P \leq 0.20$ on univariate analysis. Demographic variables, including age, gender, race, and institution, were forced into the final models. Because HMG (3-hydroxy-3-methyl-glutaryl)-CoA reductase inhibitor (statin) therapy has been shown to decrease cardiovascular events and mortality in cardiac surgical patients,[9,10] preoperative statin therapy was also forced into the final models. In addition, increased POD1 cTnI, which has been associated with increased postoperative mortality,[11] was forced into the final models (see figure legends for a final list of risk factors for each model). The proportional hazards assumption was tested by including interaction terms between preoperative CRP levels and the logarithm of follow-up time in regression models.[12] The interaction terms were not significant, suggesting that the assumption of proportionality was valid.[12] Mortality was censored at 7 yr, and HLOS was censored at 30 days. Patients who died before hospital discharge were censored at 30 days or at day of death for the HLOS analysis. Kaplan–Meier survival curves were generated for each preoperative CRP risk category.

Medians with interquartile range are used to describe nonnormally distributed data; otherwise, means and SD are presented. Wilcoxon rank-sum and Fisher's exact tests were used to compare continuous and categorical variables, respectively. A Kruskal–Wallis test was used to compare continuous variables against categorical variables with more than 2 levels. HR ± 95% confidence intervals (CI) was used to describe the effect of preoperative CRP risk categories on outcomes. $P \leq 0.05$ was considered statistically significant. JMP 7.0.2 and SAS 9.1.3 (SAS Institute, Cary, NC) were used for statistical analysis.

Results

Patient Demographics and Perioperative CRP Levels

After exclusions, 916 patients were analyzed: 365 patients in the less than 1 mg/l group, 315 patients in the 1–3 mg/l group, 138 patients in the 3–10 mg/l group, and 98 patients in the more than 10 mg/l group. Baseline demographic and clinical characteristics for each CRP category are listed in table 1. Patients in the higher CRP categories were more likely to be women, current smokers, have a higher body mass index, have a higher incidence of self-reported history of myocardial infarction less than 2 weeks before surgery, and have longer cardiopulmonary bypass times. These patients were less likely to have hypercholesterolemia or to be receiving preoperative aspirin.

Table 1. Baseline Demographic and Clinical Characteristics Across Defined Preoperative CRP Categories

	< 1 mg/l (n = 365)	1–3 mg/l (n = 315)	3–10 mg/l (n = 138)	> 10 mg/l (n = 98)	*P* Value*
Demographic data					
Age at enrollment (mean ± SD), yr	63 ± 10	64 ± 10	65 ± 10	65 ± 10	ns
Male, n (column %)	324 (89)	267 (85)	103 (74)	72 (73)	< 0.001
Caucasian, n (column %)	269 (74)	231 (73)	97 (70)	73 (74)	ns
Institution A, n (column %)	259 (71)	226 (72)	104 (72)	69 (70)	ns
Preoperative data					
Body mass index (mean ± SD), kg/m^2	29 ± 5	29 ± 5	32 ± 14	30 ± 5	< 0.001
Hypertension, n (column %)	269 (74)	231 (73)	103 (75)	81 (83)	ns
Hypercholesterolemia, n (column %)	299 (81)	223 (71)	105 (76)	66 (67)	0.001
Diabetes mellitus†, n (column %)	123 (34)	90 (29)	40 (29)	32 (33)	ns
MI < 2 wks before surgery‡, n (column %)	15 (4)	26 (8)	22 (16)	13 (13)	0.002
Creatinine, median (IQR), mg/dl	1.0 (0.9–1.2)	1.1 (0.9–1.2)	1.0 (0.9–1.2)	1.1 (0.9–1.2)	ns
Pulmonary disease§, n (column %)	36 (10)	62 (20)	21 (15)	20 (20)	0.006
Current smoker, n (column %)	23 (6)	39 (12)	23 (17)	16 (16)	0.001
LVEF, median (IQR), %	59 (50–60)	55 (50–60)	55 (45–60)	55 (44–60)	ns
cTnI, median (IQR), μg/l	0.00 (0.00–0.01)	0.00 (0.00–0.01)	0.00 (0.00–0.02)	0.00 (0.00–0.01)	ns
Preoperative medications					
Statin, n (column %)	294 (81)	243 (77)	104 (75)	69 (70)	ns
Aspirin, n (column %)	287 (79)	246 (78)	85 (62)	69 (70)	< 0.001
β-blocker, n (column %)	271 (74)	237 (75)	99 (72)	77 (78)	ns
ACE inhibitor, n (column %)	178 (49)	134 (43)	62 (45)	39 (40)	ns
Antiarrhythmic medication, n (column %)	8 (2)	6 (2)	5 (4)	5 (5)	ns
Digoxin, n (column %)	5 (1)	10 (3)	5 (4)	2 (2)	ns
Nonaspirin platelet inhibitor, n (column %)	80 (22)	60 (19)	36 (26)	18 (18)	ns
Intraoperative data					
Cardiopulmonary bypass time, median (IQR), min	92 (65–118)	86 (62–112)	102 (74–124)	93 (64–117)	0.009
Distal coronary anastomosis, n (column %)					ns
≤ 2	53 (15)	60 (19)	22 (16)	12 (12)	
3	159 (44)	139 (44)	67 (49)	44 (45)	
≥ 4	153 (42)	114 (36)	49 (36)	42 (43)	
Blood product transfusion‖, n (column %)	183 (50)	143 (45)	72 (52)	58 (40)	ns
New-onset atrial fibrillation, n (column %)	89 (24)	108 (34)	38 (28)	22 (22)	0.02

* *P* value represents significance across CRP risk categories. † Diabetes mellitus defined as either insulin or noninsulin-dependant. ‡ MI < 2 wks before surgery defined as patient-reported history of myocardial infarction before surgery; not based on measured preoperative troponin levels. § Pulmonary disease defined as chronic obstructive, asthma, or pulmonary fibrosis. ‖ Blood product transfusion was defined as any transfusion of autologous packed red blood cells or fresh-frozen plasma during the intraoperative period up until 24 h postoperatively.

ACE = angiotensin converting enzyme; CRP = C-reactive protein; cTnI = cardiac troponin I; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; ns = not significant.

Preoperative cTnI levels were less than 0.03 μg/l in all patients analyzed. POD1 cTnI levels were significantly increased in each CRP category compared with respective preoperative cTnI levels (median cTnI levels [interquartile range]: < 1 mg/l group, 1.17 [0.60–2.36] μg/l; 1–3 mg/l group, 1.02 [0.58–2.17] μg/l; 3–10 mg/l group, 1.20 [0.65–2.08] μg/l; and > 10 mg/l group, 1.14 [0.67–2.76] μg/l; $P < 0.0001$). However, POD1 cTnI levels did not differ significantly between CRP categories ($P = 0.36$). Perioperative CRP levels stratified by CRP category are shown in figure 1.

Relationship of Preoperative CRP Risk Categories to All-cause Mortality up to 7 yr after CABG Surgery

Eighty-seven patients (9.5%) died during a mean follow-up period of 4.8 ± 1.5 yr. There was a significant decrease in survival with increasing preoperative CRP category ($P = 0.002$; fig. 2). The unadjusted HRs (95% CI) for patients in the 1–3, 3–10,

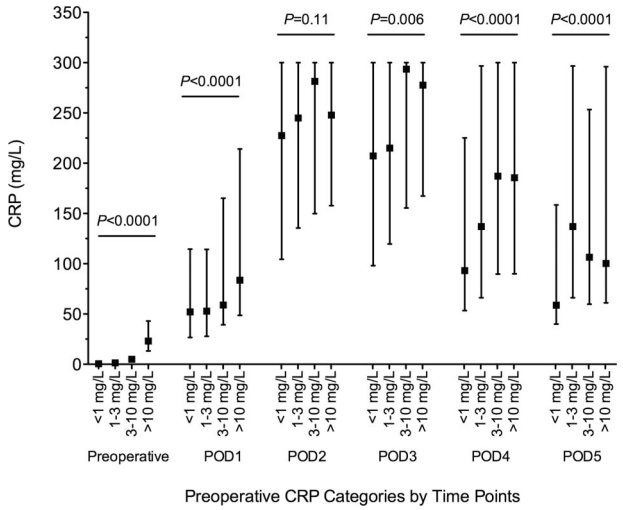


Fig. 1. Perioperative C-reactive protein (CRP) levels during coronary artery bypass graft (CABG) surgery stratified by preoperative CRP risk categories. Data are represented as median and interquartile range. *P* values in figure represent significant differences across CRP categories. Upper limit of the CRP assay was 300 mg/l. POD = postoperative day.

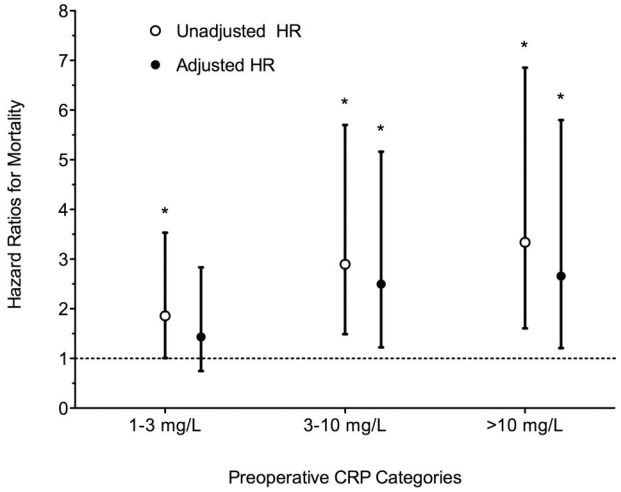
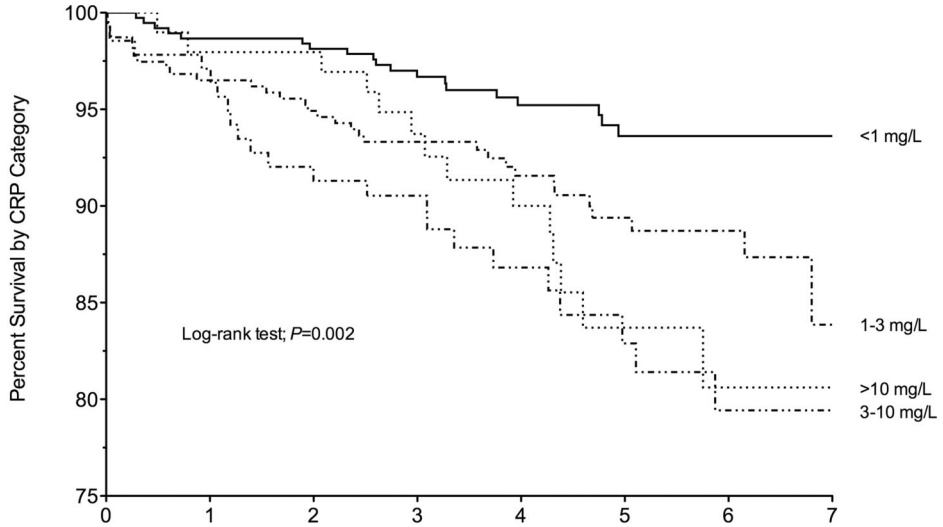


Fig. 3. Unadjusted and adjusted Cox proportional hazards ratio (HR) for all-cause mortality up to 7 yr after surgery. Data represented as HR with 95% confidence interval bars. C-reactive protein (CRP) risk category adjusted for history of myocardial infarction < 2 weeks before surgery, body mass index, diabetes mellitus, pulmonary disease, preoperative serum creatinine, preoperative left ventricular ejection fraction, number of performed coronary grafts, and new-onset postoperative atrial fibrillation. * $P \leq 0.05$ compared with preoperative CRP risk category of < 1 mg/l as reference.

and more than 10 mg/l preoperative CRP groups were 1.86 (1.01–3.53), $P = 0.05$; 2.89 (1.49–5.70), $P = 0.002$, and 3.34 (1.61–6.86), $P = 0.002$, respectively, compared with the less than 1 mg/l CRP category as the reference (fig. 3). After adjusting for clinically relevant demographic variables and perioperative risk factors, including preoperative statin use and POD1 cTnI levels, the HRs (95% CI) for patients in the 1–3, 3–10, and more than 10 mg/l preoperative CRP groups were 1.43 (0.75–2.83), $P = 0.28$; 2.50 (1.22–5.16), $P = 0.01$; and 2.66 (1.21–5.80), $P = 0.02$, respectively, compared with the less than 1 mg/l CRP category as the reference. POD1 cTnI levels ($P = 0.20$) and preoperative statin therapy ($P = 0.10$) were not independently associated with all-cause mortality after surgery.

Relationship of Preoperative CRP Risk Categories to HLOS after CABG Surgery

Nine hundred four patients (98.2%) were discharged from the hospital within 30 days of surgery. Three patients died before hospital discharge. Patients with preoperative CRP levels in the less than 1 and 1–3 mg/l range stayed a median



Patients At-Risk								
<1 mg/L	365	361	359	296	230	155	96	23
1-3 mg/L	315	305	300	256	197	136	73	19
3-10 mg/L	138	135	127	106	79	57	38	6
>10 mg/L	98	97	97	83	66	37	22	4

Fig. 2. Survival for each C-reactive protein (CRP) category for up to 7 yr after coronary artery bypass graft surgery.

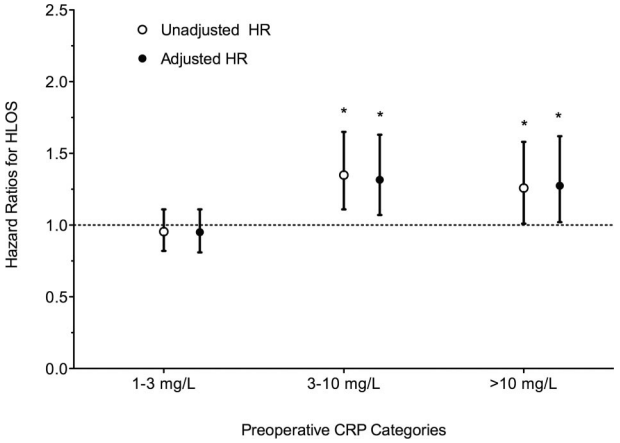


Fig. 4. Unadjusted and adjusted Cox proportional hazards ratios for hospital length of stay (HLOS). Data are represented as hazards ratios with 95% confidence interval bars. C-reactive protein (CRP) risk category adjusted for preoperative left ventricular ejection fraction, preoperative serum creatinine, preoperative use of antiarrhythmic medications, digoxin, or nonaspirin platelet inhibitors, administration of perioperative blood product, cardiopulmonary bypass time, and new-onset postoperative atrial fibrillation. * $P \geq 0.05$ compared with preoperative CRP risk category of < 1 mg/l as reference. HR = hazards ratio.

of 7 days in the hospital, whereas patients with preoperative CRP levels in the 3–10 and more than 10 mg/l range stayed a median of 8 days ($P < 0.001$). Although the clinical relevance of one additional POD in the hospital may be debatable, the costs incurred nonetheless significant. The unadjusted HRs (95% CI) for patients in the 1–3, 3–10, and more than 10 mg/l preoperative CRP groups were 0.95 (0.82–1.11), $P = 0.55$; 1.35 (1.11–1.65), $P = 0.0.003$; and 1.26 (1.01–1.58), $P = 0.04$, respectively, compared with the less than 1 mg/l CRP category as the reference (fig. 4). The adjusted HRs (95% CI) for patients in the 1–3, 3–10, and more than 10 mg/l preoperative CRP groups were 0.95 (0.81–1.11), $P = 0.20$; 1.32 (1.07–1.63), $P < 0.001$; and 1.27 (1.02–1.62), $P = 0.001$, respectively, compared with the less than 1 mg/l CRP category. After adjustment, POD1 cTnI levels were independently associated with extended HLOS (HR [95% CI]: 2.70 [1.38–5.88], $P = 0.003$).

Discussion

Preoperative CRP levels more than 10 mg/l have been previously associated with increased long-term mortality and extended HLOS in patients undergoing primary CABG-only surgery with cardiopulmonary bypass. We now extend this previous work by demonstrating for the first time that preoperative CRP levels ranging as low as 3–10 mg/l are also independent predictors of increased long-term mortality and extended HLOS, even in patients without evidence of ongoing preoperative myocardial injury. These important findings may allow for more objective risk stratification of patients who present for uncomplicated surgical coronary revascularization.

Increased CRP levels have emerged as a strong independent predictor of cardiovascular disease in apparently healthy individuals.[1,13] In patients with acute coronary syndromes, CRP predictors increased morbidity and mortality independent of increased troponin levels.[14,15] Several studies have reported increased short- and long-term morbidity and mortality in cardiac surgical patients with increased preoperative CRP levels. Palmerini *et al.*[8] showed decreased survival at 9 months of follow-up after CABG surgery in relatively high-risk patients with unprotected left main coronary artery disease and preoperative CRP levels ≥ 12.2 mg/l. Cappabianca *et al.*[6] showed increased in-hospital and 3-yr all-cause mortality in a heterogeneous patient population with preoperative CRP levels ≥ 5 mg/l undergoing cardiac surgery that included, but was not limited to, CABG surgery. Kangasniemi *et al.*[7] showed significantly increased 12-yr mortality in patients with preoperative CRP levels ≥ 10 mg/l undergoing isolated on-pump CABG surgery. However, these authors were unable to comment specifically on the effects of preoperative CRP levels less than 10 mg/l because of limitations of the CRP assay used. Although these studies add to the growing body of evidence suggesting that increased preoperative CRP levels predict increased postoperative mortality, they are not generalizable to lower-acuity cardiac surgical patients with lower-range preoperative CRP levels less than 10 mg/l undergoing CABG-only surgery. To address this gap in knowledge, we not only corroborate the findings of other by demonstrating an association between preoperative CRP levels more than 10 mg/l and increased postoperative mortality but also show that preoperative CRP levels as low as 3 mg/l are associated with decreased survival and extended HLOS in lower-acuity cardiac surgical patients free of ongoing myocardial ischemia or infarction at the time of nonemergent surgical revascularization.

We did not observe an effect of preoperative statin therapy on long-term mortality after CABG surgery. Although no study to date has examined the effects of preoperative statin therapy on long-term survival after CABG surgery, there are a number of studies that suggest a beneficial association with improved survival up to 30 days postoperatively.[9,10,16,17] In this study, more than 75% of the patients were treated preoperatively with a statin. Because of the small number of patients not on preoperative statin therapy and the relatively low mortality rate in this study, we may have been underpowered to detect a difference in long-term survival. Furthermore, in light of emerging evidence suggesting beneficial effects on short- and long-term cardiovascular morbidity and mortality in both surgical and nonsurgical cohorts,[16,18] any inference of discontinuing perioperative statin therapy should not be made based on our findings.

Emerging evidence from the nonsurgical population suggests that even slight increase in circulating CRP levels correlate with poorer cardiovascular outcomes. Similarly, our findings in the cardiac surgical population suggest that preoperative CRP levels well below levels considered increased in previous studies also carries a significant risk of increased long-term mortality and HLOS. However, because we only enrolled patients scheduled to undergo CABG surgery, we

are unable to directly compare the predictive value of CRP between surgical and nonsurgical cohorts with regards to outcome. Despite minimal variability of basal CRP levels over long periods of time,[19,20] it is conceivable that surgical coronary revascularization might alter a patients' risk profile for death by altering postoperative baseline CRP levels. These questions can only be addressed through a prospectively designed study whereby CRP levels are measured at the time of long-term follow-up.

Our findings do not support or refute the important question of whether or not CRP is a proinflammatory mediator of postoperative mortality, or merely a marker. A number of studies implicate CRP as an important mediator in the generation of atheromatous coronary plaque, including uptake of low-density lipoprotein by macrophages,[21] triggering increased expression of endothelial cell surface adhesion molecules,[22] and activating complement system proteins.[23] However, more recent studies have brought into question the biologic role of CRP as a proinflammatory pattern recognition molecule by suggesting that the *in vitro* effects of CRP noted above can be ascribed to bacterial by-product or azide contamination of commercially available CRP preparations not subsequently seen when highly purified CRP is used.[24,25] Moreover, although there is strong evidence that putative CRP gene single nucleotide polymorphisms influence systemic CRP levels, an independent association between these CRP single nucleotide polymorphisms and adverse cardiovascular events has not been definitively established.[26–28] Confirmation of a direct causal relationship between CRP and cardiovascular outcomes will require further investigation.

In this study, we show that increased preoperative CRP levels predict long-term, all-cause mortality and extended HLOS in a cohort of lower-acuity CABG-only surgical patients. These findings may allow for more objective risk stratification of patients who present for nonemergent, surgical coronary revascularization. Further delineation of the proinflammatory mechanisms of CRP will establish CRP as a potentially modifiable risk predictor in both surgical and nonsurgical patients.

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