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C-Reactive Protein and the Risk of Stent Thrombosis and Cardiovascular Events After Drug-Eluting Stent Implantation

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Background—Although C-reactive protein (CRP) has been proposed as a useful biomarker for predicting atherothrombosis, the association between CRP and stent thrombosis after drug-eluting stent implantation has not been defined.

Methods and Results—We prospectively evaluated 2691 patients treated with drug-eluting stents who had a baseline CRP measurement. The primary outcome was stent thrombosis; secondary outcomes were death, myocardial infarction (MI), death or MI, and target vessel revascularization. During follow-up (median, 3.9 years), 32 patients had definite or probable stent thrombosis, 137 patients died, 227 had an MI, and 195 underwent target vessel revascularization. In multivariable Cox proportional-hazards models, elevated levels of CRP were significantly associated with increased risk of stent thrombosis (hazard ratio, 3.86; 95% confidence interval, 1.82 to 8.18; $P<0.001$). Elevated CRP levels also significantly predicted the risks of death (hazard ratio, 1.61; 95% confidence interval, 1.13 to 2.28; $P=0.008$), MI (hazard ratio, 1.63; 95% confidence interval, 1.25 to 2.12; $P=0.001$), and death or MI (hazard ratio, 1.61; 95% confidence interval, 1.29 to 2.00; $P<0.001$) but not target vessel revascularization (hazard ratio, 1.20; 95% confidence interval, 0.90 to 1.61; $P=0.21$). The incorporation of CRP into a model with patient, lesion, and procedural factors resulted in a significant increase in the C statistic for the prediction of stent thrombosis, MI, and the composite of death or MI.

Conclusions—Elevated CRP levels were significantly associated with increased risks of stent thrombosis, death, and MI in patients receiving drug-eluting stents, suggesting the usefulness of inflammatory risk assessment with CRP. Given the relatively infrequent occurrence of stent thrombosis, death, and MI, larger studies with longer-term follow-up are required to confirm the novel relationship. (***Circulation*. 2009;120:1987-1995.**)

Key Words: C-reactive protein ■ stents ■ thrombosis

Inflammatory processes are important contributors to atherogenesis and to the vulnerability of atherosclerotic lesions.[1] C-reactive protein (CRP), a marker of systemic inflammation, has been associated with increased relative risks of cardiovascular events independently of established risk factors, suggesting that CRP is a useful biomarker for cardiovascular risk stratification in clinical practice.[2] In addition, preprocedural CRP levels are predictive of ischemic complications after percutaneous coronary intervention (PCI).[3]

Clinical Perspective on p 1995

Although drug-eluting stents (DES) have resulted in reduced rates of restenosis and repeat revascularization compared with bare metal stents, recent reports have raised safety concerns about late stent thrombosis.[4,5] Several clinical and anatomic risk factors have been reported to predict DES-related stent thrombosis.[5–7] However, these characteristics do not fully explain the risk of stent thrombosis.

CRP has been postulated to be a hemostatic risk factor predicting atherothrombosis.[8] Our previous study suggested that in patients undergoing DES implantation, CRP levels were associated with major coronary events (cardiac death or Q-wave myocardial infarction [MI]), which could reflect the major clinical manifestations of stent thrombosis.[9] Specifically, on an a priori basis, we hypothesized that elevated levels of CRP were associated with increased risk of stent thrombosis after DES implantation. However, clinical data linking CRP with the risk of stent thrombosis are limited. We therefore prospectively investigated whether CRP levels were associated with the risk of stent thrombosis and long-term clinical outcomes and evaluated the predictive usefulness of CRP among patients treated with DES.

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Table 1. Baseline Characteristics

Variable	All Patients (n=2691)	Elevated CRP Levels (≥3 mg/L) (n=970)	Nonelevated CRP Levels (<3 mg/L) (n=1721)	*P*
Demographic characteristics				
Age, y	60.8 (10.2)	61.5 (10.6)	60.4 (9.9)	0.01
Male sex, n (%)	1864 (69.3)	700 (72.2)	1164 (67.6)	0.01
Clinical characteristics, n (%)				
Diabetes mellitus	768 (28.5)	310 (32.0)	458 (26.6)	0.003
Hypertension	1412 (52.5)	550 (56.7)	862 (50.1)	0.001
Current smoking	769 (28.6)	305 (31.4)	464 (27.0)	0.01
Hypercholesterolemia	603 (22.4)	213 (22.0)	390 (22.7)	0.68
Renal insufficiency (creatinine ≥2.0 mg/dL)	70 (2.6)	46 (4.7)	24 (1.4)	<0.001
Previous PCI	508 (18.9)	179 (18.5)	329 (19.1)	0.67
Previous bypass surgery	80 (3.0)	39 (4.0)	41 (2.4)	0.02
Unstable angina	1115 (41.4)	431 (44.4)	684 (39.7)	0.02
Left ventricular ejection fraction, %	59.1 (8.4)	57.9 (9.3)	59.8 (7.8)	<0.001
Other blood biomarkers				
Homocysteine, μmol/L	14.5 (5.8)	15.0 (5.9)	14.1 (5.7)	<0.001
Lipoprotein(a), mg/dL	27.5 (27.1)	29.8 (29.7)	26.2 (25.5)	0.002
Leukocyte count, $\times 10^3/mm^3$	7.1 (2.1)	7.7 (2.3)	6.7 (1.9)	<0.001
Lesion and procedural characteristics, n (%)				
Multivessel disease	1604 (59.6)	622 (64.1)	982 (57.1)	<0.001
Left anterior descending artery	1492 (55.4)	527 (54.3)	965 (56.1)	0.38
Left main coronary artery	238 (8.8)	83 (8.6)	155 (9.0)	0.69
ACC/AHA type B2 or C lesions	2122 (78.9)	780 (80.4)	1342 (78.0)	0.14
Bifurcation treatment	554 (20.6)	190 (19.6)	364 (21.2)	0.34
Ostial lesion	302 (11.2)	104 (10.7)	198 (11.5)	0.54
Total occlusion	201 (7.5)	65 (6.7)	136 (7.9)	0.26
Type of stent				0.03
Sirolimus-eluting stent	2123 (78.9)	743 (76.6)	1380 (80.2)	
Paclitaxel-eluting stent	568 (21.1)	227 (23.4)	341 (19.8)	
Total stents per patient, n	1.96 (1.14)	2.00 (1.18)	1.93 (1.12)	0.14
Total stent length per patient, mm	49.12 (31.77)	50.79 (33.21)	48.19 (30.89)	0.05
Average stent diameter per patient, mm	3.17 (0.29)	3.16 (0.30)	3.18 (0.29)	0.20
PCI with intravascular ultrasound guidance	1842 (68.5)	624 (64.3)	1218 (70.8)	0.001
Discharge medications				
ACE inhibitor	671 (24.9)	326 (33.6)	345 (20.0)	<0.001
β-blockers	2056 (76.4)	748 (77.1)	1308 (76.0)	0.52
Calcium channel blocker	2153 (80.0)	712 (73.4)	1441 (83.7)	<0.001
Statin	1435 (53.3)	501 (51.6)	934 (54.3)	0.19
Status of dual antiplatelet therapy				
Duration of clopidogrel use, mo	10.9 (8.6)	10.9 (8.9)	10.9 (8.4)	0.54
Dual antiplatelet therapy through 6 mo, n (%)	2230 (82.9)	794 (81.9)	1436 (83.5)	0.28
Dual antiplatelet therapy through 12 mo, n (%)	713 (26.5)	251 (25.9)	462 (26.9)	0.98

ACE indicates angiotensin-converting enzyme. Data are shown as mean (SD) for continuous variables and absolute numbers (percentage) for dichotomous variables.

Methods

Study Population and Procedures

The study population included consecutive patients with de novo coronary artery disease who underwent an initial PCI with DES and had their baseline high-sensitivity CRP measured at the Asan Medical Center (Seoul, Korea) between February 2003 and February 2006. Patients who presented with acute MI (either ST- or non–ST-elevation MI) were excluded because of the possible confounding effect of myocardial necrosis on baseline CRP. Patients were also excluded if they presented with cardiogenic shock, had concomitant inflammatory conditions (such as active infection, inflammatory arthritis, inflammatory bowel disease, or connective tissue disease) or malignancies, or had recent (<2 months) surgery or major trauma.

PCI was performed according to current practice guidelines. During the study enrollment period, stenting was performed exclusively with DES.[10] The choice of the specific type of DES (sirolimus-eluting [Cypher, Cordis, Johnson and Johnson, Miami Lakes, Fla] or paclitaxel-eluting [Taxus, Boston Scientific, Natick, Mass] stents) was left to the operator's discretion. All patients undergoing PCI were prescribed aspirin (loading dose, 200 mg) plus clopidogrel (loading dose, 300 or 600 mg) before or during the coronary intervention. After the procedure, patients were prescribed aspirin (100 to 200 mg once daily) indefinitely and clopidogrel (75 mg once daily) for at least 6 months, regardless of DES type.[11] Treatment beyond this duration was at the discretion of the physician.

This study was approved by the local institutional review board of Asan Medical Center, and all patients provided written informed consent.

Measurement of CRP and Other Biomarkers

In addition to assessment of CRP, we measured some other inflammatory markers studied in coronary heart disease. Considering the biological plausibility and the reported associations with cardiovascular events, homocysteine (a marker of endothelial function and oxidant stress), lipoprotein(a) (a marker of coagulation and fibrinolytic system), and leukocyte count (a marker of systemic inflammation) were measured simultaneously in each patient. Fasting blood samples were obtained in the morning before the procedure. CRP was assayed with a latex-enhanced high-sensitivity CRP immunoassay (COBAS INTEGRA, Roche Diagnostics GmbH, Mannheim, Germany). Total plasma homocysteine was determined with a chemiluminescence immunoassay (ADVIA Centaur, Bayer Diagnostics, Tarrytown, NY). Lipoprotein(a) was measured with an ELISA (Immunozym Lp(a) kit, Immuno GmbH, Vienna, Austria). Leukocyte count was determined with an automated counter (Auto Blood Cell Analyzer, Sysmex XE-2100, TOA Medical Electronics, Kobe, Japan). All laboratory testing was performed by personnel blinded to patient information and study objectives.

End Points and Definitions

The primary end point was the occurrence of stent thrombosis assessed by the Academic Research Consortium designations of definite, probable, or possible, with the prespecified key end point being definite or probable.[12] Secondary end points were death, MI, death or MI, and target vessel revascularization (TVR). All events were based on clinical diagnoses assigned by the patient's physician and were adjudicated by an independent group of clinicians blinded to CRP values.

Definite stent thrombosis was defined as angiographic or pathological confirmation of thrombus in or within 5 mm of the stent in the presence of an acute ischemic syndrome. Probable stent thrombosis was defined as acute MI involving the target vessel territory without angiographic evidence or any unexplained death within 30 days. Possible stent thrombosis was defined as any unexplained death from 30 days after the procedure. According to timing, stent thrombosis was defined as early (0 to 30 days), late (31 days to 1 year), or very late (>1 year). Death was defined as death resulting from any cause. MI was defined as the presence of new Q waves on the ECG or an elevation of the creatine kinase-MB isoenzyme at least 3 times the upper limit of normal in at least 2 blood samples. TVR was defined as any percutaneous or surgical revascularization of the target vessel. As previously defined, CRP levels ≥3 mg/L were considered elevated,[3,13] and this cutoff point was prespecified in the study protocol before examination of the data.

Data Collection and Follow-Up

Clinical, procedural, and outcome data were prospectively collected by independent research personnel unaware of the study aims, as previously described.[14] Clinical follow-up after PCI was performed via office visit or telephone contact at 1, 6, and 12 months and then every 6 months thereafter. At each time of follow-up contact, data pertaining to patients' clinical status, interim occurrence of any adverse events, and antiplatelet drug therapy (use of aspirin and clopidogrel) were collected.

For validation of complete follow-up data, information about vital status was obtained from the National Population Registry of the Korea National Statistical Office with the use of a unique personal identification number.[10] Data on rehospitalization for follow-up MI or revascularization were obtained from the Hospital Disease Code Registration System (categorized according to the *International Classification of Disease*, 10th revision), which was merged for reimbursement in the *Health Insurance Review Agency* in Korea.

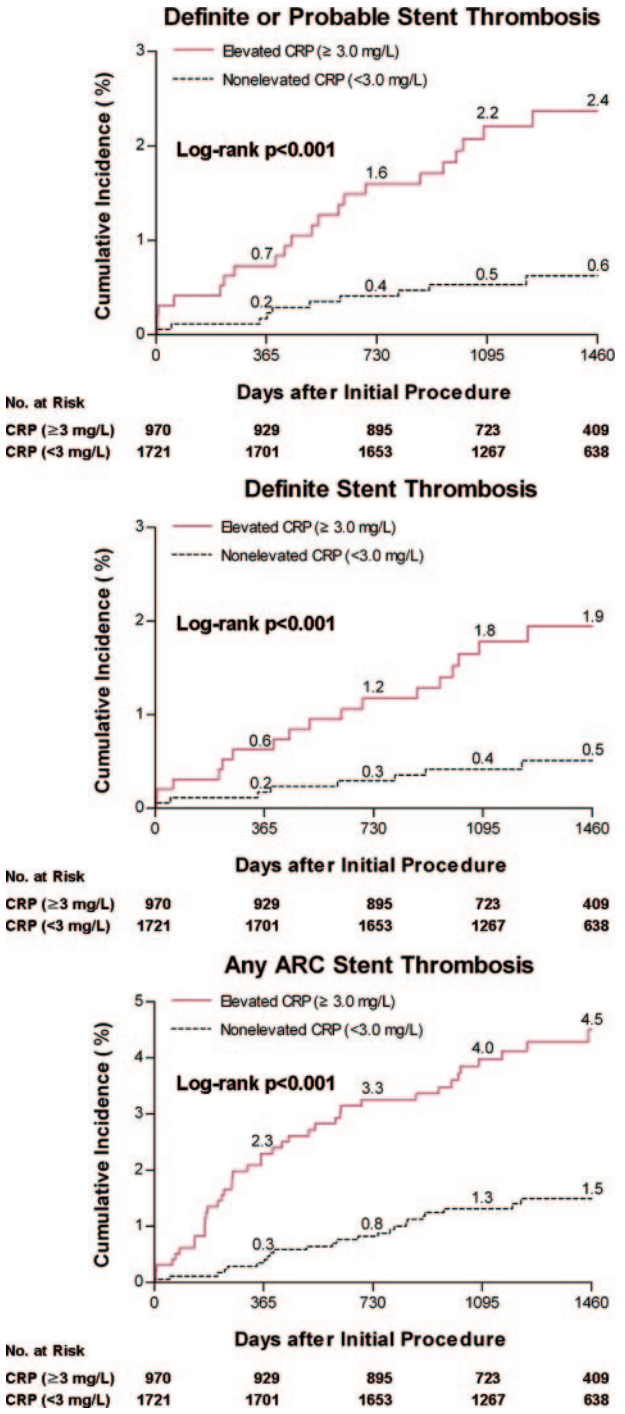

Figure 1. Kaplan–Meier curves of the cumulative probability of stent thrombosis according to elevated vs nonelevated levels of CRP.

Table 2. Crude and Multivariable Associations of Elevated CRP Levels With Stent Thrombosis and Clinical Outcomes

	Crude		Multivariable Adjusted*		Inverse Probability Weights	
Outcome	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Stent thrombosis (ARC criteria)						
Definite or probable	3.95 (1.87–8.34)	<0.001	3.86 (1.82–8.18)	<0.001	4.11 (1.80–9.37)	<0.001
Definite	4.02 (1.75–9.25)	0.001	4.16 (1.81–9.58)	<0.001	4.91 (1.97–12.22)	<0.001
Any	2.94 (1.79–4.84)	<0.001	2.55 (1.54–4.22)	<0.001	2.63 (1.49–4.66)	<0.001
Clinical outcomes						
Death	2.13 (1.52–2.98)	<0.001	1.61 (1.13–2.28)	0.008	1.51 (1.03–2.21)	0.04
MI	1.74 (1.34–2.26)	<0.001	1.63 (1.25–2.12)	<0.001	1.56 (1.17–2.07)	0.002
Death or MI	1.80 (1.45–2.22)	<0.001	1.61 (1.29–2.00)	<0.001	1.50 (1.19–1.90)	<0.001
TVR	1.17 (0.88–1.56)	0.29	1.20 (0.90–1.61)	0.21	1.24 (0.89–1.71)	0.21

ARC indicates Academic Research Consortium.

*Adjusted for age, sex, diabetes, hypertension, current smoking, hypercholesterolemia, renal insufficiency, previous PCI, previous bypass surgery, unstable angina, ejection fraction, other blood biomarkers, multivessel disease, left anterior descending artery disease, left main coronary artery disease, ACC/AHA type B2 or C lesions, bifurcation treatment, ostial lesion, total occlusion, type of stent, total number of stents, total stent length, average stent diameter, intravascular ultrasound guidance, discharge medications, dual antiplatelet therapy through 6 months, and dual antiplatelet therapy through 12 months.

Statistical Methods

Continuous variables were compared by use of the *t* test or Mann–Whitney *U* test; categorical variables were compared with the χ^2 statistics or Fisher exact test as appropriate. Logarithmic transformation was performed to normalize the distribution of the biomarkers. Cumulative probability and survival curves were constructed from Kaplan–Meier estimates and compared by use of the log-rank test.

The relations of CRP to stent thrombosis and clinical outcomes were investigated with the use of crude and multivariable Cox proportional-hazards models (by backward elimination methods) adjusted for age, sex, and all potentially available explanatory factors for stent thrombosis and each clinical outcome, which are listed in Table 1. In these models, the associations between increasing levels of CRP and outcomes were evaluated according to 3 criteria: CRP levels that were elevated or not based on prespecified cutoff points (3.0 mg/L), relative risk category of CRP recommended by the Centers for Disease Control (CDC) and the American Heart Association (AHA; low risk, <1.0 mg/L; average risk, 1 to 3 mg/L; and high risk, >3 mg/L), and a 1-SD increase in CRP levels (continuous model). Proportional-hazards assumptions were confirmed by Schoenfeld tests, and no relevant violations were found. In addition, we performed the weighted Cox proportional-hazards models with robust SEs using inverse probability-weighted estimators to enable an even more rigorous adjustment for a significant difference in patients' characteristics according to CRP category and potential confounding.[15] Two group propensity scores (elevated versus nonelevated CRP) were estimated with a nonparsimonious logistic regression model that included all the covariates listed in Table 1.

The incremental value of incorporating CRP in the context of conventional clinical and anatomic characteristics for predicting clinical events was examined. The improvement in model discrimination when CRP was added to a model with patient, lesion, and procedural risk factors was evaluated with the C index.[16] The 95% confidence intervals (CIs) for differences in the C index after the addition of CRP were obtained through bootstrap with percentile method (200 replicates).[17] To assess the calibration of the Cox models, the slope of the linear predictor (shrinkage) was computed for all models.[18] The slope of the linear predictor is a measure of how well the predicted probability reflects observed probabilities. Perfect is 1.0, and calibration is worse as the value deviates from 1.0. We also compared the global model fit using the Akaike information criterion, which is a measure based on the log-likelihood function; a low value implies a better fit.[19]

All reported *P* values are 2 sided, and values of $P<0.05$ were considered to indicate statistical significance. SAS software version 9.1 (SAS Institute, Inc, Cary, NC) and the R programming language with Design library were used for statistical analysis.

Results

Patient Characteristics

Between February 2003 and February 2006, a total of 2691 patients who received an initial PCI procedure with DES met the study inclusion criteria and none of the criteria for exclusion and had valid measurements of baseline CRP levels (see the Appendix in the online-only Data Supplement). Characteristics of the entire population and of the patients according to elevated versus nonelevated CRP levels are shown in Table 1. Elevated CRP (≥3.0 mg/L) was observed in 36% of the study population. Covariates of elevated CRP levels included older age, male sex, traditional cardiovascular risk factors, renal insufficiency, unstable angina, low ejection fraction, and multivessel disease. Elevated levels of CRP were also associated with higher levels of other blood biomarkers. Duration of clopidogrel use and the status of dual antiplatelet therapy at different time intervals did not differ between patients with and without elevated CRP levels.

Stent Thrombosis and Clinical Outcomes

The median follow-up was 3.9 years (interquartile range, 3.1 to 4.6 years). Complete follow-up data for major clinical events were obtained in 99.3% of the overall cohort. During follow-up, 26 patients had definite stent thrombosis, 6 had probable stent thrombosis, and 34 had possible stent thrombosis. Of the 32 patients with definite or probable stent thrombosis, 4 patients (13%) had early, 6 (19%) had late, and 22 (69%) had very late stent thrombosis. Four patients (13%) died at presentation, and 28 (87%) presented with nonfatal MI. Among these patients, 13 (41%) were on dual antiplatelet therapy, 11 (34%) were on aspirin monotherapy, and 8 (25%) were not on antiplatelet therapy at the time of presentation of stent thrombosis. At follow-up, the case fatality rate, including death at presentation, was 19% (6 of 32).

Overall, the increasing rates of stent thrombosis over time were significantly higher in patients with elevated CRP levels

Table 3. Multivariable-Adjusted Hazard Ratios for Stent Thrombosis and Clinical Outcomes According to CRP Levels Using the CDC/AHA Criteria and a Continuous Model

Outcome	Multivariable Adjusted* Hazard Ratio (95% CI)	P†
Stent thrombosis (ARC criteria)		
Definite or probable		
CDC/AHA criteria		0.006
Low risk (<1 mg/L)	1 (Reference)	…
Average risk (1–3 mg/L)	1.71 (0.52–5.54)	0.38
High risk (>3 mg/L)	3.81 (1.29–11.25)	0.02
Continuous model		
1-SD increment‡	1.64 (1.21–2.21)	0.001
Definite		
CDC/AHA criteria		0.011
Low risk (<1 mg/L)	1 (Reference)	…
Average risk (1–3 mg/L)	2.12 (0.56–7.99)	0.27
High risk (>3 mg/L)	4.30 (1.24–14.85)	0.02
Continuous model		
1-SD increment‡	1.55 (1.14–2.12)	0.006
Any		
CDC/AHA criteria		0.008
Low risk (<1 mg/L)	1 (Reference)	…
Average risk (1–3 mg/L)	0.92 (0.44–1.96)	0.84
High risk (>3 mg/L)	2.11 (1.09–4.10)	0.03
Continuous model		
1-SD increment‡	1.33 (1.07–1.65)	0.009
Clinical outcomes		
Death		
CDC/AHA criteria		0.01
Low risk (<1 mg/L)	1 (Reference)	…
Average risk (1–3 mg/L)	1.03 (0.61–1.72)	0.92
High risk (>3 mg/L)	1.67 (1.04–2.69)	0.03
Continuous model		
1-SD increment‡	1.29 (1.11–1.51)	0.001
MI		
CDC/AHA criteria		<0.001
Low risk (<1 mg/L)	1 (Reference)	…
Average risk (1–3 mg/L)	1.26 (0.86–1.83)	0.23
High risk (>3 mg/L)	1.84 (1.29–2.63)	<0.001
Continuous model		
1-SD increment‡	1.22 (1.08–1.38)	0.001
Death or MI		
CDC/AHA criteria		<0.001
Low risk (<1 mg/L)	1 (Reference)	…
Average risk (1–3 mg/L)	1.18 (0.87–1.61)	0.30
High risk (>3 mg/L)	1.77 (1.32–2.38)	<0.001
Continuous model		
1-SD increment‡	1.25 (1.13–1.38)	0.001
TVR		
CDC/AHA criteria		0.34
Low risk (<1 mg/L)	1 (Reference)	…
Average risk (1–3 mg/L)	1.12 (0.78–1.61)	0.53
High risk (>3 mg/L)	1.20 (0.83–1.73)	0.33
Continuous model		
1-SD increment‡	1.06 (0.92–1.22)	0.42

ARC indicates Academic Research Consortium.

*Adjusted for covariates (for a list of covariates, see Table 2 footnote).

†For comparison of 3 groups by CDC/AHA cutoff points, *P* values for trend were denoted.

‡Hazard ratios correspond to a 1-SD increment in the natural logarithm of CRP value.

compared with those with nonelevated CRP levels (Figure 1). In crude models, elevated levels of CRP were associated with an increased risk of stent thrombosis (Table 2). After multivariable adjustment for all potentially explanatory factors for stent thrombosis, an independent association between CRP and the risk of stent thrombosis was observed. In the second multivariable analysis using the inverse probability weights, an even stronger association was noted. In multivariable analyses using the Centers for Disease Control/American Heart Asssociation (CDC/AHA) CRP cutoff points and log-transformed CRP as a continuous variable, similar strong effects were observed, all of which were statistically significant (Table 3). When the relation of CRP to late-occurring definite or probable stent thrombosis was assessed, increasing CRP levels were significantly associated with increased risks of late and very late (all cases occurring >1 month) stent thrombosis (Figure 2).

During follow-up, 137 patients (5.1%) died, 227 (8.4%) had an MI, and 195 (7.2%) underwent TVR. There were progressive and significantly higher increases in death, MI, and the composite of death or MI over the follow-up periods in patients with elevated CRP levels than in those with nonelevated CRP levels (Figure 3). Elevated levels of CRP predicted death, MI, and the composite of death or MI in crude and multivariable Cox models (Table 2). However, there was no association between CRP levels and the risk of TVR. Similar results were found when CRP was assessed as CDC/AHA cutoff points and as a continuous variable (Table 3).

Incremental Usefulness of CRP Over Conventional Risk Factors for the Prediction of Stent Thrombosis and Clinical Outcomes

Table 4 summarizes the improvements in model discrimination, calibration, and global fit when CRP levels are added for the prediction of stent thrombosis and clinical outcomes. When CRP values were incorporated into a model containing the conventional clinical, lesion, and procedural risk factors, the C statistic increased significantly for the prediction of

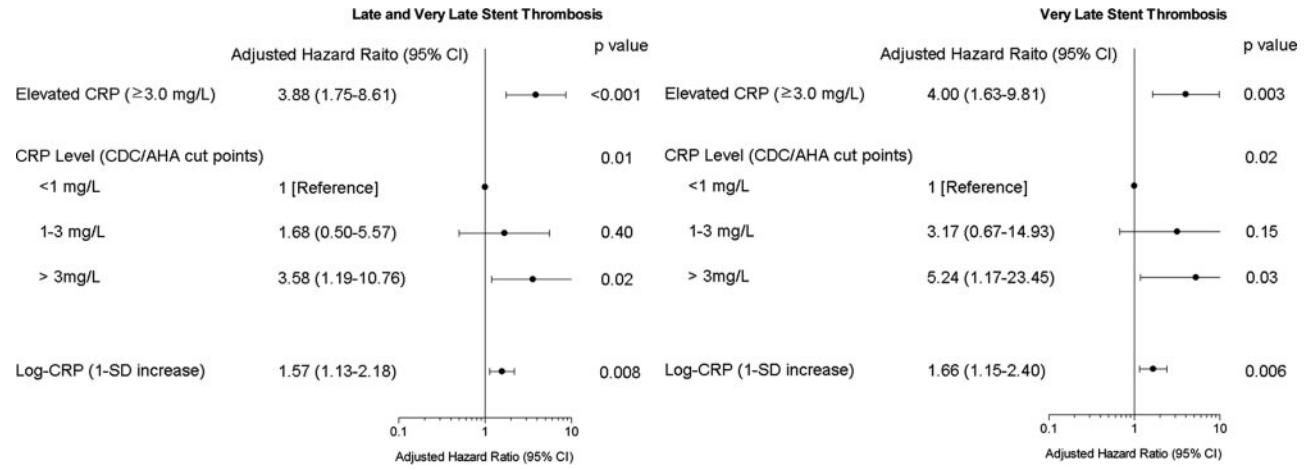

Figure 2. Multivariable-adjusted association of increasing levels of CRP for the prediction of late stent thrombosis. Models were adjusted for age, sex, diabetes mellitus, hypertension, current smoking, hypercholesterolemia, renal insufficiency, previous PCI, previous bypass surgery, unstable angina, ejection fraction, other blood biomarkers, multivessel disease, left anterior descending artery disease, left main coronary artery disease, ACC/AHA type B2 or C lesions, bifurcation treatment, ostial lesion, total occlusion, type of stent, total number of stents, total stent length, average stent diameter, intravascular ultrasound guidance, discharge medications, dual antiplatelet therapy through 6 months, and dual antiplatelet therapy through 12 months.

stent thrombosis. For clinical outcomes, the addition of CRP values to the basic models with conventional risk factors significantly improved the C statistic for predicting MI and the composite of death or MI.

The slope of the linear predictor indicated good calibration for the multivariable models with and without CRP for predicting stent thrombosis and each clinical outcome, indicating no significant deviations between predicted and ob-

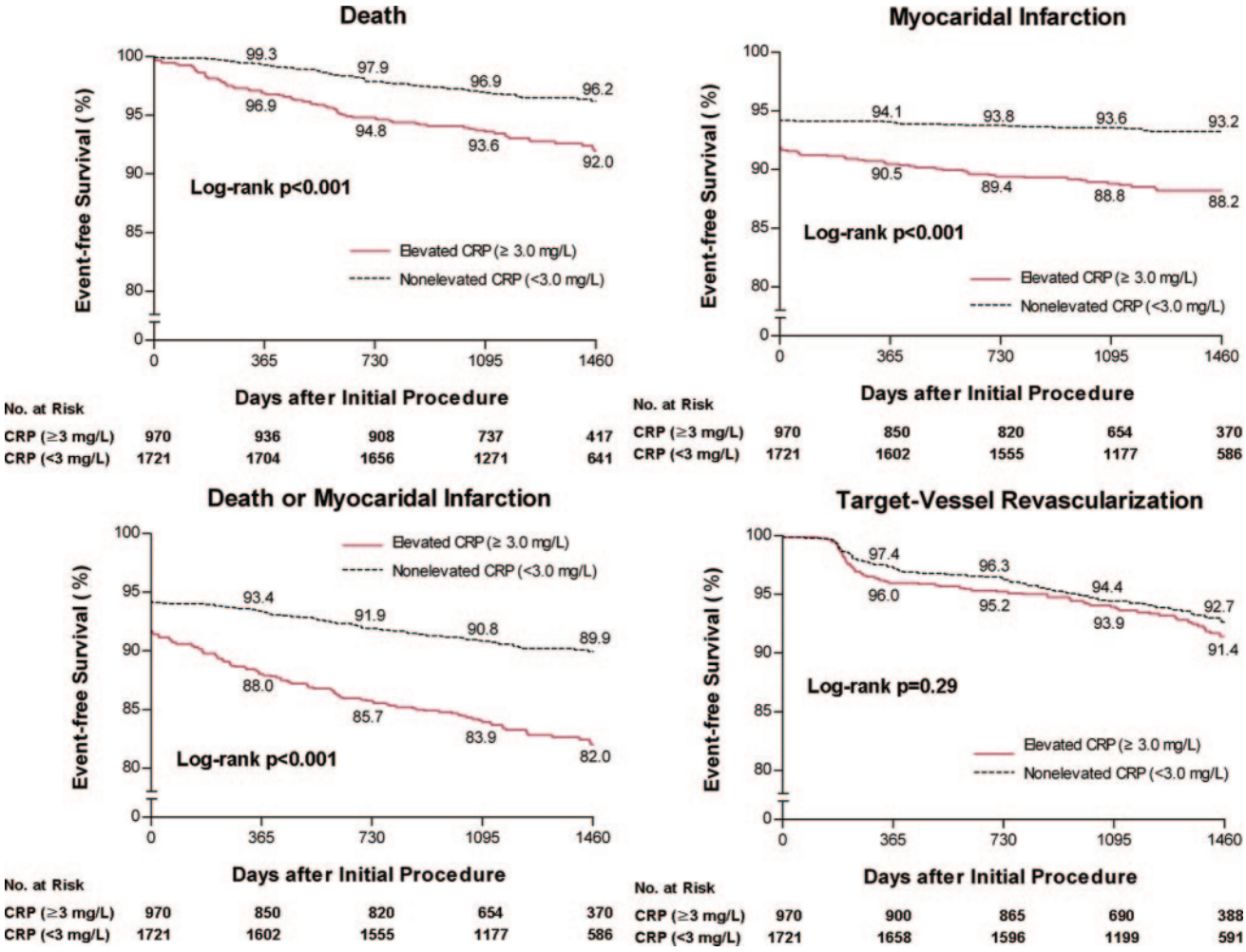

Figure 3. Kaplan–Meier curves of event-free survival of clinical outcomes according to elevated vs nonelevated levels of CRP.

Table 4. Comparison of Discrimination, Calibration, and Global Model Fit of Cox Regression Models With and Without CRP for the Prediction of Stent Thrombosis and Clinical Outcomes*

Model	Discrimination		Calibration: Slope of the Linear Predictor†	Global Model Fit: Akaike Information Criterion‡
	C-Index	Estimated Difference With the Addition of CRP (95% CI)		
Stent thrombosis				
Definite or probable				
Multivariable models using patient, lesion, and procedural factors§	0.723	Reference	0.93	481.29
Multivariable models using patient, lesion, and procedural factors plus CRP	0.772	0.049 (0.001–0.108)	0.90	473.58
Clinical outcomes				
Death				
Multivariable models using patient, lesion, and procedural factors§	0.759	Reference	0.95	1943.36
Multivariable models using patient, lesion, and procedural factors plus CRP	0.761	0.002 (−0.006–0.012)	0.94	1934.59
MI				
Multivariable models using patient, lesion, and procedural factors§	0.663	Reference	0.96	3471.20
Multivariable models using patient, lesion, and procedural factors plus CRP	0.677	0.014 (0.003–0.029)	0.96	3463.24
Death or MI				
Multivariable models using patient, lesion, and procedural factors§	0.652	Reference	0.97	5065.26
Multivariable models using patient, lesion, and procedural factors plus CRP	0.667	0.015 (0.005–0.033)	0.97	5049.85
TVR				
Multivariable models using patient, lesion, and procedural factors§	0.665	Reference	0.92	2910.05
Multivariable models using patient, lesion, and procedural factors plus CRP	0.665	−0.001 (−0.003–0.008)	0.93	2911.40

*Biomarker (CRP value) was modeled as a continuous variable.
†The slope of the linear predictor is a measure of how well the predicted probability reflected observed probabilities.
‡Akaike information criterion is a measure based on the log-likelihood function; a low value implies a better fit.
§Multivariable Cox regression models based on all the variables (listed in Table 1) without inclusion of CRP.

served outcomes. Models that incorporated CRP values for the prediction of stent thrombosis, death, MI, and the composite of death or MI had a lower value of Akaike information criterion than models containing only conventional risk factors, suggesting better overall model fit.

Discussion

In this large cohort of consecutive patients receiving DES, baseline levels of CRP were significantly associated with increased risk of stent thrombosis. The results were consistent when we assessed the relation of CRP with late or very late stent thrombosis. Elevated levels of CRP were also associated with increased risks of death or MI but not TVR. The incorporation of CRP into a model with clinical, lesion, and procedural risk factors improved the risk prediction for stent thrombosis and death or MI.

Recent observational studies suggested that periprocedural CRP levels might be a risk indicator for clinical outcomes after DES implantation.[20,21] However, these studies were hampered by small patient numbers, limited durations of follow-up, or a retrospective observational study design. The present study highlights the prognostic value and clinical usefulness of CRP among patients treated with DES in several important respects. To the best of our knowledge, this study is the first to suggest a possible relationship between CRP levels and DES-related stent thrombosis. This strong association was also apparent for the prediction of late or very late stent thrombosis, which has raised concerns about the long-term safety of DES. Second, the relation of CRP levels with risk of stent thrombosis was determined in real-world patients with off-label use of DES who were at higher risk for the condition as opposed to a clinical trial.[5,22] Third, statistical measures of model discrimination, calibration, and global model fit all supported the incremental value of CRP over conventional risk factors. Enhanced risk assessment with the addition of CRP to conventional risk factors would be of great clinical value if it could more accurately identify people at high risk for stent thrombosis and major cardiovascular events in patients receiving DES.

Although our study does not fully clarify the plausible mechanism of association of CRP with stent thrombosis, the

possible explanations include the association of CRP with platelet and clotting system activation,[23] local inflammation in the vessel wall,[24] endothelial dysfunction,[25] hypersensitivity reactions,[26] and new plaque rupture either adjacent to or within the stented site,[27] all of which have also been suggested as potential causes of DES-related thrombosis. Biologically, CRP mediates enhanced expression of adhesion molecules, a potent chemoattractant, and plasminogen activator inhibitor-1 and a reduction in nitric oxide production, thereby altering the vascular equilibrium toward a proinflammatory, prothrombotic, and vasoconstrictive state.[8] A previous study demonstrated that thrombotic occlusion occurred frequently after arterial injury in human CRP-transgenic mice, suggesting a prothrombotic action of CRP.[28] In addition, it is possible that elevated CRP levels cluster with traditional clinical risk factors for stent thrombosis such as diabetes mellitus, unstable angina, renal failure, compromised ventricular function, and complex lesions and thus function as just a marker. However, even after adjustment for these concomitant risk factors, elevated CRP levels were independently associated with increased risks of stent thrombosis and major clinical events.

A number of cardiovascular-active drugs (ie, statins, aspirin, glycoprotein IIb/IIIa inhibitors, thiazolidinediones, and β-blockers) are thought to modulate serum CRP levels.[29–33] Coupled with these findings, our study fosters the interesting hypothesis that these pharmacological interventions may reduce the risk of DES-related thrombosis, which requires future investigations. In addition, the effect of long-term clopidogrel therapy in patients with elevated CRP levels on stent thrombosis may need to be investigated.

In the present study, there was no association between CRP levels and the need for repeat revascularization in patients treated with DES. These results were consistent with previous studies reporting the lack of an association between CRP and repeat revascularization after bare metal stent treatment.[34,35]

Study Limitations

First, our study evaluated nonrandomized, observational data. Second, given the relatively infrequent occurrence of stent thrombosis, our findings warrant further investigation and should be confirmed or refuted through larger studies with longer follow-up. Although the absolute risk difference was very low among patients with or without elevated CRP because of the small number of events, a significant relative risk (almost 4 times) and the incremental predictability using CRP values may be clinically relevant to better understand how these infrequent but deadly events can be prevented. Third, because the prognostic value of CRP for predicting stent thrombosis among patients receiving bare metal stents was not addressed, the application of elevated CRP levels to guide specific stent selection for reducing stent thrombosis may be limited. Finally, because this study does not address the clinical value of lowering CRP level, the present findings should not be construed as implying a direct benefit of reducing CRP itself after DES implantation without further investigations.

Conclusions

Elevated CRP levels were significantly associated with increased risks of stent thrombosis, death, or MI among patients who received DES. Inflammatory risk stratification with CRP as an adjunct to clinical and angiographic risk factors may be useful for the identification of high-risk patients, and there may be potential for greater absolute risk reductions with established or new preventive interventions.

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Disclosures

None.

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CLINICAL PERSPECTIVE

High-sensitivity C-reactive protein (CRP) has been postulated to be a hemostatic risk factor predicting atherothrombosis. However, the association between CRP and stent thrombosis after drug-eluting stent implantation has not been defined. We prospectively investigated whether CRP levels were associated with the risk of stent thrombosis and long-term clinical outcomes and assessed the incremental usefulness of CRP for predicting these events beyond clinical and angiographic risk assessment in 2691 patients who received drug-eluting stent implantation with a median follow-up of 3.9 years. In multivariable Cox proportional-hazards models, elevated levels of CRP were significantly associated with increased risk of stent thrombosis (definite or probable; hazard ratio, 3.86; 95% confidence interval, 1.82 to 8.18; $P<0.001$). There were also independent associations of elevated CRP levels with late stent thrombosis (hazard ratio, 3.88; 95% confidence interval, 1.75 to 8.61; $P<0.001$). Elevated CRP levels significantly predicted the risks of death (hazard ratio, 1.61; 95% confidence interval, 1.13 to 2.28; $P=0.008$), myocardial infarction (hazard ratio, 1.63; 95% confidence interval, 1.25 to 2.12; $P=0.001$), and death or MI (hazard ratio, 1.61; 95% confidence interval, 1.29 to 2.00; $P<0.001$). The incorporation of CRP into a model with patient, lesion, and procedural factors resulted in a significant increase in the C statistic for the prediction of stent thrombosis, myocardial infarction, and the composite of death or myocardial infarction. Our data support the independent association of CRP with stent thrombosis and major cardiovascular events in patients receiving drug-eluting stents. Inflammatory risk assessment with CRP as an adjunct to clinical and angiographic risk factors may be useful for identifying patients at high risk who could then be targeted for preventive measure.

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SUPPLEMENTAL MATERIAL

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Park DW, et al, “C-Reactive Protein and the Risk of Stent Thrombosis and Cardiovascular Events After Drug-Eluting Stent Implantation”

Supplemental Figure Legend

Supplemental Figure. Diagram depicting study schematic and included/excluded study patients

*Indicates definite or probable stent thrombosis. Abbreviations: CRP, C-Reactive Protein; MI, myocardial infarction; TVR, target-vessel revascularization.

Supplemental Figure