ORIGINAL RESEARCH

Influence of Late Vascular Inflammation on Long-Term Outcomes Among Patients Undergoing Implantation of Drug Eluting Stents: Role of C-Reactive Protein

Masanori Shiba, MD; Hideki Itaya, MD; Raisuke Iijima, MD; Masato Nakamura, PhD

***Background*—**Elevation of C-reactive protein (CRP) as a marker of vascular inflammation at a late phase of drug-eluting stent (DES) implantation may predict subsequent major adverse cardiac events (MACE).

***Methods and Results*—**In 1234 consecutive patients undergoing DES implantation, CRP was measured both before (baseline) and 8 to 12 months after (late phase) stenting, and the relationship between elevation of CRP (>2.0 mg/L) and subsequent MACE (all cause death, nonfatal myocardial infarction, target lesion revascularization, and other additional revascularization) was assessed. As results, CRP was elevated in 38.0% of patients at baseline and in 23.6% during late phase ($P<0.0001$), and hazard ratio (HR) for MACE was 1.52 (95% confidence interval [95% CI] 1.21–1.93, $P=0.0004$) at baseline versus 4.00 (95% CI 3.16–5.05, $P<0.0001$) in late phase. By multivariable analysis, late-phase CRP elevation (HR 3.60, 95% CI: 2.78–4.68, $P<0.0001$), chronic kidney disease (CKD) (HR 1.41, 95% CI: 1.10–1.84, $P=0.01$), and number of diseased segments (HR 1.19, 95% CI: 1.08–1.30, $P=0.0002$) were positive predictors of MACE, whereas statin use (HR 0.66, 95% CI 0.50–0.87, $P=0.003$) was a negative predictor. Propensity score–matched analysis also confirmed the effect of late-phase CRP on MACE (HR 3.39, 95% CI 2.52–4.56, $P<0.0001$). In prediction of the late-phase CRP elevation, CKD (odds ratio [OR] 1.71, 95% CI 1.24–2.36, $P=0.001$) and baseline CRP elevation (OR 3.48, 95% CI 2.55–4.74, $P<0.0001$) were positive predictors, whereas newer generation DES (OR 0.59, 95% CI 0.41–0.84, $P=0.003$) and statin therapy (OR 0.68, 95% CI 0.47–0.97, $P=0.03$) were negative predictors.

***Conclusions*—**Monitoring the late-phase CRP may be helpful to identify a high-risk subset for MACE among patients undergoing DES implantation. **(*J Am Heart Assoc*. 2016;5:e003354 doi: 10.1161/JAHA.116.003354)**

Key Words: C-reactive protein • drug-eluting stent • long-term outcome

Drug-eluting stents (DES) control the development of intimal hyperplasia following stent deployment, but there are issues with respect to the long-term outcome, including late-stent thrombosis,[1] the late catch-up phenomenon,[2] and neoatherosclerosis within the stent.[3] Previous studies have revealed that these problems are more frequent in patients with DES than in those with bare metal stents (BMS) and contribute to late stent failure. A recent pathological study suggested that vascular inflammation after DES implantation may play a major role in subsequent stent failure.[4] However, there is no established marker of such inflammation that can be used in daily practice.

C-reactive protein (CRP) is a surrogate marker of vascular inflammation in relation to the progression of atherosclerosis and plaque vulnerability, and the efficacy of CRP-guided risk stratification for both primary prevention[5] and secondary prevention[6] of cardiovascular disease is widely accepted. In patients with BMS a higher CRP level prior to stent implantation has been reported to predict subsequent restenosis, but the predictive value of measuring CRP prior to DES implantation is still unclear.[7] We considered that not only the CRP value before stent deployment but also the CRP in the late phase might provide useful information about vascular inflammation associated with DES failure. However, the prevalence of the late-phase CRP elevation and its clinical impact have not been fully investigated. Accordingly, in addition to before stenting, we have measured CRP at 8 to 12 months after DES implantation and investigated the relationship between the CRP level and the long-term outcome.

From the Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan.

Correspondence to: Masanori Shiba, MD, Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, 2-17-6 Ohashi, Meguro-ku, Tokyo, Japan. E-mail: masanorishiba@hotmail.com

Received February 3, 2016; accepted August 8, 2016.

Methods

We retrospectively investigated 1563 consecutive patients who underwent implantation of DES for de novo coronary artery disease at Toho University Ohashi Medical Center from May 2003 to October 2013. Among them, 1234 patients (2483 lesions with 2183 stents) with paired CRP data (obtained before stenting and 8–12 months after stenting) were entered into this study. The primary endpoint of this study was major adverse cardiac events (MACE), comprising all-cause death, nonfatal myocardial infarction, target lesion revascularization (TLR), and other additional revascularization. The first event in each patient was employed for cumulative assessment of MACE.

Patients were treated with first-generation DES, including the Cypher stent (durable polymer sirolimus-eluting stent; Cordis, Miami Lakes, FL; n=492) and the Taxus stent (durable polymer paclitaxel-eluting stent; Boston Scientific, Natick, MA; n=310), or with newer DES, such as the Xience stent (durable polymer everolimus-eluting stent; Abbott Vascular, Santa Clara, CA; n=75), the Promus stent (durable polymer everolimus-eluting stent; Boston Scientific; n=149), and the Nobori stent (biodegradable polymer biolimus-eluting stent; Terumo Corporation, Tokyo, Japan; n=208). A total of 329 patients were excluded from this study. First, the study population was limited to patients who underwent measurement of CRP at 8 to 12 months after DES implantation. Therefore, a total of 40 patients who experienced MACE (19 died, 18 required TLR including 2 with stent thrombosis, and 3 had other additional revascularization) less than 8 months after DES implantation, 88 patients who were lost to follow-up before 8 months, and another 119 patients who did not have late-phase CRP data despite being followed were excluded. Next, a total of 66 patients who underwent implantation of an Endeavor stent (n=42, Medtronic Vascular, Santa Rosa, CA) or a Resolute Integrity stent (n=24, Medtronic Vascular) were excluded because of less frequent use than other types of DES at our hospital. In addition, 5 patients with previous DES implantation and 11 patients who received more than 1 type of stent were also excluded because those cases with mixed use of DES were not suitable for stent-type–based assessment for CRP elevation.

Baseline clinical characteristics, procedural data, and follow-up data were collected from the medical records or hospital databases. The study protocol was approved by our hospital ethics committees, and the study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from every patient.

Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI) was performed by standard techniques, and selection of stents was done by the operator. All patients received dual antiplatelet therapy (DAPT) for at least 8 months after DES implantation.

Measurement of CRP

The serum CRP level before PCI was defined as the baseline value and was measured from 1 day before up to the time of the procedure. In patients who underwent multiple PCI sessions, the CRP level measured before the first session was defined as the baseline value. The CRP level measured at 8 to 12 months after PCI was defined as the late-phase value because drug elution from the stent was expected to have been completed by this time.[8] If the patient had acute infection when CRP was measured, the value was not employed for this study. Serum CRP was measured by a turbidimetric immunoassay until November 2010, after which latex-agglutination turbidimetry was used. An elevated CRP level was defined as >2.0 mg/L based on previous reports.[6]

Definitions

A diseased segment was defined as having >50% angiographic stenosis (visual estimate) in a major epicardial artery with a reference diameter >1.5 mm. Myocardial infarction was defined as elevation of creatinine phosphokinase or creatinine kinase-myocardial isozyme to >3 times the upper limit of normal. TLR was defined as any revascularization for a stenosis within the stent or within a 5-mm border proximal and distal to the stent. Other additional revascularization was defined as revascularization that was required after completion of the procedures planned from the initial angiograms except for TLR. Stent thrombosis was assessed according to the Academic Research Consortium definition.[9] Chronic kidney disease (CKD) was defined as eGFR <60 mL/min (by modification of diet in renal disease equation).[10]

Statistical Analysis

Continuous variables are presented as the mean±1 standard deviation (SD) or as the median (25th–75th percentile), whereas categorical variables are displayed as percentages. Comparisons were performed by both paired and unpaired Student *t* test for continuous variables, and by Fisher exact test and McNemar test for categorical variables. The Kaplan-Meier method was used to estimate survival and events, while the log-rank test was employed to compare survival curves. To evaluate the independent contributions of clinical, angiographic, and procedural variables to the primary endpoints, multivariable analysis was performed with the Cox proportional hazards model. To perform landmark analysis, the landmark time was defined relative to the patient's index

Table 1. Background and Procedural Results Stratified by Late-Phase Elevation of CRP After PCI

	All Subjects	Late-Phase CRP Elevation (+)	Late-Phase CRP Elevation (−)	*P* Value
Patient characteristics				
Age, y	68.6±10.2	69.3±9.3	68.4±10.4	0.17
Male sex, %	77.9	82.8	76.4	0.02
Hyperlipidemia, %	69.8	70.0	69.8	1.00
Hypertension, %	80.3	85.2	78.7	0.03
Diabetes mellitus, %	40.5	47.4	38.3	0.001
Chronic kidney disease, %	45.9	56.7	42.6	<0.0001
Hemodialysis, %	8.5	22.0	4.4	<0.0001
Prior CABG, %	3.7	4.5	3.2	0.59
Prior PCI, %	14.9	17.9	14.0	0.13
NSTEMI, %	26.7	28.3	26.4	0.54
STEMI, %	13.5	12.1	13.9	0.49
Baseline CRP elevation, %	38.0	61.2	30.8	<0.0001
Late-phase CRP elevation, %	23.6	100	0	<0.0001
Ejection fraction, %	60.9±13.6	58.5±15.2	61.6±13.0	0.001
Medications				
Aspirin, %	99.9	100.0	99.9	1
Thienopyridine, %	99.8	99.7	99.8	0.55
β-Blocker, %	28.5	30.0	28.1	0.55
ACE-I/ARB, %	66.3	69.3	65.4	0.23
Statin, %	79.4	73.8	81.2	0.01
CCB, %	39.2	40.7	38.7	0.58
Angiographic findings				
1 vessel disease, %	38.6	33.3	40.2	0.11
2 vessel disease, %	33.5	35.9	32.8	
3 vessel disease, %	27.8	30.8	26.9	
No. of diseased segments, n	2.7±1.8	3.1±2.1	2.7±1.7	0.001
Target lesion				
LAD, %	57.6	60.5	56.7	0.28
LCX, %	24.1	27.5	23.0	0.14
RCA, %	39.6	43.3	38.5	0.15
LMT, %	11.1	12.0	10.8	0.59
No. of treated lesions, n	2.0±1.4	2.2±1.6	1.9±1.3	0.001
Details of stents				
No. of stents used, n	1.9±1.2	2.1±1.5	1.8±1.1	0.002
Stent diameter, mm	3.06±0.3	3.05±0.3	3.06±0.3	0.63
Total stent length, mm	41.3±30.0	47.2±38.0	39.5±26.8	0.0002
Cypher, %	39.8	46.4	37.8	0.001
Taxus, %	25.1	26.6	24.3	
Xience/promus, %	18.2	15.6	18.9	
Nobori, %	16.9	11.4	19.0	
First-generation DES/newer DES, %	65.2/34.8	73.6/26.4	62.6/37.4	0.001

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CRP, C-reactive protein; DES, drug-eluting stent; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

procedure. In this study a landmark was set at 2 years after PCI, and patients completing late-phase CRP assessment were analyzed with respect to events occurring after this time up to the latest follow-up. Logistic regression analysis was used to identify predictors of late-phase CRP elevation.

In addition to those analyses, to assess absolute impact of late-phase CRP elevation on clinical outcomes, we tried to adjust the baseline imbalance between patients with and without late-phase CRP elevation by using inverse probability of treatment weighting (IPTW) based on the propensity score.[11] Propensity scores of imbalanced characteristics were estimated by multiple logistic regression analysis, and inverses of those scores were entered into IPTW methods. Discrimination of that logistic regression model was assessed by C-statistics (0.72, 95% CI 0.69–0.76), and calibration was assessed by Hosmer-Lemeshow statistics (χ^2=3.51, *df*=8, *P*=0.90). The outcomes were compared by use of Cox

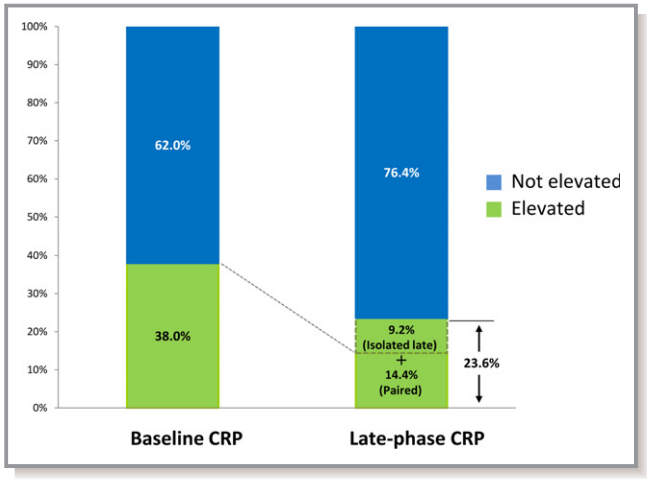

Figure 1. CRP elevation at baseline and in the late phase after DES implantation. Green shows patients with elevation of CRP. CRP indicates C-reactive protein; DES, drug-eluting stent.

regression models. In all analyses a probability (*P*) value <0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

The mean age of the patients was 68.6±10.2 years, 77.9% were men, 45.9% had chronic kidney disease, 40.2% had acute coronary syndrome, 40.5% had diabetes mellitus, and 27.8% had 3-vessel disease. At the time of discharge, statin therapy was prescribed for 79.4% of the patients (Table 1).

CRP Profile

The mean interval between baseline and late-phase measurements was 269.2±29 days. Elevation of CRP (>2.0 mg/L) at baseline was found in 38.0% of the subjects, whereas late-phase elevation of CRP was seen in only 23.6% (*P*<0.0001). CRP elevation occurred only during the late phase in 9.2% of the patients (isolated late-phase elevation), but CRP was elevated at both baseline and the late phase in 14.4% (paired elevation) (Figure 1).

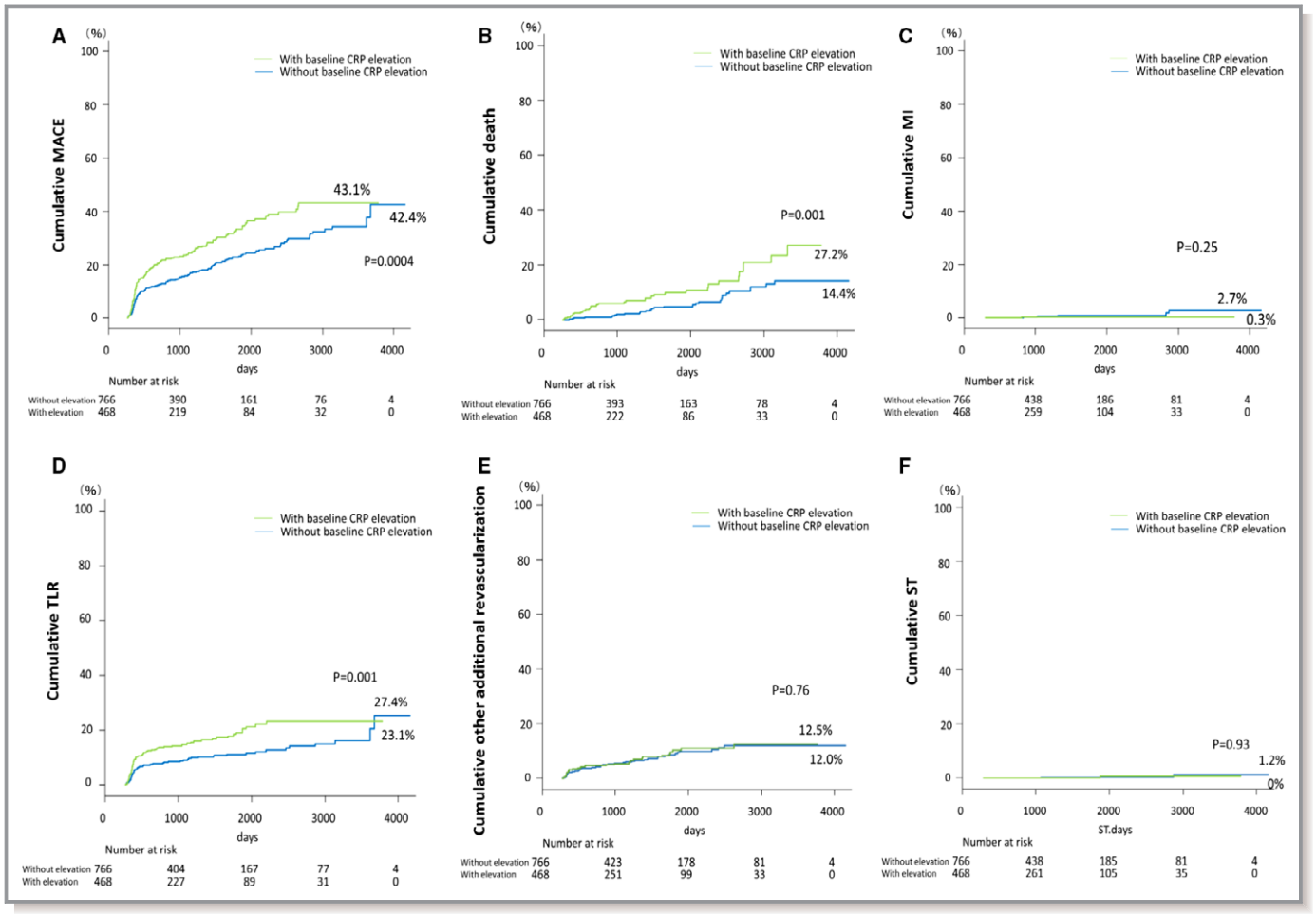

Figure 2. Cumulative event curves stratified according to baseline CRP elevation. A, MACE. B, Death. C, Myocardial infarction (MI). D, Target lesion revascularization (TLR). E, Other additional revascularization. F, Stent thrombosis (ST). CRP indicates C-reactive protein; MACE, major adverse cardiac events.

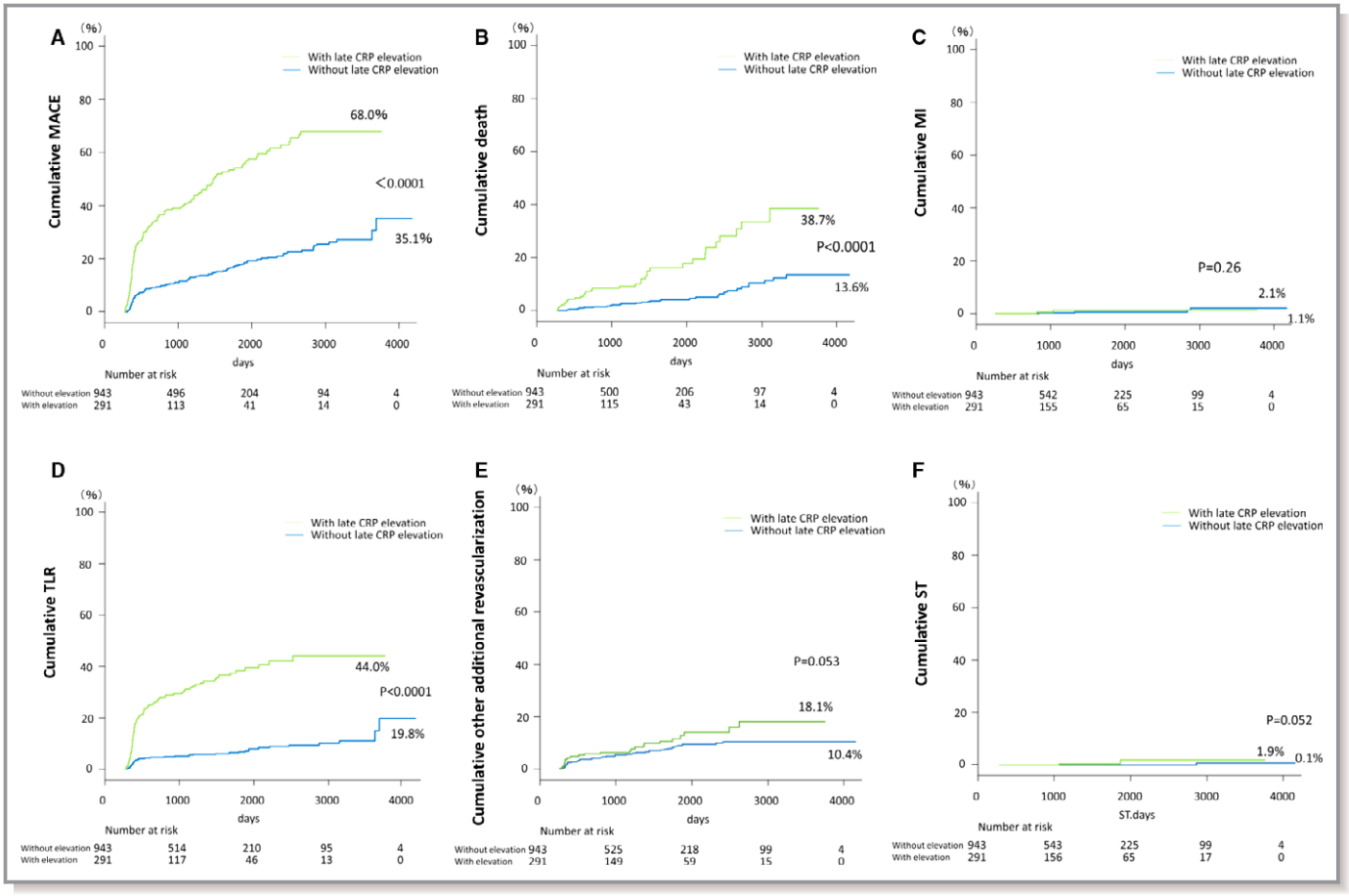

Figure 3. Cumulative event curves stratified according to late-phase CRP elevation. A, MACE. B, Death. C, Myocardial infarction (MI). D, Target lesion revascularization (TLR). E, Other additional revascularization. F, Stent thrombosis (ST). CRP indicates C-reactive protein; MACE, major adverse cardiac events.

Comparison of Patients With and Without Late-Phase CRP Elevation

A comparison of the patients with and without late-phase CRP elevation is shown in Table 1. Patients with late-phase CRP elevation were more likely to be male and were more likely to have comorbidities such as hypertension, diabetes, and CKD. They also had more diseased segments and underwent more complex PCI procedures (more lesions treated, longer total stent length, and more stents implanted). Conversely, statin use was more frequent in the patients without late-phase CRP elevation.

Long-Term Outcomes

The median follow-up period was 1185 days (interquartile range 583–1980 days). Events occurred in 282 patients during follow-up (71 patients died, 7 had nonfatal MI, 151 had TVR, and 81 had other unplanned revascularization). There were 3 cases of definite late stent thrombosis (at 982, 1790, and 2785 days after PCI). At both baseline and during the late phase, MACE were more frequent in patients with CRP elevation than in patients without CRP elevation (Figures 2 and 3). At baseline, the HR of CRP elevation for MACE was 1.52, and the 95% CI was 1.21–1.93 (P=0.0004), whereas the HR was 4.00 and the 95% CI was 3.16 to 5.05 in the late phase (P<0.0001). According to 2-year landmark analysis, there was no significant difference between the Kaplan-Meier curves for MACE associated with baseline CRP (P=0.36), but there was divergence of Kaplan-Meier curves for the association with late-phase CRP (P<0.0001) (Figure 4). As compared to patients without late-phase CRP elevation, those analyses demonstrated increasing death, TLR, and ST beyond 2 years after DES implantation among patients with late-phase CRP elevation (Figure 5).

Multivariable Analysis

Multivariable analysis revealed that late-phase CRP elevation (HR 3.60, 95% CI 2.78–4.68, P<0.0001), CKD (HR 1.41, 95% CI 1.10–1.84, P=0.01), and number of diseased segments (HR 1.19, 95% CI 1.08–1.30, P=0.0002) were positive predictors

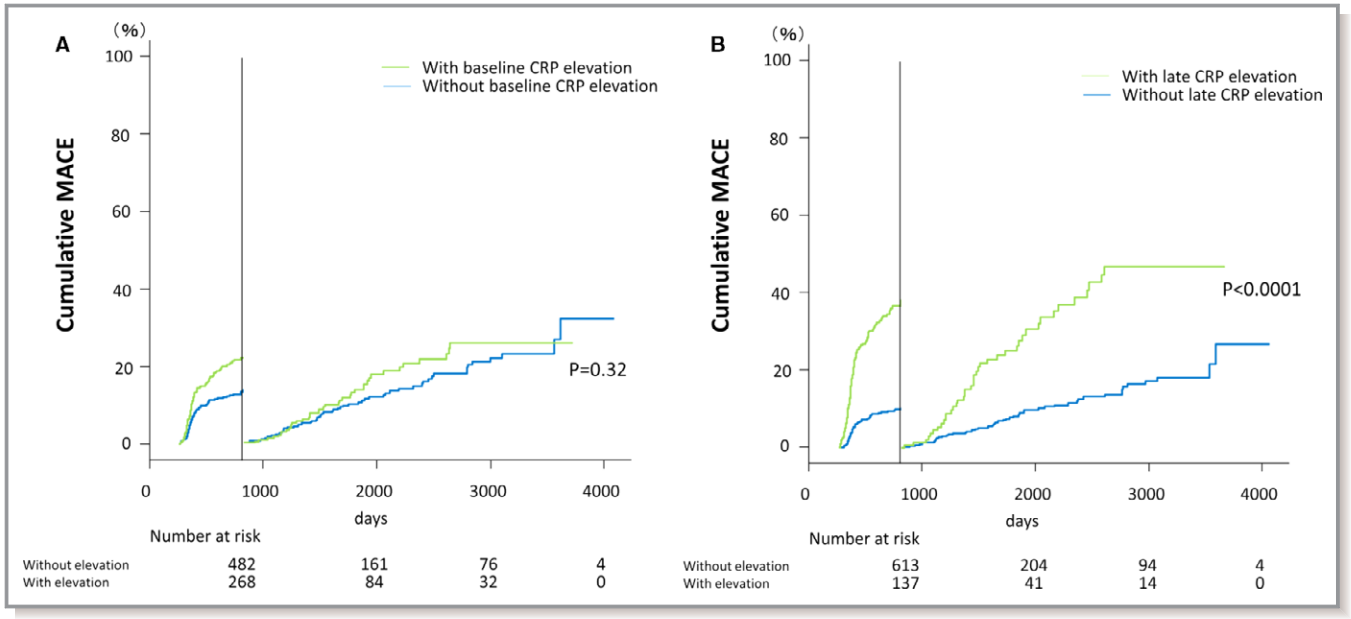

Figure 4. Landmark analysis of MACE at 2 years after DES implantation. A, Landmark analysis showed no significant difference in occurrence of MACE after 2 years between patients with baseline CRP elevation and those without elevation. B, Landmark analysis showed a significant difference in occurrence of MACE after 2 years between patients with late-phase CRP elevation and those without elevation. CRP indicates C-reactive protein; DES, drug-eluting stent; MACE, major adverse cardiac events.

of MACE, whereas statin therapy (HR 0.66, 95% CI 0.50–0.87, *P*=0.003) was a negative predictor (Table 2). When predictors of late-phase CRP elevation were investigated, it was found that CKD (OR 1.71, 95% CI 1.24–2.36, *P*=0.001) and baseline CRP elevation (OR 3.48, 95% CI 2.55–4.74, *P*<0.0001) were positive predictors, whereas newer-generation DES (OR 0.59, 95% CI 0.41–0.84, *P*=0.003) and statin therapy (OR 0.68, 95% CI 0.47–0.97, *P*=0.03) were negatively associated with late-phase CRP elevation (Table 3).

Results Based on Propensity Matching

Propensity score–matched analysis using IPTW methods revealed that, as compared to nonelevated late-phase CRP elevation, late-phase CRP elevation was associated with high frequency of occurrence of MACE (HR 3.39, 95% CI 2.52–4.56, *P*<0.0001), death (HR 2.94, 95% CI 1.61–5.38, *P*=0.0004), and TLR (HR 4.90, 95% CI 3.28–7.31, *P*<0.0001) (Table 4).

Discussion

The main findings of the present study were as follows: (1) late-phase CRP elevation was found in 23.6% of patients with DES, and it was isolated late-phase elevation in 9.2%; (2) late-phase CRP elevation was an independent predictor of future clinical events; (3) several positive and negative predictors of late-phase CRP elevation were identified; and (4) use of statins and implantation of newer DES were associated with a lower risk of CRP elevation and thus may decrease MACE.

Late-Phase CRP Elevation

In the BMS era, baseline CRP prior to stenting was a predictor of restenosis as well as the minimum luminal diameter after stenting.[12] The authors suggested that inflammation derived from atherosclerotic plaques promoted intimal hyperplasia after stent implantation. When DES was introduced, it was initially thought that these stents would prevent such inflammation and control intimal hyperplasia. However, Nebeker et al subsequently reported late stent thrombosis of DES and proposed that its mechanism involved inflammation caused by the polymer coating.[13] In addition, it was suggested that stent malapposition and uncovered stent struts serve as predictors of late stent thrombosis, related to vascular inflammation after DES implantation.[14,15] Furthermore, a recent pathological study demonstrated that neoatherosclerosis was greater after implantation of DES compared with BMS,[3] suggesting that inflammation may modify the endothelium and lead to neoatherosclerosis as well as late catch-up phenomenon.[3,16] These findings suggest that the influence of inflammation on outcomes is stronger in the DES era than the BMS era and that inflammation may predict a future cardiovascular event after DES implantation.

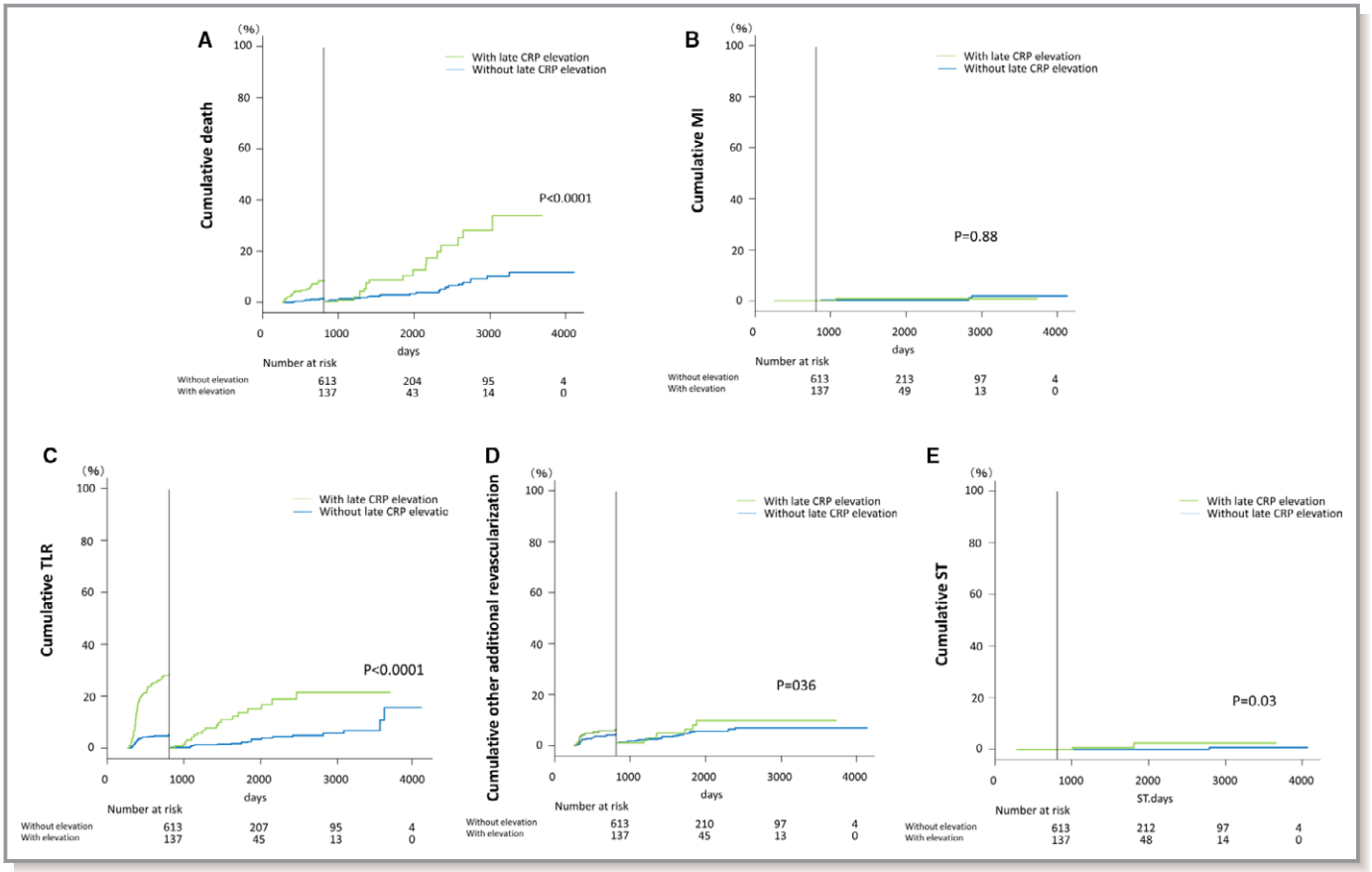

Figure 5. Landmark analysis of cardiovascular events at 2 years after DES implantation among patients with late-phase CRP elevation and those without elevation. A, Death. B, Myocardial infarction (MI). C, Target lesion revascularization (TLR). D, Other additional revascularization. E, Stent thrombosis (ST).

Recently, a positive relationship between elevation of serum CRP at follow-up and presence of neoatherosclerosis within DES[17] was reported. Thus, measurement of serum CRP may possibly estimate that inflammation and predict future cardiovascular events after DES implantation.

The present study showed that, as compared to baseline CRP elevation, late-phase CRP elevation was powerful predictor to identify high-risk patients for late cardiovascular events after DES implantation (Figure 4), and the predictive power of the late-phase CRP elevation was also confirmed by multivariable adjustment and propensity score–matched analysis (Tables 3 and 4). According to the results, about two-thirds of the patients with late-phase CRP elevation also had baseline elevation, and this may represent refractory inflammation after revascularization despite medical therapy or an excessive reaction to the stent itself. Thus, in this DES era, baseline CRP elevation indicates not only the presence of vulnerable plaque but also the risk of late vascular inflammation after DES implantation. On the other hand, isolated late-phase CRP elevation (which occurred in 9.2% of all subjects) may suggest a late vascular reaction to the stent. It seems that existence of vascular inflammation after completion of drug elution may determine the outcome, and patients with late-phase CRP elevation should be regarded as a high-risk subset.

Predictors of MACE

Apart from late-phase CRP elevation, CKD, the number of diseased segments, and statin therapy were also predictors of MACE. These are well-known prognostic indicators for patients with ischemic heart disease. It seems reasonable to consider that factors showing a positive association with MACE were surrogate markers of atherosclerosis, and progression of atherosclerosis influences long-term outcomes.

Predictors of Late-Phase CRP Elevation

Late-phase CRP elevation was a predictor of MACE, and CKD, baseline CRP elevation, use of newer-generation DES, and use of statin therapy were associated with late-phase CRP elevation. Both statin therapy and newer DES were negative predictors, which is consistent with the results of trials that

Table 2. Multivariate Analysis: Predictors of MACE After DES Implantation

Variable	HR	95% CI	*P* Value
Male sex, %	1.25	0.91 to 1.72	0.17
Hypertension, %	0.87	0.61 to 1.23	0.42
Diabetes mellitus, %	1.25	0.96 to 1.63	0.10
Chronic kidney disease, %	1.41	1.10 to 1.84	0.01
Statin therapy, %	0.66	0.50 to 0.87	0.003
Number of diseased segments, n	1.19	1.08 to 1.30	0.0002
Ejection fraction, %	1.001	0.99 to 1.01	0.83
Number of treated lesions, n	0.94	0.82 to 1.07	0.34
Number of stents used, n	1.14	0.88 to 1.46	0.32
Total stent length, mm	1.00	0.99 to 1.006	0.39
Newer DES, %	1.17	0.85 to 1.62	0.34
Late-phase CRP elevation, %	3.60	2.78 to 4.68	<0.0001

CRP indicates C-reactive protein; DES, drug-eluting stent; HR, hazard ratio; MACE, major adverse cardiac events.

have demonstrated the efficacy of statins for preventing cardiovascular events[5,6] as well as TLR.[18] The pleotropic anti-inflammatory effects of statins could reduce late-phase inflammation after DES implantation as previously reported[19] and thus decrease MACE. Moreover, a favorable effect of statins on reendothelialization after DES implantation may influence the outcome.[20]

According to recent pathological investigations, inflammation at stented sites was less severe in patients with newer DES than in those with first-generation DES,[4] and the lower CRP value in our patients with newer DES was compatible with that pathological finding. Recent use of biocompatible polymer and optimized drug dose contributes to these results of newer DES.[8] However, although late-phase CRP elevation was less frequent in patients with newer DES than in those with first-generation DES in the present study, occurrence of MACE did not differ significantly. Recent RCT suggests extended follow-up is needed to know the safety and efficacy profiles of DES.[21] Thus, sufficient study to detect the difference between those 2 stent generations is needed.

Table 3. Multivariate Analysis: Predictors of Late-Phase CRP Elevation in Patients With DES

Variable	Odds Ratio	95% CI	*P* Value
Male sex, %	1.44	0.97 to 2.13	0.07
Hypertension, %	1.38	0.90 to 2.13	0.14
Diabetes mellitus, %	1.22	0.89 to 1.67	0.21
Chronic kidney disease, %	1.71	1.24 to 2.36	0.001
Statin therapy, %	0.68	0.47 to 0.97	0.03
Baseline CRP elevation, %	3.48	2.55 to 4.74	<0.0001
Number of diseased segments, n	0.99	0.87 to 1.13	0.86
Ejection fraction, %	1.00	0.98 to 1.01	0.41
Number of treated lesions, n	1.08	0.90 to 1.29	0.41
Number of stents used, n	0.86	0.62 to 1.19	0.36
Total stent length, mm	1.01	0.99 to 1.02	0.18
Newer DES, %	0.59	0.41 to 0.84	0.003

CRP indicates C-reactive protein; DES, drug-eluting stent.

Table 4. Propensity Score–Matched Hazard Ratios of Elevated Late-Phase CRP for Long-Term Outcomes Compared With Nonelevated Late-Phase CRP

	HR	95% CI	*P* Value
MACE	3.39	2.52 to 4.56	<0.0001
Death	2.94	1.61 to 5.38	0.0004
Myocardial infarction	1.47	0.18 to 11.99	0.72
TLR	4.90	3.28 to 7.31	<0.0001
Other additional revascularization	1.51	0.67 to 2.61	0.15
Stent thrombosis	7.64	0.70 to 83.5	0.10

CRP indicates C-reactive protein; HR, hazard ratio; MACE, major adverse cardiac event; TLR, target lesion revascularization.

On the other hand, baseline CRP elevation and CKD showed a positive association with late-phase CRP elevation. Elevation of CRP is a well-known predictor of the long-term outcome in CKD,[22] and it was reported that the natural course of atherosclerosis differs between patients with CKD and other patients.[23] The CRP elevation of patients with CKD might relate to the CKD-specific atherosclerosis. In addition, a recent study demonstrated that the efficacy of statin therapy decreases as the stage of CKD advances.[24,25] In fact, statin therapy was less effective in reduction of CRP elevation among patients with hemodialysis[26] compared to the other subset.[5] Thus, pathophysiological differences and a reduced response to statin therapy may be related to refractory inflammation in patients with CKD, and that inflammation might attenuate efficacy of DES, but further investigation is needed to confirm this.

Limitations

This was a single-center retrospective study, which makes bias inevitable. First, the study population was limited to patients who underwent measurement of CRP at 8 to 12 months after DES implantation. Therefore, patients without CRP data from that period and patients with MACE before 8 months, a high risk subgroup, were not included, resulting

in possible selection bias. Also, patients who underwent BMS implantation were not included because use of BMS was limited to patients with contraindication of continuous dual antiplatelet therapy in our hospital since DES had been introduced. Second, changes in medical therapy during the past decade may have influenced the results of this study. For example, because statin therapy has become more common, pretreatment with statin therapy as general practice may have become associated with the lower-baseline CRP[27] of recent newer DES patients compared to first-generation DES patients. Third, the optimum time for measurement of CRP to assess late-phase vascular inflammation is unclear. The CRP level measured at 8 to 12 months after PCI was employed as late phase for this study because drug elution from the stent was expected to have been completed by this time.[8] However, it is possible that a time later than 8 to 12 months after PCI might have been more suitable for patients receiving newer DES because improved biocompatibility might delay the peak of inflammation. Finally, we could not completely distinguish vascular inflammation from inflammation due to acute or chronic inflammatory diseases in the patients with elevation of CRP.

Conclusion

In this study, late-phase CRP elevation after DES implantation was a strong predictor of MACE. Accordingly, monitoring the CRP may be helpful to identify a high-risk subset for MACE among patients undergoing DES implantation.

Disclosures

None.

References

1. Kimura T, Morimoto T, Nakagawa Y, Kawai K, Miyazaki S, Muramatsu T, Shiode N, Namura M, Sone T, Oshima S, Nishikawa H, Hiasa Y, Hayashi Y, Nobuyoshi M, Mitudo K; j-Cypher Registry Investigators. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. *Circulation*. 2012;125:584–591.
2. Kuriyama N, Kobayashi Y, Nakama T, Mine D, Nishihira K, Shimomura M, Nomura K, Ashikaga K, Matsuyama A, Shibata Y. Late restenosis following sirolimus-eluting stent implantation. *JACC Cardiovasc Interv*. 2011;4:123–128.
3. Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. *J Am Coll Cardiol*. 2012;59:2051–2057.
4. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, Kutys R, Ladich E, Finn AV, Kolodgie FD, Virmani R. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation*. 2014;129:211–223.
5. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
6. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005;352:20–28.
7. Niccoli G, Montone RA, Ferrante G, Crea F. The evolving role of inflammatory biomarkers in risk assessment after stent implantation. *J Am Coll Cardiol*. 2010;56:1783–1793.
8. Garg S, Serruys PW. Coronary stents: looking forward. *J Am Coll Cardiol*. 2010;56:S43–S78.
9. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.
10. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992.
11. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, Robins JM. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol*. 2006;163:262–270.
12. Inoue T, Kato T, Uchida T, Sakuma M, Nakajima A, Shibazaki M, Imoto Y, Saito M, Hashimoto S, Hikichi Y, Node K. Local release of C-reactive protein from vulnerable plaque or coronary arterial wall injured by stenting. *J Am Coll Cardiol*. 2005;46:239–245.
13. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47:175–181.
14. Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation*. 2008;118:1138–1145.
15. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, Togni M, Wenaweser P, Billinger M, Seiler C, Gay S, Meier B, Pichler WJ, Jüni P, Virmani R, Windecker S. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation*. 2009;120:391–399.
16. Otsuka F, Finn AV, Yazdani SK, Nakano M, Kolodgie FD, Virmani R. The importance of the endothelium in atherothrombosis and coronary stenting. *Nat Rev Cardiol*. 2012;9:439–453.
17. Kuroda M, Otake H, Shinke T, Takaya T, Nakagawa M, Osue T, Taniguchi Y, Iwasaki M, Nishio R, Kinutani H, Konishi A, Hirata KI. The impact of in-stent neoatherosclerosis on long-term clinical outcomes: an observational study from the Kobe University Hospital optical coherence tomography registry. *EuroIntervention*. [Epub ahead of print]
18. Natsuaki M, Nakagawa Y, Morimoto T, Ono K, Shizuta S, Furukawa Y, Kadota K, Iwabuchi M, Kato Y, Suwa S, Inada T, Doi O, Takizawa A, Nobuyoshi M, Kita T, Kimura T; CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators. Impact of statin therapy on late target lesion revascularization after sirolimus-eluting stent implantation (from the CREDO-Kyoto Registry Cohort-2). *Am J Cardiol*. 2012;109:1387–1396.
19. Hong SJ, Choi SC, Kim JS, Shim WJ, Park SM, Ahn CM, Park JH, Kim YH, Lim DS. Low-dose versus moderate-dose atorvastatin after acute myocardial infarction: 8-month effects on coronary flow reserve and angiogenic cell mobilisation. *Heart*. 2010;96:756–764.
20. Wang TJ, Yang YJ, Xu B, Zhang Q, Jin C, Tang Y, Tian Y, Mintz GS. Atorvastatin accelerates both neointimal coverage and re-endothelialization after sirolimus-eluting stent implantation in a porcine model: new findings from optical coherence tomography and pathology. *Circ J*. 2012;76:2561–2571.
21. Maeng M, Tilsted HH, Jensen LO, Krusell LR, Kaltoft A, Kelbæk H, Villadsen AB, Ravkilde J, Hansen KN, Christiansen EH, Aarøe J, Jensen JS, Kristensen SD, Bøtker HE, Thuesen L, Madsen M, Thayssen P, Sørensen HT, Lassen JF. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. *Lancet*. 2014;383:2047–2056.
22. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int*. 2005;68:766–772.

23. Rigatto C, Levin A, House AA, Barrett B, Carlisle E, Fine A. Atheroma progression in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:291–298.

24. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;15:263–275.

25. Natsuaki M, Furukawa Y, Morimoto T, Sakata R, Kimura T; CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators. Renal function and effect of statin therapy on cardiovascular outcomes in patients undergoing coronary revascularization (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). *Am J Cardiol*. 2012;110:1568–1577.

26. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395–1407.

27. Oduncu V, Tanalp AC, Erkol A, Sırma D, Dündar C, Akgün T, Türkyilmaz E, Kılıçgedik A, Gözübüyük G, Tigen K, Izgi A, Kirma C. Impact of chronic pretreatment of statins on the level of systemic inflammation and myocardial perfusion in patients undergoing primary angioplasty. *Am J Cardiol*. 2011;107:179–185.