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Original article

Clinical impact of high-sensitivity C-reactive protein during follow-up on long-term adverse clinical outcomes in patients with coronary artery disease treated with percutaneous coronary intervention

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ABSTRACT

Introduction: C-reactive protein (CRP) is an established marker for vascular inflammation and predictor of adverse cardiovascular events, but the prognostic value of preprocedural CRP in coronary artery disease (CAD) patients who have undergone percutaneous coronary intervention (PCI) remains controversial. Furthermore, the impact of CRP levels during follow-up in CAD patients after PCI on long-term adverse clinical outcomes is uncertain. We evaluated the association between high-sensitivity (hs)-CRP values at follow-up angiography and long-term clinical outcomes in CAD patients after coronary intervention.

Methods: We prospectively enrolled 3507 consecutive CAD patients who underwent first PCI between 1997 and 2011 at our institution. We identified 2509 patients (71.5%) who underwent follow-up angiography (6–8 months after PCI). Of those, 1605 patients (45.8%) who had data available for hs-CRP at follow-up angiography were stratified into three groups according to tertiles of hs-CRP level at the time of follow-up angiography. The primary endpoint was composite of all-cause death and non-fatal acute coronary syndrome (ACS).

Results: Median follow-up was 1716 days. The cumulative incidence of all-cause death and ACS differed significantly among groups (log-rank, $p = 0.0002$). Multivariate Cox regression analysis showed that a higher hs-CRP level at follow-up angiography was associated with a greater risk of all-cause death and ACS [adjusted hazard ratio (HR) for all-cause death and ACS 2.14, 95% confidence interval (CI) 1.43–3.27, $p = 0.0002$.

Conclusion: Elevated hs-CRP levels during follow-up were significantly associated with higher frequencies of adverse long-term clinical outcomes in patients with CAD after PCI.

Introduction

Cardiovascular disease (CVD) is the major cause of death and disability worldwide despite significant advances in the medical and interventional management of CVD [1]. Inflammation plays an important role in the pathogenesis of atherosclerosis, which is a cause of coronary artery disease (CAD) and its complications [2]. Various biomarkers have been highlighted in association with predictors of CAD as secondary prevention. Among these, C-reactive protein (CRP) is widely used as an inflammatory marker in clinical settings and has been recognized as an independent predictor of adverse cardiovascular events in patients with CAD [3,4]. Several studies have shown that preprocedural high-

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sensitivity (hs)-CRP levels in patients undergoing percutaneous coronary intervention (PCI) are associated with adverse cardiovascular events or all-cause mortality [5–7], which may reflect the actual atherosclerotic status. However, the association between increased hs-CRP levels in the chronic phase, which should serve as "relatively" stable CAD, and long-term mortality and cardiovascular events after PCI has not been fully evaluated. We investigated the prognostic value of hs-CRP levels at 6–8 months as a secondary prevention biomarker after PCI in patients with CAD.

Materials and methods

Study population and data collection

The present investigation is a single-center, observational, retrospective cohort study of 3507 consecutive patients who underwent their first PCI at Juntendo University Hospital (Tokyo, Japan) between January 1997 and December 2011. Of those, 2509 patients (71.5%) underwent follow-up angiography at 6-8 months after that first PCI. Exclusion criteria comprised missing hs-CRP data at follow-up angiography, cardiac events contributing to PCI occurring before planned follow-up angiography, and target vessel revascularization (TVR) at follow-up angiography simultaneously (6–8 months after first PCI). Our final study population comprised 1605 patients (45.8%). The study population was divided into three groups according to hs-CRP level at follow-up angiography: Group 1, hs-CRP <0.041 mg/dL; Group 2, hs-CRP 0.041–0.116 mg/dL; and Group 3, hs-CRP >0.116 mg/dL.

Demographic data as well as information about coronary risk factors, medications, revascularization procedure-related factors, and comorbidities were retrospectively collected and analyzed. Blood samples were collected during the early morning on the day of follow-up angiography after an overnight fast, and blood pressure (BP) was measured at the time of admission. Patients with BP > 140/90 mmHg or under antihypertensive medication were considered hypertensive. Diabetes mellitus was defined as either hemoglobin (Hb)A1c ≥ 6.5% or under medication with insulin or oral hypoglycemic drugs. Estimated HbA1c (%) was calculated as the US National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) using the formula HbA1c (%) = 1.02 × HbA1c Japan Diabetes Society (JDS) equivalent value (%) +0.25% [8]. We defined chronic kidney disease (CKD) as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, and calculated eGFR based on the Modification of Diet in Renal Disease equation modified with a Japanese coefficient using baseline serum creatinine [9]. Serum hs-CRP concentration was measured using the reagent N-latex CRP test (Dade Behring, Deerfield, IL, USA) and autoanalyzer BN (Dade Behring) (1997–2005), and the reagent auto LIA CRP test (Nissui Pharmaceutical, Tokyo, Japan) and autoanalyzer Hitachi 7170S (Hitachi, Tokyo, Japan) (2005–2011). These tests were based on a latex agglutination immunoassay method. Other markers were determined by routine laboratory methods. TVR was considered ischemia-driven if associated with stenosis of the target vessel diameter ≥75% with ischemic symptoms, or stenosis of the target vessel diameter ≥90% irrespective of documented ischemia. Target vessel diameter was angiographically measured based on American Heart Association category by cardiovascular specialists.

Written informed consent was obtained from all patients before PCI to get permission to enter our registry and use their clinical data. Our institutional review board approved the protocol of this study, which was implemented in accordance with the principles established in the Declaration of Helsinki and our institutional ethics policy.

Primary endpoint

The primary outcome was defined as a composite of all-cause death and non-fatal acute coronary syndrome (ACS). We defined ACS as ST-elevation myocardial infarction (STEMI), non-STEMI, or unstable angina pectoris. We determined STEMI based on symptoms of ischemia with ST-segment elevation on electrocardiogram (ECG) and increased serum concentrations of cardiac enzymes [troponin T, creatine kinase (CK)-MB, CK ≥2-fold increase] [10,11] and non-STEMI based on symptoms of ischemia without ST-segment elevation on ECG and increased serum levels of cardiac enzymes. Unstable angina pectoris was determined based on symptoms of ischemia at rest or having a crescendo of symptoms or new-onset symptoms associated with transient ischemic ST-segment shifts and normal serum levels of cardiac enzymes [12]. Clinical follow-up comprised analyses of office visit charts and responses to questionnaires sent to patients or their families and telephone contact. Mortality data were collected from the medical records of patients who died or who were treated at our institution, and details and causes of death were obtained from other hospitals to which patients had been admitted.

Statistical analysis

Quantitative data are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) and categorical variables are presented as frequencies. Continuous variables across groups were compared using one-way analysis of variance or the Kruskal–Wallis test. Categorical variables were compared using the chi-square test or Fisher's exact probability test. Unadjusted cumulative event rates were estimated using Kaplan–Meier curves and compared across groups using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each variable were calculated using Cox proportional hazards modeling. Predictors of all-cause death and ACS were determined by multivariable Cox regression analysis. Variables showing values of $p < 0.1$ in univariate models were included in multivariate analysis. Values of $p < 0.05$ were considered to indicate a statistically significant difference. To making further analysis about hs-CRP, log-transformed hs-CRP (natural logarithm) which is a continuous variable was used in this analysis. Multivariable analysis was adjusted by the same variables. All data were analyzed using JMP for Windows version 9.0 (SAS Institute, Cary, NC, USA).

Results

Among the 3507 patients, we enrolled 2509 patients (71.5%) who underwent follow-up angiography at 6–8 months after first PCI. We excluded patients in whom ACS contributed to additional PCI between first PCI and follow-up angiography ($n = 40$), or had missing data for hs-CRP at follow-up angiography (n = 584), or underwent TVR at follow-up angiography simultaneously ($n = 280$) (Fig. 1). Finally, of the 3507 patients, we analyzed data from 1605 eligible patients and assigned patients to three groups according to hs-CRP at follow-up angiography. Baseline clinical characteristics of subjects according to hs-CRP tertiles are shown in Table 1. Body mass index (BMI), CKD, hemodialysis (HD), creatinine, triglyceride (TG), brain natriuretic peptide (BNP), hs-CRP, and multivessel disease differed significantly among the three groups. Median duration of follow-up was 1716 days (interquartile range, 838–2495 days). In total, 163 (10.2%) all-cause deaths and ACS were identified during follow-up, including 96 (6.0%) all-cause deaths and 67 (4.2%) ACS. Each component of all-cause death and ACS among the three groups are shown in Table 2. Fig. 2 shows the cumulative event-free survival curves for all-cause death and ACS among groups. Rates of all-cause death and ACS were significantly

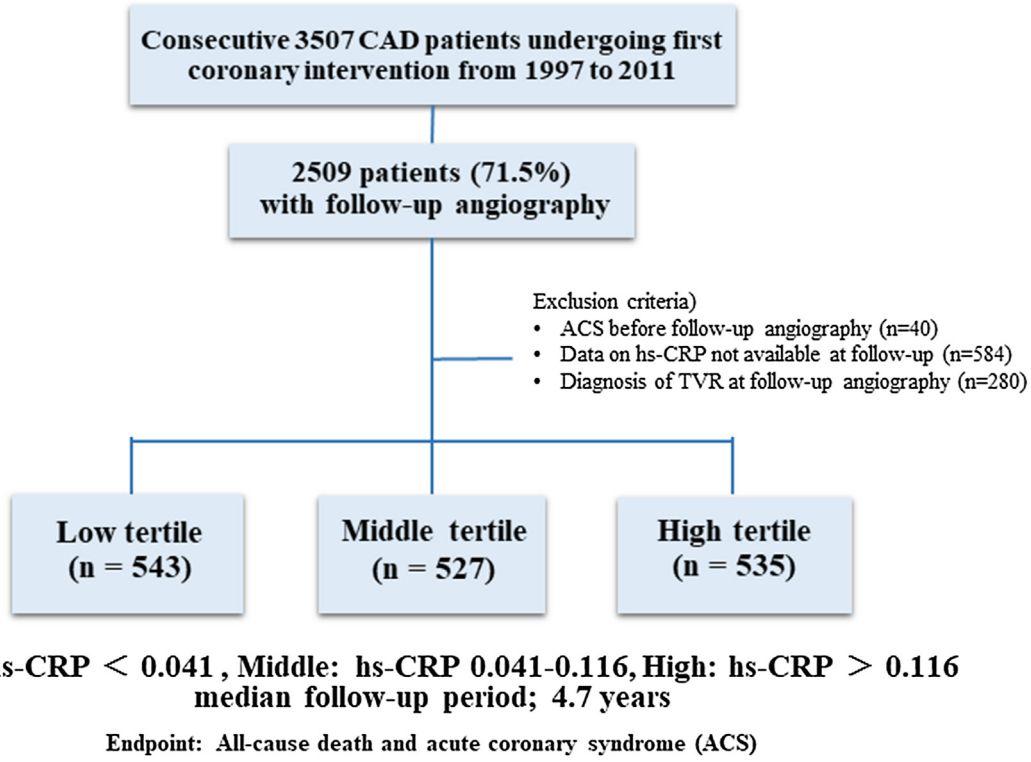

Fig. 1. Study flow chart. Study flow chart shows how patients were eligible in this study. Final cohort for analysis was 1605 patients and assigned them to three groups according to hs-CRP at follow-up angiography. ACS, acute coronary syndrome; CAD, coronary artery disease; hs-CRP, high-sensitivity C-reactive protein; TVR, target vessel revascularization.

Table 2
Event rate of composite endpoint.

hs-CRP	Group 1 (Low)	Group 2 (Middle)	Group 3 (High)	*p*
All-cause death, *n* (%)	19 (3.5)	30 (5.7)	47 (8.9)	0.0007
ACS, *n* (%)	16 (2.9)	20 (3.8)	31 (5.8)	0.03
Total event rate, *n* (%)	35 (6.4)	50 (9.5)	78 (14.6)	0.0005

ACS, acute coronary syndrome; hs-CRP, high-sensitivity C-reactive protein.

different among groups (log-rank test, $p = 0.0002$). Table 3 shows the findings of univariate and multivariate Cox hazard regression analyses for all-cause death and ACS. Variables with $p < 0.05$ in univariate analysis comprised age, BMI, fasting blood glucose, CKD, statin use, β-blocker use, multivessel disease, drug-eluting stent used, and hs-CRP levels. High hs-CRP levels at follow-up angiography (Group 3) remained significantly associated with higher rate of all-cause death and ACS (HR,2.14; 95%CI:1.43–3.27; $p = 0.0002$) even after adjustment for other covariates. Because tertile hs-CRP is a categorical variable, we used log hs-CRP (natural logarithm), which is a continuous variable, in all-cause death and ACS analysis in Table 3. Multivariable analysis was adjusted by the same variables in each analysis. Even after adjusting for other variables, increased log hs-CRP at follow-up angiography was significantly associated with higher incidence of all-cause death and ACS (HR, 1.04; 95%CI, 1.02–1.07; $p = 0.002$).

Discussion

This observational study demonstrated that increased hs-CRP levels at 6–8 months after first PCI were significantly associated with a higher incidence of long-term adverse clinical outcomes in CAD patients during a median follow-up period of 4.7 years. Even after adjusting for other independent variables, our results may indicate an association between hs-CRP levels in the chronic phase and future cardiovascular events and mortality in patients with CAD after first PCI.

PCI has been widely established as a treatment for patients with ACS or stable CAD. Furthermore, advances in stents and mechanical devices have been associated with improved clinical outcomes after PCI. However, in the REACH (Reduction of Atherothrombosis for Continued Health) Registry, the incidence of vascular events (cardiovascular death, myocardial infarction, or stroke) was reportedly higher in the population with established arterial disease than in the population with only risk factors after 3 years [13,14]. This registry indicated that secondary prevention was still important to reduce clinical events in patients with arterial disease. However, long-term clinical outcomes including cardiovascular events and death after PCI have not yet been fully evaluated. Management of clinical events in CAD patients after PCI as secondary prevention thus remains a challenge for most cardiologists.

Previous studies have focused on the importance of elevated hs-CRP levels before PCI. Oemrawsingh et al. followed 486 patients with stable CAD or ACS who underwent PCI and showed that higher hs-CRP levels immediately before the PCI procedure were significantly associated with mortality and myocardial infarction at 10 years [15]. Razzouk et al. showed that preprocedural hs-CRP was associated with mortality in 8834 patients who underwent PCI for stable or unstable disease [7]. In contrast, Almagor et al. reported that CRP levels at 20 h after elective stent implantation showed CRP levels increased 4.9-fold compared to baseline CRP levels in stable CAD patients, because of mechanical disruption of atherosclerotic coronary plaque [16]. Based on these findings, whether hs-CRP levels in the postoperative period serve as predictive markers of future cardiovascular events has not been fully elucidated. The present study investigated the association

Table 1
Baseline clinical characteristics of the study population at first PCI.

hs-CRP at follow-up angiography Variable	Group 1 low (n = 543)	Group 2 middle (n = 527)	Group 3 high (n = 535)	p-value
Age (years)	64.2 ± 9.9	65.0 ± 10.1	65.4 ± 10.0	0.15
Men (%)	454 (83.6)	435 (82.5)	444 (83.0)	0.90
Hypertension, n (%)	380 (70.0)	383 (72.7)	380 (71.0)	0.62
Diabetes mellitus, n (%)	223 (41.1)	227 (43.1)	239 (44.7)	0.49
Dyslipidemia, n (%)	402 (74.0)	394 (74.8)	394 (73.8)	0.93
Family history, n (%)	173 (31.9)	140 (26.6)	154 (28.9)	0.21
BMI, kg/m^2	24.1 ± 3.2	24.6 ± 3.3	24.6 ± 3.7	0.03
Current smoking, n (%)	126 (23.2)	144 (27.3)	150 (28.1)	0.19
CKD, n (%)	114 (21.0)	168 (31.9)	149 (28.0)	0.0002
HD, n (%)	13 (2.4)	21 (4.0)	29 (5.4)	0.03
FBG, mg/dL	115 ± 40	116 ± 41	118 ± 46	0.60
HbA1c, %	5.9 ± 1.1	6.0 ± 1.2	6.0 ± 1.3	0.15
Creatinine, mg/dL	0.9 ± 0.9	1.1 ± 1.5	1.2 ± 2.0	0.004
LDL-C, mg/dL	112 ± 33	113 ± 32	114 ± 35	0.60
TG, mg/dL	131 ± 77	140 ± 73	146 ± 110	0.03
BNP, pg/dL	37.5 (18.7, 106.3)	38.7 (19.1, 101.3)	45.3 (18.9, 117.4)	0.02
hs-CRP, mg/dL	0.05 (0.02, 0.13)	0.11 (0.06, 0.28)	0.22 (0.11, 0.53)	0.009
SBP, mmHg	133.4 ± 22.4	134.4 ± 23.2	133.4 ± 21.2	0.71
DBP, mmHg	72.8 ± 13.4	74.5 ± 40.4	72.8 ± 13.3	0.46
LVEF, %	62.4 ± 11.4	62.6 ± 11.3	61.1 ± 11.6	0.09
Multivessel disease, n (%)	290 (53.4)	288 (54.7)	326 (60.9)	0.03
ACS, n (%)	144 (26.5)	144 (27.3)	128 (24.0)	0.42
Type B2/C lesion, n (%)	448 (83.7)	455 (88.7)	449 (86.2)	0.07
LMT, n (%)	18 (3.3)	17 (3.2)	11 (2.1)	0.37
DES used, n (%)	311 (57.3)	274 (52.0)	305 (57.0)	0.15
Total stent length, mm	24.8 ± 16.4	23.2 ± 15.1	23.3 ± 15.2	0.17
Medication				
Aspirin, n (%)	491 (91.6)	481 (92.0)	498 (93.8)	0.54
β-Blockers, n (%)	258 (48.1)	253 (48.4)	246 (46.3)	0.56
Ca-channel blockers, n (%)	207 (38.6)	221 (42.3)	212 (39.9)	0.44
ACE-I/ARBs, n (%)	266 (49.0)	254 (48.2)	286 (53.5)	0.18
Statin, n (%)	337 (63.6)	316 (61.2)	308 (58.4)	0.23

ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; DBP, diastolic blood pressure; DES, drug-eluting stent; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HD, hemodialysis; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TG, triglyceride.
Continuous variables are expressed as mean ± standard deviation, except BNP and hs-CRP levels, which are expressed as median with interquartile range.

between hs-CRP levels after PCI in the chronic phase and long-term clinical outcomes, because hs-CRP in that period can reflect the stabilized atherosclerotic status and serve as a useful marker for secondary prevention. Several studies have reported the clinical impact of hs-CRP levels in the chronic phase on clinical outcomes in CAD patients who underwent PCI. Hsieh et al. reported that higher hs-CRP levels (>3.0 mg/L) at 9-month follow-up angiography after PCI were associated with higher incidence of overall mortality and future clinical cardiovascular outcomes, including restenosis [17]. Hoshida et al. reported that in 243 Japanese patients, a persistent increase in CRP at 6 ± 1 months after PCI represents a risk factor for restenosis or target lesion revascularization on follow-up angiography [18]. To the best of our knowledge, few clinical studies in Asia have investigated associations between hs-CRP at follow-up angiography and long-term future clinical events, including death and non-fatal ACS.

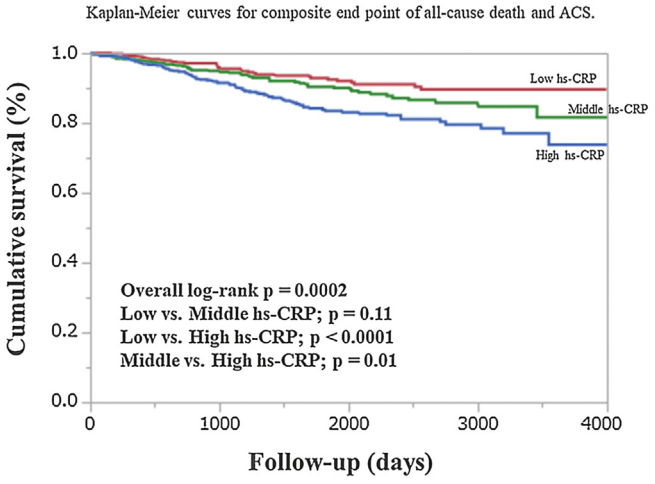

Fig. 2. Kaplan–Meier curves for all-cause death and ACS. Kaplan–Meier curves show significant difference in all-cause death and ACS among the hs-CRP groups (log-rank test, p = 0.0002). ACS, acute coronary syndrome; hs-CRP, high-sensitivity C-reactive protein.

These findings, including the present study, indicate that hs-CRP could offer a useful biomarker for predicting the risk of adverse cardiovascular events or mortality in CAD patients after PCI, although CRP is a non-specific marker of a variety of inflammatory diseases. These results are supported by the fact that inflammation underlies many of the processes contributing to atherogenesis and plaque destabilization. It has been indicated that CRP may contribute to the development of arteriosclerosis in the presence of modified low-density lipoprotein (LDL) such as oxidized LDL [19]. Lin et al. explained that modified LDL may be a potential moderator for the association of hs-CRP with cardiovascular disease in Asian populations [20]. Previous reports have shown that anti-inflammatory therapy could improve clinical outcomes in CAD patients, with statins in particular shown to indirectly reduce hs-CRP along with LDL cholesterol (LDL-C), and to improve inflammation [21,22]. However, whether hs-CRP can be used as a therapeutic target marker for statin treatment remains to

Table 3
Univariate and multivariate Cox hazard model predicting all-cause death and ACS.

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (per 1-year increase)	1.04	1.02–1.06	<0.0001	1.03	1.01–1.04	0.005
Male sex	1.18	0.78–1.87	0.43			
Family history	0.88	0.62–1.24	0.49			
Hypertension	0.90	0.65–1.25	0.52			
Current smoking	0.92	0.64–1.30	0.64			
BMI (per 1-kg/m^2 increase)	0.91	0.86–0.95	0.0001	0.93	0.88–0.98	0.004
LDL-C (per 1-mg/dL increase)	1.00	0.99–1.00	0.36			
HDL-C (per 1-mg/dL increase)	0.99	0.98–1.01	0.75			
TG (per 1-mg/dL increase)	1.00	0.99–1.00	0.11			
FBG (per 1-mg/dL increase)	1.00	1.00–1.01	0.04	1.00	0.99–1.01	0.17
CKD	1.99	1.45–2.72	<0.0001	1.56	1.11–2.17	0.01
Aspirin	0.87	0.42–2.21	0.74			
Statins	0.62	0.45–0.84	0.003	0.77	0.56–1.05	0.10
ACE-Is/ARBs	0.84	0.62–1.14	0.26			
β-blockers	0.77	0.56–1.05	0.26			
Ca-channel blockers	1.17	0.85–1.60	0.33			
SBP (per 1-mmHg increase)	1.00	0.99–1.01	0.95			
DBP (per 1-mmHg increase)	1.00	0.99–1.00	0.32			
LVEF (per 1% increase)	0.99	0.98–1.01	0.43			
Multivessel disease	1.47	1.07–2.04	0.02	1.36	0.98–1.91	0.06
Type B2/C lesion	1.12	0.70–1.89	0.65			
LMT lesion	2.13	0.90–4.21	0.08	2.50	1.06–5.00	0.04
DES used	0.67	0.48–0.93	0.02	0.63	0.45–0.89	0.009
Stent length (per 1-mm increase)	0.99	0.98–1.01	0.41			
ACS	1.00	0.70–1.40	0.99			
hs-CRP at follow-up angiography (Group 1 as reference)						
Group 2	1.41	0.92–2.19	0.11	1.37	0.88–2.16	0.16
Group 3	2.19	1.49–3.31	<0.0001	2.14	1.43–3.27	0.0002
Log hs-CRP (per 0.1-mg/dL increase)	1.05	1.03–1.08	0.0002	1.04*	1.02–1.07*	0.002*

HR, hazard ratio; 95%CI, 95% confidence interval; ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; DES, drug-eluting stent; FBG, fasting blood glucose; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TG, triglyceride.
* Adjusted for age, BMI, FBG, CKD, statins, multivessel disease, LMT lesion, DES used.

be seen. In the recent CANTOS study, treatment with canakinumab, which has direct anti-inflammatory effects and reduces hs-CRP levels, was shown to decrease the risk of recurrent cardiovascular events in patients with previous myocardial infarction and hs-CRP level >2 mg/L [23]. In that study, interleukin-1β inhibition with canakinumab markedly reduced plasma levels of interleukin-6 and hs-CRP without lowering the level of LDL-C. For this reason, these findings suggest hs-CRP-lowering treatments as an innovative approach to treating CAD patients after PCI. Intervention for residual inflammatory risk is important in CAD patients already using statins. The results of our study confirm that hs-CRP may offer a useful secondary prevention biomarker to assess the risk of death and cardiovascular events in patients with established coronary artery disease who undergo PCI. Furthermore, we demonstrated that even only a single measurement of hs-CRP at 6–8 months after PCI is sufficient to provide information on cardiovascular risk. Further study is required to investigate the prognostic value of hs-CRP levels at chronic phase as a secondary prevention biomarker in CAD patients who undergo PCI.

Several limitations to this study warrant consideration. First, this was a retrospective, observational study from a single center, and the patient population and lesion characteristics thus may have been biased. Second, information on active infection and sources of inflammation was unavailable in the present study, although we generally reschedule or never schedule follow-up angiography when patients are being treated for active infection or malignant disease. Third, although we applied multivariate Cox proportional hazards models that included several known confounding variables, other unknown confounders might have played important roles. Fourth, we did not evaluate revascularization as a clinical outcome because it was difficult to correct sufficiently by questionnaire data of patients who transferred to other hospitals. Furthermore, we had no data about other vascular events. It will be necessary to gain more information about other vascular diseases including not only ACS but also planned coronary revascularization, stroke, or peripheral artery disease. Finally, we had no information about the patient compliance with prescribed medical therapy during follow-up. There may be patients not taking statin or aspirin which affect hs-CRP levels even as secondary prevention after PCI.

In conclusion, elevated hs-CRP levels at 6-8 months after PCI were significantly associated with long-term clinical outcome. The hs-CRP levels in the chronic phase could offer a useful marker for secondary prevention in patients with coronary artery disease after PCI.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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