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Original article

Time-dependent prognostic effect of high sensitivity C-reactive protein with statin therapy in acute myocardial infarction

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ABSTRACT

Background: Elevated high sensitivity C-reactive protein (hs-CRP) in acute myocardial infarction (AMI) patients undergoing percutaneous coronary intervention (PCI) has prognostic value for future cardiovascular events. This study aimed to ascertain a valid prognostic time-period for predicting cardiovascular outcome based on baseline hs-CRP in AMI patients undergoing successful PCI on statin therapy.

Methods: Overall, 4410 AMI patients were enrolled from the Korea Acute Myocardial Infarction-National Institutes of Health (KAMIR-NIH) registry. Participants were divided into groups according to cut-off values of baseline hs-CRP (1.0, 3.0, and 10.0 mg/L) and statin therapy intensity. The primary outcome was 36-month major adverse cardiovascular events (MACE), a composite of all-cause mortality, any myocardial infarction, and repeat revascularization. The secondary outcome was MACE developed 0–6, 6–12, and 12–36 months after AMI.

Results: The overall incidence of 36-month MACE was significantly higher as baseline hs-CRP increased (by groups: 8.8% vs. 8.6% vs. 10.7% vs. 15.4%, log-rank $p < 0.001$). The prognostic effect of baseline hs-CRP was mostly confined to the first 6 months after AMI (0–6 months MACE by groups: 1.6% vs. 2.3% vs. 4.3% vs. 6.1%, log-rank $p < 0.001$) and attenuated in high-intensity statin users. Six months after AMI, this prognostic effect of baseline hs-CRP was remarkably reduced (6–12 month MACE by groups: 2.4% vs. 2.1% vs. 2.8% vs. 4.0%, log-rank $p = 0.111$, 12–36 month MACE by groups: 4.7% vs. 4.1% vs. 4.0% vs. 6.2%, log-rank $p = 0.218$); however, high-intensity statin treatment showed a consistent improvement in outcome. The observed time-dependent prognostic effects remained consistent following multivariate analysis.

Conclusions: The prognostic impact of elevated hs-CRP at baseline was most evident during the first 6 months after AMI; however, the use of high-intensity statin persistently improved the clinical outcome even after the resolution of inflammatory reactions.

Introduction

Inflammation has a pivotal role in atherosclerosis progression [1] and contributes to the development of atherosclerotic vascular disease which ultimately leads to acute coronary syndrome [2]. Among the numerous circulating biomarkers for

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atherosclerotic inflammation, the high sensitivity C-reactive protein (hs-CRP) is one of the most extensively studied molecules for cardiovascular risk stratification [3]. An abrupt increase in hs-CRP at an early stage of acute myocardial infarction (AMI) is a result of an acute inflammatory reaction induced by myocardial necrosis that has been superimposed on preexisting atherosclerotic inflammation [4,5]. This elevated hs-CRP following AMI is a well-known independent predictor of both short-term [6–8] and long-term adverse cardiovascular outcomes [4,9,10]. Increased hs-CRP since AMI is usually reduced over the subsequent several weeks [5,11,12], however, the precise duration of this prognostic effect for predicting future adverse outcome by baseline hs-CRP has not been clearly defined, especially in patients undergoing successful percutaneous coronary intervention (PCI).

Statin therapy is effective for reducing cardiovascular risk in a wide spectrum of the population [13,14]. The anti-inflammatory action of statin, which is independent of its lipid-lowering effects, plays an important role in cardiovascular risk reduction [15,16]. In the setting of secondary prevention after AMI, the use of high-intensity statin is strongly recommended [17] and the resulting reduction in hs-CRP levels achieved through statin therapy is known to produce substantial improvement in clinical outcomes [18]. Statin therapy usually decreases hs-CRP levels [19,20] and a stronger reduction is expected from the use of higher intensity therapy [21,22]. The greater anti-inflammatory action achieved using higher intensity statin treatment has a substantial role in improving outcome after AMI; however, it is unclear whether the use of high-intensity statin could make a further difference on the prognostic effects of baseline hs-CRP. Furthermore, little is known about whether the therapeutic effect of high-intensity statin treatment remains consistent after the prognostic effect of baseline hs-CRP is no longer present.

In the present study, we evaluated a valid time-frame for predicting cardiovascular outcome based on baseline hs-CRP levels in AMI patients undergoing successful PCI on statin therapy. We further investigated whether the use of high-intensity statin could alter the observed prognostic effect and influence the outcome beyond the estimated prognostic time-period.

Methods

Study protocols and population

The study subjects were enrolled from the KAMIR-NIH registry between November 2011 and December 2015. The KAMIR-NIH is a prospective, nation-wide, multicenter web-based registry, which consecutively enrolls AMI patients from 20 tertiary university hospitals in Korea. The detailed study protocol has been published previously [23]. The KAMIR-NIH protocol was approved by the Institutional Review Board and Ethical Committee at each participating center and written informed consent was provided by all participants upon enrollment.

Among the 12,341 patients enrolled in the KAMIR-NIH registry, AMI patients who underwent successful PCI were enrolled. The following patients were excluded sequentially: (1) patients with sub-acute presentation (>7 days), (2) patients with final diagnosis of unstable angina or other chest pain, (3) patients that underwent suboptimal or failed PCI, (4) patients lacking baseline laboratory data including lipid profiles, hs-CRP, and creatinine clearance, (5) patients without left ventricular ejection fraction (LVEF) values by transthoracic echocardiography, (6) patients with no prescription for statins after PCI. Ultimately, a total of 4410 patients were included in the study (Fig. 1).

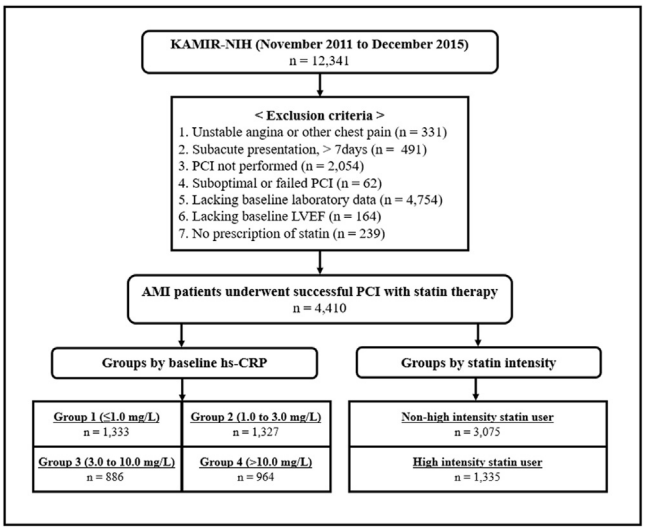

Fig. 1. Study flow chart of patient enrollment. AMI, acute myocardial infarction; hs-CRP, high sensitivity C-reactive protein; KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institute of Health; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Study definitions

The diagnosis of AMI was based on the increase in cardiac biomarkers (creatinine kinase-MB, troponin I or T) with typical changes on 12-lead electrocardiography (ECG). ST-segment elevation myocardial infarction (STEMI) was defined as new ST-segment elevation measuring ≥1 mm from ≥2 contiguous leads or new left bundle-branch block on ECG. Those with ECG findings not classified as STEMI with positive cardiac biomarkers were defined as non ST-segment elevation myocardial infarction (NSTEMI). Peripheral blood samples of baseline laboratory tests were obtained at the time of admission. Levels of hs-CRP were analyzed by immunoturbidimetric analysis (Tina-quant hs-CRP latex assay, Roche/Hitachi, Cobas, Mannheim, Germany). Lipid profiles including total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol were measured by standard enzymatic methods after 8 h of fasting. The LVEF was determined by transthoracic echocardiography at the time of admission utilizing modified Simpson's biplane method.

The statin intensity was categorized as high-intensity and non-high-intensity, which includes both moderate- and low-intensity treatment, as defined by the 2013 American College of Cardiology and American Heart Association (ACC/AHA) guidelines for blood cholesterol treatment [24]. The entire study population was divided into 4 groups according to baseline hs-CRP levels of 1.0 mg/L, 3.0 mg/L, and 10.0 mg/L: group I (G1, $n = 1333$; ≤1.0 mg/L), group II (G2, $n = 1327$; 1.0–3.0 mg/L), group III (G3, $n = 886$; 3.0–10.0 mg/L), and group IV (G4, $n = 864$; >10.0 mg/L). These pre-specified levels of hs-CRP were previously recommended as a reference value for predicting future cardiovascular outcomes by the 2003 Centers for Disease Control and Prevention and AHA statement [3]. The previous studies have widely demonstrated that these cut-off values have significant prognostic impact on patients with acute coronary syndrome including myocardial infarction [10,22,25,26].

Patient management, data collection, and follow up

All patients in the present study underwent successful PCI. The morphology of coronary artery lesion type was determined according to the ACC/AHA classification [27]. Successful PCI was defined as residual stenosis <30% with post-PCI Thrombolysis in

Myocardial Infarction (TIMI) grade 3 flow on the treated vessel. Primary PCI in STEMI was defined as emergent PCI within 12 h and early invasive PCI in NSTEMI was defined as emergent PCI within 48 h after admission. Rescue PCI was defined as emergent PCI due to failure of initial medical treatment in both STEMI and NSTEMI including thrombolysis for STEMI. Treatment strategies for multivessel involvement, such as PCI for culprit lesions only or multivessel revascularization, and single stage or stepwise PCI were left to the attending operator's discretion.

All patients were recommended to take dual antiplatelet therapy with aspirin and P2Y12 inhibitor after PCI. Medications including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins were prescribed according to the recent practice guidelines. The choice of type and dose of statin was left to the individual physician's discretion. A regular outpatient clinic visit was performed at the end of the first month, every 3–6 months after the PCI procedure, and up to 36 months in available cases. If patients did not visit on the

Table 1
Baseline characteristics at initial admission and prescribed medications according to baseline hs-CRP.

	Total (n = 4410)	G1 (n = 1333)	G2 (n = 1327)	G3 (n = 886)	G4 (n = 864)	p-value	p-value for trend
Sex (male)	3410 (77.3)	1032 (77.4)	1085 (81.7)	684 (77.2)	609 (70.4)	<0.001	<0.001
Age (years)	62.7 ± 12.4	62.0 ± 11.8	61.0 ± 12.4	63.2 ± 12.3	65.9 ± 12.9	<0.001	
Age > 60 years	2493 (56.5)	736 (55.2)	665 (50.1)	518 (58.4)	574 (66.4)	<0.001	<0.001
BMI (kg/m^2)	24.2 ± 3.3	23.9 ± 3.1	24.7 ± 3.2	24.5 ± 3.3	23.8 ± 3.5	<0.001	
SBP (mmHg)	130.7 ± 29.2	130.8 ± 29.0	133.31 ± 29.5	131.7 ± 28.3	125.6 ± 29.6	<0.001	
DBP (mmHg)	79.2 ± 18.0	79.7 ± 18.1	80.0 ± 18.4	79.8 ± 17.2	76.3 ± 17.8	<0.001	
Heart rate (bpm)	77.2 ± 18.6	74.6 ± 17.4	76.0 ± 18.2	78.5 ± 18.5	81.7 ± 20.1	<0.001	
Killip class 4	196 (4.4)	57 (4.2)	51 (3.8)	26 (2.9)	62 (7.1)	<0.001	0.016
Final diagnosis: STEMI	2484 (56.3)	808 (60.6)	751 (56.5)	473 (53.3)	452 (52.3)	<0.001	<0.001
Symptom onset to hospital arrival (h)	3.18 (1.25–9.50)	2.28 (1.00–5.61)	2.70 (1.05–7.58)	3.86 (1.55–12.69)	6.00 (2.27–24.00)	<0.001	
hs-CRP measurement within 48 h of hospitalization	4275 (96.9)	1316 (98.7)	1308 (98.5)	848 (95.7)	803 (92.9)	<0.001	<0.001
Past medical history							
Previous hypertension	2156 (48.8)	602 (45.1)	640 (48.2)	461 (52)	453 (52.4)	0.001	<0.001
Previous diabetes	1102 (24.9)	290 (21.7)	300 (22.6)	225 (25.3)	287 (33.2)	<0.001	<0.001
Previous dyslipidemia	605 (13.7)	178 (13.3)	209 (15.7)	118 (13.3)	100 (11.5)	0.041	0.154
Previous myocardial infarction	217 (4.9)	58 (4.3)	68 (5.1)	39 (4.4)	52 (6)	0.286	0.163
Previous heart failure	30 (0.6)	8 (0.6)	6 (0.4)	6 (0.6)	10 (1.1)	0.255	0.121
Previous CVA	236 (5.3)	56 (4.2)	63 (4.7)	45 (5)	72 (8.3)	<0.001	<0.001
Family history of CAD	348 (7.8)	115 (8.6)	112 (8.4)	72 (8.1)	49 (5.6)	0.058	0.019
Smoking	1978 (44.8)	557 (41.7)	633 (47.7)	441 (49.7)	347 (40.1)	<0.001	0.924
Laboratory findings							
Creatinine clearance (mL/min)	78.8 (57.9–101.6)	81.6 (63.9–103.4)	82.3 (61.6–106.4)	77.1 (55.3–98.3)	66.4 (44.1–91.4)	<0.001	
Max CK-MB (ng/mL)	78.2 (19.1–213.0)	94.4 (22.6–229.9)	87.7 (22.4–221.8)	76.2 (17.3–224.9)	51.8 (15.0–150.1)	<0.001	
Max Troponin-I (ng/mL)	21.7 (3.7–51.5)	22.2 (2.9–53.6)	25.0 (4.4–62.0)	21.1 (3.2–54.1)	18.7 (4.5–40.0)	0.017	
NT-proBNP (pg/L)	197.4 (52.3–1060.0)	105.0 (37.8–372.2)	118.6 (42.3–487.8)	396.1 (79.8–1629.0)	1793.0 (464.1–5081.0)	<0.001	
Total cholesterol (mmol/L)	4.66 (3.96–5.43)	4.57 (3.93–5.35)	4.84 (4.11–5.59)	4.71 (4.01–5.53)	4.42 (3.70–5.25)	<0.001	
Triglyceride (mmol/L)	1.21 (0.84–1.89)	1.14 (0.79–1.84)	1.35 (0.90–2.09)	1.27 (0.86–1.92)	1.10 (0.79–1.54)	<0.001	
HDLc (mmol/L)	1.06 (0.91–1.24)	1.09 (0.93–1.32)	1.06 (0.91–1.24)	1.03 (0.88–1.22)	1.06 (0.91–1.24)	<0.001	
LDLc (mmol/L)	2.92 (2.30–3.56)	2.88 (2.28–3.48)	3.01 (2.38–3.65)	3.00 (2.35–3.65)	2.73 (2.05–3.44)	<0.001	
hs-CRP (mg/L)	2.6 (0.8–6.9)	0.5 (0.3–0.7)	2.0 (1.4–2.9)	5.2 (4.0–7.1)	27.7 (16.3–57.8)	<0.001	
Fasting glucose (mmol/L)	7.94 (6.49–10.21)	7.88 (6.49–9.82)	7.94 (6.49–9.99)	7.88 (6.44–10.86)	8.16 (6.49–11.15)	0.033	
HbA1c (%)	6.0 (5.6–6.9)	5.9 (5.5–6.6)	5.9 (5.6–6.7)	6.1 (5.6–7.2)	6.1 (5.7–7.3)	<0.001	
LVEF (%)	52.5 ± 10.4	54.0 ± 9.5	53.8 ± 9.6	52.0 ± 10.9	48.7 ± 11.5	<0.001	
Medications after PCI							
Aspirin	4388 (99.5)	1329 (99.6)	1320 (99.4)	884 (99.7)	855 (98.9)	0.056	0.061
Clopidogrel	3208 (72.7)	920 (69.0	988 (74.4)	655 (73.9)	645 (74.6)	0.004	0.004
Cilostazol	552 (12.5)	147 (11.0)	134 (10.0)	121 (13.6)	150 (17.3)	<0.001	<0.001
Prasugrel	494 (11.2)	179 (13.4)	145 (10.9)	102 (11.5)	68 (7.8)	0.001	<0.001
Ticagrelor	721 (16.3)	237 (17.7)	205 (15.4)	131 (14.7)	148 (17.1)	0.191	0.471
Beta-blocker	3848 (87.2)	1163 (87.2)	1197 (90.2)	789 (89.0)	699 (80.9)	<0.001	<0.001
ACE-inhibitor and ARB	3599 (81.6)	1087 (81.5)	1091 (82.2)	735 (82.9)	686 (79.3)	0.239	0.368
Statin intensity							
High-intensity	1335 (30.2)	356 (26.7)	501 (37.7)	265 (29.9)	213 (24.6)	<0.001	0.115
Moderate-to-high intensity	2984 (67.6)	948 (71.1)	810 (61.0)	599 (67.6)	627 (72.5)	<0.001	0.262
Low-intensity	91 (2.0)	29 (2.1)	16 (1.2)	22 (2.4)	24 (2.7)	0.049	0.159
Statin subtype							
Atorvastatin	1947 (44.1)	526 (39.4)	698 (52.5)	382 (43.1)	341 (39.4)	<0.001	0.836
Rosuvastatin	1861 (42.1)	607 (45.5)	474 (35.7)	375 (42.3)	405 (46.8)		
Pravastatin	67 (1.5)	24 (1.8)	16 (1.2)	12 (1.3)	15 (1.7)		
Pitavastatin	350 (7.9)	111 (8.3)	93 (7.0)	74 (8.3)	72 (8.3)		
Fluvastatin	4 (0.0)	1 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)		
Simvastatin	181 (4.1)	64 (4.8)	44 (3.3)	43 (4.8)	30 (3.4)		

Data are expressed as n (%), mean ± SD or median (interquartile range). G1 = group 1 (hs-CRP ≤ 1.0 mg/L); G2 = group 2 (1.0 < hs-CRP ≤ 3.0 mg/L); G3 = group 3 (3.0 < hs-CRP ≤ 10.0 mg/L); G4 = group 4 (hs-CRP > 10.0 mg/L).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; CK-MB, creatinine kinase-MB; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDLc, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDLc, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; Max, maximum; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

Table 2
Procedural characteristics and treatment strategies of groups according to baseline hs-CRP.

	Total (n = 4410)	G1 (n = 1333)	G2 (n = 1327)	G3 (n = 886)	G4 (n = 864)	p-value	p-value for trend
STEMI							
Primary PCI	2436 (55.2)	794 (59.5)	738 (55.6)	469 (52.9)	435 (50.3)	<0.001	<0.001
Facilitated elective PCI	16 (0.3)	5 (0.3)	5 (0.3)	2 (0.2)	4 (0.4)	0.870	0.936
Rescue PCI after initial medical therapy	22 (0.4)	4 (0.3)	6 (0.4)	6 (0.6)	6 (0.6)	0.502	0.138
NSTEMI							
Early invasive PCI	1666 (37.7)	472 (35.4)	495 (37.3)	348 (39.2)	351 (40.6)	0.068	0.008
Elective or rescue PCI	268 (6.0)	57 (4.2)	82 (6.1)	61 (6.8)	68 (7.8)	0.004	<0.001
Procedural strategy							
Culprit lesion only PCI	954 (21.6)	276 (20.7)	264 (19.8)	190 (21.4)	224 (25.9)	0.006	0.005
Single PCI	3928 (89.0)	1187 (89.0)	1188 (89.5)	792 (89.3)	761 (88.0)	0.741	0.538
Stepwise PCI	473 (10.7)	143 (10.7)	136 (10.2)	92 (10.3)	102 (11.8)	0.688	0.489
Extent of vessel involvement							
One-vessel disease	2312 (52.4)	756 (56.7)	691 (52)	474 (53.4)	391 (45.2)	<0.001	<0.001
Two-vessel disease	1399 (31.7)	403 (30.2)	426 (32.1)	263 (29.6)	307 (35.5)	0.030	0.046
Three-vessel disease	699 (15.8)	174 (13.0)	210 (15.8)	149 (16.8)	166 (19.2)	0.001	<0.001
Infarct-related artery							
Left main	78 (1.7)	20 (1.5)	23 (1.7)	9 (1.0)	26 (3.0)	0.011	0.056
Left anterior descending	2118 (48)	647 (48.5)	628 (47.3)	432 (48.7)	411 (47.5)	0.882	0.821
Left circumflex	719 (16.3)	207 (15.5)	220 (16.5)	157 (17.7)	135 (15.6)	0.521	0.679
Right	1495 (33.9)	459 (34.4)	456 (34.3)	288 (32.5)	292 (33.7)	0.784	0.537
Left main + left anterior descending	2196 (49.7)	667 (50.0)	651 (49.0)	441 (49.7)	437 (50.5)	0.912	0.781
Stent characteristics							
Stent length (mm)	29.40 ± 13.75	28.22 ± 12.93	28.75 ± 13.03	30.01 ± 14.25	31.60 ± 15.20	<0.001	
Stent diameter (mm)	3.13 ± 0.44	3.15 ± 0.43	3.16 ± 0.46	3.14 ± 0.42	3.06 ± 0.41	<0.001	
Stent number (total)	1.50 ± 0.80	1.48 ± 0.81	1.45 ± 0.76	1.50 ± 0.80	1.60 ± 0.84	<0.001	
Other characteristics							
Lesion type B2 + C	3837 (87.0)	1139 (85.4)	1142 (86)	781 (88.1)	775 (89.6)	0.015	0.002
Initial TIMI grade 0 flow	2127 (48.2)	638 (47.8)	621 (46.7)	423 (47.7)	445 (51.5)	0.175	0.116
Final TIMI grade 3 flow	4297 (97.4)	1306 (97.9)	1295 (97.5)	862 (97.2)	834 (96.5)	0.203	0.036
Second generation DES	4240 (96.1)	1292 (96.9)	1262 (95.1)	856 (96.6)	830 (96.0)	0.085	0.587

Data are expressed as n (%) or mean ± SD. G1 = group 1 (hs-CRP ≤ 1.0 mg/L); G2 = group 2 (1.0 < hs-CRP ≤ 3.0 mg/L); G3 = group 3 (3.0 < hs-CRP ≤ 10.0 mg/L); G4 = group 4 (hs-CRP > 10.0 mg/L).
DES, drug-eluting stent; hs-CRP, high sensitivity C-reactive protein; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

scheduled date, a telephone interview was conducted to assess adverse outcomes. All data obtained during the follow-up visits were collected and input by an independent clinical research coordinator who followed the standard operation procedures of the KAMIR-NIH data administration committee.

Study outcomes

A major adverse cardiovascular event (MACE) was defined as a composite of all-cause mortality, any myocardial infarction (MI), and any repeat revascularization. The primary outcome was 36-month MACE, and the secondary outcome was MACE within the pre-specified period of 0–6 months, 6–12 months, and 12–36 months after AMI. The follow-up duration of each study participant was counted from the date of successful PCI, while those who developed MACE or were lost to follow-up were censored from the survival curve analysis. Mortality was classified as cardiac and non-cardiac death. Recurrent MI was defined as the recurrence of symptoms or typical ST-segment changes on ECG combined with a significant elevation of cardiac biomarkers. Repeat revascularization included clinically driven revascularization which occurred after discharge from the index admission.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD) and variables that did not fit a normal distribution were expressed as median with interquartile range (IQR). Data with normal distribution were compared by one-way ANOVA or unpaired Student's t-test, while non-normally distributed variables were compared by the Kruskal–Wallis H-test or Mann–Whitney U-test. Categorical variables were expressed as frequency (percent) and compared by Pearson's chi-square or Fisher's exact test. The incidence of adverse outcome by each group during the pre-specified time-period was compared by Kaplan–Meier survival curve analysis with a stratified log-rank test. Multivariate analysis with Cox proportional-hazard model was performed to validate time-dependent prognostic effects of both baseline hs-CRP and high-intensity statin for each time-period assessed. Variables known to potentially affect outcomes or that revealed a relative significance (p-value <0.100) from univariate analysis were selectively included in the multivariate analysis. The results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) and p-values. All analyses were two-tailed with clinical significance defined as p-values <0.05. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 20.0 (SPSS-PC Inc., Chicago, IL, USA).

Results

Baseline clinical, procedural characteristics, and treatment strategy

The median follow-up duration for the study population was 740.5 (391.0–1032.3) days. The rate of completing follow-up of 6, 12, and 36 months was 86.4%, 78.8%, and 25.4%, respectively. The baseline clinical, procedural characteristics and treatment strategies of the groups categorized according to baseline hs-CRP levels are summarized in Tables 1 and 2. The median time from symptom onset to hospital arrival was 3.18 (1.25–9.50) h, and hs-CRP measurement was performed within 48 h of admission in 96.9% of whole study population. The proportion of patients aged >60 years, with medical history of hypertension, diabetes, and cerebrovascular events increased with elevating baseline hs-CRP

Table 3
Thirty-six-month clinical outcome of groups according to baseline hs-CRP.

	G1 (n = 1333)		G2 (n = 1327)		G3 (n = 886)		G4 (n = 864)		Log-rank p-value
	No. at risk		No. at risk		No. at risk		No. at risk		
0–6 month outcome									
Total death	1333	4 (0.3)	1327	11 (0.9)	886	15 (1.7)	864	38 (4.5)	<0.001
Cardiac death	1333	3 (0.2)	1327	6 (0.5)	886	8 (0.9)	864	26 (3.1)	<0.001
Non-cardiac death	1333	1 (0.1)	1327	5 (0.4)	886	7 (0.8)	864	12 (1.5)	0.001
Myocardial infarction	1333	9 (0.7)	1327	8 (0.6)	886	9 (1.0)	864	9 (1.1)	0.557
Repeat revascularization	1333	14 (1.1)	1327	20 (1.6)	886	16 (1.9)	864	11 (1.3)	0.486
MACE	1333	24 (1.6)	1327	34 (2.3)	886	37 (4.3)	864	51 (6.1)	<0.001
6–12 month outcome									
Total death	1205	3 (0.3)	1175	2 (0.2)	793	5 (0.7)	763	11 (1.6)	0.001
Cardiac death	1205	2 (0.2)	1175	1 (0.1)	793	2 (0.3)	763	7 (1.0)	0.006
Non-cardiac death	1205	1 (0.1)	1175	1 (0.1)	793	3 (0.4)	763	4 (0.6)	0.111
Myocardial infarction	1196	4 (0.4)	1170	4 (0.4)	784	2 (0.3)	757	7 (1.0)	0.138
Repeat revascularization	1191	23 (2.1)	1155	19 (1.8)	778	14 (2.0)	753	16 (2.4)	0.867
MACE	1185	27 (2.4)	1154	22 (2.1)	772	20 (2.8)	750	27 (4.0)	0.111
12–36 month outcome									
Total death	1047	9 (1.4)	1008	14 (1.9)	687	7 (1.9)	632	14 (2.9)	0.096
Cardiac death	1047	6 (0.7)	1008	6 (0.7)	687	3 (0.6)	632	4 (0.8)	0.962
Non-cardiac death	1047	3 (0.7)	1008	8 (1.2)	687	4 (1.3)	632	10 (2.2)	0.025
Myocardial infarction	1036	12 (1.7)	1000	8 (1.0)	676	5 (1.3)	622	3 (0.6)	0.534
Repeat revascularization	1011	19 (2.7)	972	17 (2.2)	658	8 (1.8)	606	14 (3.3)	0.508
MACE	1006	32 (4.7)	970	30 (4.1)	651	16 (4.0)	603	27 (6.2)	0.218
0–36 month outcome									
Total death	1333	16 (1.9)	1327	27 (2.9)	886	27 (4.3)	864	63 (8.7)	<0.001
Cardiac death	1333	11 (1.1)	1327	13 (1.3)	886	13 (1.8)	864	37 (4.8)	<0.001
Non-cardiac death	1333	5 (0.8)	1327	14 (1.7)	886	14 (2.5)	864	26 (4.1)	<0.001
Myocardial infarction	1333	25 (2.7)	1327	20 (2.0)	886	16 (2.6)	864	19 (2.6)	0.657
Repeat revascularization	1333	56 (5.7)	1327	56 (5.5)	886	38 (5.5)	864	41 (6.9)	0.847
MACE	1333	83 (8.8)	1327	86 (8.6)	886	73 (10.7)	864	105 (15.4)	<0.001

Data are expressed as n (%). G1 = group 1 (hs-CRP ≤ 1.0 mg/L); G2 = group 2 (1.0 < hs-CRP ≤ 3.0 mg/L); G3 = group 3 (3.0 < hs-CRP ≤ 10.0 mg/L); G4 = group 4 (hs-CRP > 10.0 mg/L).
hs-CRP, high sensitivity C-reactive protein; MACE, major adverse cardiovascular events.

levels. The levels of cardiac biomarkers, creatinine clearance, LDL cholesterol, and LVEF level at admission decreased as the baseline hs-CRP level increased. The rate of patients that underwent PCI only for culprit lesions and with incidence of two- or three-vessel diseases, and complex lesions (type B2C) from initial angiography was higher with higher baseline hs-CRP. The baseline characteristics and procedural profiles of the groups categorized according to the use of high-intensity statin are provided in the Supplemental Tables 1 and 2.

Clinical outcome of the groups divided by baseline hs-CRP

The 36-month clinical outcomes of the groups divided by baseline hs-CRP are summarized in Table 3. The overall incidence of 36-month MACE was significantly higher as the baseline hs-CRP level increased (estimated 36-month MACE by groups: 8.8% vs. 8.6% vs. 10.7% vs. 15.4%, log-rank $p < 0.001$, Fig. 2A). The incidence of MACE during the first 6 months was significantly higher with increasing baseline hs-CRP (estimated 0–6 month MACE by groups: 1.6% vs. 2.3% vs. 4.3% vs. 6.1%, log-rank $p < 0.001$, Fig. 2B), however, the MACE developed during the subsequent 6–12 months (estimated 6–12 month MACE by groups: 2.4% vs. 2.1% vs. 2.8% vs. 4.0%, log-rank $p = 0.111$, Fig. 2C) and 12–36 months (estimated 12–36 month MACE by groups: 4.7% vs. 4.1% vs. 4.0% vs. 6.2%, log-rank $p = 0.218$, Fig. 2D) period showed no significant difference among the groups. The greater incidence of 36-month MACE at higher levels of baseline hs-CRP was largely attributed to the differences developed during the first 6 months after AMI.

In the subgroup analysis of non-high-intensity statin users, future MACE prediction by baseline hs-CRP showed consistent prognostic patterns as in the overall population (Fig. 3A). The baseline hs-CRP elevation was strongly associated with a greater risk of future MACE during the first 6 months after AMI; however, there was no prognostic impact for predicting MACE after the 6–12 month and 12–36 month periods. In the analysis confined to the high-intensity statin users, baseline hs-CRP elevation was no longer associated with a significant increase in MACE for any of the time-periods after AMI (Fig. 3B). In the subgroup analysis of statin subtypes, the baseline hs-CRP elevation lost its prognostic significance during the first 6 months period in the rosuvastatin users while maintaining its prognostic effect in both atorvastatin and other statin users (Supplemental Fig. 1). The subgroups divided by baseline LDL cholesterol level of 100 mg/dL showed a similar prognostic pattern by baseline hs-CRP as in the whole study population (Supplemental Fig. 2).

Clinical outcome by the use of high-intensity statin

The 36-month clinical outcome by the use of high-intensity statin is shown in Supplemental Table 3. The incidence of overall 36-month MACE was significantly reduced by the use of high-intensity statin (8.8% vs. 15.4%, log-rank $p < 0.001$, Fig. 4A). The use of high-intensity statin was associated with a significant decrease in MACE during the first 6 months after AMI (2.1% vs. 4.0%, log-rank $p = 0.003$, Fig. 4B). Contrary to the prognostic effect of baseline hs-CRP, the use of high-intensity statin further reduced the incidence of MACE even after the first 6 months of AMI, including both time-periods of 6–12 months (1.1% vs. 3.3%, log-rank $p < 0.001$, Fig. 4C) and 12–36 months (3.1% vs. 5.3%, log-rank $p = 0.021$, Fig. 4D).

Multivariate analysis

Supplemental Table 4 shows independent predictors for 36-month MACE and detailed results for each pre-specified

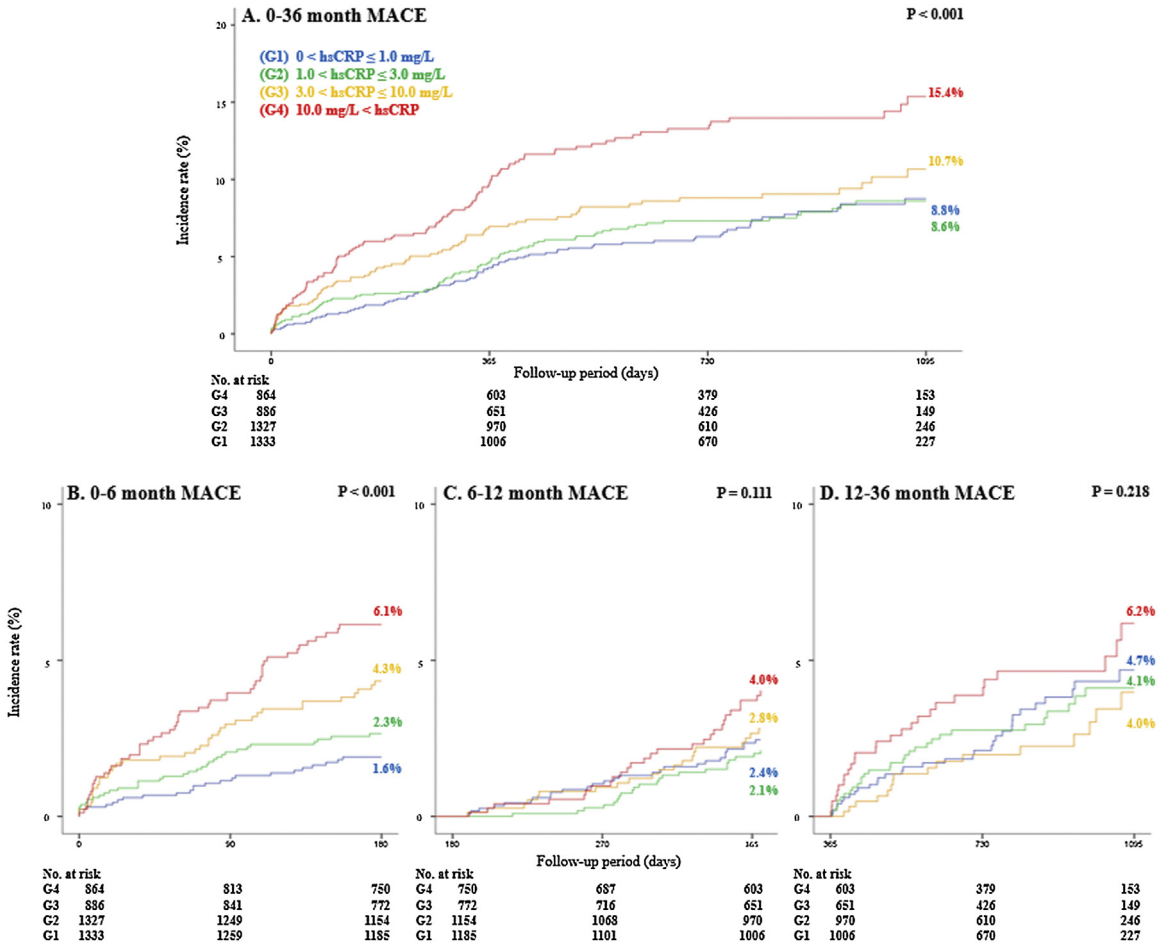

Fig. 2. Incidence of MACE according to pre-specified time-periods and baseline Hs-CRP levels. G1 = group 1 (hs-CRP ≤ 1.0 mg/L); G2 = group 2 (1.0 < hs-CRP ≤ 3.0 mg/L); G3 = group 3 (3.0 < hs-CRP ≤ 10.0 mg/L); G4 = group 4 (hs-CRP > 10.0 mg/L).
hs-CRP, high sensitivity C-reactive protein; MACE, major adverse cardiovascular events.

time-period of 0–6, 6–12, and 12–36 months are provided in Supplemental Tables 5, 6, and 7, respectively. Both baseline hs-CRP elevation and use of high-intensity statin were independent predictors of 36-month MACE. The use of high-intensity statin reduced the risk of 36-month MACE by 49% (adjusted HR: 0.51; 95% CI: 0.38–0.70) and a significant trend (p-value for trend = 0.037) of increased 36-month MACE was observed compared to baseline hs-CRP elevations. Compared to the reference group (G1), the risk of 36-month MACE was increased by 6% (G2; adjusted HR: 1.06; 95% CI: 0.78–1.44), 24% (G3; adjusted HR: 1.24; 95% CI: 0.90–1.71), and 50% (G4; adjusted HR; 1.50; 95% CI: 1.11–2.03) according to the groups of baseline hs-CRP elevations.

In the analysis of pre-specified time-periods, baseline hs-CRP elevation was effective for predicting future MACE development during the first 6 months after AMI (Fig. 5A: Forrest). However, this prognostic impact on MACE by baseline hs-CRP elevation was no longer present 6 months after AMI. Similar to the results of unadjusted analysis, the use of high-intensity statins consistently reduced the incidence of MACE throughout all time-periods including the 0–6, 6–12, and 12–36-month intervals (Fig. 5B).

Discussion

The present study demonstrated that baseline hs-CRP elevation after AMI undergoing successful PCI with statin therapy was an independent predictor for 36-month MACE development and this prognostic impact was mostly attributed to the development of MACE during the first 6 months after AMI. The time-period-specific analysis revealed that the prognostic impact of baseline hs-CRP elevation was no longer present 6 months after AMI. The use of high-intensity statins exhibited sustained improvement in MACE throughout the whole study period and this preventative action was independent of the prognostic effect of baseline hs-CRP elevation. In the subgroup analysis, prediction of future MACE development by baseline hs-CRP elevation was ineffective in the high-intensity statin users.

Prognostic implications of baseline hs-CRP elevation after AMI

To the best of our knowledge, this is the first study to demonstrate the validity of the prognostic duration of elevated baseline hs-CRP for predicting future adverse outcomes in AMI patients undergoing successful PCI. In the thrombolytic era, Pietila et al. [28] previously reported that the elevated baseline hs-CRP levels could predict increased mortality up to 6 months following infarction treated by thrombolysis. However, this finding cannot be directly applied to current medical practice due to the major therapeutic advances over the last two decades, including the widespread use of primary PCI and prescription of statins for secondary prevention. The findings of the present study support

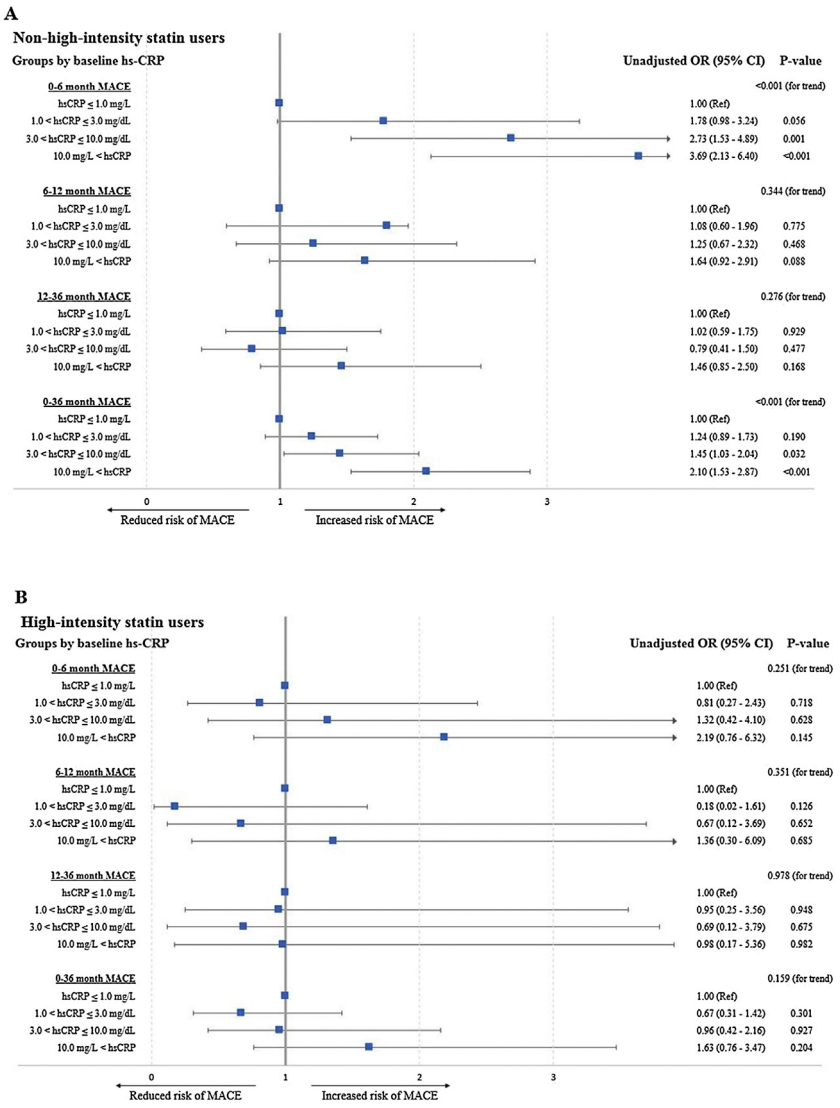

Fig. 3. Subgroup analysis of non-high-intensity (A) and high-intensity statin (B) users. Unadjusted estimated risks for MACE during pre-specified time-periods and according to groups divided by baseline hs-CRP are displayed. hs-CRP, high sensitivity C-reactive protein; MACE, major adverse cardiovascular events; OR, odds ratio.

the prognostic impact of baseline hs-CRP elevation within contemporary medicine and utilization of more detailed outcome measures provides a deeper understanding for the observed prognostic effects. In addition, the large number of participants in the current study provides greater confidence to the impact of the study results.

In patients with acute coronary syndrome (ACS), the clinical significance of achieved hs-CRP levels during statin therapy has been emphasized in the previous TIMI-22 study [18]. The dual monitoring strategy for both hs-CRP and LDL cholesterol has been recommended for those who attempt to lower cardiovascular risk by statin therapy after ACS. Besides the hs-CRP levels achieved during follow-up, hs-CRP levels at baseline could also provide valuable prognostic information regarding future adverse outcomes in the setting of initial disease presentation. In the present study, hs-CRP elevation at baseline showed significant prognostic effects for predicting future MACE development up to 36 months under statin therapy. MACE prediction based on baseline hs-CRP elevation was highly reliable for the first 6 months after AMI and this predictive effect gradually decreased over the subsequent periods.

Time-dependent activity of high-intensity statin for MACE improvement

The hs-CRP value after AMI is often elevated to levels greater than 10 mg/L which identifies the presence of myocardial necrosis [4,5] and acute vascular inflammation associated with plaque rupture and acute thrombus formation [3,29]. This acute increase in hs-CRP shortly after AMI reaches its peak value within 48–72 h and gradually decreases over the next several weeks to the chronic reference range of <10 mg/L [5,11,12]. Using higher intensity statins could produce greater therapeutic effects during the first 6 months after AMI possibly by early stabilization of acute vascular inflammation and rapid reduction of baseline hs-CRP [30,31].

The use of high-intensity statins was also associated with the continued improvement in MACE 6 months after AMI when the prognostic effect of baseline hs-CRP elevation was no longer present. Although the acute inflammatory response after AMI disappears within the initial several weeks, the use of higher intensity statin during the early stage of ACS may result in the extended suppression of the atherosclerotic plaque until the chronic stabilized phase is achieved [22,32]. Furthermore,

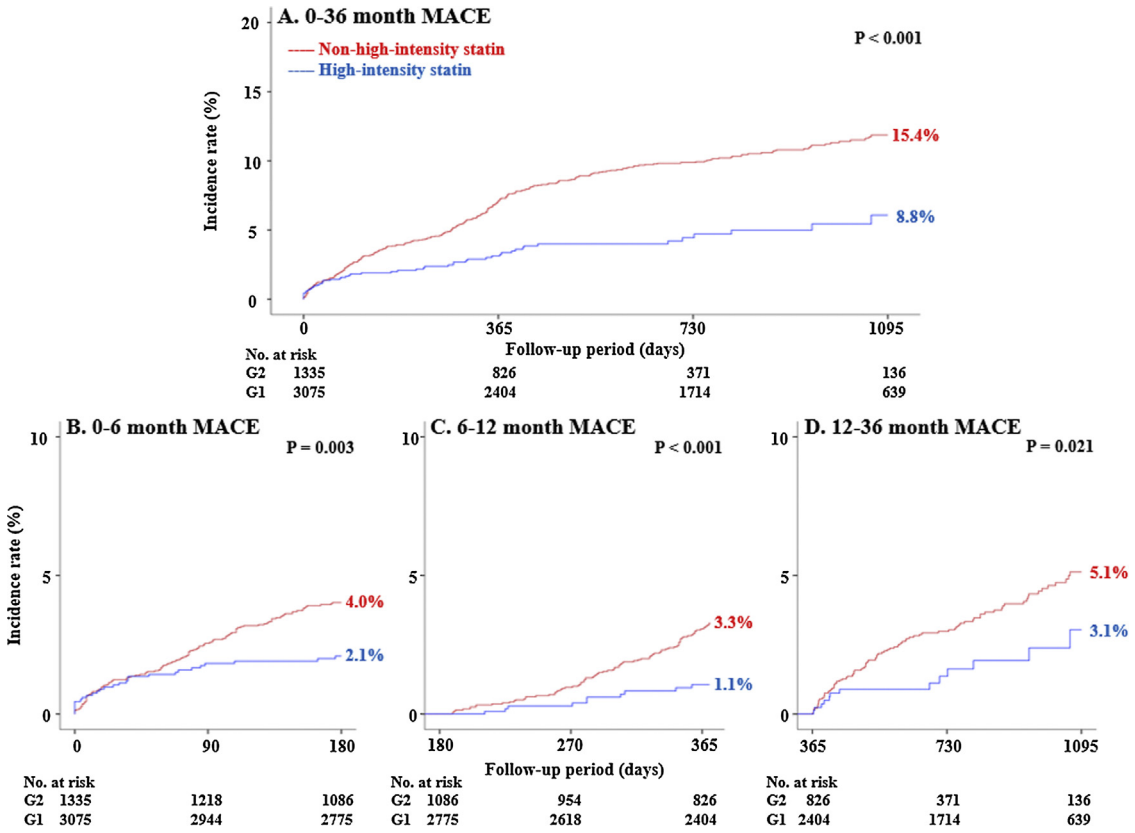

Fig. 4. Incidence of MACE during pre-specified time-periods and according to statin treatment groups. MACE developed during the following periods are displayed: 0–6 months (A), 6–12 months (B), 12–36 months (C), and 0–36 months (D). G1 = group 1 (hs-CRP ≤ 1.0 mg/L); G2 = group 2 (1.0 < hs-CRP ≤ 3.0 mg/L); G3 = group 3 (3.0 < hs-CRP ≤ 10.0 mg/L); G4 = group 4 (10.0 mg/L < hs-CRP).
hs-CRP, high sensitivity C-reactive protein; MACE, major adverse cardiovascular events.

regarding the pleiotropic effects of statin therapy, stronger lipid-lowering effects by higher intensity statin treatment could be an additional contributing factor for the improved outcome observed after stabilization of acute vascular inflammation [17].

The improvement in MACE by high-intensity statin 6 months after AMI was independent of the levels of baseline hs-CRP. This finding suggests that other types of statin actions could have been involved in this prolonged period to improve incidence of MACE compared to the earlier stage. Several clinical trials have reported that anti-inflammatory activity of high-intensity statin has earlier onset of action for improving outcome compared to its cholesterol-lowering activity [30,33,34]. Compared to the earlier phase with acute inflammatory reaction, the period of 6 months after AMI could be assumed to be a circumstance of stabilized coronary artery disease. In the setting of reduced inflammatory activity after 6 months of AMI, greater suppression of cholesterol-associated atherosclerotic process by high-intensity statin could have produced a dominant contribution for improvement in MACE. Therefore, we suggest that the observed beneficial effect of high-intensity statin treatment after AMI is mostly dependent upon both the anti-inflammatory and cholesterol-lowering effects during the early 6 months, but more dominantly upon cholesterol-lowering effects in the later periods (Graphical abstract). The findings of the subgroup analysis also support this perspective that the attenuated prognostic effects of elevated baseline hs-CRP levels with high-intensity statin therapy could also be attributed to the greater anti-inflammatory effect during the first 6 months after AMI.

Study limitations

The present study has several limitations. First, because of the non-randomized nature of the registry data, the characteristics of the groups divided by baseline hs-CRP and use of high-intensity statin showed substantial differences at baseline. Determination of treatment strategy by the attending physician's discretion also introduced a possibility of selection bias. To minimize such biases, we included potential confounding factors into the multivariate analysis; however, it was still possible that remaining confounders may have been included in the analysis. Second, despite acceptable patient compliance with follow-up visits up to 12 months after AMI, a substantial amount of follow-up loss developed after the 12–36-month period. Although similar results and study implications could be derived from the analysis limited to first 12 months, we aimed to assess the outcome measures up to 36 months in order to investigate the prognostic impact of baseline hs-CRP elevation over a prolonged period. The incidence of MACE occurrence between 12 to 36 months could have been overestimated by the low rate of follow-up visits during this period. Third, future MACE development was solely estimated based on baseline characteristics and profiles without reflecting detailed changes occurring in laboratory results and medication status during the follow-up periods. The results of the present study should be interpreted with caution, because only baseline profiles were assessed as variables affecting the occurrence of future cardiovascular events.

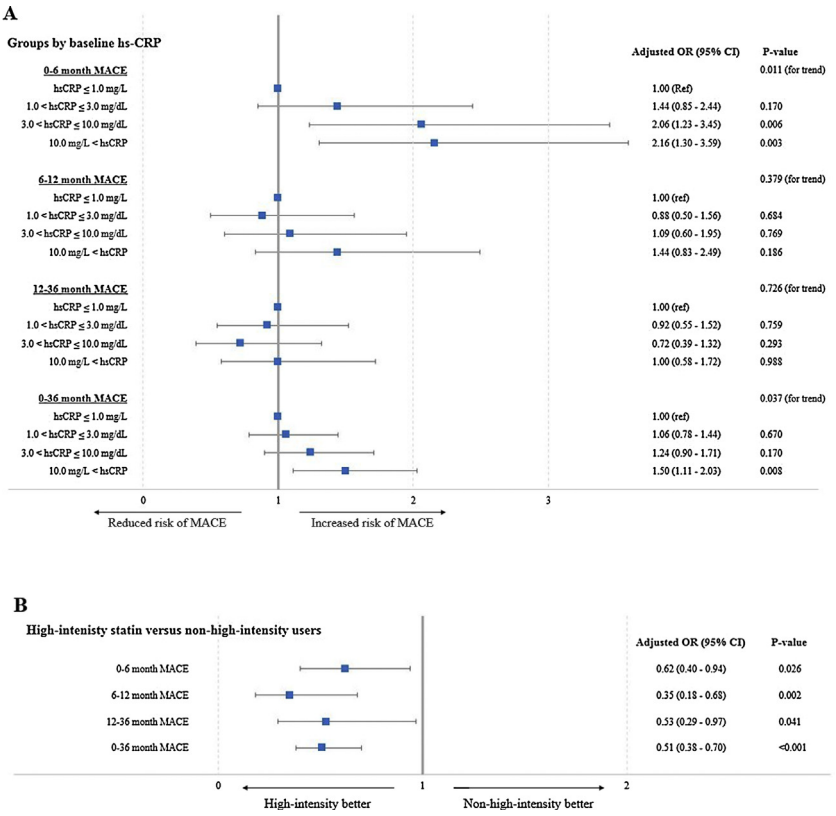

Fig. 5. Adjusted estimated risk for MACE during pre-specified time-periods and according to baseline Hs-CRP levels (A) and statin intensity (B). Results are adjusted for the following variables: sex, age >60 years, previous hypertension, previous diabetes, previous myocardial infarction, Killip class 4, creatinine clearance LVEF <50%, LDLc >160 mg/mL, three-vessel disease, IRA of left main or LAD, complex lesion (type B2 + C), second generation DES. hs-CRP, high sensitivity C-reactive protein; IRA, infarct-related artery; DES, drug-eluting stent; LAD, left anterior descending artery; LDLc, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; OR, odds ratio.

Conclusion

The prognostic impact of baseline hs-CRP at the time of admission was most evident during the first 6 months after AMI occurrence, and diminished subsequently over the following periods under statin therapy. However, the use of high-intensity statin persistently improved the clinical outcome over the extended follow-up periods, which was highly independent of the baseline hs-CRP levels.

Author contributions

D.O.K., Y.P., J.H.S., and H.S.S. designed and conceptualized the study. D.O.K., W.Y.J., W.K., E.J.P., and B.G.C. contributed to data acquisition, analysis, and interpretation. M.H J., S.C.C., T.H.A., and H. S.S. contributed to project administration, supervision, validation, and discussion. D.O.K. and Y.P. wrote the original manuscript. J.O. N., C.U.C., E.J.K., S-W.R., C.G.P., and H.S.S. reviewed and edited the manuscript.

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Conflict of interest

None.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.12.022.

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