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Differential statin intensity and outcomes in patients following myocardial infarction with very low low-density lipoprotein cholesterol

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Abstract

Background: *Despite increasing evidence on the benefits of statin therapy for acute myocardial infarction (AMI), differential outcomes in accordance with statin intensity have not been evaluated in patients with AMI and low-density lipoprotein cholesterol (LDL-C) levels < 55 mg/dL. Therefore, this study aimed to compare the clinical outcomes of high- and moderate-intensity statin therapy in this population.*

Methods: *A total of 752 participants with AMI and LDL-C levels < 55 mg/dL from a Korean nationwide multicenter observational cohort (2016–2020) were included and categorized into two groups: high-intensity statin group (n = 384) and moderate-intensity statin group (n = 368). The primary outcome was 1-year major adverse cardiac and cerebrovascular events (MACCEs). Propensity score matching (PSM) and Cox models were used to determine whether statin intensity independently influenced the primary outcome.*

Results: *Compared to the moderate-intensity statin group, the high-intensity statin group had a comparable risk of MACCE in all Cox models and PSM-adjusted analyses. The cumulative incidence of MACCE was comparable between the two groups.*

Conclusions: *Statin intensity appeared to have no significant impact on clinical outcomes in AMI patients with LDL-C levels < 55 mg/dL. These results underscore the need for further investigations aimed at refining treatment strategies for this specific patient cohort, potentially reducing treatment-related burdens without compromising clinical effectiveness.* (Cardiol J 2024; 31, 6: 802–813)

Keywords: comparative study, LDL cholesterol, myocardial infarction, statins, treatment outcome

Introduction

Over the past five years, multiple lines of evidence have shown that low-density lipoprotein cholesterol (LDL-C) drives the development of atherosclerotic cardiovascular diseases (ASCVDs) [1–3]. With numerous studies having shown that LDL-C-lowering therapies have been beneficial in lowering the risk of ASCVDs [2, 3], LDL-C has become the primary target for lipid management; therefore, several international guidelines recommend intensifying LDL-C reduction efforts [4–6].

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Among various LDL-C-lowering therapies, statins are the first-line therapy for both primary and secondary prevention of ASCVDs, including acute coronary syndrome (ACS) [5, 7, 8]. Since the clinical benefits of statins have been well-established in the setting of ACS, current guidelines endorse the effective and prompt use of statins [9]. In particular, in acute myocardial infarction (AMI), one of the most severe forms of ACS that requires timely reperfusion, rapid optimized medical treatment may benefit greatly from its initiation [10–13]. Furthermore, the benefits of statins appear to extend even to patients with AMI and extremely low LDL-C levels [11, 12].

These benefits of statins in patients with AMI are attributed not only to their LDL-C-lowering effects but also to their diverse biological effects on the cardiovascular system [14, 15]. Nonetheless, a significant gap exists in clinical evidence concerning comparative outcomes according to differential statin intensity in patients with AMI and extremely low LDL-C levels. Since these patients are expected to have a lesser magnitude of absolute or relative reduction in LDL-C levels, the difference in the clinical outcomes of high-intensity statins versus those of moderate-intensity statins may be attenuated in this population.

Therefore, in this study, the aim was to evaluate the association between differential statin intensity and clinical outcomes in AMI patients with extremely low LDL-C levels.

Methods

Korean nationwide multicenter AMI cohort — the Korea Acute Myocardial Infarction Registry-V (KAMIR-V) registry

This study was a *post-hoc* analysis of a subgroup of patients with AMI from the KAMIR-V, which is a Korean nationwide observational cohort (from January 2016 to June 2020). The KAMIR-V registry involved participation of 33 tertiary cardiovascular institutions capable of performing percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery [16]. The study protocol of the KAMIR-V registry was designed in accordance with the Declaration of Helsinki 2013 and was approved by the ethics committee or institutional review board of each participating institution [16]. The requirement for informed consent was waived owing to the retrospective nature of the study. These registries have not been registered on ClinicalTrials.gov because of the nature of observational studies.

Study scheme and population

A total of 15,501 patients with AMI were initially selected from the KAMIR-V registry. After exclusion of (a) patients with LDL-C levels ≥ 55 mg/dL, (b) patients who did not survive during the index hospitalization, and (c) patients treated with no statins, 752 patients were ultimately enrolled. These patients were allocated to two groups according to statin intensity: (a) high-intensity statin group (n = 384) and (b) moderate-intensity statin group (n = 368) (Fig. 1). The research reported in this paper adhered to CONSORT guidelines.

Definition of high- and moderate-intensity statins

The LDL-C-lowering agents available for statistical analysis included statins and ezetimibe. In this study, high-intensity statins were defined as ≥ 40 mg per day of atorvastatin or ≥ 20 mg per day of rosuvastatin, in accordance with the current guidelines [5].

Definition of AMI

Regarding the diagnostic criteria of the current guidelines [4, 6], AMI was defined as ischemic myocardial injury evidenced by an increase in cardiac biomarker levels and at least one of the following: (a) myocardial ischemia-related clinical symptoms or signs, (b) myocardial ischemia-related abnormalities found on 12-lead surface electrocardiogram (ECG) suggesting myocardial ischemia, and (c) any manifestations suggesting either a lack of myocardial perfusion or regional wall motion abnormalities on cardiovascular imaging modalities. ST-segment elevation myocardial infarction (STEMI) was defined as AMI with newly detected ST-segment elevation in at least two continuous leads on 12-lead surface ECG [4, 6].

Definition of other baseline covariates

Definitions of covariates in the baseline characteristics were summarized in a previously published article based on the KAMIR-V registry [17]. The patient-reported smoking status was categorized as smoker (current smoker or ex-smoker) versus nonsmoker. The body mass index (BMI) was computed based on the patient's weight and height. Medical history included hypertension, diabetes mellitus, dyslipidemia, prior coronary artery disease, and prior cerebrovascular accident (CVA). Left ventricular systolic function was evaluated based on left ventricular ejection fraction measured using two-dimensional transthoracic echocardiography. The final diagnoses included both STEMI and non-STEMI cases. The discharge medications

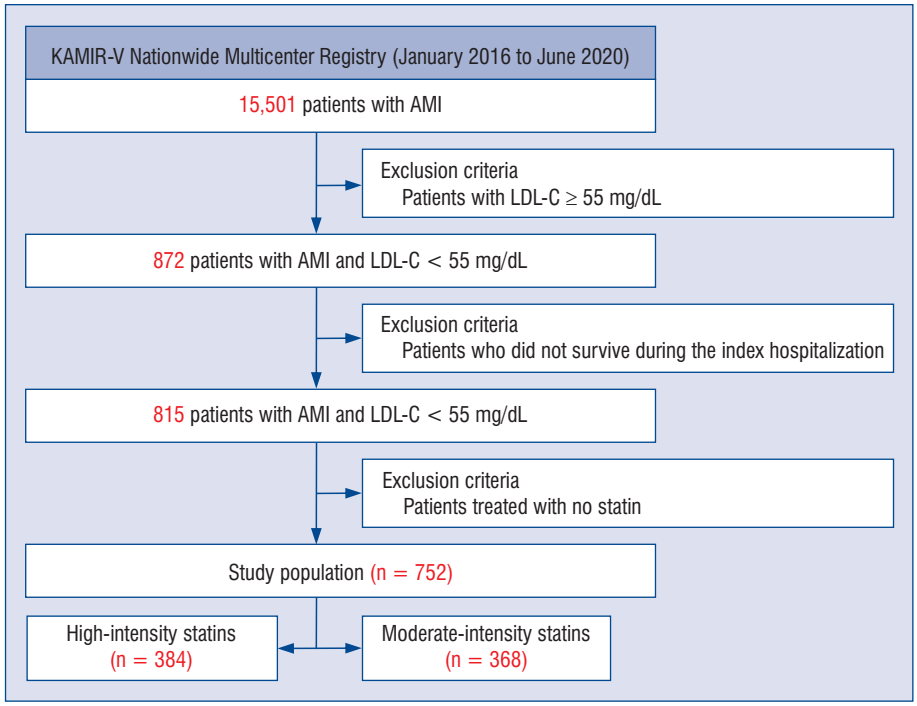

Figure 1. Flowchart of the study. AMI — acute myocardial infarction; KAMIR-V — Korea Acute Myocardial Infarction Registry-V; LDL-C — low-density lipoprotein cholesterol

of interest included aspirin, P2Y12 inhibitors, beta-blockers, renin-angiotensin-aldosterone system inhibitors, and ezetimibe.

Left main coronary artery (LMCA) disease was defined as ≥ 50% diameter stenosis of the LMCA, whereas multivessel disease was defined as LMCA disease along with ≥ 70% diameter stenosis of one epicardial coronary artery or ≥ 70% diameter stenosis of two or more epicardial coronary arteries. Antegrade intracoronary flow was quantitatively stratified by the Thrombolysis in Myocardial Infarction (TIMI) flow grade [18, 19]. Intracoronary imaging during PCI was defined as the use of either intravascular ultrasound or optical coherence tomography.

Treatment outcomes and follow-up

Differences in treatment outcomes between the two groups were assessed. The primary outcome was the occurrence of 1-year major adverse cardiac and cerebrovascular events (MACCEs), defined as all-cause death, a composite of all-cause death, nonfatal myocardial infarction (NFMI), any revascularization, CVA, and stent thrombosis. Revascularization was defined as PCI or CABG.

All participants were instructed to complete the follow-up for approximately 12 months, and the follow-up was censored on the date of the study outcome, date of death, or end of the study period. As stated in a previously published article, clinical follow-ups were conducted via outpatient visits or whenever any adverse cardiovascular events occurred [20].

Exploratory outcomes related to the control of LDL-C levels

In addition to assessing the 1-year treatment outcomes, the degree of control of LDL-C levels in patients using statins of two different intensities were compared. They included two different LDL-C target goals and LDL-C changes from baseline during the 1-year follow-up interval. The absolute LDL-C target goal was defined as an LDL-C level < 70 mg/dL, whereas the relative LDL-C target goal was defined as a reduction in the LDL-C level from an initial level of > 50%. These definitions are based on the International Lipid Management Guidelines of the 2016 European Society of Cardiology/European Atherosclerosis Society and the 2018 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines [5, 21].

Statistical analysis

Data manipulation and analyses were executed using SPSS version 25.0 (SPSS Inc., Armonk, NY, United States) and STATA version 15.0 (StataCorp,

College Station, TX, United States). Continuous variables are described as means and standard deviations and were analyzed using the student t-test or Mann–Whitney U test, whereas categorical variables are described as numbers with percentages and were analyzed using Pearson's chi-square test, the Fisher exact test, or Mantel––Haenszel linear-by-linear association. Statistical significance was defined as $p < 0.05$.

Because differences in baseline covariates influence treatment outcomes, propensity score matching (PSM) was performed to reduce the effects of selection bias or confounders. Propensity scores were calculated using 31 baseline covariates of interest (age, sex, smoking history, use of emergency medical service, Killip functional class, body mass index, past medical history, family history of coronary artery disease, serum creatinine level, left ventricular ejection fraction, a final diagnosis, discharge medications, LMCA disease, multivessel disease, infarct-related artery, the ACC/AHA lesion characteristics, TIMI coronary flow, use of intracoronary imaging, and type of PCI strategies), and the standardized mean differences post-PSM were < 25% for all matched background covariates.

In addition, a multivariable Cox proportional hazards regression model was used to determine the association between the differential statin intensity and clinical outcomes in the study population. Diverse Cox models were used to assess the robustness and consistency of the findings.

Statement of human rights

The present study adhered to the principles of the Declaration of Helsinki developed by the World Medical Association. The study protocol was reviewed and approved by the Institutional Review Board of Chonnam National University Hospital (IRB No. CNUH-2023-361). The requirement for informed consent was waived due to the retrospective nature of this study.

Results

Baseline patient characteristics

Among the 752 study participants, 384 (51.1%) received high-intensity statins and 368 (48.9%) received moderate-intensity statins. Table 1A summarizes the baseline clinicopathological characteristics of the study participants. Notably, the high-intensity statin group was characterized by a younger age, a higher prevalence of cigarette smoking, and elevated LDL-C levels, but it exhibited a lower likelihood of having prior CVA and receiving ezetimibe compared with that in the moderate-intensity statin group. Table 1B summarizes the baseline angiographic and procedural characteristics of patients. This demonstrates that the high-intensity statin group underwent more intracoronary imaging and stent implantation procedures than did their counterparts. Importantly, these group-by-group differences were statistically significant after PSM analysis.

Treatment outcomes

Among the study population, 51 patients were lost to follow-up, resulting in the analysis of a total of 701 study participants for treatment outcomes. The incidence of all treatment outcomes and their association with statin intensity are summarized in Table 2. The median follow-up duration was 360 days. The incidences of all treatment outcomes were statistically similar between both the groups. Compared with the moderate-intensity statin group, the high-intensity statin group had a comparable risk of each treatment outcome in all Cox models and PSM-adjusted analyses. As illustrated in Figures 2 and 3, the cumulative incidences of treatment outcomes were comparable between the two groups in both the pre- and post-PSM analyses.

Discussion

This study used data from Korean AMI patients with extremely low LDL-C levels treated with either high- or moderate-intensity statins from a Korean nationwide multicenter observational cohort and then evaluated 1-year treatment outcomes. The main finding was that treatment with moderate-intensity statins seemed to have outcomes comparable to those of treatment with high-intensity statins.

Cholesterol is the major structural element of human cell membranes [22, 23], and serves as the direct precursor of both bile acids and steroid hormones [23]. Nonetheless, excessively high cholesterol levels are associated with elevated risk of cardiovascular diseases, as endorsed in many landmark trials from the Framingham Heart Study and the Multiple Risk Factor Intervention Trial [24–26]. Despite dietary sources contributing to cholesterol levels, approximately two-thirds of the body's cholesterol is synthesized in the liver [27]. Hence, the inhibition of this biosynthesis pathway has been recognized as the key therapeutic target for altering plasma cholesterol levels [27].

In the cholesterol biosynthesis pathway, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)

Table 1. Baseline characteristics*

	Before propensity score matching			After propensity score matching		
	High--intensity statins	Moderate--intensity statins	P-value	High--intensity statins	Moderate--intensity statins	P-value
	(n = 384)	(n = 368)		(n = 170)	(n = 170)	
Clinicodemographic characteristics						
Demographics						
Age ≥ 75 years	112 (29.2)	137 (37.2)	0.019	63 (37.1)	54 (31.8)	0.304
Male sex	299 (77.9)	280 (76.1)	0.563	132 (77.7)	133 (78.2)	0.896
Smoking history	208 (56.5)	166 (47.7)	0.018	90 (52.9)	86 (50.6)	0.664
Use of EMS	78 (20.3)	73 (19.8)	0.871	36 (21.2)	36 (21.2)	1.000
Killip class III–IV	44 (11.5)	57 (15.5)	0.105	22 (12.9)	23 (13.5)	0.873
BMI ≥ 25 kg/m^2	119 (32.9)	114 (33.5)	0.854	58 (34.1)	61 (35.9)	0.733
Past medical history						
Hypertension	264 (68.8)	253 (68.8)	1.000	115 (67.7)	119 (70.0)	0.640
Diabetes mellitus	197 (51.3)	208 (56.5)	0.151	91 (53.5)	98 (57.7)	0.445
Dyslipidemia	111 (28.9)	89 (24.2)	0.143	49 (28.8)	52 (30.6)	0.722
Prior CAD	128 (33.3)	131 (35.6)	0.514	59 (34.7)	60 (35.3)	0.909
Prior CVA	35 (9.2)	52 (14.3)	0.030	23 (13.5)	23 (13.5)	1.000
Family history of CAD	29 (7.8)	24 (6.6)	0.542	9 (5.3)	10 (5.9)	0.813
LDL-C level, mg/dL	44.42 ± 8.89	42.63 ± 9.56	0.008	43.64 ± 9.59	43.84 ± 8.79	0.841
Serum creatinine ≥ 1.5 mg/dL	77 (20.1)	95 (26.0)	0.054	37 (21.8)	39 (22.9)	0.795
LVEF < 40%	54 (14.4)	63 (17.8)	0.206	29 (17.1)	26 (15.3)	0.659
STEMI as a final diagnosis	157 (40.9)	130 (35.3)	0.117	73 (42.9)	74 (43.5)	0.913
Discharge medications						
Aspirin	382 (99.5)	366 (99.5)	1.000	170 (100.0)	170 (100.0)	–
P2Y12 inhibitors	379 (98.7)	363 (98.6)	1.000	170 (100.0)	170 (100.0)	–
Beta-blockers	289 (75.3)	272 (73.9)	0.671	132 (77.7)	132 (77.7)	1.000
RAAS inhibitors	275 (71.6)	262 (71.2)	0.899	130 (76.5)	125 (73.5)	0.531
Ezetimibe	18 (4.7)	64 (17.4)	< 0.001	15 (8.8)	11 (6.5)	0.414
Angiographic and procedural characteristics						
Angiographic findings						
LMCA disease	32 (8.4)	35 (9.6)	0.562	12 (7.1)	17 (10.0)	0.332
Multivessel disease	209 (54.7)	202 (55.3)	0.863	105 (61.8)	109 (64.1)	0.653
Infarct-related artery			0.948			0.828
LMCA or LAD	191 (53.6)	165 (53.4)		94 (55.3)	92 (54.1)	
LCX or RCA	165 (46.4)	144 (46.6)		76 (44.7)	78 (45.9)	
ACC/AHA lesion type B2/C	277 (82.2)	249 (83.8)	0.583	133 (78.2)	136 (80.0)	0.689
TIMI 0–I as the initial coronary flow	167 (47.8)	155 (51.0)	0.424	86 (50.6)	84 (49.4)	0.828
Procedural findings						
Use of thrombolysis	3 (0.8)	0 (0.0)	0.249	0 (0.0)	0 (0.0)	–
Use of intracoronary imaging	127 (33.1)	62 (16.8)	< 0.001	38 (22.3)	42 (24.7)	0.609
Type of PCI strategies			0.001			1.000
Stent implantation	321 (83.6)	279 (75.8)		154 (90.6)	155 (91.2)	
Balloon angioplasty alone	31 (8.1)	25 (6.8)		14 (8.2)	13 (7.6)	
Others	32 (8.3)	64 (17.4)		2 (1.2)	2 (1.2)	

*Values are presented as percentages (numbers) for categorical values and as means ± standard deviations for continuous values; ACC/AHA — the American College of Cardiology/the American Heart Association; BMI — body mass index; CAD — coronary artery disease; CVA — cerebrovascular accident; EMS — emergency medical service; LAD — left anterior descending coronary artery; LCX — left circumflex coronary artery; LMCA — left main coronary artery; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention; RAAS — renin-angiotensin-aldosterone system; RCA — right coronary artery; STEMI — ST-segment elevation myocardial infarction; TIMI — thrombolysis in myocardial infarction

Table 2. HRs and 95% CI showing associations between high- and moderate-intensity statins groups and the incidence of treatment outcomes with respect to each Cox model and PSM model

	Total participants	Events		Model 1*	Model 2**	Model 3***	Model 4	PSM-adjusted analysis
		High-intensity statins	Moderate-intensity statins					
	701	362	339	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
MACCE	94 (13.4)	42 (11.6)	52 (15.3)	1.33 (0.88–1.99)	1.25 (0.83–1.88)	1.01 (0.63–1.64)	0.90 (0.54–1.53)	0.90 (0.49–1.65)
All-cause death	36 (5.1)	15 (4.1)	21 (6.2)	1.49 (0.77–2.90)	1.19 (0.61–2.32)	1.08 (0.49–2.35)	0.89 (0.36–2.19)	0.88 (0.32–2.43)
NFMI	21 (3.0)	10 (2.8)	11 (3.2)	1.18 (0.50–2.77)	1.23 (0.52–2.90)	1.41 (0.44–4.49)	1.34 (0.38–4.71)	2.03 (0.51–8.12)
Any re-vascular-ization	44 (6.3)	24 (6.6)	20 (5.9)	0.88 (0.49–1.59)	0.89 (0.49–1.61)	0.66 (0.32–1.33)	0.84 (0.39–1.81)	0.63 (0.27–1.45)
CVA	10 (1.4)	4 (1.1)	6 (1.8)	1.60 (0.45–5.66)	1.43 (0.40–5.09)	0.64 (0.11–3.58)	0.10 (0.00–4.07)	0.50 (0.05–5.56)
Stent thrombo-sis	8 (1.1)	3 (0.8)	5 (1.5)	1.79 (0.43–7.51)	1.83 (0.44–7.70)	3.13 (0.43–22.73)	2.94 (0.25–34.14)	1.53 (0.26–9.14)

*Model 1 — crude model, **Model 2 — adjusted for age and sex; ***Model 3 — adjusted for all components in Model 2 plus use of EMS, Killip functional class, BMI, smoking status, past medical history, family history of CAD, LDL-C, serum creatinine level, LVEF, final diagnosis, and discharge medications; ****Model 4 — adjusted for all components in Model 3 plus angiographic and procedural characteristic variables; BMI — body mass index; CAD — coronary artery disease; CI — confidence interval; CVA — cerebrovascular accident; EMS — emergency medical service; HR — hazard ratio; IDR — ischemia-driven readmission; LDL-C — low-density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; MACCE — major adverse cardiac and cerebrovascular event; NFMI — nonfatal myocardial infarction; PSM — propensity score matching

reductase stands as the rate-limiting step, catalyzing the conversion of HMG-CoA to mevalonate, which is further metabolized into farnesyl pyrophosphate, a precursor of cholesterol and sterol [28]. Statins reversibly bind to the active site of HMG-CoA reductase then inhibit endogenous cholesterol biosynthesis [27]. Many clinical trials and analyses have proven that statins have their beneficial effects in both the primary and secondary prevention of clinical ASCVDs, including ACS [27, 29]. Hence, current guidelines endorse recommendations for initiating statins for targeting the optimal therapeutic threshold of an LDL-C level < 55 mg/dL in very-high-risk patients with clinical ASCVDs [30, 31]. Given the remarkable efficacy of statins in lowering LDL-C levels, they have rapidly become the standard of care for patients with ACS, with recommendations for initiating high-intensity statins as quickly as possible upon presentation in all ACS patients [4, 6].

Furthermore, several studies have explored the clinical benefits of statins in patients with ACS who already have sufficiently low LDL-C levels, attaining or nearly attaining the LDL-C target goal [11, 12]. Lee and his colleagues showed that statins are associated with a lower incidence of the composite of all-cause mortality, NFMI, and coronary revascularization among patients with AMI and LDL-C levels < 70 mg/dL [11]. Additionally, Piao and his colleagues reported that these benefits of statins extend even to patients with AMI and LDL-C levels < 50 mg/dL [12]. Results from these two studies are consistent with those of a comparative study published by Leeper and his colleagues [32]. Despite the precise mechanisms behind these benefits not being fully elucidated, authors from these two clinical studies speculated that these benefits may be driven by their cholesterol-independent or "pleiotropic effects" [11, 12]. In addition to their cholesterol-dependent effects, statins improve endothelial function, promote atherosclerotic plaque stabilization, reduce inflammation, and inhibit thrombogenic responses [27], which may contribute to clinical benefits in patients with extremely low LDL-C levels.

Despite the aforementioned clinical advantages of statin therapy and the compelling evidence of a graded association between statin

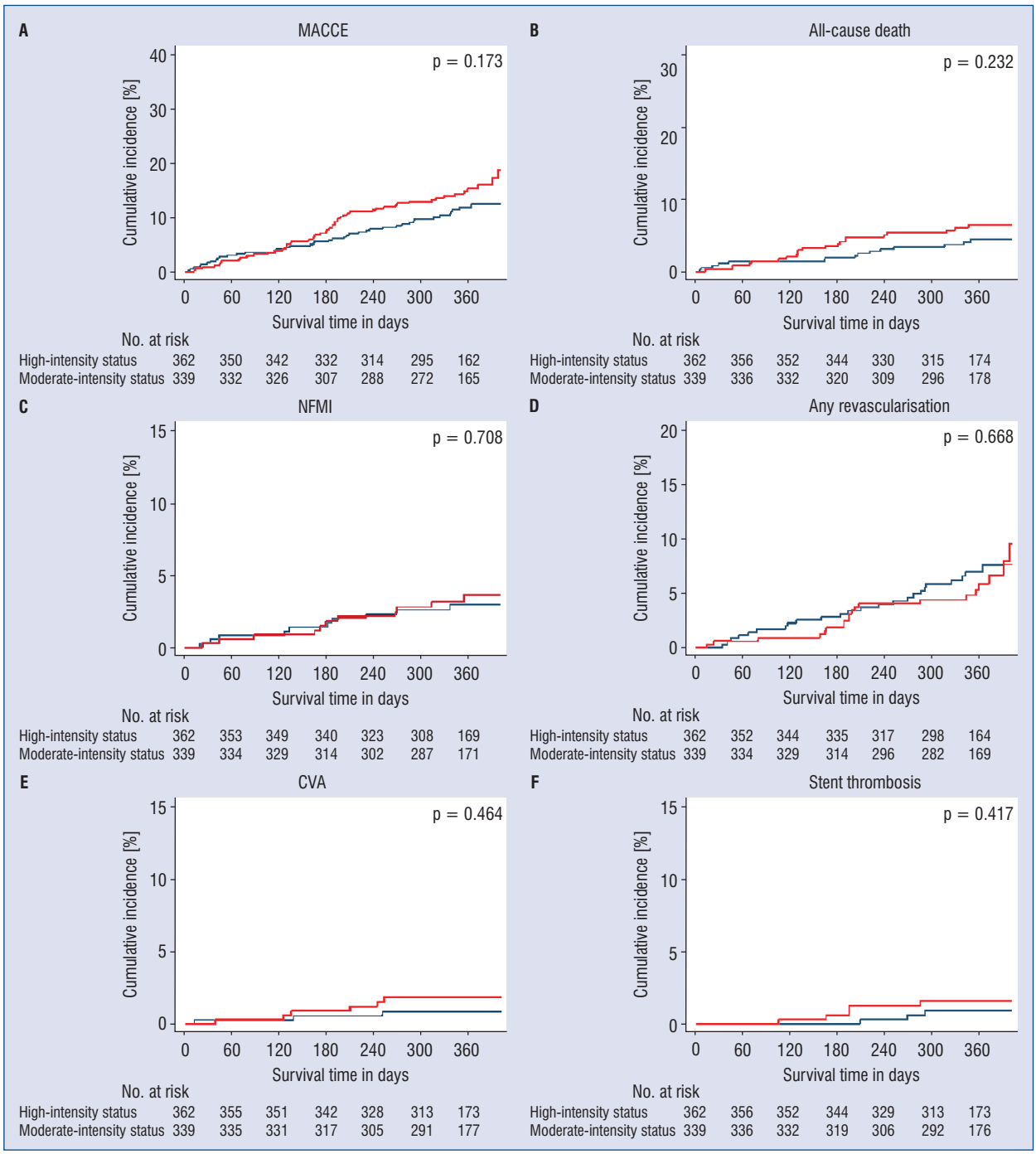

Figure 2. Cumulative incidence of each treatment outcome; CVA — cerebrovascular accident; MACCE — major adverse cardiac and cerebrovascular events; NFMI — nonfatal myocardial infarction

intensity and survival outcomes in patients with ASCVDs [33, 34], the clinical efficacy of high-intensity statins has not been well established in patients with extremely low LDL-C levels. Moreover, considering statin's "pleiotropic effects", it can be reasonably be hypothesized that high-intensity statins may exert better survival outcomes than moderate-intensity statins. Nonetheless, the present analysis underscores the fact that this graded association may be attenuated in patients with AMI and extremely low LDL-C levels. That is, although high-intensity statin users had a numerically lower risk of MACCE than did their counterparts, the treatment outcomes

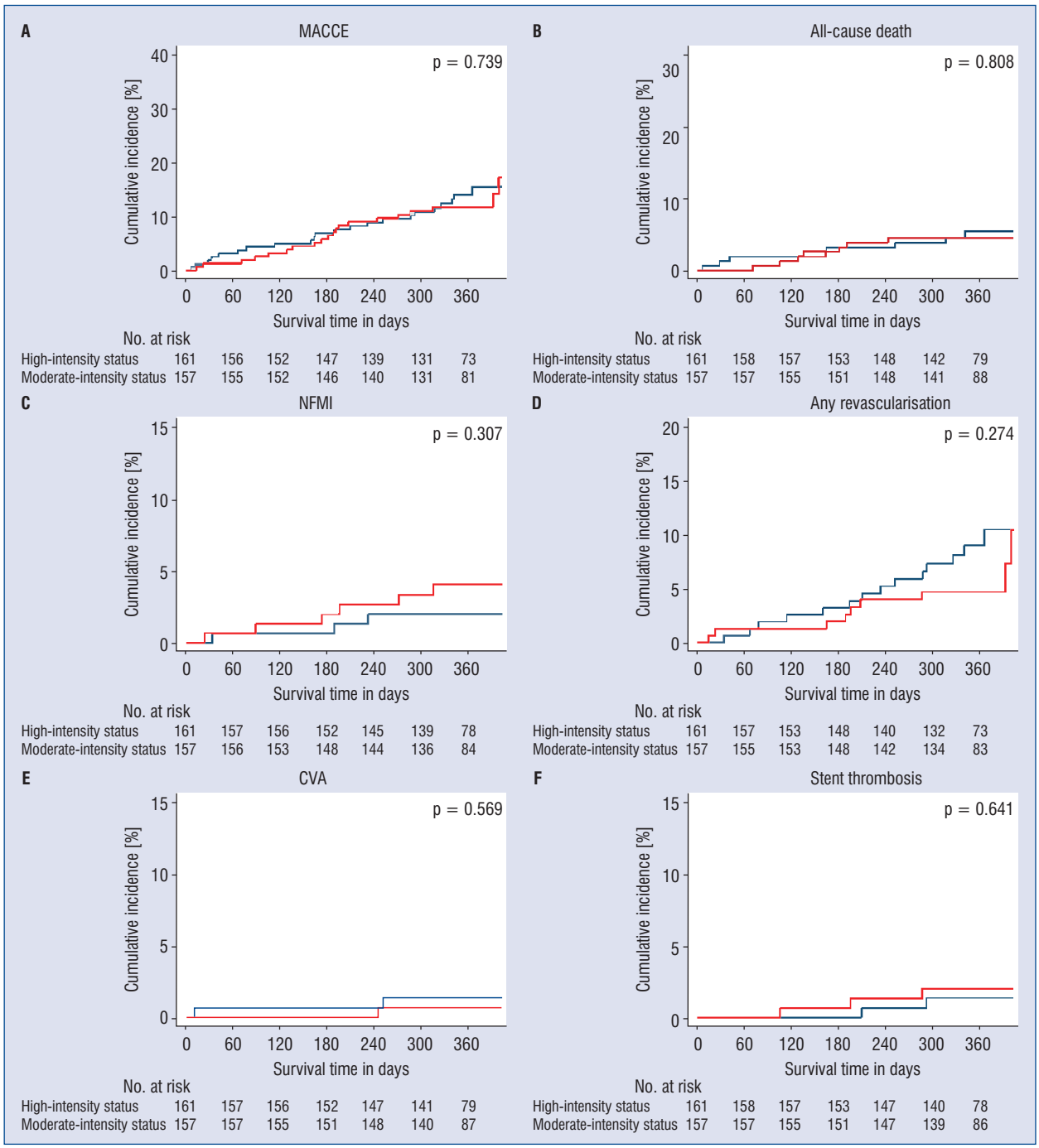

Figure 3. Cumulative incidence of each treatment outcome (after PSM); CVA — cerebrovascular accident; MACCE — major adverse cardiac and cerebrovascular events; NFMI — nonfatal myocardial infarction; PSM — propensity score matching

were statistically similar, irrespective of statin intensity. Primarily, it may be driven by similar one-year LDL-C levels. In other words, as shown in Table 3, two different statin-intensity groups demonstrated similar results in terms of change of LDL-C from baseline and attainment rates of LDL-C target goals. These similarities of LDL-C-lowering effects seem to have contributed to the similar incidence of MACCEs, as they outweighed different potentials of aforementioned "pleiotropic effects".

Moreover, Cho et al. [35] reported that attainment of the relative LDL-C target goal would be of superior importance to that of the absolute LDL-C

Table 3. One-year exploratory outcomes in propensity score-matched patients

Characteristics	Before PSM			After PSM		
	High-intensity statins	Moderate-intensity statins	P-value	High-intensity statins	Moderate-intensity statins	P-value
	(n = 181)	(n = 144)		(n = 81)	(n = 78)	
The LDL-C target goals						
Absolute target goal	92 (50.8)	80 (55.6)	0.396	46 (56.8)	40 (51.3)	0.486
Relative target goal	1 (0.5)	4 (2.8)	0.175	1 (1.2)	2 (2.6)	0.616
Changes of LDL-C levels from baseline	11.10 ± 18.68	10.85 ± 20.61	0.911	10.30 ± 19.29	10.84 ± 20.20	0.863

LDL-C — low-density lipoprotein cholesterol; PSM — propensity score matching

target goal, these observations may be moderately circumstantiated by the very poor attainment of the percent reduction in LDL-C levels in this population. That is, although more than half of the patients in both groups attained the absolute target goals of LDL-C, they had extremely low attainment rates of the relative target goals of LDL-C (0.5% vs. 2.8%), which may weaken the superior efficacy of high-intensity statins highlighted in previous studies.

Meanwhile, focus should be on the different utilization rates of ezetimibe, a non-statin LDL-C-lowering agent. Given that the combination of moderate-intensity statins and ezetimibe demonstrated comparable clinical efficacy to that of high-intensity statin monotherapy [36], and that the current study showed that the moderate-intensity statin group received more ezetimibe than did its counterparts, it is theoretically possible that these similarities may have been contaminated by interventions in group-by-group proportional disparities of ezetimibe treatment, although they were statistically attenuated in post-PSM analysis. Notwithstanding, an additional analysis demonstrated that similar trends also persisted consistently in the dataset excluding ezetimibe (**Suppl. Table 1**).

According to a PSM-based post-hoc analysis of the ODYSSEY OUTCOMES trials, patients with two strata of extremely low LDL-C levels, those with LDL-C levels of 25–50 mg/dL and those with levels below 25 mg/dL, showed a similar absolute risk reduction with alirocumab [37]. Herein, additional analysis of clinical outcomes per tertiles of LDL-C values may align with these data (**Suppl. Table 2**).

Interestingly, a *post-hoc* retrospective analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) cohort, an earlier version of the KAMIR-V cohort, demonstrated the dose-dependent efficacy of statin therapy in Korean AMI patients with baseline LDL-C levels < 70 mg/dL [38]. In other words, patients receiving a more intensive statin regimen had better clinical prognosis with significantly lower LDL-C levels than did those receiving less-intensive statin regimen. However, the present study showed that this was not evident in the more stringent LDL-C target level of < 55 mg/dL. Although not fully explicable, this contradiction may be explained by another study conducted based on the KAMIR-NIH cohort [39], which suggested that a further reduction in the LDL-C target to < 55 mg/dL did not show additional clinical benefits in patients with AMI. Given that an East Asian descent is considered a risk factor for statin intolerance [40], and since the current study encompasses Korean patients, who are generally considered part of a northeast Asian group, the present study may support the notion that the use of moderate-intensity statins is also one of the reasonable treatment options and is associated with treatment outcomes comparable to those of high-intensity statins for patients with very low LDL-C levels at presentation. Nonetheless, further investigations are required to elucidate this not a fully explicable issue.

This study had some limitations. First, each treatment outcome may have been affected by confounders based on group-by-group differences in the baseline patient characteristics. To minimize selection bias, while diligently adjusted for these disparities using various Cox models and PSM, the possibility of residual or unmeasured

confounders or missing data cannot be entirely excluded. Second, although several recent clinical studies have emphasized that cumulative LDL-C and time-weighted average LDL-C levels are related to the risk of ASCVDs [41, 42], the present analysis did not provide detailed information regarding previous cumulative exposure to LDL-C. Upon further investigation, the duration and prior treatment of dyslipidemia in both the groups, demonstrating comparable group-by-group results (**Suppl. Table 3**). Third, no information about other lipid-lowering therapeutics such as proprotein convertase subtilisin/kexin type 9 inhibitors or bempedoic acid was provided. Finally, because a causal relationship could not be fully confirmed owing to the retrospective and non-randomized nature of this study, the results should be interpreted with caution.

Conclusions

In conclusion, despite compelling evidence of a graded association between statin intensity and survival outcomes in patients with ASCVD, the variation in statin intensity appeared to have no significant impact on clinical outcomes in AMI patients with LDL-C levels < 55 mg/dL. Further randomized prospective studies should be conducted.

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