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Impact of statin intensity on adverse cardiac and cerebrovascular events in older adult patients with myocardial infarction

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ABSTRACT

BACKGROUND There is insufficient evidence regarding the effect of high-intensity statin therapy in older adults. This study aimed to investigate the effects of high-intensity statin treatment on the clinical outcomes in older adults with myocardial infarction (MI).

METHODS Consecutive patients with MI aged at least 75 years were analyzed retrospectively. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause death, MI, rehospitalization due to unstable angina, repeat revascularization, and ischemic stroke. The high-intensity group was compared to the low-to-moderate intensity group in the propensity score-matched cohort.

RESULTS Average age of total 546 patients was 81 years. Among them, 84% of patients underwent percutaneous coronary intervention. The unadjusted seven-year MACCE rate differed by statin intensity (high-intensity statin group: 38%, moderate-intensity statin group: 42%, low-intensity statin group: 56%, and no-statin group: 61%, P = 0.004). However, among these groups, many baseline characteristics were significantly different. Among the 74 propensity score-matched pairs, which lacked any significant differences in all baseline characteristics, the high-intensity group had a significantly lower rate of MACCE than the low-to-moderate intensity group (37% *vs.* 53%, P = 0.047). Follow-up low-density lipoprotein cholesterol levels were significantly lower in the high-intensity group than that in the low-to-moderate intensity group (69.4 ± 16.0 mg/dL *vs.* 77.9 ± 25.9 mg/dL, P = 0.026).

CONCLUSIONS In older adult patients with MI, the use of high-intensity statin caused significantly less occurrence of MACCE in comparison to that in low-to-moderate intensity for up to seven years of follow-up.

The prevalence and mortality of atherosclerotic cardiovascular disease increase with age.[1] The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol recommend moderate-intensity statin as secondary prevention to reduce atherosclerotic cardiovascular risk in adults aged over 75 years.[2] Prior to the publication of the guidelines, statins were prescribed based on risk factors and cholesterol levels according to the National Cholesterol Education Program Adult Treatment Panel III guideline.[3] The guideline recommended lowering low-density lipoprotein cholesterol (LDL-C) to less than 100 mg/dL in patients with coronary heart disease, and this concept was contained in the 2004 ACC/AHA guidelines for the management of patients with ST-segment elevation myocardial infarction (MI).[4] In 2004, National Cholesterol Education Program released a modification report, adding an optional goal of LDL-C less than 70 mg/dL in very high risk patients.[5] And, this optional goal was included in the 2007 ACC/AHA

guidelines for the management of patients with unstable angina (UA)/non-ST-segment elevation MI.[6]

Although more recent guidelines recommend high-intensity statin for high-risk older adult MI patients,[7,8] the supporting reference showed only a marginal reduction in the risk of major vascular events.[9,10] Moreover, the patients enrolled in the randomized trials comparing statin intensities were not older than 75 years or 80 years.[11–14] Therefore, there is a lack of evidence on the use of high-intensity statins for patients with MI at least 75 years old and whether a high-intensity statin is sufficiently effective for secondary prevention in comparison with low-to-moderate intensity statins. Therefore, we aimed to investigate the prescription intensities of statins in real-world practice and the long-term cardiac and cerebrovascular outcomes according to statin intensity in older adult patients with MI.

METHODS

Selection of Study Patients

We enrolled consecutive patients aged ≥ 75 years admitted with MI between 2005 and 2015 at the Seoul National University Bundang Hospital, Seongnam, South Korea. Irrespective of ST-segment changes, MI included type I MI, according to its universal definition.[15] Those who died in-hospital and within thirty days after discharge were excluded. The study protocol was approved by the Institutional Review Board (No.B-2009-636-101), and written informed consent was waived by the Institutional Review Board because of the retrospective design and minimal hazard to the subjects. The study complied with the principles of the Declaration of Helsinki.

Classification of Study Patients

Similar to the 2013 ACC/AHA guideline on the treatment of blood cholesterol, statin intensity was classified as either high-intensity, moderate-intensity, or low-intensity. Atorvastatin of 40–80 mg and rosuvastatin of 20–40 mg were categorized as high-intensity statins, and simvastatin of 10 mg, pravastatin of 10–20 mg, lovastatin of 20 mg, fluvastatin of 20–40 mg, and pitavastatin of 1 mg were classified in low-intensity statins, and the others were categorized as moderate-intensity statins. Data on statin intensity were acquired as the main intensity of three years, which is the intensity of statin prescribed for the longest period within the first three years of follow-up after discharge from the index hospitalization. Patients were classified into four groups according to their three-year main intensity: high-intensity statin group, moderate-intensity statin group, low-intensity statin group, and no-statin group. Non-statin lipid-lowering agents, including Niemann-Pick C1-like 1 inhibitor or fibric acid derivatives, were not considered to affect the intensity-based categorization of statins significantly. Furthermore, proprotein convertase subtilisin/kexin type 9 inhibitors were not introduced to the country until the end of the enrollment period.

Clinical Outcomes

The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), defined as a composite endpoint of all-cause death, recurrent MI, rehospitalization due to UA, repeat revascularization (including percutaneous coronary intervention and coronary artery bypass graft surgery), and ischemic stroke (including transient ischemic attack) during the follow-up period of thirty days to seven years after discharge. The secondary endpoints included the components of MACCE: all-cause death, recurrent MI, rehospitalization due to UA, repeat revascularization, ischemic stroke, and the last follow-up lipid profiles.

Data Acquisition and Analysis Scheme

The all-cause death data of all the study patients were collected by requesting the Ministry of Public Administration and Security the date of resident registration cancelation to avoid missing the deaths at home or other hospitals. Rehospitalization due to heart failure or non-cardiovascular cause was not classified as an occurrence of the study outcome events.

After analyzing the baseline characteristics and outcomes in the four unadjusted statin-intensity groups, we compared the outcomes in patients with low-to-moderate intensity statin versus high-intensity statin. Differences in baseline demographics and comorbid conditions were corrected through propensity score matching.

Statistical Analysis

The continuous variables are presented as mean ± SD, and the categorical variables are presented as

frequency or percentage. To compare the four statin groups, the Pearson's chi-squared test or Fisher's exact test was used for the categorical variables, while the one-way ANOVA or Kruskal-Wallis H test was used for the continuous variables. Kaplan-Meier analysis was performed to calculate the cumulative incidence of the primary and secondary outcomes.

To compare the variables of the high-intensity statin group and the low-to-moderate intensity statin group, the Pearson's chi-squared test or Fisher's exact test was used for the categorical variables, and Student's *t*-test or Mann-Whitney *U* test was used for the continuous variables.

Propensity score matching was initiated in 437 patients after excluding the no-statin group (n = 100), the patient without baseline coronary angiography (n = 1), the patient whose baseline body mass index data were missing (n = 1), and the patient without baseline lipid profile (n = 1). The matching variables comprised mostly of the baseline characteristics, including age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking history, prior MI, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke, prior congestive heart failure, prior chronic kidney disease, height, body weight, body mass index, admission systolic blood pressure, diastolic blood pressure, heart rate, Killip class, clinical diagnosis, troponin I, creatine kinase-MB isoform, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), LDL-C, plasma glucose, echocardiographic left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and left ventricular ejection fraction. One-to-one matching was performed for each group without replacement, and a caliper width with a standard deviation of 0.05 was used.

Baseline and follow-up lipid profiles were compared using the paired *t*-test after performing a normality test. Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (SPSS, Chicago, NY, USA), and graphs were drawn using R statistical version 3.6.

RESULTS

Baseline Patient Characteristics

Of the 2,753 patients admitted with MI, 665 patients were aged at least 75 years, with 119 patients dying in the hospital or within thirty days after discharge. Finally, 546 patients were included in this study (Figure 1). The average age of the whole study population was 81 years, and 51% of patients were male (Table 1). Among all the patients, 46% of patients had ST-segment elevation MI, 84% of patients underwent percutaneous coronary intervention, and 10% of patients underwent coronary artery bypass graft surgery. The proportions of Killip classes 3 and 4 were 14% and 8%, respectively.

Prescription Pattern of Statins

The proportion of high-intensity statin prescription at discharge was 24%. However, 35% of the patients had their statin intensity changed after discharge. The trends of the three-year main intensity according to discharge year showed that the pre-

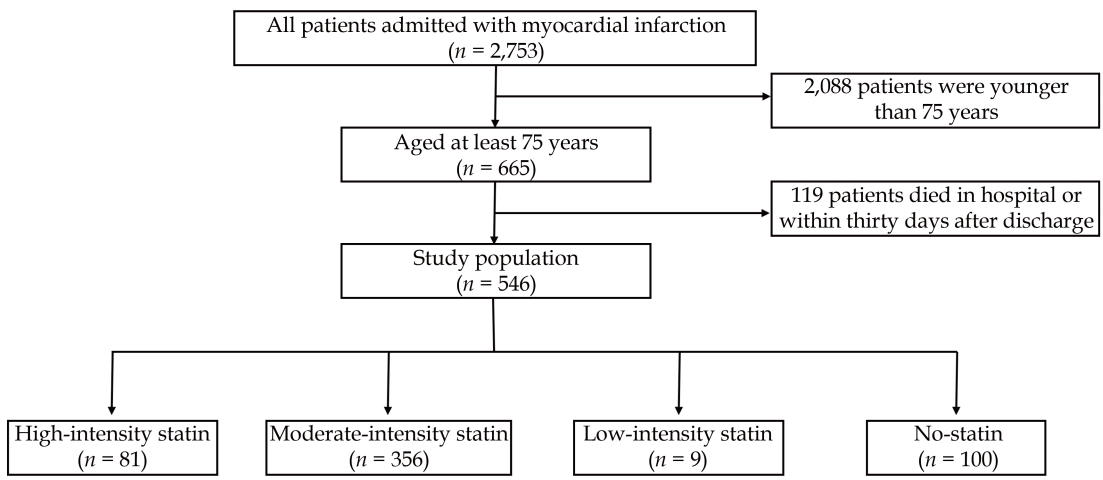

Figure 1 Flow chart of the study population selection.

scription of high-intensity statin significantly increased each year ($P < 0.001$) (Figure 2). Meanwhile, the proportion of high-intensity statin according to the three-year main intensity was not significantly different among the age groups divided by five years (75–79 years: 14%, 80–84 years: 17%, 85–89 years:

Table 1 Baseline characteristics of the whole study population.

Characteristics	High-intensity statin (*n* = 81)	Moderate-intensity statin (*n* = 356)	Low-intensity statin (*n* = 9)	No-statin (*n* = 100)	Total (*n* = 546)	*P*-value
General characteristics						
Age, yrs	80.3 ± 3.9	80.2 ± 4.3	83.1 ± 7.2	81.1 ± 5.1	80.5 ± 4.5	0.107
Sex, male	37 (45.7%)	184 (51.7%)	6 (66.7%)	50 (50.0%)	277 (50.7%)	0.595
Body mass index, kg/m^2	23.1 ± 3.4	22.8 ± 3.9	21.5 ± 4.2	21.3 ± 3.1	22.6 ± 3.8	0.002
Height, cm	157.7 ± 7.9	158.8 ± 8.8	161.1 ± 7.6	158.0 ± 9.8	158.5 ± 8.9	0.556
Weight, kg	57.3 ± 9.6	57.4 ± 11.2	56.3 ± 13.3	53.5 ± 10.4	56.7 ± 11.0	0.015
Lipid profiles						
Total cholesterol, mg/dL	173.4 ± 42.3	164.1 ± 39.9	133.4 ± 22.0	143.9 ± 41.3	161.3 ± 41.4	< 0.001
Triglyceride, mg/dL	99.0 ± 48.4	105.3 ± 64.4	69.9 ± 22.9	89.6 ± 56.6	100.9 ± 60.7	0.053
HDL-C, mg/dL	45.0 ± 9.2	44.2 ± 13.8	46.2 ± 12.2	43.2 ± 12.6	44.2 ± 12.9	0.779
LDL-C, mg/dL	106.4 ± 35.1	97.6 ± 33.2	67.8 ± 16.2	81.7 ± 34.0	95.6 ± 34.4	< 0.001
Clinical presentation						
STEMI/NSTEMI	40/41 (49.4%/50.6%)	163/193 (45.8%/54.2%)	6/3 (66.7%/33.3%)	41/59 (41.0%/59.0%)	250/296 (45.8%/54.2%)	0.403
Killip class I/II/III/IV	55/6/13/7 (67.9%/7.4%/16.0%/8.6%)	233/53/45/25 (65.4%/14.9%/12.6%/7.0%)	5/0/1/3 (55.6%/0/11.1%/33.3%)	60/14/19/7 (60.0%/14.0%/19.0%/7.0%)	353/73/78/42 (64.7%/13.4%/14.3%/7.7%)	0.087
Risk factors						
Hypertension	57 (70.4%)	232 (65.2%)	7 (77.8%)	70 (70.0%)	366 (67.0%)	0.607
Diabetes mellitus	22 (27.2%)	109 (30.6%)	2 (22.2%)	31 (31.0%)	164 (30.0%)	0.877
Dyslipidemia	20 (24.7%)	70 (19.7%)	0	16 (16.0%)	106 (19.4%)	0.224
Smoking current/former/never	10/20/51 (12.3%/24.7%/63.0%)	54/102/200 (15.2%/28.7%/56.2%)	2/3/4 (22.2%/33.3%/44.4%)	17/30/53 (17.0%/30.0%/53.0%)	83/155/308 (15.2%/28.4%/56.4%)	0.862
Prior MI	2 (2.5%)	20 (5.6%)	1 (11.1%)	8 (8.0%)	31 (5.7%)	0.382
Prior PCI	13 (16.0%)	50 (14.0%)	2 (22.2%)	8 (8.0%)	73 (13.4%)	0.291
Prior CABG	4 (4.9%)	9 (2.5%)	0	4 (4.0%)	17 (3.1%)	0.604
Prior stroke	7 (8.6%)	36 (10.1%)	2 (22.2%)	12 (12.0%)	57 (10.4%)	0.590
Prior CHF	2 (2.5%)	1 (0.3%)	0	5 (5.0%)	8 (1.5%)	0.005
Prior CKD	4 (4.9%)	19 (5.3%)	0	11 (11.0%)	34 (6.2%)	0.157
Laboratory findings						
CK-MB, ng/mL	56.7 ± 130.3	51.6 ± 102.1	58.8 ± 116.5	53.0 ± 84.1	52.8 ± 103.8	0.979
Troponin-I, ng/mL	75.9 ± 117.4	60.6 ± 94.0	49.1 ± 62.9	63.2 ± 111.6	63.2 ± 100.6	0.636
NT-proBNP, pg/mL	5231.5 ± 8794.3	5286.7 ± 11590.9	2812.1 ± 4426.8	9769.7 ± 21349.5	6055.3 ± 13584.0	0.044
Serum creatinine, mg/dL	1.16 ± 0.84	1.24 ± 0.96	1.06 ± 0.34	1.46 ± 1.19	1.27 ± 0.98	0.154
eGFR by MDRD, mL/min per 1.73 m^2	65.3 ± 25.9	62.7 ± 26.8	68.7 ± 26.4	57.6 ± 29.9	62.2 ± 27.3	0.216
Glucose, mg/dL	92.0 ± 28.6	88.3 ± 21.7	88.7 ± 18.5	87.6 ± 27.9	88.7 ± 24.0	0.618
Hemoglobin A1c, %	5.9 ± 0.7	5.9 ± 0.7	5.9 ± 0.5	5.9 ± 0.9	5.9 ± 0.7	0.674
LVEF, %	48.5 ± 13.1	51.2 ± 12.4	51.5 ± 16.2	48.7 ± 12.8	50.3 ± 12.7	0.164
LVEDD, mm	47.4 ± 5.3	47.7 ± 6.4	49.8 ± 11.7	47.3 ± 6.4	47.6 ± 6.3	0.686
LVESD, mm	34.0 ± 7.0	33.0 ± 7.5	35.7 ± 13.0	33.6 ± 7.3	33.3 ± 7.5	0.502

Continued

Characteristics	High-intensity statin (*n* = 81)	Moderate-intensity statin (*n* = 356)	Low-intensity statin (*n* = 9)	No-statin (*n* = 100)	Total (*n* = 546)	*P*-value
Systolic BP, mmHg	138.0 ± 29.0	138.3 ± 33.1	126.6 ± 27.2	138.0 ± 32.0	138.0 ± 32.2	0.760
Diastolic BP, mmHg	74.7 ± 19.5	74.4 ± 18.7	69.2 ± 14.2	74.0 ± 14.6	74.3 ± 18.1	0.856
Heart rate, beat/ mim	77.0 ± 19.8	77.1 ± 22.3	85.1 ± 33.6	83.0 ± 23.2	78.3 ± 22.4	0.086
CAG findings						
CAD extent 0/1/2/3 vessel disease	0/15/26/40 (0/18.5%/32.1%/49.4%)	1/87/109/159 (0.3%/24.4%/30.6%/44.7%)	0/3/3/2 (0/37.5%/37.5%/25.0%)	1/21/26/52 (1.0%/21.0%/26.0%/52.0%)	2/126/164/253 (0.4%/23.1%/30.1%/6.4%)	0.729
Left main disease	6 (7.4%)	30 (8.4%)	0	13 (13.0%)	49 (9.0%)	0.370
Treatment strategy						
Thrombolysis	1 (1.2%)	7 (2.0%)	0	4 (4.0%)	12 (2.2%)	0.542
PCI	73 (90.1%)	304 (85.4%)	7 (77.8%)	72 (72.0%)	456 (83.5%)	0.004
CABG	3 (3.7%)	31 (8.7%)	0	19 (19.0%)	53 (9.7%)	0.002
Discharge medication						
Aspirin	81 (100.0%)	355 (99.7%)	9 (100.0%)	98 (98.0%)	543 (99.5%)	0.186
$P2Y_{12}$ inhibitor	81 (100.0%)	346 (97.2%)	9 (100.0%)	96 (96.0%)	532 (97.4%)	0.351
Beta blocker	65 (80.2%)	233 (65.4%)	6 (66.7%)	58 (58.0%)	362 (66.3%)	0.017
ACEI	50 (61.7%)	210 (59.0%)	7 (77.8%)	47 (47.0%)	314 (57.5%)	0.074
ARB	14 (17.3%)	78 (21.9%)	2 (22.2%)	27 (27.0%)	121 (22.2%)	0.478
ACEI or ARB	62 (76.5%)	278 (78.1%)	9 (100.0%)	72 (72.0%)	421 (77.1%)	0.225
Calcium channel blocker	11 (13.6%)	60 (16.9%)	0	23 (23.0%)	94 (17.2%)	0.172
Loop diuretics	27 (33.3%)	162 (45.5%)	3 (33.3%)	54 (54.0%)	246 (45.1%)	0.041
Spironolactone	11 (13.6%)	44 (12.4%)	1 (11.1%)	18 (18.0%)	74 (13.6%)	0.539
Vitamin K antagonist	6 (7.4%)	18 (5.1%)	0	8 (8.0%)	32 (5.9%)	0.540

Data are presented as means ± SD or *n* (%). ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; CABG: coronary artery bypass surgery; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; CK-MB: creatine kinase-myocardial band; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEDD: left ventricular end diastolic dimension; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic dimension; MDRD: modification of diet in renal disease; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

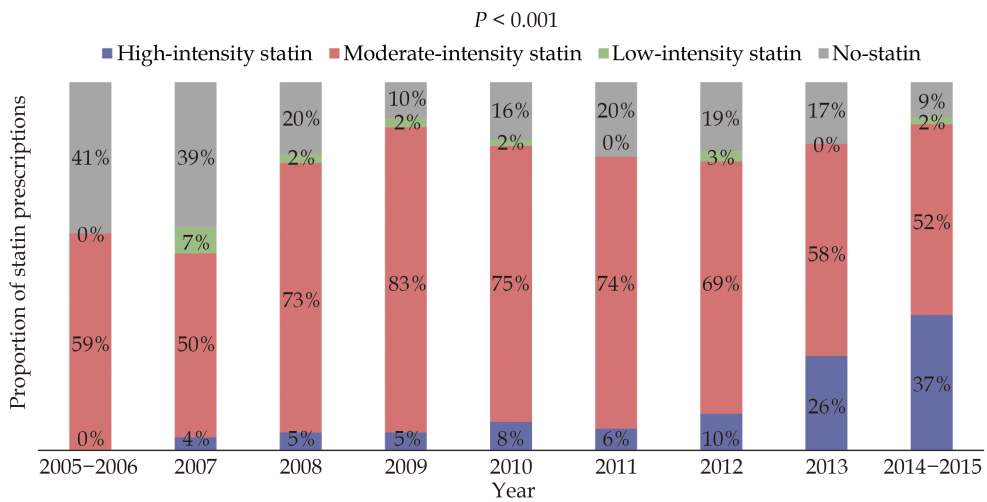

Figure 2 Three-year main statin intensity according to discharge year. The proportion of high-intensity statin prescriptions gradually increased ($P < 0.001$).

12%, and at least 90 years: 14%; $P = 0.856$) (Figure 3).

Comparison of Baseline Characteristics in Four Statin-intensity Groups

Among the four statin-intensity groups, body weight, body mass index, history of prior heart failure, dyslipidemia, lipid profiles, N-terminal-pro-brain natriuretic peptide, revascularization strategy, and discharge medication were significantly different (Table 1). The unadjusted seven-year MACCE rate was also significantly different between the four groups (high-intensity statin group: 38%, moderate-intensity statin group: 42%, low-intensity statin group: 56%, and no-statin group: 61%, $P = 0.004$) (Figure 4).

Comparison of Baseline Characteristics Between the High-intensity Statin Group and the Low-to-moderate Intensity Statin Group in the Whole Study Population

When the patients were re-grouped into high-intensity group and low-to-moderate intensity

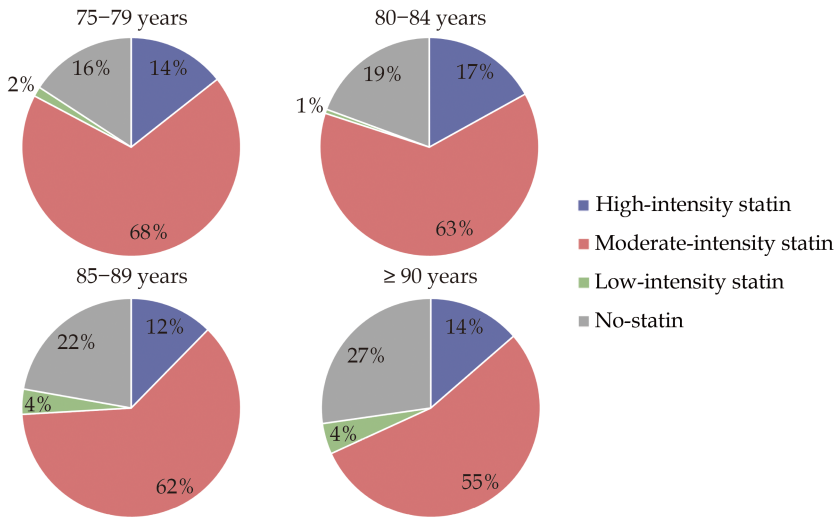

Figure 3 Distribution of three-year main statin intensities, grouped by five years of age. The frequencies of high-intensity statin were not significantly different between the age groups (75–79 years: 14%, 80–84 years: 17%, 85–89 years: 12%, and at least 90 years: 14%; $P = 0.856$).

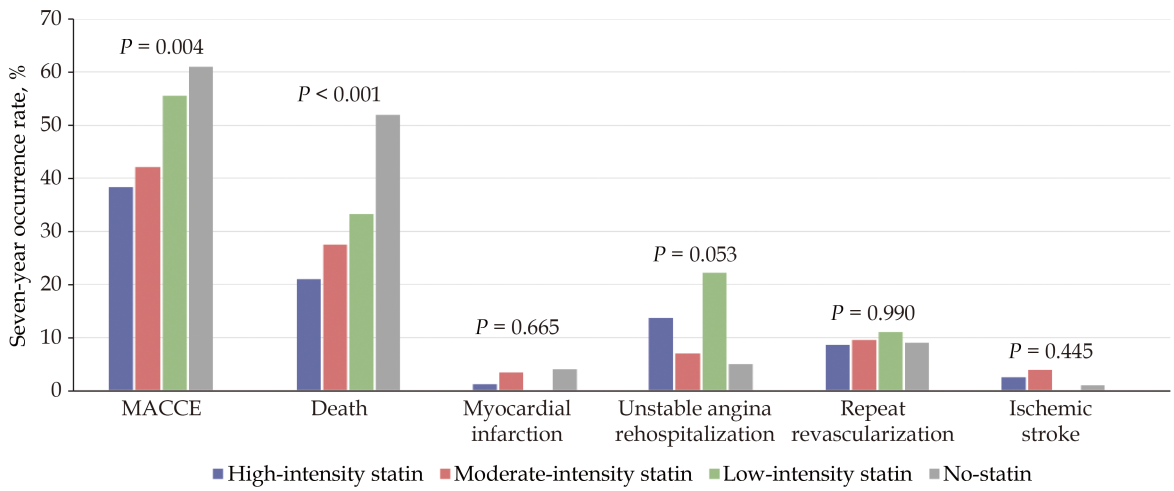

Figure 4 Unadjusted seven-year MACCE and its components in the four groups according to the three-year main intensity of statins. The MACCE rates (38% *vs.* 42% *vs.* 56% *vs.* 61%, $P = 0.004$) and all-cause death rates (21% *vs.* 28% *vs.* 33% *vs.* 52%, $P < 0.001$) were significantly different among the four statin intensity groups (high-intensity statin, moderate-intensity statin, low-intensity statin, and no-statin). However, myocardial infarction, unstable angina rehospitalization, repeat revascularization, and ischemic stroke rates did not differ significantly. MACCE: major adverse cardiac and cerebrovascular events.

group after excluding the no-statin group, significant differences in the baseline total cholesterol, LDL-C, and discharge prescription of beta-blockers were still noted (Table 2).

Comparison of MACCE Between the High-intensity Statin Group and the Low-to-moderate Intensity Statin Group in the Propensity Score-matched Cohort

Among the 74 propensity score-matched pairs, which lacked any significant differences in all the baseline characteristics (Table 3), the high-intensity group had a significantly lower rate of seven-year MACCE compared to that in the low-to-moderate intensity group (37% *vs.* 53%, $P = 0.047$), showing a risk reduction of 31%. Furthermore, the high-intensity group had numerically less events in the MACCE components, including the rate of all-cause death (21% *vs.* 29%, $P = 0.250$), MI (1% *vs.* 3%, $P = 1.000$), UA rehospitalization (12% *vs.* 15%, $P = 0.631$), repeat revascularization (10% *vs.* 18%, $P = 0.149$), and ischemic stroke (3% *vs.* 5%, $P = 0.681$) (Figure 5). In the incidence curve analysis, the occurrence of MACCE within the seven-year follow-up period was numerically lower in the high-intensity group than that in the low-to-moderate intensity group, with a hazard ratio of 0.698 (95% CI: 0.426–1.143, $P = 0.153$) (Figure 6).

Changes in Lipid Profile

In the follow-up lipid profiles, performed a median of 2.4 years after index MI, both groups saw significant decreases in the total cholesterol (high-intensity group: 169.6 ± 40.9 mg/dL to 133.9 ± 25.3 mg/dL, $P < 0.001$; low-to-moderate intensity group: 171.6 ± 44.7 mg/dL to 148.8 ± 33.1 mg/dL, $P < 0.001$) and the LDL-C (high-intensity group: 101.2 ± 31.6 mg/dL to 69.4 ± 16.0 mg/dL, $P < 0.001$; low-to-moderate intensity group: 100.4 ± 34.9 mg/dL to 77.9 ± 25.9 mg/dL, $P < 0.001$). Among the follow-up lipid profiles, both total cholesterol (133.9 ± 25.3 mg/dL *vs.* 148.8 ± 33.1 mg/dL, $P = 0.005$) and LDL-C (69.4 ± 16.0 mg/dL *vs.* 77.9 ± 25.9 mg/dL, $P = 0.026$) levels were significantly lower in the high-intensity group

Table 2 Baseline characteristics of high-intensity statin group versus low-to-moderate intensity statin group.

Characteristics	High-intensity statin ($n = 81$)	Low-to-moderate intensity statin ($n = 365$)	*P*-value
General characteristics			
Age, yrs	80.3 ± 3.9	80.3 ± 4.4	0.954
Sex, male	37 (45.7%)	190 (52.1%)	0.299
Body mass index, kg/m^2	23.1 ± 3.4	22.8 ± 3.9	0.491
Height, cm	157.7 ± 7.9	158.8 ± 8.8	0.303
Weight, kg	57.3 ± 9.6	57.4 ± 11.3	0.937
Lipid profiles			
Total cholesterol, mg/dL	173.4 ± 42.3	163.4 ± 39.8	0.043
Triglyceride, mg/dL	99.0 ± 48.4	104.4 ± 64.0	0.475
HDL-C, mg/dL	45.0 ± 9.2	44.2 ± 13.7	0.551
LDL-C, mg/dL	106.4 ± 35.1	96.9 ± 33.2	0.021
Clinical presentation			
STEMI/NSTEMI	40/41 (49.4%/50.6%)	169/196 (46.3%/53.7%)	0.615
Killip class I/II/III/IV	55/6/13/7 (67.9%/7.4%/16.0%/8.6%)	238/53/46/28 (65.2%/14.5%/12.6%/7.7%)	0.615
Risk factors			
Hypertension	57 (70.4%)	239 (65.5%)	0.399
Diabetes mellitus	22 (27.2%)	111 (30.4%)	0.563
Dyslipidemia	20 (24.7%)	70 (19.2%)	0.263
Smoking, current/former/never	10/20/51 (12.3%/24.7%/63.0%)	56/105/204 (15.3%/28.8%/55.9%)	0.503

Continued

Characteristics	High-intensity statin (*n* = 81)	Low-to-moderate intensity statin (*n* = 365)	*P*-value
Prior MI	2 (2.5%)	21 (5.8%)	0.401
Prior PCI	13 (16.0%)	52 (14.2%)	0.677
Prior CABG	4 (4.9%)	9 (2.5%)	0.267
Prior stroke	7 (8.6%)	38 (10.4%)	0.633
Prior CHF	2 (2.5%)	1 (0.3%)	0.086
Prior CKD	4 (4.9%)	19 (5.2%)	1.000
Laboratory findings			
CK-MB, ng/mL	56.7 ± 130.3	51.8 ± 102.3	0.710
Troponin-I, ng/mL	75.9 ± 117.4	60.3 ± 93.3	0.196
NT-proBNP, pg/mL	5231.5 ± 8794.3	5232.1 ± 11483.8	1.000
Serum creatinine, mg/dL	1.16 ± 0.84	1.24 ± 0.95	0.528
eGFR by MDRD, mL/min per 1.73 m^2	65.3 ± 25.9	62.8 ± 26.8	0.440
Glucose, mg/dL	92.0 ± 28.6	88.3 ± 21.6	0.200
Hemoglobin A1c, %	5.85 ± 0.73	5.95 ± 0.68	0.282
LVEF, %	48.5 ± 13.1	51.2 ± 12.5	0.079
LVEDD, mm	47.4 ± 5.3	47.7 ± 6.5	0.620
LVESD, mm	34.0 ± 7.0	33.1 ± 7.6	0.300
Systolic BP, mmHg	138.0 ± 29.0	138.0 ± 33.0	0.987
Diastolic BP, mmHg	74.7 ± 19.5	74.2 ± 18.6	0.846
Heart rate, beat/ mim	77.0 ± 19.8	77.3 ± 22.6	0.896
CAG findings			
CAD extent, 0/1/2/3 vessel disease	0/15/26/40 (0/18.5%/32.1%/49.4%)	1/90/112/161 (0.3%/24.7%/30.8%/44.2%)	0.630
Left main disease	6 (7.4%)	30 (8.2%)	0.803
Treatment strategy			
Thrombolysis	1 (1.2%)	7 (1.9%)	1.000
PCI	73 (90.1%)	311 (85.2%)	0.247
CABG	3 (3.7%)	31 (8.5%)	0.142
Discharge medication			
Aspirin	81 (100.0%)	364 (99.7%)	1.000
$P2Y_{12}$ inhibitor	81 (100.0%)	355 (97.3%)	0.132
Beta blocker	65 (80.2%)	239 (65.5%)	0.010
ACEI or ARB	62 (76.5%)	287 (78.6%)	0.680
Calcium channel blocker	11 (13.6%)	60 (16.4%)	0.525
Loop diuretics	27 (33.3%)	165 (45.2%)	0.051
Spironolactone	11 (13.6%)	45 (12.3%)	0.758
Vitamin K antagonist	6 (7.4%)	18 (4.9%)	0.412

Data are presented as means ± SD or *n* (%). ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; CABG: coronary artery bypass surgery; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; CK-MB: creatine kinase-myocardial band; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEDD: left ventricular end diastolic dimension; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic dimension; MDRD: modification of diet in renal disease; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

Table 3 High-intensity statin group versus low-to-moderate intensity statin group in propensity score matched cohort.

Characteristics	High-intensity statin (n = 74)	Low-to-moderate intensity statin (n = 74)	Total (n = 148)	P-value
General characteristics				
Age, yrs	80.4 ± 3.8	80.5 ± 4.7	80.4 ± 4.3	0.893
Sex, male	36 (48.6%)	39 (52.7%)	75 (50.7%)	0.622
Body mass index, kg/m^2	23.1 ± 3.4	23.5 ± 3.3	23.3 ± 3.3	0.486
Height, cm	158.2 ± 8.1	159.4 ± 8.0	158.8 ± 8.0	0.341
Weight, kg	57.6 ± 9.8	59.8 ± 10.2	58.7 ± 10.0	0.181
Lipid profiles				
Total cholesterol, mg/dL	169.6 ± 39.7	171.8 ± 43.9	170.7 ± 41.7	0.748
Triglyceride, mg/dL	98.6 ± 47.4	97.1 ± 46.5	98.0 ± 46.8	0.853
HDL-C, mg/dL	44.8 ± 9.0	46.7 ± 11.8	45.8 ± 10.5	0.279
LDL-C, mg/dL	103.5 ± 33.0	100.8 ± 34.0	102.1 ± 33.4	0.629
Clinical presentation				
STEMI/NSTEMI	38/36 (51.4%/48.6%)	33/41 (44.6%/55.4%)	71/77 (48.0%/52.0%)	0.411
Killip class I/II/III/IV	52/5/12/5 (70.3%/6.8%/16.2%/6.8%)	52/9/10/3 (70.3%/12.2%/13.5%/4.1%)	104/14/22/8 (70.3%/9.5%/14.9%/5.4%)	0.610
Risk factors				
Hypertension	51 (68.9%)	53 (71.6%)	104 (70.3%)	0.719
Diabetes mellitus	19 (25.7%)	26 (35.1%)	45 (30.4%)	0.211
Dyslipidemia	18 (24.3%)	25 (33.8%)	43 (29.1%)	0.205
Smoking, current/former/never	9/20/45 (12.2%/27.0%/60.8%)	5/20/49 (6.8%/27.0%/66.2%)	14/40/94 (9.5%/27.0%/63.5%)	0.519
Prior MI	1 (1.4%)	4 (5.4%)	5 (3.4%)	0.366
Prior PCI	11 (14.9%)	19 (25.7%)	30 (20.3%)	0.102
Prior CABG	3 (4.1%)	3 (4.1%)	6 (4.1%)	1.000
Prior stroke	7 (9.5%)	13 (17.6%)	20 (13.5%)	0.149
Prior CHF	0	1 (1.4%)	1 (0.7%)	1.000
Prior CKD	4 (5.4%)	7 (9.5%)	11 (7.4%)	0.347
Laboratory findings				
CK-MB, ng/mL	60.4 ± 135.5	53.7 ± 104.9	57.0 ± 120.8	0.737
Troponin-I, ng/mL	77.9 ± 121.0	62.5 ± 113.4	70.2 ± 117.1	0.426
Serum creatinine, mg/dL	1.20 ± 0.86	1.40 ± 1.62	1.30 ± 1.30	0.345
eGFR by MDRD, mL/min per 1.73 m^2	63.9 ± 25.4	63.1 ± 28.0	63.5 ± 26.6	0.856
Glucose, mg/dL	88.5 ± 17.7	89.2 ± 21.3	88.8 ± 19.5	0.831
LVEF, %	48.8 ± 13.2	51.0 ± 11.6	49.9 ± 12.4	0.284
LVEDD, mm	47.4 ± 5.2	47.3 ± 6.8	47.4 ± 6.0	0.930
LVESD, mm	33.7 ± 6.9	32.8 ± 7.3	33.2 ± 7.1	0.477
Systolic BP, mmHg	139.3 ± 27.6	142.6 ± 30.4	141.0 ± 29.0	0.486
Diastolic BP, mmHg	75.4 ± 19.0	74.6 ± 19.1	75.0 ± 19.0	0.792
Heart rate, beat/ mim	76.6 ± 20.4	74.5 ± 19.5	75.5 ± 20.0	0.508
CAG findings				
CAD extent, 0/1/2/3 vessel disease	15/25/34 (20.3%/33.8%/45.9%)	19/23/32 (25.7%/31.1%/43.2%)	34/48/66 (23.0%/32.4%/44.6%)	0.735
Left main disease	6 (8.1%)	7 (9.5%)	13 (8.8%)	0.772

Continued

Characteristics	High-intensity statin (n = 74)	Low-to-moderate intensity statin (n = 74)	Total (n = 148)	P-value
Treatment strategy				
Thrombolysis	1 (1.4%)	1 (1.4%)	2 (1.4%)	1.000
PCI	66 (89.2%)	67 (90.5%)	133 (89.9%)	0.785
CABG	3 (4.1%)	3 (4.1%)	6 (4.1%)	1.000
Discharge medication				
Aspirin	74 (100.0%)	74 (100.0%)	148 (100.0%)	–
$P2Y_{12}$ inhibitor	74 (100.0%)	74 (100.0%)	148 (100.0%)	–
Beta blocker	58 (78.4%)	57 (77.0%)	115 (77.7%)	0.843
ACEI or ARB	58 (78.4%)	57 (77.0%)	115 (77.7%)	0.843
Calcium channel blocker	10 (13.5%)	14 (18.9%)	24 (16.2%)	0.372
Loop diuretics	24 (32.4%)	22 (29.7%)	46 (31.1%)	0.722
Spironolactone	10 (13.5%)	4 (5.4%)	14 (9.5%)	0.092
Vitamin K antagonist	5 (6.8%)	6 (8.1%)	11 (7.4%)	0.754

Data are presented as means ± SD or n (%). ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; CABG: coronary artery bypass surgery; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; CK-MB: creatine kinase-myocardial band; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEDD: left ventricular end diastolic dimension; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic dimension; MDRD: modification of diet in renal disease; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

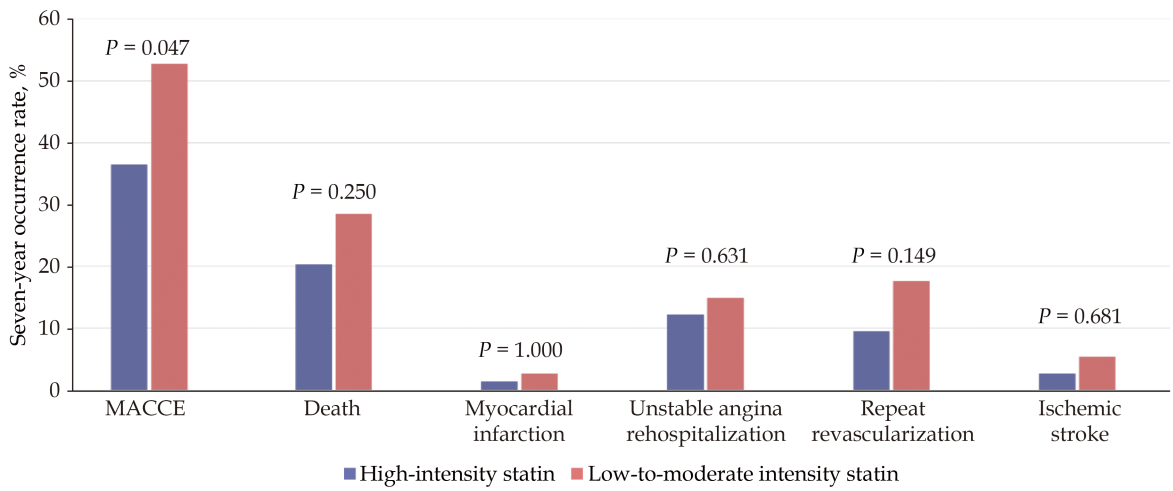

Figure 5 Seven-year MACCE and its components in the high-intensity and low-to-moderate intensity statin groups in propensity score-matched cohort. There were significantly fewer occurrence of MACCE in the high-intensity statin group than that in the low-to-moderate intensity statin group (37% *vs.* 53%, P = 0.047). MACCE: major adverse cardiac and cerebrovascular events.

than that in the low-to-moderate intensity group (Figure 7). In triglyceride or HDL-C, no significant changes from baseline and no significant difference in follow-up level were observed between the two groups.

Subgroup Analysis

The subgroup analysis according to the age of 80 years, sex, type of index MI, and baseline LDL-C level of 100 mg/dL showed no significant differences in the risk of MACCE among the subgroups (Table 4).

DISCUSSION

In this study, the frequency of prescription of high-intensity statin in older adult patients with MI increased annually during the study period. The high-intensity statin group showed significantly

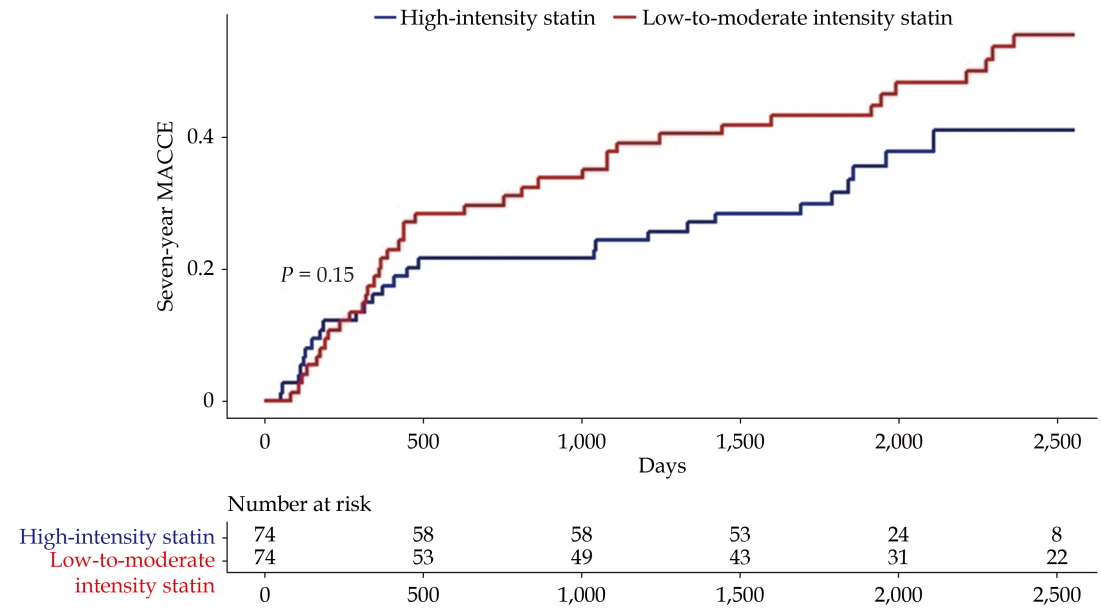

Figure 6 Incidence curve of MACCE for up to seven years in propensity score-matched cohort. During the seven-year follow-up, the high-intensity statin group had lower incidences of MACCE (hazard ratio of 0.698, 95% CI: 0.426–1.143) than that in the low-to-moderate intensity statin group. MACCE: major adverse cardiac and cerebrovascular events.

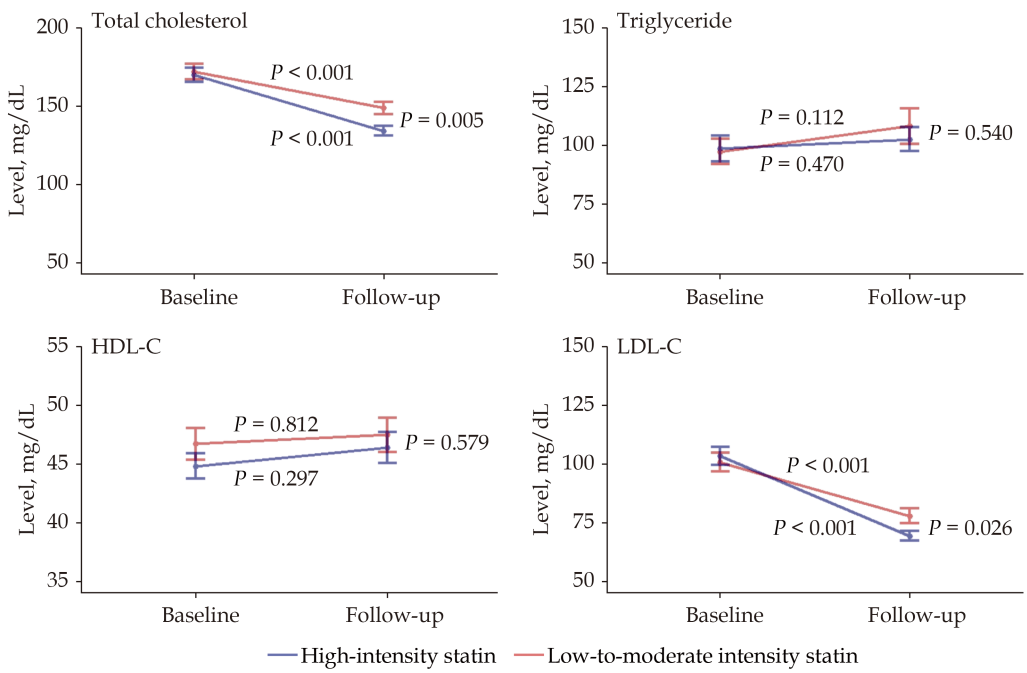

Figure 7 Lipid profiles at baseline and at follow-up in the high-intensity and low-to-moderate intensity statin groups. The total cholesterol (high-intensity group: 169.6 ± 40.9 mg/dL to 133.9 ± 25.3 mg/dL, $P < 0.001$; low-to-moderate intensity group: 171.6 ± 44.7 mg/dL to 148.8 ± 33.1 mg/dL, $P < 0.001$) and LDL-C (high-intensity group: 101.2 ± 31.6 mg/dL to 69.4 ± 16.0 mg/dL, $P < 0.001$; low-to-moderate intensity group: 100.4 ± 34.9 mg/dL to 77.9 ± 25.9 mg/dL, $P < 0.001$) levels were reduced significantly in both groups. However, among the follow-up lipid profiles, both total cholesterol (133.9 ± 25.3 mg/dL *vs.* 148.8 ± 33.1 mg/dL, $P = 0.005$) and LDL-C (69.4 ± 16.0 mg/dL *vs.* 77.9 ± 25.9 mg/dL, $P = 0.026$) levels were significantly lower in the high-intensity group than that in the low-to-moderate intensity group. The changes in the HDL-C and triglycerides were not significant. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Table 4 Estimates of the hazard ratio for the seven-year major adverse cardiac and cerebrovascular events in the high-intensity group as compared with the low-to-moderate intensity group, in various subgroups according to major baseline characteristics.

Characteristics	Number of patients	Hazard ratio	95% CI	*P*-value
Age, yrs				
75–79	74	0.598	0.275–1.299	0.194
≥ 80	74	0.778	0.409–1.482	0.445
Sex				
Male	75	0.678	0.339–1.355	0.271
Female	73	0.728	0.360–1.475	0.379
Index myocardial infarction				
ST-segment elevation myocardial infarction	77	0.525	0.252–1.096	0.086
Non-ST-segment elevation myocardial infarction	71	0.905	0.465–1.760	0.769
Low-density lipoprotein cholesterol, mg/dL				
≥ 100	74	0.546	0.269–1.107	0.093
< 100	74	0.919	0.460–1.838	0.842

lower MACCE than that in the low-to-moderate intensity statin group in the propensity score-matched cohort. Furthermore, high-intensity statins effectively lowered total cholesterol and LDL-C compared to low-to-moderate intensity statins.

Prescription Pattern of Statins

In our study, the annual prescription of high-intensity statin increased stiffly especially after the release of the 2013 ACC/AHA guideline on the treatment of blood cholesterol recommending its use for secondary prevention of MI. This trend was consistent with those seen in other East Asian countries, with both the frequency of statin prescription and the proportion of high-intensity statins seeing an increase.[16]

In our data, the proportion of high-intensity statin at discharge was 24%, similar to the 23.5% reported in a previous United States nationwide report on the use of high-intensity statin as secondary prevention of atherosclerotic cardiovascular disease for patients aged over 75 years.[17] There were no age-related differences in the frequency of statin prescription as the rate of prescription of high-intensity statins was similar in extremely old patients over 90 years. There was a previous report on the tendency of physicians to prescribe fewer statins in patients whose life expectancies were expected to be short, such as high-risk patients and extremely old ages.[18] However, this was not observed in our data.

Reduced Adverse Cardiovascular Events in the High-intensity Statin Group in Propensity Score-matched Cohort

Recent primary prevention studies have demonstrated the effect of statin on all-cause and cardiovascular mortalities,[19] and on composite of cardiovascular death, MI, and stroke,[20] in adults at least 75 years old. In the aspect of secondary prevention in older adults, however, previous Korean reports have shown that the effect of high-intensity statin was not significantly better than that of low-to-moderate intensity statin in older adult patients.[21–23] Above-mentioned studies, however, have tended to classify patients based on the dosages of statins prescribed at the time of discharge. Meanwhile, our data revealed that statin intensity changed at least once during the follow-up period in almost one-third of the patients. Therefore, classifying the patient groups according to the discharge medications may lead to incorrect conclusions. We classified the patients based on the dosages prescribed for most of the follow-up period, the three-year main intensity. As such, in contrast with the previous data, our results showed that the seven-year MACCE occurred less in the high-intensity statin group, suggesting that this might be beneficial in older adult patients with MI.

Changes in Lipid Profile

In this study, the total cholesterol and LDL-C

levels were significantly decreased from baseline in both statin intensity groups, with a more significant decline seen in the high-intensity statin group. These findings were consistent with the changes in lipid profiles in previous prospective statin intensity trials.[11–13,24] Meanwhile, no significant changes were noted in the triglyceride and HDL-C levels, consistent with the varying results in previous reports.[11,24]

LIMITATIONS

This study had some limitations. Firstly, this was a retrospective study. Therefore, the baseline characteristics of the patients were not well balanced. However, we tried to investigate and adjust as many baseline characteristics as possible through a thorough medical record review and by utilizing propensity score matching, although there might have been hidden unadjusted confounding variables. Secondly, there were no data on the adverse effects of statins, which may be important due to the previous reports of higher frequency of adverse effects in high-intensity statins compared to low-to-moderate intensity statins.[11,13,14] However, another report suggested that adverse effects did not increase in the older adult patients compared to those in younger patients.[17] Therefore, it might be possible to assume that older adult patients have adverse effects similar to those in younger patients. Thirdly, the exact cause of death was not investigated since many patients died at home or in other hospitals. Last but not least, the size of the study population was small, especially after propensity score matching. To overcome this limitation, we investigated longer-term follow-up data than previous reports,[21–23] which showed outcome differences as early as six months to two years.[24,25]

CONCLUSIONS

In older adult patients with MI, the use of high-intensity statin significantly reduced the occurrence of MACCE in comparison to low-to-moderate intensity for up to seven years of follow-up. It is anticipated that further large-scale prospective studies on statin intensity, especially in older adult patients, will confirm our results and reinforce statin treatment in older adult patients.

DISCLOSURE

All authors had no conflicts of interest to disclose.

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