ORIGINAL RESEARCH

High-Intensity Versus Non-High-Intensity Statins in Patients Achieving Low-Density Lipoprotein Cholesterol Goal After Percutaneous Coronary Intervention

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***Background*—**Whether use of high-intensity statins is more important than achieving low-density lipoprotein cholesterol (LDL-C) target remains controversial in patients with coronary artery disease. We sought to investigate the association between statin intensity and long-term clinical outcomes in patients achieving treatment target for LDL-C after percutaneous coronary intervention.

***Methods and Results*—**Between February 2003 and December 2014, 1746 patients who underwent percutaneous coronary intervention and achieved treatment target for LDL-C (<70 mg/dL or >50% reduction from baseline level) were studied. We classified patients into 2 groups according to an intensity of statin prescribed after index percutaneous coronary intervention: high-intensity statin group (atorvastatin 40 or 80 mg, and rosuvastatin 20 mg, 372 patients) and non-high-intensity statin group (the other statin treatment, 1374 patients). The primary outcome was a composite of cardiac death, myocardial infarction, or stroke. Difference in time-averaged LDL-C during follow-up was significant, but small, between the high-intensity statin group and non-high-intensity statin group (59±13 versus 61±12 mg/dL; P=0.04). At 5 years, patients receiving high-intensity statins had a significantly lower incidence of the primary outcome than those treated with non-high-intensity statins (4.1% versus 9.9%; hazard ratio, 0.42; 95% confidence interval, 0.23–0.79; P<0.01). Results were consistent after propensity-score matching (4.2% versus 11.2%; hazard ratio, 0.36; 95% confidence interval, 0.19–0.69; P<0.01) and across various subgroups.

***Conclusions*—**Among patients achieving treatment target for LDL-C after percutaneous coronary intervention, high-intensity statins were associated with a lower risk of major adverse cardiovascular events than non-high-intensity statins despite a small difference in achieved LDL-C level. **(*J Am Heart Assoc*. 2018;7:e009517. DOI: 10.1161/JAHA.118.009517)**

Key Words: cardiovascular events • low-density lipoprotein cholesterol • percutaneous coronary intervention • secondary prevention • statin

High-intensity statins have demonstrated consistent benefits for secondary prevention of adverse cardiovascular events compared with moderate-intensity statins in several randomized trials.[1,2] Therefore, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on treatment of blood cholesterol recommends high-intensity statins, including atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg, for patients with atherosclerotic cardiovascular disease.[3] However, whether beneficial effects of high-intensity statins can be attributable to statin intensity per se or to merely lower low-density lipoprotein cholesterol (LDL-C) level achieved by high-intensity statins compared with moderate-intensity statins is uncertain. It has been reported that lowering of LDL-C with statin therapy reduces major cardiovascular events regardless of types or intensities of statins.[4] Therefore, European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for management of dyslipidemia still propose the

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Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009517

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Clinical Perspective

What Is New?

- In patients undergoing coronary revascularization who achieved a low-density lipoprotein-cholesterol <70 mg/dL, high-intensity statin therapy was significantly associated with a lower risk of primary outcome compared with non-high-intensity statin therapy.

What Are the Clinical Implications?

- In patients undergoing percutaneous coronary intervention, high-intensity statin therapy is associated with additional lowering of risk of major adverse cardiovascular events beyond what may be achieved by low-density lipoprotein cholesterol target alone.

target goal for LDL-C of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% from baseline for subjects at very high risk without specific recommendation for type or intensity of statin.[5] The differences between the 2 guidelines have caused many debates and much confusion in daily practice.[6] To date, it remains controversial whether outcomes differ according to statin intensity in patients with similar LDL-C level. Therefore, we sought to investigate the association between statin intensity and long-term clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) and achieving treatment target for LDL-C.

Methods

Study Population

The study population was selected from the Samsung Medical Center (Seoul, Korea) PCI registry. Between February 2003 and December 2014, 8148 patients underwent PCI with drug-eluting stents. Patients were ineligible for the study if there were no data on blood cholesterol level or medication information at discharge. Exclusion criteria were: (1) <20 years of age; (2) on maintenance hemodialysis; (3) had a history of liver cirrhosis; (4) received treatment for human immunodeficiency virus infection; (5) had undergone any organ transplantation; (6) had cardiopulmonary resuscitation or mechanical circulatory support during PCI; or (7) taking statin and ezetimibe combination therapy. After exclusion of 4013 patients, whether treatment target for LDL-C was achieved or not during follow-up after index PCI was reviewed in 4135 patients. We calculated time-averaged LDL-C using follow-up LDL-C levels measured from 4 weeks to 3 years after index PCI and regarded target for LDL-C being achieved when time-averaged LDL-C was <1.8 mmol/L (70 mg/dL) or reduced at least 50% from baseline during follow-up after index PCI based on the ESC/EAS guideline.[5] Time-averaged LDL-C was calculated by the formula:

$$\text{Time-averaged LDL-C} = \frac{\sum_{i=1}^{n} \text{Li} \times \text{Ti}}{\sum_{i=1}^{n} \text{Ti}}$$

where Li=consecutively measured follow-up LDL-C level, Ti=time period of measurement between Li-1 and Li, and T1=time period between index PCI and L1.

Finally, 1746 patients who achieved target for time-averaged LDL-C during follow-up were included in this study. We classified patients into 2 groups according to the intensity of statin prescribed at hospital discharge from admission for the index PCI: high-intensity statin group (n=372) and non-high-intensity statin group (n=1374). Definition of statin intensity was based on the guideline from ACC/AHA.[3] Atorvastatin 40 or 80 mg and rosuvastatin 20 mg were defined as high-intensity statins, and the other statins were classified as non-high-intensity statins. (Details about statins used in the non-high-intensity statin group are shown in Table S1.) Rosuvastatin 40 mg has not been approved in Korea. The exclusion and division of the study is shown in a flow diagram in Figure 1. The Institutional Review Board of Samsung Medical Center approved this study and waived the requirement for written informed consent. The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data Collection and Follow-up

Baseline characteristics and clinical outcome data were prospectively collected in our PCI registry by trained research coordinators using a standardized case report form and protocol. Patients were routinely followed up at 1, 6, and 12 months after the index procedure and annually thereafter. Further information was collected by telephone contact or medical records, if necessary. Data on statin intensity were collected from the electronic prescribing system of Samsung Medical Center. To assess whether the intensity of statin was maintained during follow-up, information on medications that had been prescribed during the 3 years after index PCI were collected. We also collected high-sensitivity C-reactive protein (hs-CRP) level measured during the 3 years after index PCI. Time-averaged hs-CRP was calculated by the same formula used in calculating time-averaged LDL-C. Follow-up was considered complete if mortality was confirmed from the National Population Registry of the Korea National Statistical Office using a unique personal identification number or if the patient was contacted at the planned follow-up interval.

Study Outcomes and Definition

The primary outcome was the occurrence of major adverse cardiovascular events (MACEs) during follow-up, defined as a composite of cardiac death, myocardial infarction (MI), or

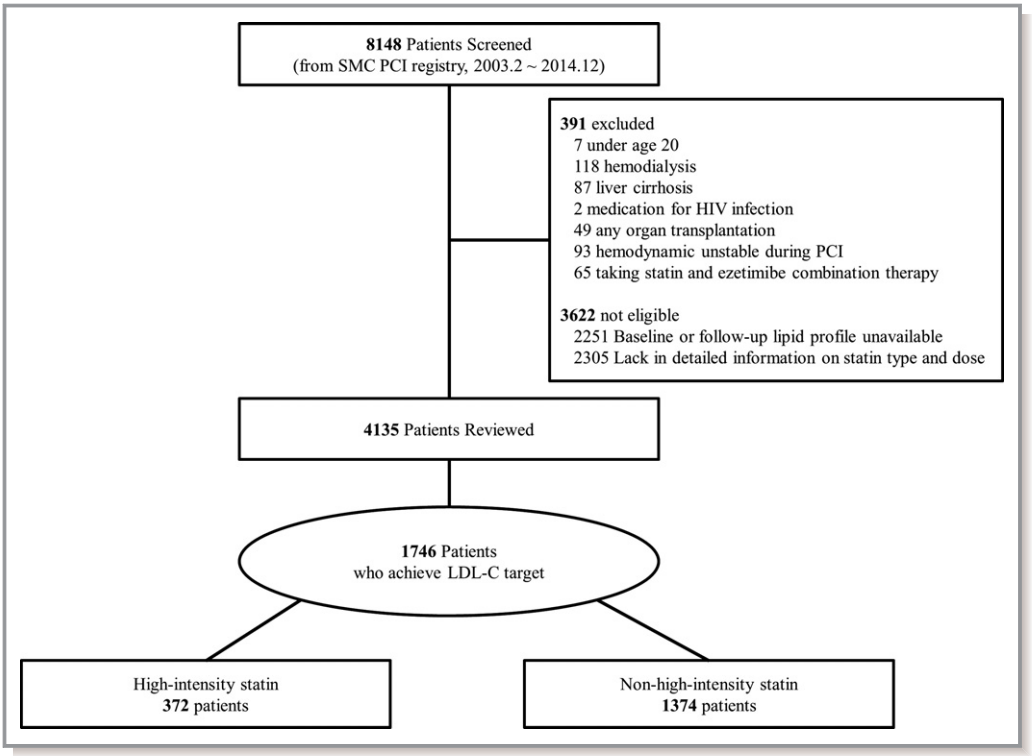

Figure 1. Scheme of group distribution. HIV indicates human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; SMC, Samsung Medical Center.

stroke. Secondary outcomes included all-cause death, target lesion revascularization, target vessel revascularization, and individual components of the primary outcome. All deaths were considered to be cardiac death unless a definite noncardiac cause could be established.[7] MI was defined as elevated cardiac enzymes (troponin or myocardial band fraction of creatinine kinase) greater than the upper-normal limit with ischemic symptoms or electrocardiography findings indicative of ischemia or MI at readmission requiring subsequent hospitalization (defined as emergency admission with principal diagnosis of MI).[8,9] Stroke was defined as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.[10] Target lesion revascularization was defined as repeat PCI of the lesion within 5 mm of stent deployment or bypass graft surgery of the target vessel. Target vessel revascularization was repeat revascularization of the target vessel by PCI or bypass graft surgery.[7,8] All end points in this study were censored at 5 years after index PCI.

Statistical Analysis

Categorical variables are presented as numbers of events and percentages and were compared using the chi-square test or Fisher's exact test (for sparse data). Continuous variables are presented as mean±SD and were compared using the *t* test or Wilcoxon rank-sum test. We assessed survival curves using the Kaplan–Meier method, along with a log-rank test. We estimated the hazard ratios (HRs) of high versus non-high-intensity statin group in both univariate and multiple Cox regression models. In multiple Cox regression, variables that appeared to be related in the univariate analysis with a $P<0.2$ were considered in a step-wise method to select predictors of outcomes. HRs of high versus non-high-intensity statin group were reported with their 95% confidence intervals (CIs).

In addition, to adjust the 2 groups for any inherent imbalance in their demographic and clinical characteristics, we advocated the propensity score method and balanced the 2 groups so that they were comparable with no undue influences from confounding factors. Propensity scores, which are the probability of being treated with a high-intensity statin for each patient, were estimated using predicted probabilities from a multiple logistic regression analysis. Typically a full nonparsimonious model was fit using all variables in Table 1 (except aspirin and $P2Y_{12}$ inhibitors) and baseline lipid profile in Table 2 to predict the probability to be treated with a high-intensity statin. The variable ratio, parallel, and pair-wise nearest neighbor matching method created a matched data set to avoid a significant data loss from unmatched patients. A standardized mean difference of less than 10% for each matching covariate suggested an appropriate balance between the groups, as did a variance ratio near 1.0 between the 2 groups. To confirm the balance, McNemar's or Bowker's

Table 1. Baseline and Procedural Characteristics of the Patients

	Total Population				Propensity-Matched Population			
	High-Intensity Statin (n=372)	Non-High-Intensity Statin (n=1374)	*P* Value	Standardized Difference	High-Intensity Statin (n=367)	Non-High-Intensity Statin (n=798)	*P* Value	Standardized Difference
Age, y	62.0±11.8	62.6±10.7	0.63	−5.4	62.0±11.8	62.1±11.1	0.90	−0.7
Sex (male)	302 (81.2)	1079 (78.5)	0.26	6.3	298 (81.2)	639 (80.1)	0.65	2.9
BMI ≥25 kg/m^2	170 (45.7)	573 (41.8)	0.17	9.0	172 (46.9)	366 (45.9)	0.76	1.9
Medical history								
Diabetes mellitus	212 (57.0)	631 (45.9)	<0.01	22.8	209 (57.0)	442 (55.4)	0.61	3.2
Hypertension	205 (55.1)	760 (55.3)	0.94	−0.3	202 (55.0)	438 (54.9)	0.97	0.3
Current smoker	133 (35.8)	349 (25.4)	<0.01	21.7	132 (36.0)	269 (33.7)	0.46	4.6
Chronic kidney disease	18 (4.8)	92 (6.7)	0.19	−8.4	18 (4.9)	37 (4.7)	0.87	1.1
Previous history of MI	38 (10.2)	172 (12.5)	0.23	−7.5	38 (10.4)	83 (10.4)	1.00	0.0
Previous history of PCI	23 (6.2)	116 (8.4)	0.15	−9.5	23 (6.3)	62 (7.8)	0.36	−6.2
Previous history of CABG surgery	3 (0.8)	34 (2.5)	0.06	−18.8	3 (0.8)	5 (0.6)	0.73	2.0
Previous CVA	24 (6.5)	55 (4.0)	0.04	10.2	24 (6.5)	51 (6.4)	0.91	0.7
Peripheral artery disease	3 (0.8)	22 (1.6)	0.33	−9.0	3 (0.8)	5 (0.6)	0.66	2.5
Family history of CAD	41 (11.0)	128 (9.3)	0.32	5.3	39 (10.6)	89 (11.1)	0.80	−1.6
Previous statin use	67 (18.0)	272 (19.8)	0.44	−4.6	67 (18.3)	125 (15.7)	0.27	7.0
Clinical presentation			<0.01				0.75	
Stable ischemic heart disease	119 (32.0)	706 (51.4)			119 (32.4)	266 (33.4)		
Acute coronary syndrome	253 (68.0)	668 (48.6)		41.7	248 (67.6)	532 (66.6)		2.0
Disease extent			0.16				0.95	
1-vessel disease	159 (42.7)	568 (41.3)			156 (42.5)	341 (42.8)		
2-vessel disease	140 (37.6)	473 (34.4)		6.8	138 (37.6)	293 (36.7)		1.8
3-vessel disease	73 (19.6)	333 (24.2)		−11.5	73 (19.9)	163 (20.5)		−1.5
Concomitant therapies at hospital discharge								
Aspirin	369 (99.2)	1367 (99.4)	0.45	−3.7	364 (99.2)	795 (99.7)	0.25	−5.7
P2Y$_{12}$ inhibitors*	372 (100.0)	1368 (99.6)	0.35	9.4	367 (100.0)	794 (99.6)	0.20	9.9
DAPT	369 (99.2)	1361 (99.1)	1.00	1.5	364 (99.2)	791 (99.1)	1.00	0.7
β-blockers	215 (57.8)	765 (55.7)	0.47	4.4	210 (57.2)	445 (55.8)	0.64	2.9
ACE inhibitors or ARBs	241 (64.8)	869 (63.3)	0.58	3.1	236 (64.3)	496 (62.2)	0.49	4.4
DAPT duration, mo	18.1±17.2	18.9±18.2	0.47	−4.3	18.0±17.1	17.4±20.2	0.63	3.2

Continued

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Table 1. Continued

	Total Population				Propensity-Matched Population			
	High-Intensity Statin (n=372)	Non-High-Intensity Statin (n=1374)	*P* Value	Standardized Difference	High-Intensity Statin (n=367)	Non-High-Intensity Statin (n=798)	*P* Value	Standardized Difference
Procedural characteristics								
First-generation DES†	32 (8.6)	449 (32.7)	<0.01	−85.0	32 (8.7)	75 (9.4)	0.73	−2.3
No. of stents	1.4±0.7	1.5±0.8	0.53	−9.5	1.4±0.7	1.4±0.7	0.72	2.3
Mean stent diameter, mm	3.1±0.4	3.1±0.4	0.27	−7.7	3.1±0.4	3.1±0.4	0.63	−3.2
Intervention on LM or LAD	233 (62.6)	847 (61.6)	0.73	1.9	230 (62.7)	499 (62.6)	0.98	0.2
SYNTAX score at baseline	14.3±8.3	14.6±9.6	0.63	−2.8	13.9±11.4	14.4±8.3	0.39	−5.1
Population with available LV ejection fraction data	(n=256)	(n=957)			(n=253)	(n=576)		
LV ejection fraction at baseline, %	59±11	60±11	0.32	7.0	59±11	60±28	0.55	3.8

Values are mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; LAD, left anterior descending artery; LM, left main coronary artery; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

*$P2Y_{12}$ inhibitors included clopidogrel, ticagrelor, prasugrel, and ticlopidine.

†First-generation DES included sirolimus-eluting stents and paclitaxel-eluting stents.

test of symmetry were used to compare categorical variables, whereas continuous variables were compared using a paired *t* test. Using the matched data set, the risk of outcomes was assessed using a conditional Cox regression model to obtain another set of HRs. For all analyses, we used SAS (version 9.2; SAS Institute Inc., Cary, NC) and R software (version 3.3; "MatchIt" and "survival" packages; R Foundation for Statistical Computing, Vienna, Austria) for Windows for statistical analyses.

Results

Baseline Characteristics

Overall population

Baseline and procedure characteristics between the high-intensity statin group (n=372) and the non-high-intensity statin group (n=1374) are presented in Table 1. The high-intensity statin group had a higher prevalence of diabetes mellitus, current smoker, previous cerebrovascular accident event, and acute coronary syndrome on admission. Aspirin, $P2Y_{12}$ inhibitors, beta blockers, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were similarly prescribed at hospital discharge in both groups. At index PCI, first-generation coronary stents were more frequently used in the non-high-intensity statin group. But total number of stents, mean stent diameter, and whether stents were implanted on the left main coronary artery or left anterior descending artery and were not different between the 2 groups.

Propensity-matched population

After performing propensity-score matching for the entire population, 367 patients in the high-intensity statin group and 798 in the non-high-intensity statin group were matched using a variable 1:N matching (Table 1). There were no significant differences in baseline characteristics, medications at hospital discharge, and procedural characteristics for the propensity-matched subjects.

Adherence to Statin Treatment

Information about statin intensity during follow-up is shown in Table 3 and Table S2. In the high-intensity statin group, adherence to high-intensity statin was 98.5% at 2 years and 87.3% at 3 years after the index PCI. In the non-high-intensity statin group, adherence to non-high-intensity statin was 99.2% at 2 years and 94.8% at 3 years after the index PCI. At the 3 years of follow-up, adherence in the high-intensity statin group was significantly lower than in the non-high-intensity statin group (87.3% versus 94.8%; $P<0.01$).

Table 2. Baseline Lipid Profile and Changes in LDL-C and hs-CRP

	Total Population			Propensity-Matched Population		
	High-Intensity Statin (n=372)	Non-High-Intensity Statin (n=1374)	*P* Value	High-Intensity Statin (n=367)	Non-High-Intensity Statin (n=798)	*P* Value
Baseline lipid profile, mg/dL						
LDL-C	126±41	112±41	<0.01	125±41	123±41	0.54
HDL-C	46±12	45±12	0.14	46±12	46±12	0.89
Triglycerides	155±114	151±102	0.57	155±114	154±97	0.90
Time-averaged LDL-C, mg/dL*	59±13	61±12	0.04	59±13	62±13	0.03
Reduction from baseline LDL-C, mg/dL	66±36	51±35	<0.01	66±36	61±35	0.10
Percent reduction from baseline LDL-C, %	48.0	39.4	<0.01	47.9	42.9	<0.01
Population with available hs-CRP data	(n=292)	(n=924)		(n=287)	(n=556)	
Baseline hs-CRP, mg/L	9.6±35.3	6.9±21.5	0.22	9.7±35.6	6.2±16.9	0.11
Time-averaged hs-CRP, mg/L*	3.0±9.0	4.8±15.7	0.01	3.0±9.0	4.1±13.7	0.15
Reduction from baseline hs-CRP, mg/L	6.6±34.8	2.1±24.6	0.04	6.7±35.1	2.1±19.0	0.04

Values are mean±SD. HDL-C indicates high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.
*Time-averaged LDL-C and time-averaged hs-CRP were calculated from follow-up LDL-C and hs-CRP values collected during the periods from 4 weeks to 3 years after index PCI.

Changes in LDL-C and hs-CRP

Overall population

Baseline lipid profile, time-averaged LDL-C, and hs-CRP between the high-intensity statin group and non-high-intensity statin group are shown in Table 2. The high-intensity statin group showed higher baseline LDL-C than the non-high-intensity statin group (126±41 versus 112±41 mg/dL; *P*<0.01). Baseline level of high-density lipoprotein cholesterol and triglyceride were similar between the 2 groups. Difference in the time-averaged LDL-C during follow-up was significant, but small (59±13 versus 61±12 mg/dL; *P*=0.04). A high-intensity statin lowered LDL-C further from baseline by approximately 15 mg/dL than a non-high-intensity statin, and the difference between the 2 groups in percent reduction from baseline LDL-C was 8.6% (48.0% versus 39.4%; *P*<0.01). Reduction from baseline hs-CRP was significantly greater in the high-intensity statin group than in the non-high-intensity statin group (6.6±34.8 versus 2.1±24.6 mg/L; *P*=0.04).

Propensity-matched population

Baseline level of LDL-C was similar in the 2 groups (125±41 versus 123±41 mg/dL; *P*=0.54). In the high-intensity statin group, time-averaged LDL-C was significantly lower than that of the non-high-intensity statin group (59±13 versus 62±13 mg/dL; *P*=0.03). A high-intensity statin lowered LDL-C further from baseline by approximately 5 mg/dL than a non-high-intensity statin, and the difference between the 2 groups in percent reduction from baseline LDL-C was 5.0% (47.9% versus 42.9%; *P*<0.01). Reduction from

Table 3. Maintenance of Statin Intensity During Follow-up

	Total Population		Propensity-Matched Population	
Year of Follow-up*	High-Intensity Statin (n=372)	Non-High-Intensity Statin (n=1374)	High-Intensity Statin (n=367)	Non-High-Intensity Statin (n=798)
1 y	302/303 (99.7%)	1127/1133 (99.5%)	297/298 (99.7%)	645/649 (99.4%)
2 y	191/194 (98.5%)	869/876 (99.2%)	187/190 (98.4%)	480/486 (98.8%)
3 y	124/142 (87.3%)	620/654 (94.8%)	122/139 (87.8%)	313/333 (94.0%)

PCI indicates percutaneous coronary intervention.
*We investigated the maintenance of statin intensity in the patients who were not censored and had information about the follow-up medication at 1, 2, and 3 years after index PCI, respectively. The denominators of each cell were calculated by subtracting the number of patients without statin information from the patients under follow-up at each year. The numbers of patients under follow-up and without statin information are summarized in Table S2.

Table 4. Clinical Outcomes

	High-Intensity Statin	Non-High-Intensity Statin	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
Total population (n=1746)	(n=372)	(n=1374)				
Primary end point						
Cardiac death, MI, stroke	11 (4.1)	108 (9.9)	0.44 (0.24–0.82)	0.01	0.42 (0.23–0.79)	<0.01
Secondary end points						
All-cause death	12 (5.0)	100 (9.6)	0.56 (0.31–1.02)	0.06	0.56 (0.30–1.01)	0.06
Cardiac death	3 (0.8)	50 (4.8)	0.27 (0.09–0.87)	0.03	0.29 (0.09–0.94)	0.04
MI	4 (1.4)	26 (2.4)	0.64 (0.22–1.83)	0.40	0.64 (0.22–1.84)	0.41
Stroke	5 (2.2)	46 (4.2)	0.48 (0.19–1.20)	0.12	0.45 (0.18–1.13)	0.09
Target lesion revascularization	11 (4.2)	65 (5.2)	0.66 (0.35–1.26)	0.21	0.68 (0.36–1.29)	0.24
Target vessel revascularization	15 (5.4)	110 (9.0)	0.54 (0.31–0.92)	0.02	0.64 (0.37–1.11)	0.11
Propensity-matched population (n=1165)	(n=367)	(n=798)				
Primary end point						
Cardiac death, MI, stroke	11 (4.2)	66 (11.2)	0.39 (0.20–0.75)	<0.01	0.36 (0.19–0.69)	<0.01
Secondary end points						
All-cause death	12 (5.1)	50 (9.0)	0.57 (0.30–1.07)	0.08	0.58 (0.31–1.07)	0.08
Cardiac death	3 (0.9)	27 (4.9)	0.26 (0.08–0.86)	0.03	0.27 (0.08–0.90)	0.03
MI	4 (1.4)	15 (2.6)	0.56 (0.18–1.72)	0.31	0.53 (0.17–1.63)	0.27
Stroke	5 (2.3)	33 (5.6)	0.40 (0.19–1.03)	0.06	0.41 (0.16–1.06)	0.07
Target lesion revascularization	11 (4.3)	37 (4.8)	0.68 (0.34–1.34)	0.26	0.67 (0.34–1.34)	0.26
Target vessel revascularization	15 (5.4)	52 (7.3)	0.66 (0.37–1.19)	0.17	0.66 (0.37–1.19)	0.17

Values are n (%). CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction.
*The adjusted HRs are adjusted using all variables listed in Table 1 and baseline lipid profile in Table 2, eliminating insignificant variables.

baseline hs-CRP was significantly greater in the high-intensity statin group than in the non-high-intensity statin group (6.7±35.1 versus 2.1±19.0 mg/L; *P*=0.04).

Clinical Outcomes

Overall population

Median follow-up duration was 4.2 years (interquartile range, 2.2–5.0). Observed clinical outcomes are shown in Table 4. MACEs occurred in 119 patients, including 53 cardiac deaths, 30 MIs, and 51 strokes. Incidence of MACEs was significantly lower in the high-intensity statin group than that of the non-high-intensity statin group (4.1% versus 9.9%; adjusted HR, 0.42; 95% CI, 0.23–0.79; *P*<0.01; Figure 2A). Cardiac death also occurred less frequently in the high-intensity statin group than the non-high-intensity statin group (0.8% versus 4.8%; adjusted HR, 0.29; 95% CI, 0.09–0.94; *P*=0.04). However, in the analysis that we classified only those deaths proven to have a definite cardiac etiology as "cardiac death," incidence of cardiac death was not significantly different between the 2 groups (0.6% versus 2.8%; adjusted HR, 0.31; 95% CI, 0.07–1.34; *P*=0.12). Although all-cause death and stroke tended to occur less frequently in the high-intensity statin group than in the non-high-intensity statin group, statistically significance was not achieved.

Propensity-matched population

There were 77 instances of MACEs with a median follow-up of 4.1 years (interquartile range, 2.1–5.0) in the matched patients. Incidence of MACEs was significantly lower in the high-intensity statin group than that of the non-high-intensity statin group (4.2% versus 11.2%; adjusted HR, 0.36; 95% CI, 0.19–0.69; *P*<0.01; Table 4; Figure 2B). Cardiac death also occurred less frequently in the high-intensity statin group than the non-high-intensity statin group (0.9% versus 4.9%; adjusted HR, 0.27; 95% CI, 0.08–0.90; *P*=0.03). Although all-cause death and stroke tended to occur less frequently in the high-intensity statin group than in the non-high-intensity statin group, statistically significance was not achieved.

Subgroup Analysis

To determine whether the treatment benefits of high-intensity statin observed in the overall population were consistent, we calculated the unadjusted HR for the MACEs in various

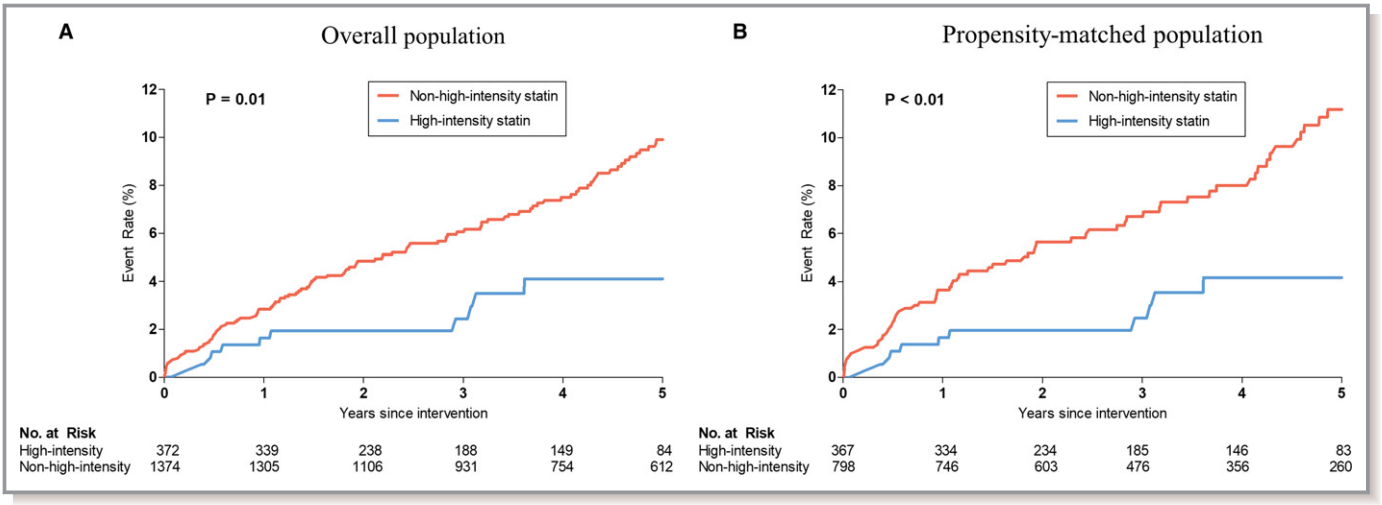

Figure 2. Kaplan–Meier estimates of the incidence of the primary end point in overall and propensity-matched population. **A,** Kaplan–Meier curves for major cardiovascular events (a composite of cardiac death, myocardial infarction, or stroke) in the high-intensity statin group vs the non-high-intensity statin group in the overall population. **B,** Kaplan–Meier curves for major cardiovascular events (a composite of cardiac death, myocardial infarction, or stroke) in the high-intensity statin group vs the non-high-intensity statin group in the propensity-matched population.

subgroups (Figure 3). Benefits of high-intensity statin were consistent, and there was no significant interaction between statin intensity and primary outcome in any subgroups.

Discussion

In the present study, we compared the long-term clinical outcomes according to intensity of statin in patients achieving treatment target for LDL-C during follow-up after PCI. The major findings of this study were: (1) Patients in the high-intensity statin group had a significantly lower incidence of MACEs than those in the non-high-intensity statin; (2) this finding was consistently observed in the propensity-matched population and the various subgroups; (3) time-averaged LDL-C, which was calculated from follow-up LDL-C values after index PCI, was significantly lower in the high-intensity statin group than in the non-high-intensity statin group, but the difference was small; and (4) reduction from baseline hs-CRP was significantly greater in the high-intensity statin group than in the non-high-intensity statin group.

Limited Data on Comparison Between Statin Intensity-Based Strategy Versus LDL-C Target-Based Strategy

Statin therapy should be initiated as early as possible to all patients who undergo coronary revascularization for coronary artery disease, regardless of baseline serum cholesterol level.[11–13] However, 2 major guidelines from the ACC/AHA and ESC/EAS recommend different lipid-lowering strategies for secondary prevention in patients who undergo PCI.[3,5] Whereas the ESC/EAS guideline focuses on decreasing LDL-C to specific treatment target, ACC/AHA recommends the treatment using evidence-based intensity statin therapy without specific cholesterol target.[14] Such a distinction between the 2 guidelines has led to confusion in the clinical setting.[6] During the study period, a high-intensity statin was prescribed in 14.2% (774 of 5452) of all patients with available information on statin type and dose in our PCI registry. Although the rate of prescription of a high-intensity statin increased to 41.9% (137 of 327) after the ACC/AHA published the guideline on the treatment of blood cholesterol in November 2013, non-high-intensity statins have still been used frequently for secondary prevention in patients undergoing PCI. These observations imply a lack of consensus in the treatment of LDL-C for secondary prevention. In a meta-analysis by the Cholesterol Treatment Trialists' Collaboration, each 1-mmol/L (approximately 40 mg/dL) reduction in LDL-C reduced the risk of major vascular events by around 22%, regardless of statin type and dose.[4] Moreover, recent trials demonstrated that nonstatin lipid-lowering drugs, such as ezetimibe and cholesteryl ester transfer protein inhibitor, when added to statin, can further decrease LDL-C and improve outcomes.[15,16] These findings support LDL-C target-based strategy. However, several landmark studies on statin therapy for secondary prevention compared high-intensity statin versus moderate-intensity statin, not target LDL-C, and demonstrated that high-intensity statin was superior to moderate-intensity statin for reducing the incidence of MACEs.[1,2] So far, there are limited data on comparison between statin intensity-based strategy versus LDL-C target-based strategy, especially in patients with similar LDL-C levels. Therefore, we compared long-term clinical outcomes

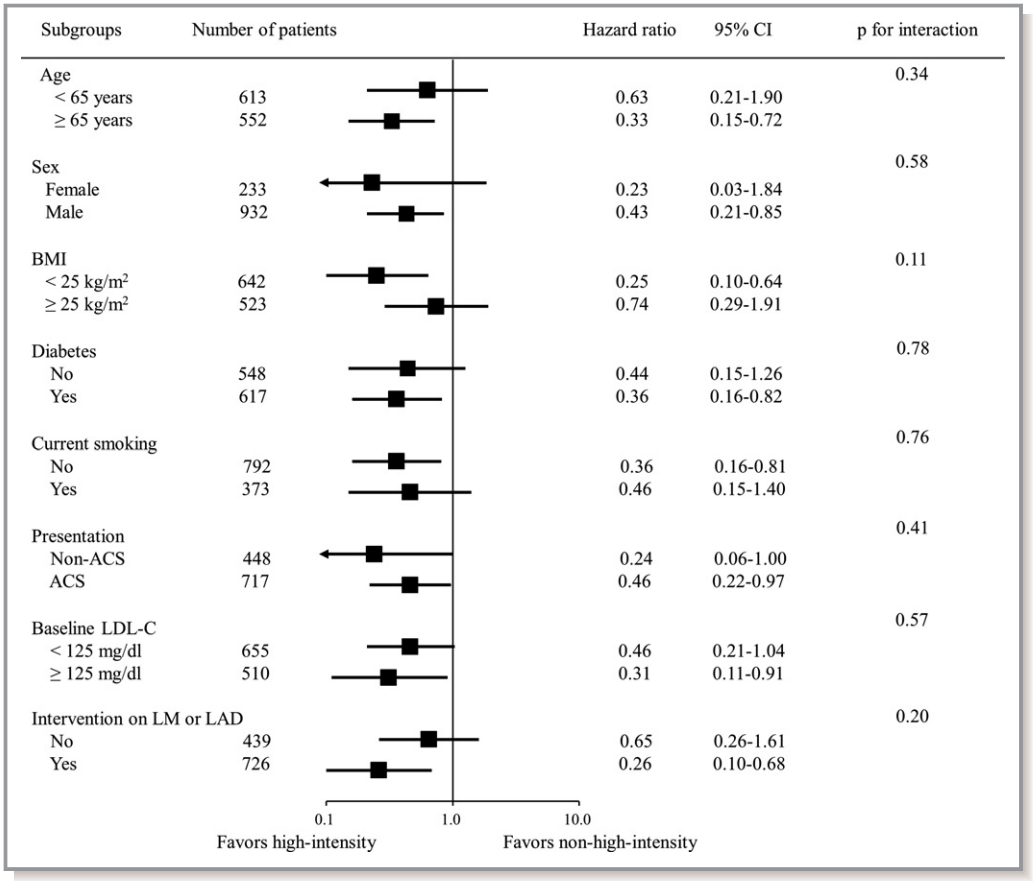

Figure 3. Comparative unadjusted hazard ratios of primary end point for subgroups. ACS indicates acute coronary syndrome; BMI, body mass index; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LAD, left anterior descending artery; LM, left main coronary artery.

between the high-intensity statin group and the non-high-intensity statin group among patients who achieved LDL-C target after PCI.

Plausible Explanations for the Benefit of High-Intensity Statin Therapy

In the present study, high-intensity statin therapy was more effective in preventing MACE than non-high-intensity statin therapy in patients achieving treatment target for LDL-C after PCI. There are several plausible explanations for our results. First, level of follow-up time-averaged LDL-C was lower in the high-intensity statin group than in the non-high-intensity statin group. As mentioned above, greater reduction in LDL-C resulted in greater reduction in risk of MACE in meta-analyses and randomized controlled trials. Second, percent LDL-C reduction was greater in the high-intensity statin group than in the non-high-intensity statin group. In a pooled individual patient-level analysis of 3 large statin trials, Bangalore et al have reported that, among patients with attained LDL-C ≤70 mg/dL, those with percent LDL-C reduction of <50% had a significantly higher risk of cardiovascular event when compared with the group with percent LDL-C reduction of ≥50%.[17] Greater percent LDL-C reduction in the high-intensity statin group, compared with the non-high-intensity statin group, might have partly explain difference in the risk of MACEs. Third, however, observed benefit in the high-intensity statin group was greater than expected benefit from the difference in time-averaged LDL-C between the 2 groups, when compared with previous data from meta-analyses.[4] This finding suggests that observed benefit in the high-intensity statin group could not be explained by only the lipid-lowering effect of statins and might be, at least partly, attributable to a non-lipid-mediated mechanism or pleotropic effects of statins. Statins have been reported to have diverse protective effects on the cardiovascular system: improvement of endothelial dysfunction[18]; modulation of inflammatory response and thrombogenesis[19]; and stabilization of plaque.[20] In particular, several trials demonstrated that pleotropic effects of statins are more potent in high-intensity statins than in non-high-intensity statin.[21–23] In the present study, we investigated follow-up hs-CRP to compare anti-inflammatory effects between the 2 groups. Follow-up hs-CRP was significantly lower and reduction from baseline hs-CRP was significantly

greater in the high-intensity statin group than in the non-high-intensity statin group, suggesting benefit from non-lipid-lowering effects of high-intensity statins. Additionally, to find an explanation for the extreme differences between the 2 groups, we compared the clinical outcomes between the high-intensity statin group (n=618) and the non-high-intensity statin group (n=3517) in all reviewed patients (n=4135), including the patients who failed to achieve treatment target for LDL-C. Unlike the results of the patients who achieved LDL-C goal, incidence of the primary outcome was not significantly different between the 2 groups (7.3% versus 10.0%; adjusted HR, 0.80; 95% CI, 0.55–1.16; *P*=0.24). Although it is difficult for us to explain the exact causes, the relatively small sample size, especially for the high-intensity statin group, and nonrandomized nature of our study may have resulted in the extreme differences between the 2 groups.

Limitations

Our study had several limitations. First, the study was a nonrandomized, observational study. Statin intensity was determined at the discretion of the attending physician and might have been influenced by several factors such as underlying demographics, clinical presentation at admission, baseline lipid values, and physician's preference. Although we performed propensity-score–matched analysis and adjustments to overcome the potential bias that can influence the study outcome, unmeasured factors might have affected study outcomes. Second, 3622 patients were excluded because of lack of information on statin prescription and LDL-C during follow-up, although 8148 patients were screened at first. For this reason, a selection bias could have influenced the study results. Third, patients' compliance to statin was not accurately evaluated. To evaluate the compliance indirectly, we used information of medication prescribed during follow-up after PCI. As shown in Table 3, statin intensity at discharge after PCI was well maintained during follow-up. Moreover, because we included only patients who achieved treatment target for LDL-C, we believe most patients might have a good compliance to statins. The main cause of sudden drop of adherence to high-intensity statin at the 3 years of follow-up might be that some physicians reduced the intensity of statin from high to moderate because LDL-C level had been well maintained under the treatment target during follow-up. Fourth, hs-CRP data were only available for 69.6% of the total population (1216 of 1746). Fifth, the median follow-up duration of the high-intensity statin group was shorter than that of the non-high-intensity statin group (3.1 [1.4–4.9] versus 4.5 [2.5–5.0] years). To assess whether difference in follow-up duration influenced the study outcome, we truncated follow-up period to 3 years and re-evaluated the clinical outcome. Incidence of primary outcome was significantly lower in the high-intensity statin group than that of the non-high-intensity statin group (2.4% versus 6.1%; adjusted HR, 0.41; 95% CI, 0.20–0.86; *P*=0.02). An adjusted HR of the primary outcome obtained from 3-year follow-up data was similar to that using 5-year follow-up data. Based on this similarity, we could estimate that the difference in follow-up duration between the 2 groups did not significantly affect the clinical outcome. Last, MI and stroke might be relatively under-reported given that this was not a randomized, controlled trial with rigorous follow-up. However, ratios of MI and stroke to cardiac death or all-cause death were comparable to, or higher than, those of the randomized, controlled trials[24,25] conducted in Korea. Moreover, it was highly unlikely that MI and stroke were selectively under-reported in the high-intensity statin group than in the non-high-intensity statin group.

Conclusions

In patients who the achieved LDL-C target recommended by the ESC/EAS guideline for secondary prevention after PCI, patients treated with high-intensity statin had a significantly lower incidence of MACE than those treated with non-high-intensity statin. Our data suggest that high-intensity statins should be considered even in patients achieving LDL-C target with non-high-intensity statins.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Statins used in the non-high-intensity statin group.

	All patients who reviewed (n=4135)	Patients who achieved LDL-C target (n=1746)
Non-high-intensity statins*	(n=3517)	(n=1374)
Moderate-intensity statins	3377 (96.0)	1359 (98.9)
Atorvastatin 10mg	1480 (42.1)	562 (40.9)
Rosuvastatin 10mg	754 (21.4)	386 (28.1)
Atorvastatin 20mg	446 (12.7)	219 (15.9)
Simvastatin 20mg	386 (11.0)	91 (6.6)
Pitavastatin 2mg	109 (3.1)	36 (2.6)
Fluvastatin XL 80mg	90 (2.6)	33 (2.4)
Simvastatin 40mg	63 (1.8)	19 (1.4)
Pravastatin 40mg	49 (1.4)	13 (0.9)
Low-intensity statins	140 (4.0)	15 (1.1)
Pravastatin 10mg	120 (3.4)	12 (0.9)
Lovastatin 20mg	13 (0.4)	3 (0.2)
Pravastatin 20mg	7 (0.2)	-

Values are n (%).

* Definition of statin intensity was based on the guideline from 2013 ACC/AHA guideline on the treatment of blood cholesterol.

LDL-C = low-density lipoprotein cholesterol

Table S2. The number of patients under follow-up and without statin information.

Year of follow-up*		Total population		Propensity-matched population	
		High-intensity statin (n=372)	Non-high-intensity statin (n=1374)	High-intensity statin (n=367)	Non-high-intensity statin (n=798)
1 year	Patients under follow-up	343	1331	338	765
	Lack in information on statin type and dose	40	198	40	116
	Denominator in Table 3	303	1133	298	649
2 years	Patients under follow-up	241	1140	237	626
	Lack in information on statin type and dose	47	264	47	140
	Denominator in Table 3	194	876	190	486
3 years	Patients under follow-up	189	961	186	495
	Lack in information on statin type and dose	47	307	47	162
	Denominator in Table 3	142	654	139	333

*The denominators of Table 3 were calculated by subtracting the number of patients without statin information from the patients under follow-up at each year.