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Different diabetogenic effect of statins according to intensity and dose in patients with acute myocardial infarction: a nationwide cohort study

Jieun Lee[1,21], Jah Yeon Choi[1,21], Byoung Geol Choi[1], You-Jung Choi[1], Soohyung Park[1], Dong Oh Kang[1], Eun Jin Park[1], Ji Bak Kim[1], Seung Young Roh[1], Jin Oh Na[1], Cheol Ung Choi[1], Eung Ju Kim[1], Chang Gyu Park[1], Myung Ho Jeong[2], Jin-Yong Hwang[3], Seung-Ho Hur[4], Jin-Ok Jeong[5], SeokKyu Oh[6], Seung-Woon Rha[1]✉ & KAMIR NIH Investigators*

Statin is crucial for acute myocardial infarction (AMI) patients. However, the risk of new-onset diabetes mellitus (NODM) associated with statin is a concern. This study aimed to determine the incremental diabetogenic effects of statins according to their intensity and dose in AMI patients undergoing percutaneous coronary intervention (PCI). Among 13,104 patients enrolled in the Korea AMI Registry between 2011 and 2015, 6152 patients without diabetes mellitus (DM) who underwent PCI and received moderate-to-high-intensity atorvastatin and rosuvastatin were selected for the study. The endpoints were NODM and major adverse cardiovascular events (MACE), composite of all-cause mortality, recurrent MI, and revascularization up to 3 years. Among the participants, 3747 and 2405 received moderate- and high-intensity statins, respectively. The Kaplan–Meier curves demonstrated a higher incidence of NODM in patients with high-intensity statins than those with moderate-intensity. High-intensity statin was a significant predictor of NODM after adjusting for other co-variables (HR = 1.316, 95% CI 1.024–1.692; P < 0.032). Higher dose of rosuvastatin was associated with a higher cumulative incidence of NODM, but this dose-dependency was not apparent with atorvastatin. Cumulative incidence of MACE decreased dose-dependently only with atorvastatin. High-intensity statin was associated with a higher cumulative incidence of NODM in AMI patients, and this association was more evident in rosuvastatin. The different diabetogenic effects of the two statins provide supporting evidence for understanding the nuanced nature of statin treatment in relation to NODM.

Keywords Statin intensity, New-onset diabetes mellitus, Acute myocardial infarction

Abbreviations

AMI	Acute myocardial infarction
LDL	Low-density lipoprotein
ASCVD	Atherosclerotic cardiovascular disease
NODM	New-onset diabetes mellitus

[1]Division of Cardiology, Department of Internal Medicine, Korea University Guro Hospital, 148, Gurodong-Ro, Guro-Gu, Seoul 08308, South Korea. [2]Chonnam National University Hospital, Gwangju, South Korea. [3]Department of Internal Medicine, Gyeongsang National University School of Medicine, Gyeongsang National University Hospital, Jinju, South Korea. [4]Keimyung University Dongsan Medical Center, Cardiovascular Medicine, Deagu, South Korea. [5]Department of Internal Medicine, College of Medicine, Chungnam National University Hospital, Chungnam National Univeresity, Daejeon, South Korea. [6]Division of Cardiology, Department of Internal Medicine, Wonkwang University School of Medicine, Iksan, South Korea. [21]These authors contributed equally: Jieun Lee and Jah Yeon Choi. *A list of authors and their affiliations appears at the end of the paper. ✉email: swrha617@yahoo.co.kr

KAMIR	Korea Acute Myocardial Infarction Registry
MACE	Major adverse cardiac events
BMI	Body Mass Index
HR	Hazard ratio
CI	Confidence interval

Statins are must-have agents used in patients with acute myocardial infarction (AMI), particularly following percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DESs). The risk of cardiovascular events can be reduced not only by lowering the low-density lipoprotein (LDL) cholesterol levels but also multiple pleiotropic effects beyond lipid lowering effect with statin treatment. Statins inhibit the pathways of atherosclerosis by inhibiting HMG-CoA reductase inside of endothelial cells and vascular smooth muscle cells[1]. Clinical studies have shown multiple benefits of statins which are LDL-cholesterol-independent (or pleiotropic)[2]. Statin treatments have shown to significantly reduce not only LDL cholesterol levels but also CRP levels[3], and also reduced degree of inflammation in other systemic diseases such as periodontal disease or rheumatoid arthritis[4]. Finally, statin treatments have significantly reduced cardiovascular mortality and morbidity in numerous previous studies[5–7]. The clinical efficacy of statins in primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) has been proven by numerous studies[8]. Further, the current guidelines recommend high-intensity statins for patients with AMI[9,10].

However, since the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial first raised the issue of an increased risk of new-onset diabetes mellitus (NODM) associated with statin treatment[3], this has been a major concern when treating AMI patients with statins. A meta-analysis of randomized trials has shown that statin therapy is associated with an approximately 10% increased risk of NODM[11]. Moreover, it revealed that intensive-dose statin therapy is associated with an increased risk of NODM compared with moderate-dose statin treatment[12]. Observational studies have also supported this finding[1,13].

Although statins play a crucial role in the secondary prevention of AMI, the increasing concern for NODM associated with statin treatment is understandable due to DM being a potent risk factor for ASCVD. However, there are still unresolved questions regarding this issue. It remains uncertain whether statins genuinely contribute to the development of DM, or if patients who are subscribed statins merely belong to a high-risk group for NODM due to factors such as advanced age and numerous comorbidities, including hypertension, dyslipidemia, or obesity.

Moreover, there is ongoing argument regarding whether the diabetogenic effect of statins is a class effect. Furthermore, considering that patients with AMI need higher intensity statin treatment than the rest of the population, it is important to identify whether higher intensity statin treatment has a higher incremental diabetogenic effect. However, comprehensive understanding of this association is yet to be achieved.

To address this knowledge gap, we used the national AMI registry data and investigated the dose-dependent diabetogenic effects of atorvastatin and rosuvastatin, both of which offer various moderate- and high-intensity dosages as per the 2018 American Heart Association (AHA) guideline on the management of blood cholesterol[10].

Methods

Study population

The Korea Acute Myocardial Infarction Registry (KAMIR) is a prospective multicenter national database supported by the Korean Society of Cardiology. Data on patients with AMI from 20 PCI capable tertiary or community hospitals in Korea were registered online. Patient data were gathered by well-trained study coordinators using a standardized case report form. The KAMIR registry was approved by the medical ethics committee of each participating center, and all study participants provided written informed consent. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

A total of 13,104 patients with AMI enrolled in the KAMIR between November 2011 and May 2015 were reviewed. Among the AMI patients without DM at enrollment and those who had undergone successful PCI with DESs, individuals taking either atorvastatin or rosuvastatin, which are available in various doses ranging from moderate to high intensity, were included in the analysis. Patients who had experienced in-hospital major adverse cardiac events (MACE) and those lacking information about statin intensity were excluded. Ultimately, a total of 6152 patients were considered in the final analysis. We investigated the cumulative incidence of NODM and MACE based on the intensity of statins, as well as the individual doses within atorvastatin and rosuvastatin group (Fig. 1).

Study endpoints

The primary endpoint of this study was the cumulative incidence of NODM according to statin intensity during 3 years of follow-up. NODM was defined as glycated hemoglobin (HbA1c) levels ≥ 6.5% or newly treated with oral hypoglycemic agents or insulin during follow-up. The secondary endpoint was MACE which was defined as a composite of all-cause mortality, myocardial infarction (MI), and any revascularization according to statin intensity during 3 years of follow-up.

Patient clinical data were obtained through chart reviews, face-to-face interviews at the outpatient clinic, or telephone interviews.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Student's t-test was used to analyze the differences between the two groups. Dichotomous variables are presented as percentages, and the chi-square test or Fisher's exact test was used to analyze the differences.

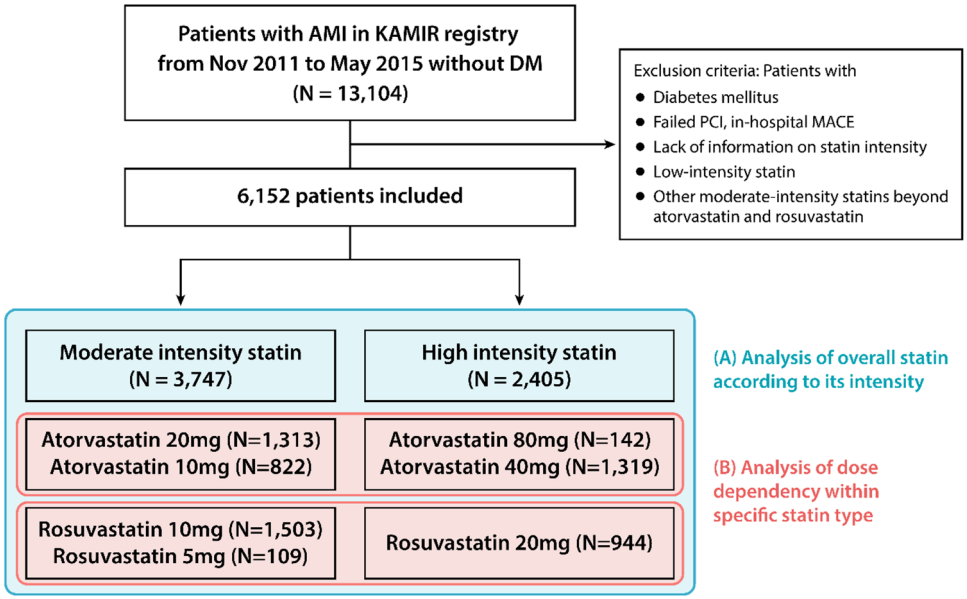

Figure 1. Study schema. A total of 6152 AMI patients who were treated with moderate-to-high intensity atorvastatin and rosuvastatin were included in the final analysis. *AMI* acute myocardial infarction, *KAMIR* Korea Acute Myocardial Infarction Registry, *PCI* percutaneous coronary intervention; *MACE* major adverse cardiac events.

The Kaplan–Meier method with log-rank test was used to compare the cumulative incidence of NODM and MACE between the two groups. Cox proportional hazard models were used to identify potential prognostic factors for NODM and MACE, and the results were presented as hazard ratios (HR) and 95% confidence intervals (CI). For multivariate analysis, variables with *P*-values (< 0.05) in the univariate analysis were included.

All analyses were performed using the SPSS software (version 22.0, Inc. Chicago, IL, USA). Statistical significance was set at a *P*-value of < 0.05.

Ethics approval and consent to participate

The KAMIR registry was approved by the medical ethics committee (Institutional Review Board) of each participating center, and all study participants provided written informed consent. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Results

Baseline characteristics

The baseline characteristics of the study participants are presented in Table 1. Among the 6152 study participants, 3747 and 2405 received moderate- and high-intensity statins, respectively. The mean age was significantly higher in the moderate-intensity statin group than in the high-intensity statin group (63.7 ± 12.8 vs. 60.5 ± 12.6; $P < 0.001$). The high-intensity statin group had a higher prevalence of male sex and current smokers, higher systolic and diastolic blood pressure, higher body mass index (BMI) ($P < 0.001$), and larger abdominal circumference ($P = 0.011$). The levels of total and LDL cholesterol were significantly higher in the high-intensity statin group (195.5 ± 44.6 vs. 178.2 ± 41.3; $P < 0.001$ and 127.8 ± 38.7 vs. 112.0 ± 38.3; $P < 0.001$, respectively); however, the levels of triglycerides were significantly higher in the moderate-intensity statin group (145.7 ± 126.5 vs. 123.8 ± 109.2; $P < 0.001$). There were no statistically significant intergroup differences in ST-segment elevation MI, non-ST segment elevation MI, high-density lipoprotein cholesterol, random blood glucose, and creatinine levels.

More than 99% of the study population was taking aspirin. The prescription rate of ticagrelor was significantly higher in the high-intensity statin group, whereas those of clopidogrel and cilostazol were higher in the moderate-intensity statin group. Prescription of β-blockers and renin–angiotensin–aldosterone system inhibitors was more frequent in the moderate-intensity group. The total number of implanted coronary stents was similar between the two groups. However, the high-intensity statin group had a slightly higher number of coronary stents than the moderate-intensity statin group, and this difference was statistically significant.

Clinical outcomes

The Kaplan–Meier curve for the cumulative incidence of NODM are presented in Figs. 2 and 3, and Supplemental Table S1. The high-intensity statin group had a significantly higher cumulative incidence of NODM than the moderate-intensity statin group (7.8% vs. 5.8%; log-rank $P = 0.002$) (Fig. 2). Figure 3 presents the cumulative incidence of NODM according to the intensity and dose for atorvastatin and rosuvastatin. Regarding groups treated with atorvastatin, study population treated with high-intensity atorvastatin showed a significantly higher cumulative incidence of NODM than the moderate-intensity atorvastatin group (7.2% vs. 5.8%, $P = 0.002$) (Fig. 3A).

Variables	Moderate intensity(n = 3747)	High intensity (n = 2405)	P-value
Men	2841 (75.8%)	1966 (81.7%)	< 0.001
Age (years)	63.7 ± 12.8	60.5 ± 12.6	< 0.001
Systolic BP	130.3 ± 26.8	133.7 ± 26.6	< 0.001
Diastolic BP	79.4 ± 15.9	81.6 ± 17.0	< 0.001
BMI	23.7 ± 3.2	24.5 ± 3.3	< 0.001
Abdominal circumstance	86.5 ± 8.6	87.5 ± 8.4	0.011
Smoking	2240 (59.8%)	1580 (65.7%)	< 0.001
Current smoker	1564 (41.7%)	1119 (46.5%)	< 0.001
Ex-smoker	676 (18.0%)	461 (19.2%)	0.266
Pack year	30.8 ± 23.8	27.6 ± 18.4	< 0.001
LV ejection fraction (%)	52.5 ± 10.3	54.1 ± 9.8	< 0.001
LVEDD	49.5 ± 6.1	49.8 ± 5.5	0.054
LVESD	34.7 ± 7.7	34.8 ± 9.8	0.959
Myocardial infarction			
ST-segment elevation	1979 (52.8%)	1284 (53.4%)	0.660
Non-ST-segment elevation	1768 (47.2%)	1121 (46.6%)	0.660
Laboratory findings			
Total cholesterol (mg/dl)	178.2 ± 41.3	195.5 ± 44.6	< 0.001
Triglyceride (mg/dl)	145.7 ± 126.5	123.8 ± 109.2	< 0.001
HDL-cholesterol (mg/dl)	43.5 ± 11.9	44.0 ± 11.5	0.138
LDL-cholesterol (mg/dl)	112.0 ± 38.3	127.8 ± 38.7	< 0.001
Glucose (mg/dl)	139.3 ± 45.9	137.6 ± 37.8	0.121
Creatinine (mg/dl)	0.98 ± 0.93	0.96 ± 0.81	0.429
Medication			
Aspirin	3731 (99.6%)	2391 (99.4%)	0.394
Clopidogrel	2705 (72.2%)	1443 (60.0%)	< 0.001
Prasugrel	409 (10.9%)	267 (11.1%)	0.819
Ticagrelor	595 (15.9%)	680 (28.3%)	< 0.001
Cilostazol	373 (10.0%)	95 (4.0%)	< 0.001
Calcium channel blockers	210 (5.6%)	123 (5.1%)	0.407
β blockers	3264 (87.1%)	2049 (85.2%)	0.033
RAAS inhibitor	3157 (84.3%)	1907 (79.3%)	< 0.001
ACEi	2172 (58.0%)	1096 (45.6%)	< 0.001
ARB	1003 (26.8%)	825 (34.3%)	< 0.001
Atorvastatin	2135 (57.0%)	1461 (60.7%)	< 0.001
10 mg	822 (21.9%)	0 (0.0%)	
20 mg	1313 (35.0%)	0 (0.0%)	
40 mg	0 (0.0%)	1319 (54.8%)	
80 mg	0 (0.0%)	142 (5.9%)	
Rosuvastatin	1612 (43.0%)	944 (39.3%)	< 0.001
5 mg	109 (2.9%)	0 (0.0%)	
10 mg	1503 (41.1%)	0 (0.0%)	
20 mg	0 (0.0%)	944 (39.3%)	
Procedural characteristics			
Total stent length (mm)	28.5 ± 12.4	28.4 ± 12.7	0.748
Total stent number	1.08 ± 0.48	1.11 ± 0.49	0.018

Table 1. Baseline patient clinical and medical characteristics. Values are mean ± SD, %, or n (%), unless noted otherwise. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *BP* blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LV* left ventricle, *LVEDD* left ventricular end diastolic diameter, *LVESD* left ventricular end systolic diameter, *RAAS* renin–angiotensin–aldosterone system.

Further, the study population treated with the highest dose (80 mg) of atorvastatin showed the highest cumulative incidence of NODM (7.7%), followed by the second highest dose (40 mg) (7.1%). On the other hand, the other two groups, treated with lower doses (20 mg and 10 mg) of atorvastatin showed a relatively lower cumulative

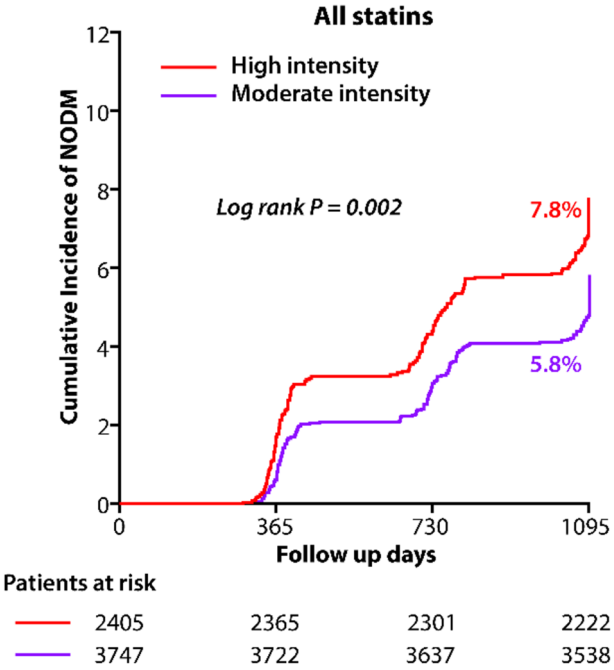

Figure 2. Cumulative incidence of NODM according to the statin intensity. The Kaplan–Meier curve showed the high-intensity statin group had a significantly higher cumulative incidence of NODM than the moderate-intensity statin group (7.8% vs. 5.8%; log-rank P = 0.002). *NODM* new-onset diabetes mellitus.

incidence of NODM (5.8% and 5.7%), even though the association was statistically insignificant ($P = 0.484$) (Fig. 3B). In terms of rosuvastatin, the high-intensity rosuvastatin group showed a significantly higher cumulative incidence of NODM than moderate-intensity rosuvastatin group (8.3% vs. 5.8%, $P = 0.004$) (Fig. 3C). The dose dependency of diabetogenicity of rosuvastatin was more prominent than that of atorvastatin. A higher dose of rosuvastatin was significantly associated with higher cumulative incidence of NODM, which was statistically significant (20 mg vs. 10 mg vs. 5 mg: 8.3% vs. 5.5% vs. 2.8%, $P = 0.008$) (Fig. 3D).

The results of the Cox regression analysis of NODM showing the potential prognostic factors are presented in Table 2. Body mass index (BMI) and abdominal circumference were positively associated with the incidence of NODM in a univariate model. Plasma glucose and triglyceride levels were also positively associated with the incidence of NODM in a univariate model, whereas the association with the amount of smoking was not statistically significant. In the multivariate model, BMI (HR 1.071; 95% CI 1.040–1.103; $P < 0.001$), plasma glucose level (HR 1.007; 95% CI 1.005–1.008; $P < 0.001$) and triglyceride (HR 1.001; 95% CI 1.000–1.001; $P = 0.035$) were positively associated with the incidence of NODM. When we compared the incidence of NODM between the high- and moderate-intensity statin groups, the hazard ratios were significantly higher in the high-intensity statin group than in the moderate-intensity statin group in both univariate (HR 1.360; 95% CI 1.115–1.659; $P = 0.002$) and multivariate (HR 1.306; 95% CI 1.056–1.617; $P = 0.014$) analyses. Regarding specific statins, atorvastatin at different doses did not show a significant impact on NODM ($P = 0.486$). In contrast, rosuvastatin demonstrated a significant difference in NODM occurrence ($P = 0.009$). When comparing different doses of rosuvastatin, several dose-dependent effects were observed, with some being statistically significant in the univariable model (e.g., 10 mg vs. 20 mg with a HR 1.514; 95% CI 1.111–2.062; $P = 0.009$) and one remaining significant in the multivariable model (e.g., 10 mg vs. 20 mg with a HR 1.430; 95% CI 1.020–2.004; $P = 0.038$).

The Kaplan–Meier curve for the cumulative incidence of NODM are presented in Fig. 4 and Supplemental Fig. S1, and Supplemental Table S1. The cumulative incidence of MACE was significantly lower in the high-intensity statin group than in the moderate-intensity group ($P = 0.004$) (Fig. 4A). Among patients treated with atorvastatin, the study population treated with the highest dose (80 mg) showed the lowest cumulative incidence of MACE, followed by those treated with the second (40 mg) and third (20 mg) highest doses (Fig. 4B). The study population treated with the lowest dose (10 mg) of atorvastatin had the highest cumulative incidence of MACE among all groups. In patients treated with 5, 10, and 20 mg rosuvastatin, there was no dose-dependent association between the cumulative incidence of MACE and rosuvastatin ($P = 0.503$) (Supplemental Fig. S1). Supplemental Table S2 presents the results of the Cox regression analysis of MACE in univariate and multivariate models. When compared with the moderate-intensity statin group, the high-intensity statin group was associated with lower MACE (HR 0.809; 95% CI 0.700–0.935; $P = 0.004$). The multivariate model showed a similar tendency; however, the difference was not statistically significant ($P = 0.252$).

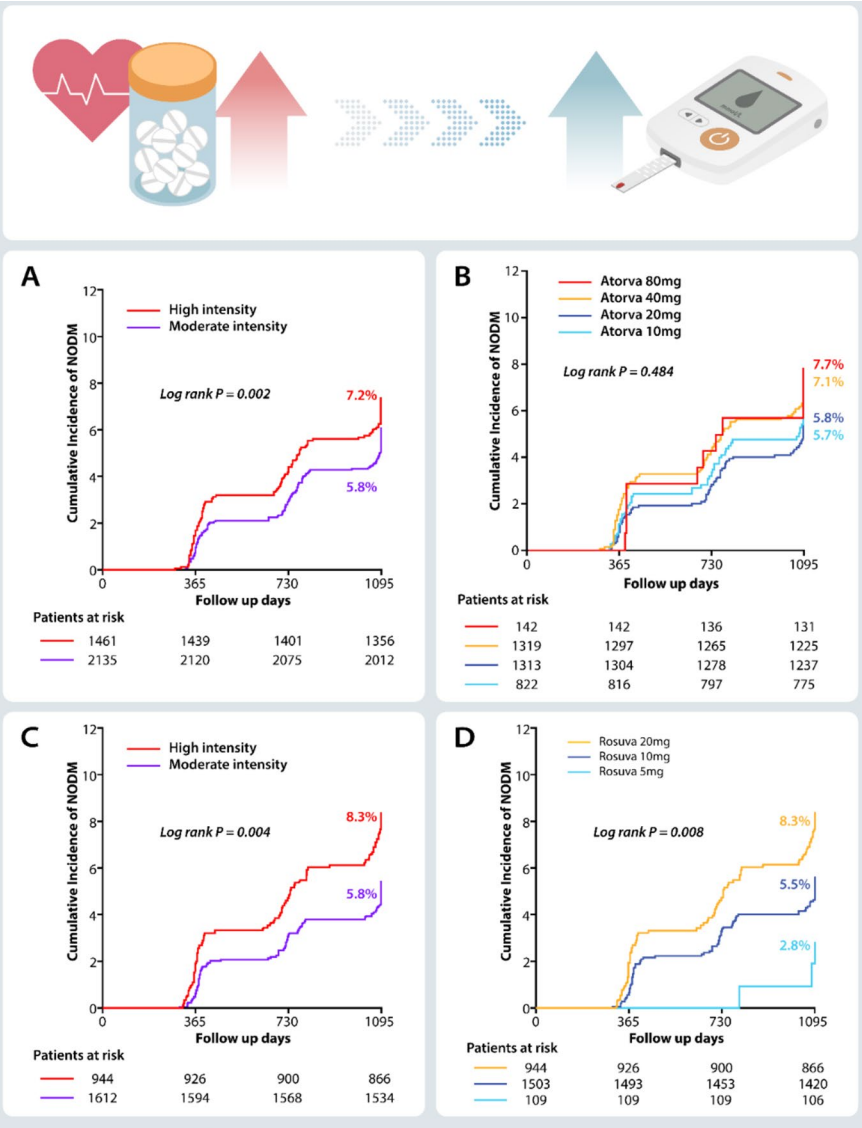

Figure 3. Cumulative incidence of NODM according to the statin intensity and dose. (**A**) Cumulative incidence of NODM according to the atorvastatin intensity. Patients treated with high-intensity atorvastatin showed a significantly higher cumulative incidence of NODM compared to the moderate-intensity atorvastatin group (7.2% vs. 5.8%, P = 0.002). (**B**) Cumulative incidence of NODM according to the atorvastatin dose. Patients treated with the 80 mg of atorvastatin had the highest cumulative incidence of NODM, followed by those on 40 mg, 20 mg and 10 mg of atorvastatin (7.7% vs. 7.1% vs. 5.8% vs. 5.7%, respectively, P = 0.484) (**C**) Cumulative incidence of NODM according to the rosuvastatin intensity. Patients treated with high-intensity rosuvastatin had a significantly higher cumulative incidence of NODM compared to the moderate-intensity rosuvastatin group (8.3% vs. 5.8%, P = 0.004). (**D**) Cumulative incidence of NODM according to the rosuvastatin Dose. Patients treated with the 20 mg of rosuvastatin showed the highest cumulative incidence of NODM, followed by 10 mg, 5 mg of rosuvastatin (8.3% vs. 5.5% vs. 2.8%, P = 0.008). *NODM* new-onset diabetes mellitus.

Discussion

In this prospective and multicenter study based on a national database, higher-intensity statin therapy was associated with a higher cumulative incidence of NODM and a lower cumulative incidence of MACE in patients with AMI underwent PCI with DES up to 3 years follow up. To the best of our knowledge, the current study is the first to demonstrate the dose-dependency of the diabetogenic effect of statins, especially in AMI patients with rosuvastatin.

Statins are critical agents for cardiovascular risk reduction, and their effect has been shown to be positively associated with statin intensity[14,15]. Therefore, current guidelines strongly recommend high-intensity or maximally tolerated-intensity statins for patients with AMI[9]. However, the association between statin therapy and an increased risk of NODM has always been a significant concern. As shown in the review article by Newman et al.,

	Univariable		Multivariable[a]		Multivariable[b]	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age	0.994 (0.986–1.001)	0.113				
Male gender	1.183 (0.918–1.523)	0.193				
BMI	1.082 (1.052–1.114)	< 0.001	1.071 (1.040–1.103)	< 0.001	1.096 (1.046–1.148)	< 0.001
Abdominal circumference	1.036 (1.016–1.056)	< 0.001				
Smoking (PY)	1.004 (1.000–1.007)	0.059				
Glucose	1.007 (1.006–1.008)	< 0.001	1.007 (1.005–1.008)	< 0.001	1.009 (1.007–1.011)	< 0.001
Triglyceride	1.001 (1.000–1.001)	0.001	1.001 (1.000–1.001)	0.035	1.001 (1.000–1.002)	0.261
β blockers	0.917 (0.691–1.217)	0.550				
Statin intensity						
Moderate vs. High	1.360 (1.115–1.659)	0.002	1.306 (1.056–1.617)	0.014		
Atorvastatin		0.486				
10 mg vs. 20 mg	1.001 (0.696–1.441)	0.994				
10 mg vs. 40 mg	1.222 (0.861–1.735)	0.261				
10 mg vs. 80 mg	1.295 (0.672–2.497)	0.440				
20 mg vs. 40 mg	1.221 (0.902–1.652)	0.196				
20 mg vs. 80 mg	1.294 (0.687–2.434)	0.425				
40 mg vs. 80 mg	1.061 (0.568–1.981)	0.854				
Rosuvastatin		0.009				0.066
5 mg vs. 10 mg	2.046 (0.646–6.472)	0.223			1.625 (0.512–5.162)	0.410
5 mg vs. 20 mg	3.097 (0.977–9.811)	0.055			2.313 (0.725–7.373)	0.156
10 mg vs. 20 mg	1.514 (1.111–2.062)	0.009			1.430 (1.020–2.004)	0.038

Table 2. Cox regression of new-onset diabetes mellitus. *BMI* body mass index, *CI* confidence interval, *PY* pack years. [a]Analysis was done in total patients by adjusting variables with $P < 0.05$ in the univariate analysis and imputing statin intensity as a categorical variable. [b]Analysis was done in the rosuvastatin group by adjusting variables with $P < 0.05$ in the univariate analysis and imputing rosuvastatin dose as a categorical variable.

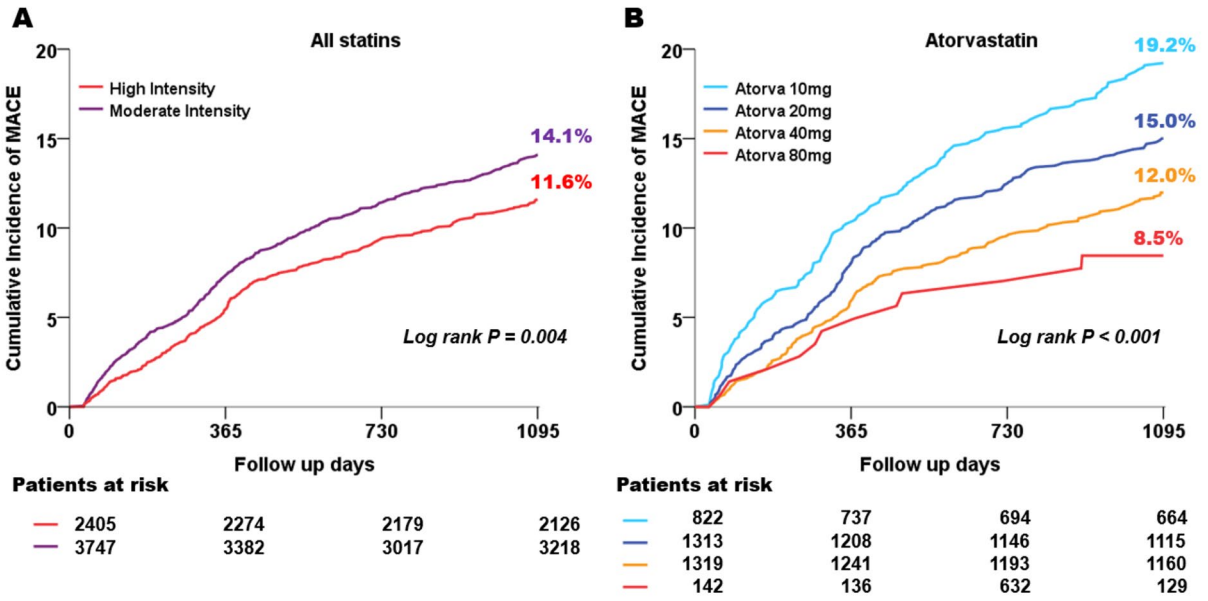

Figure 4. Cumulative incidence of MACE according to the statin intensity and dose. (**A**) Cumulative incidence of MACE according to the statin intensity. Patients treated with high-intensity statin showed a significantly lower cumulative incidence of MACE compared to the moderate-intensity statin group (11.6% vs. 14.1%, P = 0.004). (**B**) Cumulative incidence of MACE according to the atorvastatin dose. A higher dose was associated with a lower cumulative incidence of MACE (80 mg vs. 40 mg vs. 20 mg vs. 10 mg: 8.5% vs. 15.0% vs. 12.0% vs. 8.5%, respectively, P < 0.001). *MACE* major adverse cardiac events.

the absolute risk of NODM with statin therapy in major trials is around 0.2% per year[16]. Several randomized controlled trials have suggested that the risk of NODM increases by 10% with statin therapy[11,17].

Although previous studies have demonstrated the association between statin treatment and incident DM, the exact underlying mechanisms are still unclear. The hyperglycemic state associated with statins can be induced by increased insulin resistance, possibly associated with changes in free fatty acids[18], harmful effects on beta cell function, or possibly a combination of the two[19,20]. One genetic study suggested that statin therapy is associated with an increased risk of NODM and body weight via the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase[21].

Whether statins have a genuine diabetogenic effect is controversial because patients prescribed statins may already be a high-risk population for NODM because of their old age and several comorbidities. As these patients have more components of metabolic syndrome, including hypertension, dyslipidemia, or obesity, the risk of developing DM in association with statin use escalates, as demonstrated in various studies[22,23]. The relatively higher cumulative incidence of NODM of our study compared to other major trials[16] could be attributed to the patient demographics; those with AMI are more likely to have comorbidities that inherently pose risk factors of NODM. In our study, high-intensity statin treatment exhibited a greater cumulative incidence of NODM than moderate-intensity statin treatment among patients with AMI and many comorbidities, and was a significant predictive value for NODM after adjusting other covariables. Furthermore, rosuvastatin exhibited a clear trend of dose-dependent increases in HRs compared to atorvastatin which might elucidate their diabetogenic effect. However, the lack of statistical significance can be attributed to the limited sample size of rosuvastatin 5 mg (n = 109), which may have affected the ability to detect significant associations.

Regarding whether the diabetogenic effect of statins is a class effect, unlike other statins, pravastatin and pitavastatin are not generally considered as having deleterious effects on glycemic control[24,25]. In our study, a dose-dependency of statins in NODM was observed in patients treated with rosuvastatin; however, this tendency was not evident in atorvastatin. This difference in the pattern of dose dependency between atorvastatin and rosuvastatin suggests varying degrees of diabetogenicity for different statins. This tendency of rosuvastatin to have the highest risk of NODM compared with other statins was also shown in the Irish Health Services Executive Primary Care Reimbursement Services national pharmacy claims database[26]. A randomized study also showed that rosuvastatin was associated with increased fasting insulin and HbA1c levels and decreased insulin sensitivity and plasma adiponectin levels, whereas pravastatin showed opposite effects[27]. It has been suggested that lipophilic statins like atorvastatin are more likely to adversely affect insulin metabolism compared to hydrophilic statins like pravastatin by crossing the blood–brain barrier[27]. However, even though rosuvastatin is less hydrophilic than pravastatin[27], this hydrophilicity of statins cannot entirely explain rosuvastatin's apparent dose-dependent association with NODM, especially considering the fact that atorvastatin is more lipophilic than rosuvastatin. One possible mechanism for higher diabetogenic effect of rosuvastatin is that it demonstrates a stronger bonding interaction with HMG-CoA reductase than atorvastatin[19,28]. Future studies are welcomed to investigate this subtle nature of different statins.

Even though the high-risk patients have developed NODM, several observational studies have demonstrated that these patients had fewer macrovascular and microvascular complications of DM while receiving statins[29]. Undoubtedly, the net benefit of statins for cardiovascular diseases is irreplaceable, even though DM is a major cardiovascular risk factor[30,31]. In our study, the cumulative incidence of MACE was significantly lower in the high-intensity statin group, and the dose-dependency of the cumulative incidence of MACE was apparent in the atorvastatin group but not the rosuvastatin group. The relatively small number of patients treated with rosuvastatin 20 mg might have contributed to this lack of association of the cumulative incidence of MACE with rosuvastatin treatment.

Study limitations

This study has several limitations. First, although the KAMIR can provide a representation of real-world clinical data due to its enrollment of patients from various hospitals across the country, the presence of selection bias is inevitable. In addition, given the clinical context of the study population being ACS, it remains unclear whether the baseline glucose levels were obtained in a fasting state or not. Second, since the study was conducted between 2011 and 2015, there were relatively small number of patients taking high-intensity statins (n = 2405 compared to 3747 patients with moderate-intensity statins). Furthermore, the absence of rosuvastatin 40 mg in the Korean market prevented the collection of data on this specific dosage, potentially contributing to the lack of an observable dose-dependent association between MACE and rosuvastatin. In contrast, atorvastatin showed an apparent dose-dependent effect on MACE, which is consistent of current understanding of statins: the lower LDL cholesterol, the better MACE outcomes. Nevertheless, the dose-dependency of rosuvastatin in NODM was still evident, which suggests the diabetogenic effect of rosuvastatin as well as its dose-dependency. The secondary analysis of LODESTAR trial that compare the rosuvastatin and atorvastatin also demonstrated higher risk of NODM in rosuvastatin group, which is consistent with our study[32].

While our study highlights the relationship between dose-dependency of statins and NODM in patients with AMI, it is essential to replicate this dose-dependency effect in lower risk population. Such a demonstration becomes particularly significant when comparing the risk–benefit profile of statins in this population against higher-risk groups or patients with established ASCVD.

Conclusions

Treatment with high-intensity atorvastatin and rosuvastatin was associated with a higher incidence of NODM and a lower incidence of MACE than moderate-intensity treatment in patients with AMI underwent PCI with DES up to 3 years. In terms of the dose-dependency of each statin, a higher dose of rosuvastatin was significantly

associated with a higher cumulative incidence of NODM which supports the genuine diabetogenic effect of rosuvastatin; however, this association was not observed with atorvastatin. The different characteristics of the two statins could provide supporting evidence to understand the delicate nature of statins, and this might help physicians further refine statin treatment.

Data availability

The dataset generated and/or analyzed during the current study are available from the corresponding author on a reasonable request.

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Author contributions

JEL and JYC contributed to the conception and design of the work, analyzed the data, and wrote the manuscript; BGC analyzed the data; YJC, SHP, DOK, EJP, JBK, SYR, JON, CUC, EJK, and CGP contributed to the acquisition of the data; MHJ, JYH, SHH, JOJ, and SKO critically revised the manuscript; SWR contributed to the acquisition and interpretation of the data, and critically revised the manuscript. All authors read and approved the final manuscript for publication. SWR has full access to the data in the study and has responsibility for the integrity of the data and accuracy of the data analysis.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to S.-W.R.

KAMIR NIH Investigators

Seung-Woon Rha[1], Tae Hoon Ahn[7], Junghan Yoon[8], Hyo-Soo Kim[9], Ki-Bae Seung[10], Hyeon-Cheol Gwon[11], Shung Chull Chae[12], Chong-Jin Kim[13], Kwang Soo Cha[14], Jung-Hee Lee[15], Jei Keon Chae[16], Seung-Jae Joo[17], Chang-Hwan Yoon[18], Seung-Ho Hur[4], In-Whan Seong[5], Kyung-Kuk Hwang[19], Doo-Il Kim[20], Seok Kyu Oh[6], Jin-Yong Hwang[3] & Myung Ho Jeong[2]

[7]Gachon University Gil Medical Center, Incheon, South Korea. [8]Wonju Severance Christian Hospital, Wonju, South Korea. [9]Seoul National University Hospital, Seoul, South Korea. [10]Seoul St. Mary's Hospital, Seoul, South Korea. [11]Samsung Medical Center, Seoul, South Korea. [12]Kyungpook National University Hospital, Daegu, South Korea. [13]Kyunghee University Hospital At Gangdong, Seoul, South Korea. [14]Pusan National University Hospital, Busan, South Korea. [15]Yeungnam University Medical Center, Daegu, South Korea. [16]Chonbuk National University Hospital, Jeongju, South Korea. [17]Jeju National University Hospital, Jeju, South Korea. [18]Seoul National University Bundang Hospital, Bundang, South Korea. [19]Chungbuk National University Hospital, Cheongju, South Korea. [20]Inje University Haeundae Paik Hospital, Busan, South Korea.