Comparative Effects Between High-intensity Atorvastatin and Rosuvastatin on New Onset Diabetes Mellitus and Cardiovascular Outcome

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Abstract

Background: High-intensity statin is typically used in patients with acute myocardial infarction (AMI) for secondary prevention; however, concern regarding its association with diabetes mellitus has been consistent. We investigated and compared the impact of high-intensity atorvastatin on new-onset diabetes mellitus (NODM) and cardiovascular outcomes with that of high-intensity rosuvastatin for a 3-year follow-up period.

Methods: Data from the Korea Acute Myocardial Infarction Registry were collected from November 2011 to October 2015, and 13,104 AMI patients were enrolled from major cardiovascular centers. Among them, 2,221 patients without diabetes who had been administered with high-intensity atorvastatin (40–80 mg) and rosuvastatin (20 mg) were investigated. The atorvastatin and rosuvastatin groups were compared and evaluated for the incidence of NODM and major adverse cardiac event (MACE) including total death, myocardial infarction, and revascularization cases in the following 3 years.

Results: Baseline characteristics were comparable between two groups. Event-free survival rate of NODM and MACE was not significantly different between the atorvastatin and rosuvastatin groups (92.5% vs. 90.8%, respectively; Log-rank P-value = 0.550). The event-free survival rate of MACE was also not significantly different between atorvastatin and rosuvastatin groups (89.0% vs. 89.6%, respectively; Log rank p-value = 0.662). Multivariable Cox analysis revealed that the statin type was not a prognostic factor in the development of NODM and MACE.

Conclusions: Administering high-intensity atorvastatin and rosuvastatin in AMI patients produced comparable effects on NODM and clinical outcome, suggesting their clinical equivalence in secondary prevention.

Background

Statins typically prevent cardiovascular events by lowering total and low-density lipoprotein (LDL) cholesterol levels in the serum. Considering their rapid and sustained clinical advantages, the current guideline recommends administration of high-intensity statin in AMI patients for secondary prevention. However, there has been consistent concern regarding its association with new-onset diabetes mellitus (NODM) [1]. Clinical trials, meta-analyses of randomized controlled trials (RCT), and observational studies have demonstrated a 10–12% increase in NODM among patients receiving statins [2, 3]. Meta-analysis of 5 large-scale trials comparing intensive and moderate doses of statin have demonstrated that the risk of NODM further increases in intensive therapy group [4]. However, it is unclear if the diabetogenic effect of statins is a class effect. Considering their mandatory role for secondary prevention in acute myocardial infarction (AMI) patients, it would be important to identify the specific statin that can provide protective cardiovascular effects without deteriorating the glycemic status. In Korea, atorvastatin 40–80 mg and rosuvastatin 20 mg are currently available as high-intensity statins for clinical use. Here, we investigated
and compared the impact of high-intensity atorvastatin and rosuvastatin on cardiovascular outcome and NODM in AMI patients for a 3-year follow-up period.

**Methods**

**Data collection and study population**

The Korea Acute Myocardial Infarction Registry (KAMIR), a Korean prospective, multicenter, nationwide database supported by the Korean Society of Cardiology, reflects real-world treatment practices and outcomes in Asian patients diagnosed with AMI. Twenty university or community hospitals have participated in the registry. Data collection at the institution level is performed by a well-trained study coordinator using a standardized case report form. The collected data is managed using web-based systems. All participants provided written informed consent, and the study was approved by the ethics committee at each participating institution.

A total of 13,104 AMI patients were enrolled in the KAMIR registry between November 2011 and October 2015. A total of 6,728 patients without a history of diabetes mellitus (DM) with successful percutaneous coronary intervention (PCI) with drug-eluting stent implantation and high-intensity statin treatment were eligible for our study. Patients were selected considering the following exclusion criteria: history of DM or initial HbA1c level $\geq 6.5\%$, bare metal stent implantation, plain old balloon angioplasty, or failed PCI. Additionally, we did not include patients with in-hospital major adverse cardiac events (MACE) to specifically include AMI survivors. Finally, 2,221 patients with AMI and high-intensity atorvastatin or rosuvastatin, treatment, according to 2014 ACC/AHA Release Updated Guideline, were enrolled in this study. Of them, 60.7% (1,349/2,221) of patients had received 40–80 mg atorvastatin and 39.3% (872/2,221) had received 20 mg rosuvastatin (Fig. 1).

**Clinical Outcome And Definition**

The primary endpoint was the incidence of NODM and the incidence of MACE during the 3 years of clinical follow-up. Secondary endpoints were each component of MACE, reasons for mortality, MI, and revascularization. Diagnosis of NODM was defined as a HbA1c level $\geq 6.5\%$ or newly administration of oral hypoglycemic agents. Clinical data of the enrolled patients were obtained through face-to-face interviews during regular outpatient visits, medical chart reviews, and telephonic interviews.

**Statistical analysis**

For continuous variables, differences between the two groups were evaluated by Student's t-test. Data were expressed as mean ± standard deviation (SD). For discrete variables, differences were expressed as counts and percentages and analyzed using the Chi-square test or Fisher's exact test. The cumulative incidence of NODM and MACE was estimated using the Kaplan–Meier method, and the intergroup differences were determined using the log-rank test. Cox-proportional hazard models were used to
identify potential prognostic factors for NODM and MACE, and assess the hazard ratio (HR) of the atorvastatin group compared with the rosuvastatin group. Multivariable analysis was performed by including variables with significant P-values in the univariate analysis (P < 0.05). For all analyses, a P-value of < 0.05 was considered statistically significant. The data were processed using SPSS (version 22.0, Inc Chicago, IL).

Results

Baseline characteristics

Baseline clinical, laboratory, and angiographic characteristics are shown in Table 1. We did not observe any significant intergroup differences with regard to age, gender, LV systolic function, incidence of STEMI, and underlying disease such as hypertension, cerebrovascular accidents. Patients in the rosuvastatin group had higher levels of LDL cholesterol and peak CK-MB and a longer total stent length than those in the atorvastatin group. Dual antiplatelet therapy rate was above 99% in both groups.
Table 1
Baseline clinical characteristics and angiographic and procedural characteristics

| Variables                        | Atorvastatin (n = 1349) | Rosuvastatin (n = 872) | P-value |
|----------------------------------|-------------------------|------------------------|---------|
| Men                              | 1105 (81.9%)            | 720 (82.6%)            | 0.693   |
| Age (years)                      | 61.0 ± 12.5             | 61.0 ± 12.6            | 0.918   |
| LV ejection fraction (%)         | 54.1 ± 9.9              | 54.0 ± 9.6             | 0.906   |
| Body mass index (kg/m²)          | 24.5 ± 3.2              | 24.4 ± 3.4             | 0.442   |
| Myocardial infarction            |                         |                        |         |
| ST-segment elevation             | 719 (53.3%)             | 478 (54.8%)            | 0.483   |
| Non-ST-segment elevation         | 630 (46.7%)             | 394 (45.2%)            |         |
| Hypertension                     | 549 (40.7%)             | 329 (37.7%)            | 0.162   |
| Cerebrovascular accidents        | 42 (3.1%)               | 29 (3.3%)              | 0.781   |
| Total cholesterol (mg/dl)        | 195.5 ± 42.0            | 196.6 ± 45.6           | 0.563   |
| Triglyceride (mg/dl)             | 146.5 ± 120.3           | 145.4 ± 139.1          | 0.852   |
| HDL-cholesterol (mg/dl)          | 44.1 ± 11.1             | 44.0 ± 11.1            | 0.790   |
| LDL-cholesterol (mg/dl)          | 126.5 ± 36.3            | 130.6 ± 40.3           | 0.020   |
| CK-MB (mg/dl)                    | 125.2 ± 159.2           | 139.9 ± 145.1          | 0.029   |
| Glucose (mg/dl)                  | 136.7 ± 37.4            | 138.8 ± 37.9           | 0.216   |
| Creatinine (mg/dl)               | 0.97 ± 0.94             | 0.94 ± 0.42            | 0.340   |

**Discharge medications**

| Medication | Atorvastatin (n = 1349) | Rosuvastatin (n = 872) | P-value |
|------------|-------------------------|------------------------|---------|
| Aspirin    | 1343 (99.6%)            | 865 (99.2%)            | 0.280   |
| Clopidogrel| 855 (63.4%)             | 473 (54.2%)            | < 0.001 |
| Prasugrel  | 188 (13.9%)             | 68 (7.8%)              | < 0.001 |
| Ticagrel   | 302 (22.4%)             | 325 (37.3%)            | < 0.001 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, Creatine Kinase-MB; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle
| Variables                  | Atorvastatin (n = 1349) | Rosuvastatin (n = 872) | P-value |
|---------------------------|-------------------------|------------------------|---------|
| Cilostazol                | 57 (4.2%)               | 29 (3.3%)              | 0.283   |
| Calcium channel blockers  | 63 (4.7%)               | 45 (5.2%)              | 0.600   |
| β-blockers                | 1181 (87.5%)            | 714 (81.9%)            | < 0.001 |
| ACEi                      | 687 (50.9%)             | 321 (36.8%)            | < 0.001 |
| ARB                       | 426 (31.6%)             | 336 (38.5%)            | 0.001   |

**Procedural characteristics**

|                        | Atorvastatin (mm) | Rosuvastatin (mm) | P-value  |
|------------------------|-------------------|-------------------|----------|
| Total stent length     | 27.6 ± 12.2       | 39.8 ± 13.4       | < 0.001  |
| Total stent number     | 1.17 ± 0.41       | 1.20 ± 0.45       | 0.077    |
| Stent diameter (mm)    | 3.20 ± 0.44       | 3.14 ± 0.44       | 0.062    |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, Creatine Kinase-MB; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle

**Clinical outcomes**

Kaplan–Meier curves for the cumulative incidence of NODM up to 3 years are presented in Fig. 2A and Table 2. There was no significant difference in the event-free survival rate of NODM between the atorvastatin and rosuvastatin groups (92.5% vs. 90.8%, respectively; Log-rank P-value = 0.550). Kaplan–Meier curves for the cumulative incidence of MACE up to a period of 3 years are presented in Fig. 2B and Table 2. There was no significant difference between atorvastatin and rosuvastatin groups regarding the event free survival rate of MACE (89.0% vs. 89.6%, respectively; Log rank p-value = 0.662), reasons for mortality, myocardial infarction, and revascularizations. Comparing 40 mg and 80 mg of atorvastatin with 20 mg of rosuvastatin revealed no significant differences in the event-free survival rate of NODM and MACE (see Additional file 1: Fig. S1A and B).
Table 2
Cardiovascular Outcomes at 3 Years

| Clinical outcome                   | Atorvastatin (n = 1349) | Rosuvastatin (n = 872) | p value |
|------------------------------------|-------------------------|------------------------|---------|
| New onset diabetes mellitus        | 99 (7.5)                | 70 (9.2)               | 0.550   |
| MACE                               | 149 (11.0)              | 91 (10.4)              | 0.662   |
| All cause of mortality             | 49 (3.6)                | 25 (2.9)               | 0.335   |
| Cardiac death                      | 19 (1.4)                | 14 (1.6)               | 0.710   |
| Non-cardiac death                  | 30 (2.2)                | 11 (1.3)               | 0.103   |
| Any myocardial infarction          | 30 (2.3)                | 15 (1.8)               | 0.409   |
| STEMI                              | 8 (0.6)                 | 1 (0.1)                | 0.083   |
| NSTEMI                             | 22 (1.7)                | 14 (1.6)               | 0.956   |
| Any revascularization              | 98 (7.4)                | 62 (7.2)               | 0.892   |
| TLR                                | 24 (1.9)                | 21 (2.5)               | 0.312   |
| TVR                                | 48 (3.7)                | 34 (4.0)               | 0.692   |
| NTVR                               | 51 (3.9)                | 31 (3.7)               | 0.788   |
| Stroke                             | 27 (2.0)                | 10 (1.2)               | 0.127   |

MACE, major adverse cardiovascular event; STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non-ST-segment elevation myocardial infarction; NTVR, non-target vessel revascularization; TLR, target lesion revascularization; TVR, target vessel revascularization

Potential prognostic factors for NODM were identified via univariate Cox regression analysis. Higher random glucose and triglyceride levels were both significant prognostic factors for NODM in univariable and multivariable analysis. However, the type of statin used was not (HR = 1.098, 95% confidence interval [Cl]: 0.808–1.491, P = 0.551, Table 3). Conventional risk factor including older age, lower left ventricular ejection fraction (LVEF), and higher creatinine levels were associated with a higher incidence of MACE. The type of high-intensity statin, atorvastatin or rosuvastatin, was not a potential prognostic factor for MACE (HR = 0.944% confidence interval [Cl]: 0.727–1.225, P = 0.662, Table 3).
Table 3  
Cox regression of clinical outcome

|                | Univariable |             |             | Multivariable |             |             |
|----------------|-------------|-------------|-------------|---------------|-------------|-------------|
|                | Hazard ratio (95% CI) | p value     | Hazard ratio (95% CI) | p value       |             |             |
| NODM           |             |             |             |               |             |             |
| Age            | 0.988 (0.976–1.000) | 0.052       |             |               |             |             |
| Male gender    | 1.307 (0.848–2.013) | 0.225       |             |               |             |             |
| Glucose        | 1.009 (1.006–1.011) | < 0.001     | 1.009 (1.006–1.011) | < 0.001       |             |             |
| Triglyceride   | 1.001 (1.000–1.002) | 0.011       | 1.001 (1.000–1.002) | 0.021         |             |             |
| β blocker      | 0.768 (0.517–1.139) | 0.189       |             |               |             |             |
| Statin type    | 1.098 (0.808–1.491) | 0.551       |             |               |             |             |
| MACE           |             |             |             |               |             |             |
| Age            | 1.026 (1.016–1.037) | < 0.001     | 1.022 (1.0109–1.034) | 0.002         |             |             |
| Male gender    | 0.964 (0.695–1.336) | 0.824       |             |               |             |             |
| LVEF           | 0.974 (0.961–0.986) | < 0.001     | 0.979 (0.966–0.993) | 0.002         |             |             |
| Glucose        | 1.003 (1.000–1.006) | 0.089       |             |               |             |             |
| Creatinine     | 1.155 (1.080–1.235) | < 0.001     | 1.216 (1.074–1.377) | 0.002         |             |             |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction
### Discussion

To the best of our knowledge, this is the first study to compare the impact of high-intensity statin treatment on the development of NODM and MACE in AMI patients. Our results indicated that high-intensity atorvastatin and rosuvastatin therapies showed no significant difference with regard to the incidence of NODM and cardiovascular events.

Statins reduce serum LDL cholesterol level and the risk of cardiovascular events. As numerous studies revealed that the degree of cardiovascular risk reduction is proportional to the statin intensity [5, 6], the current guideline strongly recommended high-intensity or maximally tolerated intensity statin therapy in AMI patients in the absence of contraindications [7, 8]. Several studies have that suggested that statin may increase the incidence of NODM [3, 9]. The issue has started attracting attention since the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial reported a higher incidence of NODM in patients treated with rosuvastatin for primary prevention [10]. Numerous observational studies [11, 12] and meta-analyses of major RCT [3, 13] have consistently reported an increased incidence of NODM in patients receiving statin treatment. In Korea, a population-based cohort study using the Korean National Health Insurance claims database has shown an increased incidence of NODM in statin-treated groups [2].

Whether the diabetogenic effect of statin is a class effect has been a controversial subject. Typically, atorvastatin and rosuvastatin are thought to unfavorably influence glycemic parameters, while pitavastatin and pravastatin have relatively neutral effects on glycemic control regardless of the presence or absence of DM [1]. Our group recently published a report regarding the favorable glycemic effects of
moderate intensity pitavastatin in comparison to those of moderate intensity atorvastatin and rosuvastatin in AMI patients [14]. However, the current guideline recommends high-intensity or maximally tolerated statin for secondary prevention to achieve cardiovascular improvements in AMI patients [7, 8], and to the best of our knowledge, there is no study that has compared the diabetogenic and cardiovascular effects of different high-intensity statins.

Several studies were conducted regarding the cardiovascular outcome after high-intensity statin therapy. In patients with acute coronary syndrome, both the atorvastatin and rosuvastatin groups had comparable effects on lipid parameters [15, 16], although patients with familial hypercholesterolemia in the rosuvastatin group demonstrated a greater reduction in LDL cholesterol levels than those in the atorvastatin group [17]. Some studies has reported more favorable effects of rosuvastatin on reducing atherosclerotic plaque volume [15, 18] and plaque stabilization [15] than atorvastatin, however, there has been no significant difference with regard to the cardiovascular outcome in both groups [17, 19]. In line with previous studies, we could not identify the differences between the effects of high-intensity atorvastatin and rosuvastatin administration on major cardiovascular events.

Several studies have suggested the possible mechanisms underlying the effect of statin on glucose metabolism. Some studies have suggested the interconnection between glucose and lipid metabolisms by demonstrating gene variants affecting glucose metabolism [20–22], cholesterol-dependent conformational change in glucose transporter protein [23], or deleterious effect on islet β cells [24] by statins. There is scarce data regarding the mechanisms of different diabetogenic effects of various statins and further study would be needed.

This study has several limitations. First, our study is not an RCT, which inevitably leads to selection bias and an imbalance of baseline characteristics. However, as KAMIR is a prospective registry that enrolls AMI patients in Korean, it can represent real-word clinical data. Second, there is no data on rosuvastatin 40 mg and a relatively small number of patients have been treated with atorvastatin 80 mg; hence, dose-dependent increases in NODM could not be demonstrated in our study. Third, this study lacks data regarding the compliance of statin during the follow-up period. Despite its limitations, to the best of our knowledge, this is the first study from a multicenter registry that demonstrated detailed real-world data on the effect of high-intensity statin type on incidence of NODM and MACE in AMI patients. Although further studies with prospective randomized trials with a larger sample size are needed, our results provide adequate supportive evidence to compare the diabetogenic and cardioprotective effects of the currently available high-intensity statins.

**Conclusions**

In conclusion, high-intensity atorvastatin therapy showed similar incidence of NODM and cardiovascular events when compared with high-intensity rosuvastatin therapy in AMI patients. Although prospective, randomized trials with larger study population are needed to clarify our results, the outcomes presented
here provide supportive evidence for the diabetogenic and cardio protective effect of high-intensity statins in AMI patients.

**List Of Abbreviations**

AMI: acute myocardial infarction; KAMIR: Korea Acute Myocardial Infarction Registry; LDL: low-density lipoprotein; MACE: major adverse cardiac events; NODM: new-onset diabetes mellitus; PCI: percutaneous coronary intervention; RCT: randomized controlled trials

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of Korea University (IRB No. 2016GR0740) and all participants provided written informed consent.

**Consent for publication**

Not applicable

**Availability of data and materials**

We cannot upload the data that has been used in the research because it is confidential

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

**Jah Yeon Choi**: conception and design of the work, acquisition/analysis/interpretation of data, writing-Original draft preparation, **Byoung Geol Choi**: acquisition/analysis/interpretation of data, **Yoonjee Park**, **Dong Oh Kang**, **Won Young Jang**, and **Woohyeun Kim**: acquisition/analysis of data, **Jin Oh Na**, **Jin Won Kim**, **Eung Ju Kim**, **Seung-Woon Rha**, **Chang Gyu Park** and **Hong Seog Seo**: acquisition of data, **Myung Ho Jeong**, **Sung-Chull Chae**, **In-Whan Seong**, **Chang-Hwan Yoon**, **Kwang Soo Cha**, **Seok Kyu Oh**: conception of the work, acquisition of data, **Cheol Ung Choi**: conception and design of the work, supervision, reviewing and editing, acquisition/analysis of data.

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**Figures**

**Figure 1**

Patient flow chart AMI: Acute myocardial infarction, DM: diabetes mellitus, KAMIR: Korea Acute Myocardial Infarction Registry, MACE: major adverse cardiac events, PCI: percutaneous coronary intervention, POBA: plain old balloon angioplasty
Figure 2

Kaplan–Meier curves for event-free survival rate of new-onset diabetes mellitus (A) and major adverse cardiac events (B) according to statin type

Supplementary Files

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