Effects of Statin Intensity on Clinical Outcome in Acute Myocardial Infarction Patients

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Background: There has been debate regarding the added benefit of high-intensity statins compared with low-moderate-intensity statins, especially in patients with acute myocardial infarction (AMI).

Methods and Results: The Korea Acute Myocardial Infarction Registry-National Institutes of Health consecutively enrolled 13,104 AMI patients. Of these, a total of 12,182 patients, who completed 1-year follow-up, were included in this study, and all patients were classified into 3 groups (no statin; low-moderate-intensity statin; and high-intensity statin). The primary outcome was major adverse cardiac event (MACE) including cardiac death, non-fatal MI, and repeat revascularization at 1 year. Both low-moderate-intensity and high-intensity statin significantly reduced low-density lipoprotein cholesterol (LDL-C; all P<0.001). Compared with the no statin group, both statin groups had significantly lower risk of MACE (low-moderate intensity: HR, 0.506; 95% CI: 0.413–0.619, P<0.001; high intensity: HR, 0.464; 95% CI: 0.352–0.611, P<0.001). The risk of MACE, however, was similar between the low-moderate- and high-intensity statin groups (HR, 0.917; 95% CI: 0.760–1.107, P=0.368). Multivariable adjustment, propensity score matching, and inverse probability weighted analysis also produced the same results.

Conclusions: When adequate LDL-C level is achieved, patients on a low-moderate-intensity statin dose have similar cardiovascular outcomes to those on high-intensity statins.

Key Words: Acute myocardial infarction; Outcome; Percutaneous coronary intervention; Prognosis; Statin
by just over a fifth.\textsuperscript{6} All previous studies included in the meta-analysis, however, were performed during the first-generation drug-eluting stent (DES) era. In addition, of 5 RCT that directly compared lower intensity and higher intensity statin regimens,\textsuperscript{2,3,11–13} only 2 evaluated patients with ACS,\textsuperscript{2,3} while others evaluated patients with stable coronary artery disease (CAD). To date, there has been no dedicated study on AMI that directly compared low-moderate- and high-intensity statin in contemporary practice. The question of whether high-intensity statins would have significant additional prognostic benefit compared with low-moderate-intensity statins is still unanswered, especially with regard to AMI patients.

The aim of this study was therefore to investigate the prognostic effects of statin intensity in post-AMI patients in contemporary practice, using the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH), a nationwide, multicenter, prospective registry for AMI patients.

**Methods**

**Subjects**
The KAMIR-NIH consecutively enrolled 13,104 patients diagnosed with AMI between November 2011 and October 2015.\textsuperscript{14} The purpose of the KAMIR-NIH, a Korean nationwide, multicenter, prospective AMI registry, was to investigate the prognosis and surveillance index of patients admitted to 20 tertiary university hospitals. As described previously, AMI was defined as increased cardiac biomarkers (at least one had to be above the 99th percentile of the upper reference limit) accompanied by at least one of the following: ischemic symptoms; electrocardiogram (ECG) changes (ST elevation, left bundle branch block, ST change without ST elevation), and imaging suggestive of MI (loss of viable myocardium or new regional wall motion abnormality).\textsuperscript{7,8}

Of the 13,104 patients enrolled in the KAMIR-NIH, 922 patients were excluded for the following reasons: (1) death in hospital, n=504 (3.8%); (2) stopping of statins before 1 year, n=186 (1.4%); (3) loss to follow up, n=218 (1.7%); and (4) statin dose not clear, n=14 (0.01%). Finally, a total of 12,182 patients were included in this study (Figure 1). The study protocol was approved by the ethics committee at each participating center and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

**Statin Intensity**
The type of statin and dose were decided on physician’s discretion. All patients were classified into 3 groups according to statin intensity at admission (Figure 1). Only atorvastatin (40–80 mg) and rosuvastatin (20–40 mg) were considered high-intensity statins; the others, including combined agents of simvastatin and ezetimibe (n=575; 4.7% of total group) were low-moderate-intensity statins.\textsuperscript{15}

**Data Collection and Follow-up**
In KAMIR-NIH, independent clinical research coordinators from each center collected data using Web-based Internet-based Clinical Research and Trial management system (iCReaT) case report forms, a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (iCReaT Study No. C110016). The definitions of all patient- and lesion-related variables, clinical diagnoses, and clinical events were standardized. An external clinical events adjudication committee reviewed and adjudicated all relevant medical records for any clinical events.

**Endpoints**
The primary outcome, major cardiac adverse event (MACE), was a composite of cardiac death, non-fatal MI, and repeat revascularization at 1-year follow-up. The secondary outcomes consisted of the individual MACE components. All deaths without undisputed non-cardiac cause were considered cardiac. MI was defined as elevated cardiac enzymes, including troponin and myocardial band fraction of creatine kinase, with ischemic symptoms or ECG indicative of ischemia not related to index procedure.
Revascularization was considered clinically indicated for stenosis $\geq 50\%$ diameter and if one of the following occurred: (1) recurrence of angina symptoms; (2) positive non-invasive test; (3) positive invasive physiologic test; or (4) stenosis $\geq 70\%$ diameter, even in the absence of other criteria. All clinical outcomes were defined according to the Academic Research Consortium criteria.16,17

### Statistical Analysis

Categorical variables are presented as number and relative frequency. Continuous variables are presented as mean $\pm$ SD or median (IQR: Q1–Q3) according to distribution, which was checked on Kolmogorov-Smirnov test. Chi-squared test was used to evaluate non-random associations between categorical variables, and analysis of variance was used to compare continuous variables between the 3 groups. The analysis was performed in 2 parts. First, analysis and comparison of primary and secondary clinical outcomes were conducted in the original patient group. Kaplan-Meier analysis was performed to calculate cumulative incidence of primary and secondary outcomes, and log-rank test was used to compare group differences. Univariate Cox proportional hazard regression modeling was used to calculate the effect of statin intensity. Second, sensitivity analysis using multivariable adjusted Cox proportional hazard regression, propensity score matching, and inverse

<table>
<thead>
<tr>
<th>Table 1. AMI Patient Baseline Characteristics vs. Statin Intensity</th>
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<td><strong>General characteristics</strong></td>
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<tr>
<td>(n=814)</td>
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<td>Age (years)</td>
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<td>Male</td>
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<td>SBP (mmHg)</td>
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<td>Dual antiplatelet</td>
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<td>ACEI/ARB</td>
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Data given as mean±SD or n (%). ACEI/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; AMI, acute myocardial infarction; BB, $\beta$-blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.
probability weighted (IPW) analysis was performed to adjust for baseline differences between the 3 groups. All analyses incorporated participating centers as a random effect.

The following patient characteristics were included in multivariable adjusted Cox proportional hazard regression modeling: age; ejection fraction (EF); ST-elevation MI; hypertension; diabetes mellitus; dyslipidemia; previous MI; previous heart failure; treatment strategy; and discharge medication (aspirin, dual antiplatelet therapy, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [ACEI/ARB], calcium channel blocker). For propensity score matching and IPW analysis, logistic regression modeling was used to calculate propensity scores incorporating all the measured covariates. Standardized mean differences for each variable, before and after adjustment, are given in Table S1. Standardized mean differences after propensity-score matching or IPW adjustment were less than 0.10 across all matched covariates, indicating successful balance between comparator groups (Table S1).

Multivariable adjusted Cox proportional hazard regression modeling was used for subgroup analysis and evaluation of independent predictors of MACE. In order to explore the prognostic impact of admission LDL-C level continuously according to statin intensity, estimated MACE risk derived from the multivariable adjusted Cox regression model was plotted against admission LDL-C level, using the locally weighted scatterplot smoothing (LOWESS) regression line. All probability values were 2-sided, and \( P<0.05 \) was considered statistically significant. R, version 3.4.0 (Comprehensive R Archive Network) was used for statistical analysis.

Figure 2. Low-density lipoprotein cholesterol (LDL-C) changes at 1 year according to statin intensity.

Figure 3. Cumulative incidence of major adverse cardiac events (MACE) at 1 year (A) for the no statin, low-moderate-intensity, and high-intensity statin groups; and (B) for the low-moderate and the high-intensity groups, excluding patients whose statin intensity was changed before 1 year.
Results

Baseline Characteristics
A total of 12,182 patients were classified into 3 groups according to statin intensity: no statin, n=814, 6.7%; low-moderate intensity, n=7,703, 63.2%; and high intensity, n=3,665, 30.1% (Figure 1). The specific reasons for not using statins in the no statin group are listed in Table S2. The most common reasons were end-stage renal disease, advanced age ≥75, severe heart failure with Killip class III–IV, or liver function abnormality. Table 1 lists baseline characteristics of the 3 groups. While LDL-C at baseline was the highest in the high-intensity statin group, LDL-C at 1 year was the lowest (Table 1). Of the statin groups, 7,331 patients in the low-moderate-intensity statin group (95.0%) and 2,270 patients in the high-intensity statin group (61.9%) consistently maintained the initial dose up to 1 year. From a procedural standpoint, 96.3% of patients were treated with second-generation DES.

LDL-C Change According to Statin Intensity
LDL-C was significantly decreased in both statin groups (all P<0.001), while LDL-C in the no statin group was similar between index admission and at 1-year follow-up (P=0.059; Figure 2). In the statin groups, reduction of 1-year LDL-C was significantly greater in the high-intensity group than in the low-moderate-intensity group (37.6% vs. 23.8%, P<0.001). Nevertheless, 1-year LDL-C was similar between the low-moderate- and high-intensity groups (76.2 ± 25.6 mg/dL and 71.6 ± 25.0 mg/dL, respectively; Figure 2).

Clinical Outcomes: No Statin vs. Statin
Compared with the no statin group, both the low-moderate- and the high-intensity statin groups had significantly lower risk of MACE at 1 year (Figure 3A). The cumulative incidence of MACE at 1 year was 14.1%, 7.5%, and 6.7% in the no statin, low-moderate-intensity-, and the high-intensity groups, respectively. On unadjusted analysis, significant risk reduction was noted for statin (low-moderate intensity: HR, 0.506; 95% CI: 0.413–0.619, P<0.001; high intensity: HR, 0.464; 95% CI: 0.352–0.611, P<0.001), compared with the no statin group. Multivariable adjustment, propensity score matching, and IPW analysis also produced the same results (Table 2). The significantly lower risk of MACE in the low-moderate- or the high-
Prognostic Impact of Statin After AMI

were not significantly different (Table 2). Sensitivity analyses using multivariable adjustment, propensity score matching, and IPW also produced the same results. When excluding patients whose statin intensity was changed before 1 year, the risk of MACE was also similar between the low-moderate- and the high-intensity groups (7.6% vs. 8.0%; adjusted HR, 1.175; 95% CI: 0.954–1.449, P=0.130; Figure 3B). Although the high-intensity statin group had a significantly higher rate of LDL-C reduction for the whole range of baseline LDL-C, the risk of MACE was similar between the low-moderate-intensity and the high-intensity statin groups, regardless of baseline LDL-C level (Table S3).

The lack of added benefit of high-intensity statin was consistently observed in various subgroups and the overall results did not change, even after excluding patients with statin and ezetimibe complex agent (Table 3). Furthermore, when the patients were classified into 3 statin intensity groups (low; moderate; high), the risk of MACE was similar between the low and moderate intensity groups, and between the low and high intensity groups (Table S4).

Figure 4 shows the association between continuous

intensity statin groups was mainly driven by the lower risk of cardiac death in these 2 groups. The benefit of statins was consistently observed across the various subgroups, except for patients with low EF (<40%; Table 3). Interaction P-values were not significant in all subgroups.

Clinical Outcome: Low-Moderate vs. High-Intensity Statin

Both the low-moderate- and the high-intensity statin groups had a similar risk of MACE (7.5% vs. 6.7%; HR, 0.917; 95% CI: 0.760–1.107, P=0.368). All individual outcomes, including cardiac death, MI, and repeat revascularization,
initial LDL-C level and estimated 1-year MACE risk. For the whole range of initial LDL-C, both the low-moderate- and the high-intensity statin groups had significantly lower risk of MACE than the no statin group, but there was no significant difference between the low-moderate- and the high-intensity statin groups. In addition, absolute risk reduction and number needed to treat to prevent 1-year MACE were also similar between the low-moderate- and the high-intensity statin groups (Figure 4).

Independent Predictors of MACE After AMI

Table 4 lists independent predictors of MACE after successful AMI treatment. On multivariable analysis, statin use significantly reduced the risk of MACE, regardless of intensity (low-moderate intensity: HR, 0.688; 95% CI: 0.603–0.785, P<0.001; high intensity: HR, 0.701; 95% CI: 0.577–0.854, P<0.001). Other independent predictors of MACE were older age, hypertension, diabetes mellitus and non-use of ACEI/ARB and β-blocker.

Discussion

The current study evaluated the prognostic effects of statin intensity in post-AMI patients using a large-scale, nationwide, multicenter, prospective, dedicated registry for AMI, the KAMIR-NIH. The principal findings are as follows: first, both low-moderate-intensity statin and high-intensity statin significantly lowered LDL-C to around 70 mg/dL at 1 year. Second, the use of statins significantly lowered the risk of MACE at 1 year compared with the no statin group, regardless of intensity. Third, the risk of MACE was similar between the low-moderate- and the high-intensity groups. The similar risk of MACE between these 2 groups was also consistently observed when excluding patients whose statin intensity was changed during follow-up. Last, the similar risk of MACE between the low-moderate- and the high-intensity groups was also shown consistently for various baseline LDL-C levels and subgroups.

Current Evidence for Statin Use After AMI

Since the discovery of the role of LDL-C in the development of CAD in the 1950s and 1960s, LDL-C reduction has been an important treatment target in patients with CAD.\(^{18}\) By reducing the plasma LDL-C, statins reduce the risk of death and cardiovascular events across the range of LDL-C.\(^{1}\) Recent RCT reported that a higher intensity statin dosing regimen was more beneficial than standard intensity statin in ACS or stable angina.\(^{2,6,10}\) A recent meta-analysis also noted higher benefit of high-intensity statin in reducing the risks of coronary death, MI, revascularization and stroke.\(^{6}\) In this regard, current ACCF/AHA and ESC guidelines state the initiation of high-intensity statin after AMI as a class I recommendation.\(^{7,10}\)

Several points from the previous studies, however, need to be considered. First, most of the previous RCT were conducted in non-AMI patients. Of 5 RCT that directly compared lower intensity and higher intensity statins,\(^{2,11-13}\) only 2 RCT evaluated patients with ACS,\(^{23}\) while the others evaluated patients with stable CAD. Second, all the previous RCT were conducted in the first-generation DES era, therefore, the results might not reflect contemporary practice using second-generation DES. Third, although the most recent meta-analysis showed no added risk of cancer after high-intensity statin treatment,\(^{6}\) the risk of hemorrhagic stroke was significantly increased. In addition, several observational studies have suggested increased risks of adverse side-effects of high-intensity statins, such as diabetes mellitus, liver dysfunction, myopathy including rhabdomyolysis, and acute kidney disease.\(^{20-24}\)

In this regard, more evidence is needed to clarify the added prognostic benefit of high-intensity statins compared with low-moderate-intensity statins, especially in patients with AMI who are being treated in contemporary practice.

Effect of Statin Intensity in Post-AMI Patients

In this nationwide, dedicated prospective registry for AMI, both low-moderate- and high-intensity statin dosing regimens significantly reduced the risk of MACE at 1 year, with multiple sensitivity analyses showing consistent results. LDL-C was significantly decreased in both the low-moderate-intensity statin group and the high-intensity statin group, and the degree of reduction was significantly higher in the high-intensity group. The risks of MACE and all individual clinical outcomes, however, were similar between the 2 statin intensity groups. These results were consistently found across the range of baseline LDL-C and various subgroups.

These interesting findings from the registry require careful explication. First, although current guidelines recommend universal use of high-intensity statin after AMI, regardless of baseline LDL-C level, many clinicians still prescribe low-moderate-intensity statin for patients whose LDL-C level is relatively low. In the current study, baseline LDL-C between the low-moderate- and the high-intensity groups was significantly different (108.5±38.5 mg/dL vs. 123.2±40.2 mg/dL, P<0.001). Despite the fact that the degree of LDL-C reduction was significantly higher in the high-intensity group (high intensity: 37.6% vs. low-moderate intensity 23.8%, P<0.001), both groups had similar 1-year LDL-C, around 70 mg/dL. This indicates that if LDL-C is adequately lowered, regardless of baseline LDL-C level, the low-moderate-intensity statin would have similar prognostic benefits to the high-intensity statin.\(^{25,26}\) Second, although previous meta-analyses and RCT provided robust evidence for high-intensity statin use in CAD,\(^{2,5,6}\) we have to consider that these studies were performed in the first-generation DES era. The enhanced safety and efficacy of second-generation DES might dilute the benefit of high-intensity statins in contemporary practice.\(^{27,29}\) Third, it should be noted that approximately 40% of patients who were initially prescribed high-intensity statins actually lowered their dose before 1-year follow-up, while only 5% of patients in the low–moderate-intensity statin group changed the dose. This suggests that patients may have had intolerance to high-intensity statin. Even after excluding patients whose statin intensity was changed, the similar risk of MACE between the low-moderate- and high-intensity statins was maintained. All these results seem indicative of the importance of patient-specific management rather than one-size-fits-all statin treatment in post-AMI patients.

Clinical Implications

This study evaluated a large-scale real-world AMI group from a nationwide, dedicated, multicenter registry. As with previous studies, statin use had a significant prognostic benefit after AMI, regardless of intensity, in post-AMI patients. Although baseline LDL-C was significantly different between the low-moderate- and the high-intensity statin groups, both groups achieved adequate lowering of LDL at 1 year. Regarding clinical outcome, both groups
had similar risk of MACE at 1 year. Despite the universal recommendation of high-intensity statins in AMI patients, a substantial proportion of patients were prescribed low-moderate-intensity statins according to baseline LDL level, and those patients had similar risk of 1-year MACE, compared with those prescribed a high-intensity statin dosing regimen. Hence, if the low-moderate-intensity statin dosing regimen reduces LDL-C adequately, the prognostic benefit of low-moderate-intensity statin might be similar to that of high-intensity statin.8,35 Furthermore, considering the potential risk of high-intensity statins, such as intolerability due to adverse side-effects, the universal use of a high-intensity statin dosing regimen should instead be evaluated on an individual basis.

Study Limitations
This study had several limitations. First, the inherent limitation of a non-randomized controlled study should be considered. Although we performed multiple sensitivity analyses, the possibility of unobserved confounders should be considered. Second, of the total group, 11.2% of patients who were initially prescribed statins, had changed their statin dose by 1 year. Regardless of whether these patients were included or excluded from analysis, however, the risk of MACE was similar between the low-moderate and the high-intensity groups. Third, this study did not consider individual specific effects of the different types of statins.

Conclusions
The use of statins, regardless of intensity, was associated with a significantly lower MACE risk in post-AMI patients compared with the no statin group. When adequate LDL-C level was achieved, post-AMI patients on a low-moderate-intensity statin dosing regimen had similar cardiovascular outcomes to those on high-intensity statins.

Acknowledgments
This research was supported by a fund (2016-ER6304-01) by Research of Korea Centers for Disease Control and Prevention.

Disclosures
The authors declare no conflict of interest.

References


**Supplementary Files**

**Supplementary File 1**

**Table S1.** Standardized mean differences vs. statin intensity

**Table S2.** Reasons for not using statin in the no statin group

**Table S3.** LDL-C reduction rate and MACE rate vs. baseline LDL-C

**Table S4.** Final LDL-C and clinical outcome vs. statin intensity