J Lipid Atheroscler. 2020 Sep;9(3):362-379
https://doi.org/10.12997/jla.2020.9.3.362
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Review

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Clinical Benefit of Statins in Korean Patients with Acute Myocardial Infarction: Experience of the Korea Acute Myocardial Infarction Registry

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OPEN ACCESS

Received: May 22, 2020
Revised: Jul 10, 2020
Accepted: Jul 24, 2020

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Funding
This study was funded by the Korean Society of Lipid and Atherosclerosis, and supported by the Chonnam National University Hospital Biomedical Research Institute (BCRI-20075).

Conflict of Interest
The authors have no conflicts of interest to declare.

Author Contributions
Conceptualization: Jeong MH; Data curation: Cho KH, Jeong MH; Formal analysis: Cho

ABSTRACT

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) are among the most important medications for treating patients with acute myocardial infarction (AMI). Herein, we review the clinical benefit and future scope of statin therapy in Korean patients with AMI from the experience of the Korea AMI Registry. Statins are effective and safe in AMI patients, even in those with very low low-density lipoprotein cholesterol (LDL-C). Peri-procedural statin treatment could reduce the incidence of early stent thrombosis in patients with AMI after percutaneous coronary intervention. Reduction of high sensitivity C-reactive protein levels in patients with AMI plays an important role in the beneficial effect of statins on regression and compositional change of coronary plaques. Obtaining ≥50% reduction in LDL-C is associated with better clinical outcomes after AMI, whereas achieving <70 mg/dL LDL-C is not. Statin therapy has positive effects on clinical outcomes in patients with cardiogenic shock, ischemic heart failure, chronic kidney disease, and vasospasm. The combination of high-dose statin plus N-acetyl cysteine is associated with lower incidence of contrast-induced nephropathy in patients who underwent primary percutaneous coronary intervention. Moderate-intensity pitavastatin therapy is associated with a lower incidence of new-onset diabetes mellitus in patients with AMI and has similar clinical outcomes to moderate-intensity atorvastatin and rosuvastatin therapy. Future studies are required to assess the optimal intensity and LDL-C target concerning statin therapy, and the implementation of guidelines based cholesterol lowering practice in Korean patients with AMI.

Keywords: Acute myocardial infarction; Statins; Prognosis

INTRODUCTION

Coronary artery disease, especially acute myocardial infarction (AMI), is a leading cause of death in the Asia-Pacific region. The Korea Acute Myocardial Infarction Registry (KAMIR) is the first nationwide, prospective, multicenter registry of Korean patients with AMI.[1-3] Since the KAMIR first began in November 2005, more than 75,250 patients have been enrolled, and 271 (The Science Citation Index: 250) papers have been published (as of March 2020). Moreover, published data from the KAMIR have revealed different characteristics from those of Western AMI registries regarding risk factors, interventional strategies, and clinical outcomes. As a

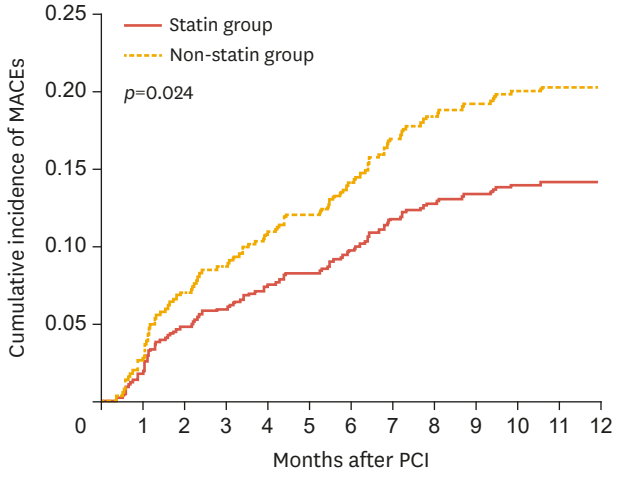
KH, Jeong MH; Funding acquisition: Jeong MH; Investigation: Cho KH, Jeong MH; Methodology: Cho KH, Jeong MH; Project administration: Cho KH, Jeong MH; Resources: Cho KH, Jeong MH; Software: Jeong MH; Supervision: Jeong MH; Visualization: Cho KH, Jeong MH; Writing - original draft: Cho KH, Jeong MH; Writing - review & editing: Jeong MH.

result, the KAMIR study has improved the outcomes of percutaneous coronary intervention (PCI) and reduced mortality.[4] We propose the use of the KAMIR score in predicting 1-year mortality and KAMIR-DAPT score for guiding selection of potent P2Y12 inhibitors (https://kamirscore.com).[5,6] Clinical benefits and future scope of statin therapy in Korean patients with AMI will be provided in this narrative review from the experience of the KAMIR.

EFFICACY OF STATIN THERAPY IN PATIENTS WITH AMI

1. Statin therapy in AMI with very low LDL-C

We investigated whether statin therapy is beneficial in patients with AMI who have baseline low-density lipoprotein cholesterol (LDL-C) levels below 70 mg/dl. Intensive lipid-lowering therapy with a target LDL-C value <70 mg/dL is recommended in patients with very high cardiovascular risk. However, whether to use statin therapy in patients with baseline LDL-C levels below 70 mg/dL remains controversial. We analyzed 1,054 patients from the KAMIR with AMI who had baseline LDL-C levels below 70 mg/dL and survived at discharge between November 2005 and December 2007. They were divided into 2 groups according to prescription of statins at discharge (statin group n=607; non-statin group n=447). The primary endpoint was composite of 1-year major adverse cardiac event (MACE), including death, recurrent MI, target vessel revascularization, and coronary artery bypass grafting. Statin therapy significantly reduced the risk of composite primary endpoint (adjusted hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.34 to 0.89; p=0.015). During the 12-month follow-up period, a primary endpoint event occurred in 58 patients (14.5%) in the statin group and 57 patients (20.4%) in the non-statin group (log-rank p=0.024) (**Fig. 1**). Statin therapy reduced the risk of cardiac death (HR, 0.47; 95% CI, 0.23 to 0.93; p=0.031) and coronary revascularization (HR, 0.45; 95% CI, 0.24 to 0.85; p=0.013). However, there were no differences in the risk of composite all-cause death, recurrent myocardial infarction, and repeated PCI rate.



No. at risk	1,054	894	780	680
Statin group	607	529	457	400
Non-statin group	447	365	323	280

Fig. 1. Estimates of the rate of the primary endpoint events. The primary endpoint was the composite of death, recurrent myocardial infarction, and coronary revascularization.
Adapted from Fig. 1 in Lee et al.[7]
MACE, major adverse cardiac event; PCI, percutaneous coronary intervention.

https://doi.org/10.12997/jla.2020.9.3.362

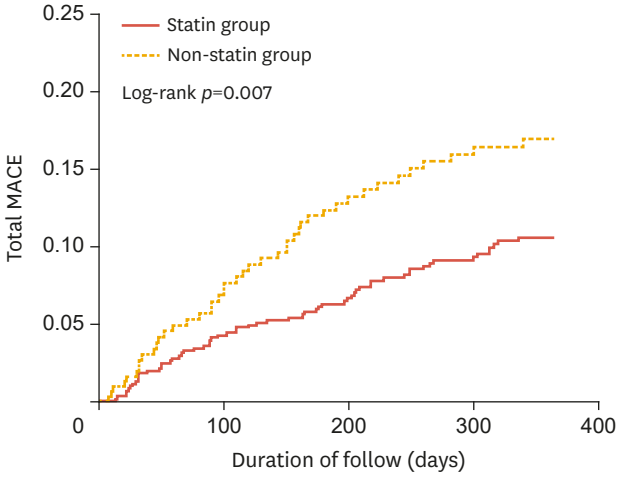


Fig. 2. Kaplan-Meier curves for 12-month probability of MACE in patients in statin and nonstatin groups.
Adapted from Fig. 2 in Piao et al.[8]
MACE, major adverse cardiac event.

Subgroup analysis showed that the beneficial effects of statin therapy appeared to be prominent in men, the elderly, those without diabetes mellitus, those without hypertension, those without prior dyslipidemia, smokers or ex-smokers, those with an initial diagnosis of ST-segment elevation myocardial infarction (STEMI), and those with higher serum levels of high-sensitivity C-reactive protein. Statin therapy in patients with AMI and baseline LDL-C levels below 70 mg/dL was associated with improved clinical outcome.[7]

Previous trials have found that statin therapy reduces LDL-C level and the risk of cardiovascular events. However, the benefit of statin therapy in patients with baseline LDL-C levels ≤50 mg/dL is less clear. Therefore, we assessed whether patients with AMI who have baseline LDL-C levels ≤50 mg/dL benefit from statin therapy in real-world clinical practice. The clinical data of 1,048 patients (67.3±12.6 years, 69.6% men) with AMI and baseline LDL-C levels ≤50 mg/dL from KAMIR data between November 2005 and May 2014 were analyzed. Patients were divided into 2 groups based on whether or not they were prescribed statins at discharge (statin and non-statin groups, n=738 and 310, respectively). The primary end point was MACE, defined as the composite of all-cause mortality, recurrent myocardial infarction, and repeated PCI or coronary artery bypass grafting. MACE occurred in 11.8% of the statin group versus 19.3% of the non-statin group during the 12-month follow-up (**Fig. 2**). Statin therapy significantly reduced the risk of MACE (HR, 0.60; 95% CI, 0.39 to 0.94; p=0.025) and coronary artery bypass grafting (HR, 0.27; 95% CI, 0.08 to 0.96; p=0.043). There was a trend of reduced cardiac death in the statin group compared with the non-statin group (HR, 0.52; 95% CI, 0.26 to 1.02; p=0.059). The subgroup analysis revealed that the beneficial effects of statin therapy were especially evident in the men and the elderly, as well as those with diabetes mellitus, multivessel disease, initial diagnosis of STEMI, and higher serum levels of high-sensitivity C-reactive protein. Statin therapy for patients with AMI and LDL-C levels ≤50 mg/dL was associated with improved outcomes. Therefore, statin therapy might be feasible and effective, even in patients with AMI and extremely low levels of LDL-C.[8]

2. Effects of statin intensity on clinical outcome in AMI

The added benefit of high intensity statins compared with low-moderate intensity statins has been debated, especially in patients with AMI. KAMIR- National Institute of Health (NIH) consecutively enrolled 13,104 patients with AMI. Of these, a total of 12,182 patients who

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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). Only atorvastatin 40–80 mg and rosuvastatin 20–40 mg were considered high-intensity statins (n=3,665; 30.1% of total group); the others were considered low-moderate-intensity statins (n=7,703; 63.2% of total group). The primary outcome was MACE including cardiac death, non-fatal MI, and repeat revascularization at 1 year. Both low-moderate intensity and high intensity statins significantly reduced 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 to 0.619; $p<0.001$; high intensity, HR, 0.464; 95% CI, 0.352 to 0.611; $p<0.001$). The risk of MACE, however, was similar between low-moderate and high intensity statin groups (HR, 0.917; 95% CI, 0.760 to 1.107; $p=0.368$). Multivariable adjustment, propensity score matching, and inverse probability weighted analysis also produced the same results. 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.[9]

Data on the intensity of statin therapy for patients with AMI and very low baseline LDL-C level are lacking. We assessed the impact of statin intensity in patients with AMI and LDL-C <70 mg/dL. A total of 1,086 patients with AMI and baseline LDL-C <70 mg/dL from the KAMIR-NIH database were divided into less intensive statin (expected LDL reduction <40%, n=302) and more intensive statin (expected LDL-C reduction ≥40%, n=784) groups. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCEs), a composite of cardiac death, MI, revascularization occurring at least 30 days after admission, and stroke at 12 months. After 1:2 propensity matching, differences were not observed between less intensive (n=302) and more intensive statin (n=604) groups in incidence of cardiac death (0.3% vs. 0.3%) and hemorrhagic stroke (0.3% vs. 0.5%, $p=0.727$) at 12 months. Compared with the less intensive statin group, the more intensive statin group showed lower target-vessel revascularization (4.6% vs. 1.8%, $p=0.027$) and MACCEs (11.6% vs. 7.0%, $p=0.021$). Major bleeding was not different between less intensive and more intensive statin groups (1.0% vs. 2.6%, $p=0.118$). The beneficial treatment effects of more intensive statins were evident in the female, the elderly, NSTEMI, low Killip class, low creatinine clearance, low ejection fraction, high GRACE score, and higher baseline high-sensitivity CRP (>3 mg/L). More intensive statin therapy was associated with significantly lower major adverse cardiovascular events in patients with AMI and very low LDL-C compared with less intensive statin therapy.[10]

3. Statin therapy for prevention of stent thrombosis in AMI

We investigated whether statin therapy and high-sensitivity C-reactive protein (hs-CRP) levels were associated with the risk of stent thrombosis in patients with AMI. A total of 9,162 patients with AMI who underwent coronary stent implantation were analyzed in the KAMIR. The study population was divided into four groups according to level of hs-CRP and peri-procedural statin treatment: low hs-CRP (≤2.0 mg/L) and high hs-CRP (>2 mg/L) with or without statin therapy. The incidence of early stent thrombosis was compared among groups. Statin therapy did not significantly affect the development of early stent thrombosis in the low hs-CRP group. In the high hs-CRP group, however, the incidence of early stent thrombosis significantly decreased with statin treatment. In a subgroup analysis of the high hs-CRP group, patients aged less than 65 years, without diabetes, with high body mass index, and with high Killip class benefited more from statin therapy. In multivariable Cox regression analysis of the high hs-CRP group, lack of statin therapy was a significant predictor of stent thrombosis incidence. Peri-procedural statin treatment might reduce the incidence of early stent thrombosis in patients with AMI and high levels of hs-CRP.[11]

https://doi.org/10.12997/jla.2020.9.3.362

4. Statin therapy for prevention of ventricular arrhythmia in AMI

We evaluated whether prior statin therapy reduces in-hospital ventricular tachycardia/ventricular fibrillation (VT/VF) in PCI patients with AMI. Among 1,177 patients from the KAMIR-NIH, 823 (70%) patients received prior statin therapy. Prior statin therapy was associated with a reduced risk of VT/VF events in both adjusted propensity score analysis (OR, 0.414; 95% CI, 0.198 to 0.865; p=0.019) and adjusted inverse probability of treatment weight analysis (OR, 0.463; 95% CI, 0.216 to 0.994; p=0.048). The risk of in-hospital death did not differ significantly between those with or without prior statin therapy (HR, 0.416; 95% CI, 0.112 to 1.548; p=0.191). MACE occurred in 116 (8.9%) patients during follow-up. Prior statin therapy was associated with a lower risk of MACE during the follow-up period (HR, 0.486; 95% CI, 0.243 to 0.974; p=0.042); however, this was mainly driven by reduced noncardiac death. Prior statin therapy might reduce the incidence of serious cardiac tachyarrhythmia, such as VT/VF, in patients with AMI undergoing PCI. However, the reduction in VT/VF due to prior statin therapy did not improve short- and long-term clinical outcomes.[12]

5. Statin therapy for plaque regression in AMI

There are few data regarding the effect of statins on regression and compositional changes of plaque according to reduction of hs-CRP levels in patients with AMI. Serial virtual histology-intravascular ultrasound was used to assess the efficacy of pitavastatin (dosage: 2 mg/day) on plaque regression and compositional changes according to degree of reduction in hs-CRP levels from baseline to follow-up (≥1 mg/dL [n=62] vs. <1 mg/dL [n=32]) in non-intervened non-infarct related arteries in patients with AMI who were enrolled in the Livalo in acute myocardial infarction study (LAMIS). Total atheroma and percent atheroma volumes decreased more significantly in patients with ≥1 mg/dL reduction in hs-CRP compared to those with <1 mg/dL reduction in hs-CRP (−1.7±12.4 mm^3 vs. +2.7±7.8 mm^3 p<0.015, and −0.4±3.4% vs. +0.4±4.8%, p<0.001, respectively). Absolute and % necrotic core volumes decreased significantly more in patients with ≥1 mg/dL reduction in hs-CRP compared to those with <1 mg/dL reduction in hs-CRP (−0.4±3.5 mm^3 vs. +1.9±3.4mm^3, p=0.038, and −1.1±4.9% vs. +2.7±4.7%, p=0.016, respectively). Reduction in hs-CRP ≥1 mg/dL at follow-up was an independent predictor of reduced percent atheroma volume and % necrotic core volume at follow-up (odds ratio [OR], 2.228; 95% CI, 1.390 to 2.977; p=0.016, and OR, 2.204; 95% CI, 1.512 to 2.916; p=0.020, respectively). Reduction in hs-CRP levels in patients with AMI could play an important role in the beneficial effects of statins on regression and compositional change of coronary plaques.[13]

6. Comparison of hydrophilic and lipophilic statins in AMI

Controversy exists about which statin is preferable for patients with AMI, and the clinical impacts of different statins according to lipophilicity have not been established. A total of 1,124 patients with AMI included in the present study were divided into hydrophilic- and lipophilic-statin groups. In-hospital complications (defined as death, cardiogenic shock, ventricular arrhythmia, infection, bleeding, renal insufficiency, and other fatal arrhythmias), MACE, all-cause death, re-myocardial infarction, re-PCI, and surgical revascularization were analyzed during 1 year of clinical follow-up. Baseline characteristics were similar between the two groups, and in-hospital complication rates showed no between-group differences (11.7% vs. 12.8%, p=0.688). Although MACE at 1- and 6-month clinical follow-ups occurred more in the hydrophilic statin group I (1 month: 10.0% vs. 4.4%, p=0.001; 6 months: 19.9% vs. 14.2%, p=0.022), no significant difference in MACE was observed at the 1-year follow-up (21.5% vs. 17.9%, p=0.172). Both statin groups showed similar efficacy for reducing serum lipid concentrations. A Cox-regression analysis showed that the use of hydrophilic statin did

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not predict 1-year MACE, all-cause death, AMI, or re-PCI. Although short-term cardiovascular outcomes were better in the lipophilic statin group, 1-year outcomes were similar in patients with AMI who were administered hydrophilic and lipophilic statins. In other words, the type of statin did not influence 1-year outcomes in patients with AMI.[14]

7. Timing of statin therapy in AMI

Although current guidelines recommend early initiation of statins in patients with AMI, there is no consensus for optimal timing of statin initiation. A total of 3,921 statin-naïve patients undergoing PCI were analyzed and divided into 3 groups according to statin initiation time: group 1 (statin initiation <24 hours after admission), group 2 (24–48 hours) and group 3 (≥48 hours). Three stratified models were made to reduce bias: model 1 (<24 hours vs. ≥24 hours), model 2 (<48 hours vs. ≥48 hours), and model 3 (<24 hours vs. 24–48 hours). The endpoint was MACE (a composite of cardiac death, myocardial infarction and target-vessel revascularization) during a median of 3.8 years. During follow-up, incidence of MACE was lower in the early statin group in both model 1 (14.3% vs. 18.4%, HR, 0.77; 95% CI, 0.66 to 0.91; p=0.002) and model 2 (14.6% vs. 19.7%, HR, 0.81; 95% CI, 0.67 to 0.97; p=0.022). After propensity-score matching, results remained unaltered. Statin initiation <24 hours reduced MACE compared to statin initiation ≥24 hours in model 1. Statin initiation <48 hours also reduced MACE compared to statin initiation later in model 2. However, there was no difference in incidence of MACE between statin initiation <24 hours and 24–48 hours in model 3. Early statin therapy within 48 hours after admission in statin-naïve patients with AMI could reduce long-term clinical outcomes compared with later statin initiation.[15]

8. Two LDL-C target goals in AMI: <70 mg/dL vs. ≥50% reduction from baseline

The effects of two LDL-C goals for secondary prevention after AMI were compared in real-world practice. Of 3,091 consecutive patients with AMI who had baseline LDL-C levels ≥70 mg/dL and underwent successful PCI, 1,305 eligible patients who received discharge statin prescriptions were analyzed. Patients were categorized into 2 groups according to LDL-C values obtained at 1 year by two different manners using percent reduction from baseline (≥50% reduction, n=428 vs. <50% reduction, n=877) and fixed levels (<70 mg/dL, n=625 vs. ≥70 mg/dL, n=680). The primary outcome was defined by the composite of 2-year MACE including cardiac death, non-fatal myocardial infarction, PCI, and coronary artery bypass grafting after hospital discharge. At 2 years, MACE occurred in 139 patients (10.7%). Compared with <50% LDL-C reduction from baseline, patients with ≥50% LDL-C reduction had a 47% risk reduction in MACE (adjusted HR, 0.53; 95% CI, 0.36 to 0.79; p=0.002) (**Fig. 3**). Compared with LDL-C levels ≥70 mg/dL at 1 year, patients with LDL-C levels <70 mg/dL at 1 year had a similar risk of major cardiac events (adjusted HR, 0.96; 95% CI, 0.68 to 1.34; p=0.793). Subgroup analysis revealed that obtaining a ≥50% LDL-C reduction from baseline was significantly associated with fewer MCEs at 2 years in male patients, those less than 65 years of age, those without diabetes mellitus, those with multivessel coronary disease, and those receiving high-intensity statins. Obtaining ≥50% reduction in LDL-C was associated with better clinical outcomes after AMI in real-world practice, whereas achieving <70 mg/dL was not.[16]

9. Prognostic effect of hs-CRP with statin therapy in AMI

Elevated hs-CRP in patients with AMI undergoing PCI has prognostic value for future cardiovascular events. This study aimed to ascertain a valid prognostic time period for predicting cardiovascular outcome based on baseline hs-CRP in patients with AMI undergoing successful PCI on statin therapy. Overall, 4,410 patients with AMI were enrolled from the KAMIR-NIH registry. Participants were divided into groups according to cut-off values of

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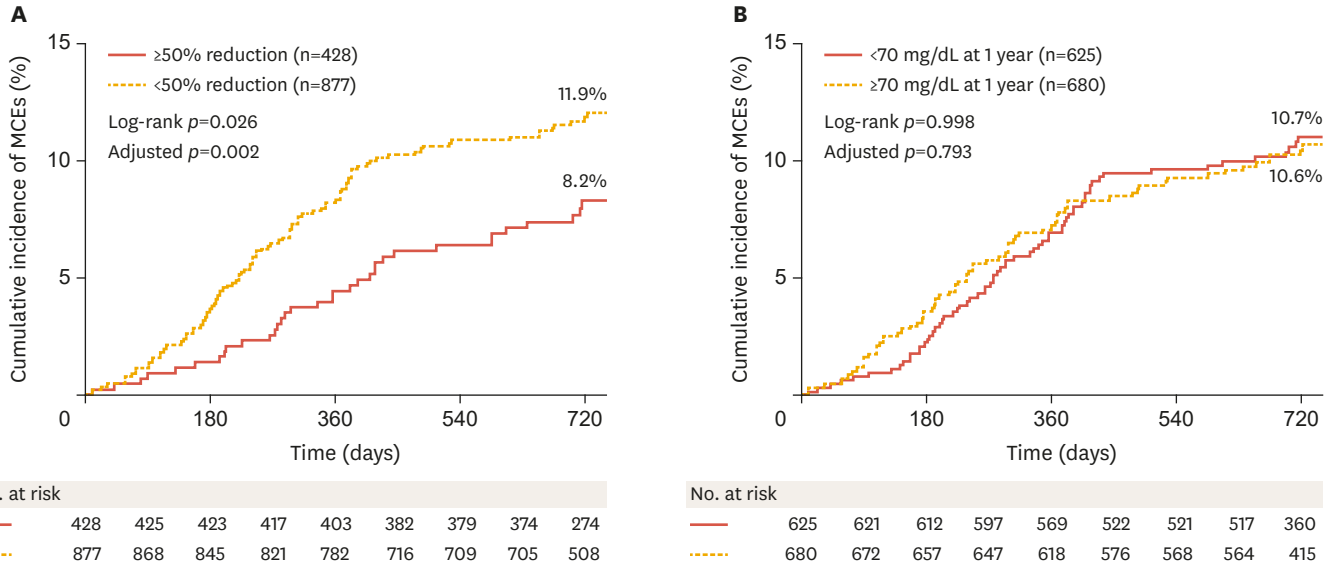

Fig. 3. Kaplan-Meier cumulative MCE curves through 24months of follow-up. (A) Percent reduction goal setting in LDL-C (≥50% reduction from baseline vs. <50% reduction at 1 year). (B) Fixed goal setting in LDL-C (<70 mg/dL vs. ≥70 mg/dL at 1 year).
Adapted from Fig. 2 in Cho et al.[16]
LDL-C, low-density lipoprotein cholesterol; MCEs, major cardiac events.

baseline hs-CRP (1.0, 3.0, and 10.0 mg/L) and statin therapy intensity. The primary outcome was 36-month MACE, a composite of all-cause mortality, any myocardial infarction, and repeat revascularization. The secondary outcome was MACE developed 0–6, 6–12, and 12–36 months after AMI. The overall incidence of 36-month MACE was significantly higher as baseline hs-CRP increased (by groups: 8.8% vs. 8.6% vs. 10.7% vs. 15.4%, log-rank p<0.001). The prognostic effect of baseline hs-CRP was mostly confined to the first 6 months after AMI (0–6 months MACE by groups: 1.6% vs. 2.3% vs. 4.3% vs. 6.1%, log-rank p<0.001) and attenuated in high-intensity statin users. Six months after AMI, the prognostic effect of baseline hs-CRP was remarkably reduced (6–12 month MACE by groups: 2.4% vs. 2.1% vs. 2.8% vs. 4.0%, log-rank p=0.111, 12–36 month MACE by groups: 4.7% vs. 4.1% vs. 4.0% vs. 6.2%, log-rank p=0.218); however, high-intensity statin treatment showed consistent improvements in outcome. The observed time-dependent prognostic effects remained consistent following multivariate analysis. The prognostic impact of elevated hs-CRP at baseline was most evident during the first 6 months after AMI; however, the use of high-intensity statin might persistently improve clinical outcomes even after the resolution of inflammatory reactions.[17]

EFFICACY OF STATIN THERAPY IN SPECIAL PATIENT GROUPS WITH AMI

1. Different statin effects on STEMI vs. NSTEMI

Intensive statin therapy reduces cardiovascular events in acute coronary syndrome. Data concerning the long-term clinical impacts of statin therapy between STEMI and non-STEMI (NSTEMI) after drug-eluting stent implantation are limited. The 2-year clinical outcomes between these 2 groups after statin therapy were compared. A total of 30,616 Korean patients with AMI were enrolled. Among them, 13,686 patients were classified as group A (STEMI statin user), 3,824 patients were classified as group B (STEMI statin nonuser), 10,398 patients were classified as group C (NSTEMI statin user), and 2,708 patients were classified as group

https://doi.org/10.12997/jla.2020.9.3.362

D (NSTEMI statin nonuser). The major clinical endpoint was the occurrence of MACE defined as all-cause death, recurrent myocardial infarction, and any repeat revascularization during a 2-year follow-up period. After adjustment, the cumulative risks of MACE (adjusted HR, 1.112; 95% CI, 1.002 to 1.235; p=0.047), all-cause death (adjusted HR, 1.271; 95% CI, 1.054 to 1.532; p=0.012), and target vessel revascularization (adjusted HR, 1.262; 95% CI, 1.049 to 1.518; p=0.014) in group C were significantly higher than in group A. The cumulative risks of MACE, all-cause death, and cardiac death of the statin non-user group (groups B and D) were significantly higher compared with the statin user group (groups A and C). Statin therapy was more effective in reducing the cumulative risks of MACE, all-cause death, and target vessel revascularization in the STEMI group than in the NSTEMI group in Korean patients with AMI after successful drug-eluting stent implantation.[18]

2. Statin therapy in AMI complicated by cardiogenic shock

The benefit of early statin treatment following AMI complicated by cardiogenic shock has not been well studied. We assessed the effect of early statin therapy in patients with cardiogenic shock complicating AMI. A total of 553 statin-naive patients with AMI and cardiogenic shock (Killip class IV) who underwent revascularization therapy between November 2005 and January 2008 at 51 hospitals in the KAMIR were studied. Patients were divided into 2 groups: those who received statins during hospitalization (n=280) and those who did not (n=273). The influence of statin treatment on 12-month clinical outcome was examined using matched-pairs analysis (n=200 in each group) based on the propensity for receiving statin therapy during hospitalization. Before adjustment, patients receiving statins had a more favorable clinical profile, were less likely to suffer procedural complications, and more likely to receive adequate medical therapy compared to those not receiving statins. Patients receiving statins had lower unadjusted in-hospital mortality and composite rate of mortality, myocardial infarction, and repeat revascularization at 12 months, which remained significantly lower after adjustment for patient risk, procedural characteristics, and treatment propensity. In patients with cardiogenic shock and AMI undergoing revascularization therapy, early statin treatment initiated during hospitalization was associated with lower rates of in-hospital death and 12-month adverse cardiac events.[19]

3. Statin therapy in AMI with ischemic heart failure

The benefit of statin therapy in patients with higher grades of heart failure has yet to be determined. We investigated whether statin therapy affects MACE and all-cause mortality in patients with AMI within 1 year after AMI according to plasma natriuretic peptide levels and left ventricular ejection fraction (LVEF). A total of 11,492 patients with AMI from two nationwide registry databases in Korea were analyzed. Patients with AMI were divided into quartiles by plasma levels of B-type NP (BNP) or N-terminal pro-BNP at admission. Patients with LVEF <40% on initial echocardiography were also evaluated. Total mortality and MACE within 12 months of AMI, including death, nonfatal myocardial infarction, and revascularization, were assessed. Among patients with AMI, statin therapy was included in the discharge medications for 9,075 (79.0%) patients, but not for the remaining 2,417 patients (21.0%). Statin therapy was associated with a 27.8% lower risk of MACE. After adjusting for risk factors, statin therapy was associated with lower HRs for MACE and all-cause mortality in only the third and fourth natriuretic peptide quartile subgroups, and was effective only with moderate- to high-intensity statin therapy. However, statins did not modify outcomes in patients with LVEF <40%. Our results show that moderate- to high-intensity statin therapy was associated with a lower risk of MACE and all-cause mortality in patients with AMI and higher plasma BNP, but not in patients with AMI and decreased LVEF.[20]

https://doi.org/10.12997/jla.2020.9.3.362

The effect of statins on the prognosis of patients with left ventricular systolic dysfunction remains controversial. The effect of statin treatment on clinical outcomes in patients with AMI and left ventricular systolic dysfunction was assessed. A total of 5,119 patients with AMI and LVEF less than 50% on initial echocardiogram were analyzed in the KAMIR. The study population was divided into 4 groups according to level of hs-CRP and statin treatment as low hs-CRP (hs-CRP≤2.0 mg/L) and high hs-CRP (hs-CRP>2 mg/L) with or without statin therapy. The incidence of MACE including cardiac death, re-infarction, target lesion revascularization, and coronary artery bypass grafting was evaluated for a 12-month period in each group. Statin therapy did not significantly prevent MACE in the low hs-CRP groups (with statin: 10.1% vs. without statin: 12.0%, p=0.249). In the high hs-CRP groups, however, the incidence of MACE significantly decreased with statin treatment (with statin: 11.3%, without statin: 20.8%, p<0.001). These findings were consistently observed in all subgroups of the high-hs CRP group, including the subgroup with LVEF less than 40%. In a multivariable logistic regression analysis of the high hs-CRP group, lack of statin therapy was a significant predictor of MACE incidence (OR, 1.573; 95% CI, 1.079–2.293; p=0.018). Statin treatment was associated with better outcome in AMI and left ventricular dysfunction in patients with hs-CRP≥2 mg/dL.[21]

4. Statin therapy in AMI with CKD

Statins reduce MACE and mortality in patients with acute coronary syndrome. The effectiveness of statin therapy in reducing MACE was investigated in patients with AMI and renal dysfunction. A total of 12,853 patients with AMI were categorized into 4 groups: group I, statin therapy and no renal dysfunction (estimated glomerular filtration rate ≥60 mL/min/1.73 m^2); group II, neither statin therapy nor renal dysfunction; group III, statin therapy and renal dysfunction; group IV, no statin therapy but renal dysfunction. The primary end points were death and complications during the hospital course. The secondary end points were MACE during 1 year of follow-up after AMI. Significant differences in composite MACE during 12 months of follow-up were observed among the 4 groups (group I, 11.7%; group II, 19.0%; group III, 26.7%; and group IV, 45.5%; p<0.001) (**Fig. 4**). In a Cox proportional hazards

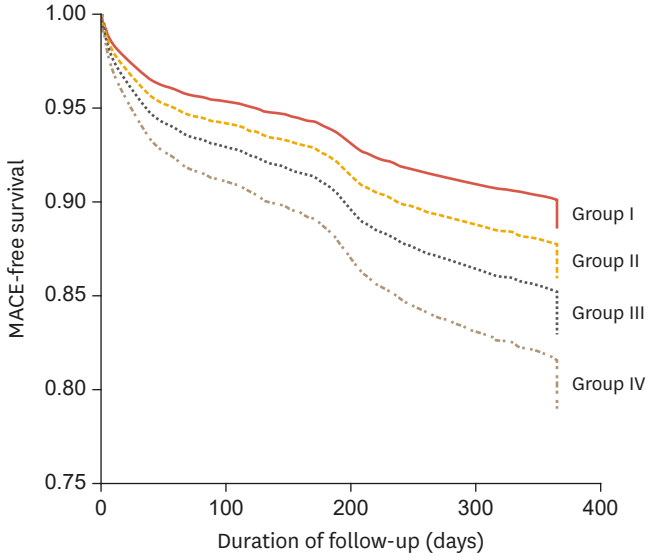

Fig. 4. Cox regression survival curves for major adverse cardiac events (MACE: death, myocardial infarction, and target lesion revascularization) among the 4 study groups.
Adapted from Fig.1 in Lim et al.[22]
MACE, major adverse cardiac event.

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model, mortality at 12 months increased stepwise from group II to IV compared to group I. Moreover, MACE-free survival in the severe renal dysfunction group (estimated glomerular filtration rate <30 mL/min/1.73 m^2) was also greater in the statin treated group. In conclusion, statin therapy might reduce MACE at 1 year of follow-up in patients with AMI regardless of renal dysfunction.[22]

5. Statin therapy in AMI with spasm

Coronary artery spasm is associated with vascular smooth muscle hyper-reactivity. Statins suppress coronary spasm by inhibiting vascular smooth muscle contraction. However, it is unclear whether statin therapy benefits patients with coronary spasm-induced AMI. A total of 501 (median age 57 years; male/female, 346/155) patients with coronary spasm-induced AMI with non-obstructive coronary arteries (stenosis severity<50%) from the KAMIR was analyzed between November 2005 and October 2013. They were divided into two groups according to statin prescription at discharge (statin group n=292; non-statin group n=209). The primary endpoint was the composite of 12-month MACE, including all causes of death, non-fatal myocardial infarction, and target vessel revascularization. The primary endpoint occurred in 17 patients during 12 months of follow-up. Statin therapy significantly reduced the risk of the composite primary endpoint (adjusted HR, 0.30; 95% CI, 0.09 to 0.97; p=0.045). Statin therapy reduced the risk of myocardial infarction (HR, 0.19; 95% CI, 0.04 to 0.93; p=0.040). However, there was no significant difference in the risk of composite all-cause death. Statin therapy in patients with coronary spasm-induced AMI with non-obstructive coronary arteries was associated with improved clinical outcome, which was predominantly accounted for by reducing the incidence of myocardial infarction.[23]

6. Statin therapy in AMI with non-obstructive coronary arteries

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a heterogeneous disease entity. Its prognosis and predictors of mortality remain unclear. The prognosis between MINOCA and myocardial infarction with obstructive coronary artery disease was compared, and factors related to all-cause death in MINOCA were identified using a nation-wide, multicenter, and prospective registry. Among 13,104 consecutive patients enrolled, patients without previous history of significant coronary artery disease who underwent coronary angiography were selected. The primary outcome was 2-year all-cause death. Secondary outcomes were cardiac death, non-cardiac death, re-infarction, and repeat revascularization. Patients with MINOCA (n=396) and myocardial infarction with obstructive coronary artery disease (n=10,871) showed similar incidence of all-cause death (9.1% versus 8.8%; HR, 1.04; 95% CI, 0.74 to 1.45; p=0.83). Risks of cardiac death, non-cardiac death, and re-infarction were not significantly different between the 2 groups (HR, 0.82; 95% CI, 0.53 to 1.28; p=0.38; HR, 1.55; 95% CI, 0.93 to 2.56; p=0.09; HR, 1.23; 95% CI, 0.65 to 2.31; p=0.38, respectively). Patients with MINOCA had lower incidence of repeat revascularization (1.3% vs. 7.2%; HR, 0.17; 95% CI, 0.07 to 0.41; p<0.001). Results were consistent after multivariable regression and propensity-score matching. In a multivariate model, several significant predictors of all-cause death of MINOCA were found, including nonuse of renin-angiotensin system blockers (HR, 2.63; 95% CI, 1.08 to 6.25; p=0.033) and statins (HR, 2.17; 95% CI, 1.04 to 4.54; p=0.039). Patients with MINOCA and those with myocardial infarction with obstructive coronary artery disease had comparable clinical outcomes. Use of renin-angiotensin system blockers and statins was associated with lower mortality in patients with MINOCA.[24]

https://doi.org/10.12997/jla.2020.9.3.362

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OTHER MAJOR ISSUES WITH STATIN THERAPY IN PATIENTS WITH AMI

1. Statin therapy for prevention of contrast-induced nephropathy in patients undergoing primary PCI

AMI is a risk factor for contrast-induced nephropathy (CIN). We investigated whether pretreatment with statins, N-acetylcysteine, and sodium bicarbonate reduces the risk of CIN. A prospective trial that enrolled a total of 334 patients with STEMI was conducted. Patients were divided into four groups: Group I (statin 40 mg), Group II (statin 80 mg), Group III (statin 80 mg plus N-acetylcysteine 1,200 mg), and Group IV (regimen of group III plus sodium bicarbonate 154 mEq/L). CIN was defined as ≥25% or ≥0.5 mg/dL increase in serum creatinine from baseline within 72h after PCI. CIN occurred in 72 (21.6%) patients. The incidence of CIN was lowest in group III (14.3%), and multivariate analysis showed a lower incidence of CIN in group III compared to Group I (OR, 0.29; 95% CI, 0.13 to 0.64; p=0.002). Admission hyperglycemia (>198 mg/dL) (OR, 2.20; 95% CI, 1.20 to 3.68; p=0.011) and the use of intra-aortic balloon pump (OR, 4.20; 95% CI, 1.38 to 12.78; p=0.016) were independent predictors for CIN. CIN (OR, 9.00; 95% CI, 1.30 to 62.06; p=0.026) was an independent predictor for in-hospital mortality. Combination of high-dose statin plus N-acetylcysteine was associated with lower incidence of CIN in patients with STEMI who underwent primary PCI compared to statin only.[25]

2. Statin-induced new-onset diabetes mellitus in AMI

Although statin use in patients with AMI is mandatory, it has been suggested to be associated with new-onset diabetes mellitus (NODM). In real world practice, moderate-intensity statin therapy is more commonly used than high-intensity statin therapy. In this study, we investigated the impact of moderate-intensity pitavastatin (2 to 4 mg) compared to moderate-intensity atorvastatin (10 to 20 mg) and rosuvastatin (5 to 10 mg) on the development of NODM during a follow-up period of up to 3 years. Between November 2011 and May 2015, 2,001 patients with AMI who did not have diabetes mellitus were investigated. The cumulative incidence of NODM was evaluated in all groups. To adjust for potential confounders, multinomial propensity scores were used. Cox proportional hazard models were used to assess the HR of NODM in atorvastatin and rosuvastatin groups compared with the pitavastatin group. The cumulative incidence of NODM was significantly lower in the pitavastatin group compared with the atorvastatin and rosuvastatin groups (3.0% vs 8.4% vs 10.4%, respectively; Log-rank p=0.001) (**Fig. 5**). After weighting baseline characteristics of the 3 statin groups by multinomial propensity scores, atorvastatin (HR, 2.615; 95% CI, 1.163 to 5.879) and rosuvastatin (HR, 3.906, 95% CI, 1.756 to 8.688) were associated with a higher incidence of NODM compared with pitavastatin therapy on multivariable analysis. Moderate-intensity pitavastatin therapy is associated with a lower incidence of NODM in patients with AMI and has similar clinical outcomes to moderate-intensity atorvastatin and rosuvastatin therapy.[26]

3. Simvastatin combined with ezetimibe vs. high intensity statins in AMI

It is unclear whether simvastatin-ezetimibe is an acceptable alternative therapy to high-intensity statin therapy in high-risk patients. The aim of this study was to compare clinical outcomes of simvastatin-ezetimibe and high-intensity statin therapy in patients with AMI, and especially in those with high-risk factors. A total of 3,520 patients with AMI in the KAMIR were classified into the simvastatin-ezetimibe group (n=1,249) and high-intensity statin group (n=2,271). Multivariate analysis and propensity-score matching analysis were performed. The primary endpoint was MACE at 12-month follow-up. In overall patients

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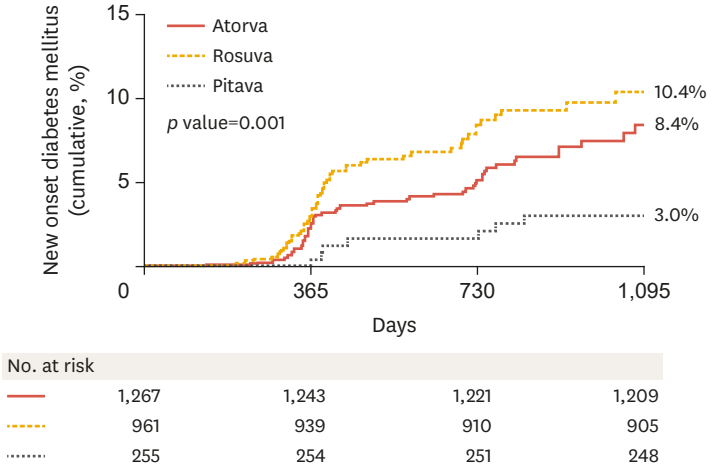

Fig. 5. Kaplan-Meier curves for the cumulative probabilities of new-onset diabetes mellitus.
Adapted from Fig.2 in Choi et al.[26]
Aotrva, atorvastatin; Pitava, pitavastatin; Rosuva, rosuvastatin.

with AMI, MACE occurred in 116 patients (9.3%) in the simvastatin-ezetimibe group and 116 patients (5.1%) in the high-intensity statin group. The difference in MACE between groups was driven by repeat revascularization (5.9% vs. 2.2%). After propensity matching analysis, simvastatin-ezetimibe was associated with a higher incidence of MACE than high-intensity statin therapy (adjusted HR, 3.090; 95% CI, 1.715 to 5.566; p<0.001). However, in patients with high-risk factors, such as diabetes, old age, or heart failure, simvastatin-ezetimibe showed a similar incidence of MACE compared with high-intensity statin therapy in further adjusted analysis. In overall patients with AMI, high-intensity statin therapy had better clinical outcomes than simvastatin-ezetimibe. However, in patients with high-risk factors, simvastatin-ezetimibe had comparable clinical outcomes to high-intensity statin therapy. Therefore, simvastatin-ezetimibe could be used as an alternative to high-intensity statin therapy in such patients.[27]

4. Comparison of statins with ACE inhibitor vs. ARB in STEMI

Studies of comparative clinical outcomes between use of statins with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in patients with STEMI are limited. We compared 2-year clinical outcomes between statins with ACEI or ARB therapy in patients with STEMI after successful PCI with drug-eluting stents. A total of 11,706 patients with STEMI were enrolled and separated into two groups: ACEI group (statin + ACEI, n=8,705) and ARB group (statin + ARB, n=3,001). The primary endpoint was MACE defined as all-cause death, recurrent myocardial infarction, and any coronary revascularization. Secondary endpoints were the individual components of MACE and target vessel failure. After propensity score-matched analysis, two groups (2,729 pairs; n=5,458; C-statistic: 0.675) were generated. The cumulative incidences of MACE, re-myocardial infarction, and any coronary revascularization were similar between the two groups. However, the cumulative incidences of all-cause death (HR, 1.548; 95% CI, 1.091 to 2.197; p=0.014) and cardiac death (HR, 1.850; 95% CI, 1.218 to 2.811; p=0.004) were significantly higher in the ARB group compared with the ACEI group after propensity score-matched analysis. The possible explanation of these results are as follows; first, ACEI, not ARB, prevent the breakdown of bradykinin, which upregulates nitric oxide synthase activity with the subsequent formation of vasodilatory nitric oxide and other relaxing factors, such as prostaglandins, prostacyclin, and endothelium-derived hyperpolarizing factor.[28] Second, the selective activity of the ARB on the angiotensin II type

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1 receptors leads to increased angiotensin II type 2 activity resulting in increased endothelial apoptosis and coronary vasoconstriction. The combination of statin with ACEI may be preferred over the use of statin with ARB to reduce mortality rates in patients with STEMI after successful PCI with drug-eluting stent during a 2-year follow-up period.[29]

FUTURE SCOPE

1. Statin withdrawal in AMI

Despite its necessity, many patients discontinue statin use after AMI. However, limited data are available describing the clinical impact of statin withdrawal after AMI. This study enrolled 3,807 patients in the Korean multicenter registry who survived for 1 year after AMI. All patients were prescribed statins at discharge and were divided into 2 groups on the basis of statin withdrawal history; 603 patients had a history of statin discontinuation and 3,204 patients continued statin therapy. The primary outcome was mortality from any cause. The incidence of cardiac death, nonfatal myocardial infarction, any revascularization, and stroke was also analyzed. The duration of follow-up was 4 years after AMI. Statin withdrawal was associated with higher mortality than continued statin treatment (HR, 3.45; 95% CI, 2.81 to 4.24; p<0.001), primarily resulting from increased cardiac mortality (HR, 4.65; 95% CI, 3.14 to 6.87; p<0.001) (**Fig. 6**). However, the incidences of nonfatal myocardial infarction, any revascularization, and stroke were not different between groups. Analysis by propensity score matching did not affect the results. In conclusion, many patients experienced statin withdrawal after AMI, which significantly increased long-term mortality in the present study. Careful education and monitoring are needed to reduce adverse cardiac outcomes in patients with AMI.[30]

2. Low rate of LDL-C target achievement in Korea and need for PCSK9 inhibitor

According to the KAMIR experience and other clinical reports, target goal achievement rate (LDL-C <70 mg/dL) in Korean patients with AMI is about 50% during 3-year clinical follow-up.[31] When patients were sub-divided according to their pre-acute coronary syndrome risk

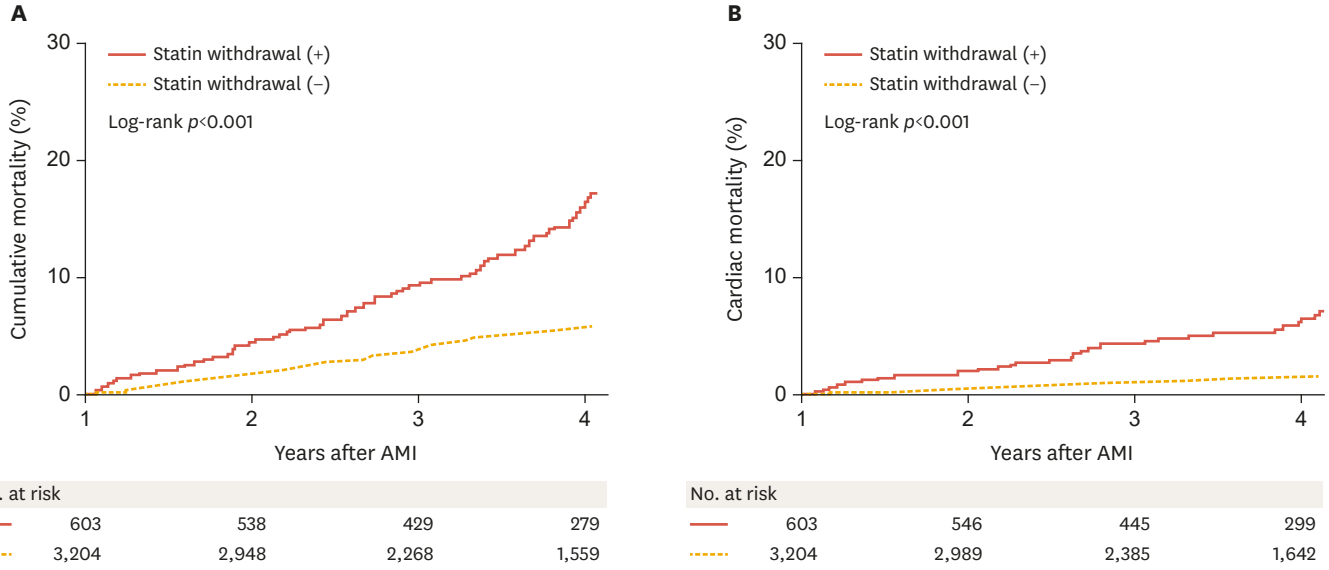

Fig. 6. Cumulative incidence of all-cause mortality (A) and cardiac mortality (B) in crude population.
Adapted from Fig.1 in Kim et al.[30]
AMI, acute myocardial infarction.

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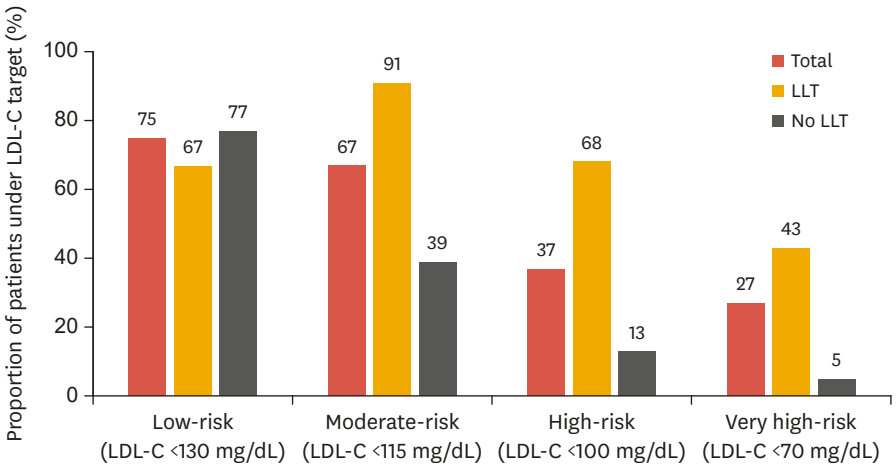

Fig. 7. Under-target rate of patients with ACS classified by pre-ACS risk status. Risk categories and corresponding LDL-C targets specified in the 2011 European Society of Cardiology/European Atherosclerosis Society guidelines. Reprinted from Fig. 2 in Lee et al.[31]
LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein-cholesterol; ACS, acute coronary syndrome.

status, under-target rates were 66.7%, 91.4%, 68.4%, and 42.9% for low, moderate, high, and very high-risk groups, respectively (**Fig. 7**). Proprotein convertase subtilisin/kexin type 9 (PCSK9) targets degradation of LDL receptors. The results of recent clinical trials involving Korean patients with acute coronary syndrome revealed that the PCSK9 monoclonal antibody, alirocumab, reduced the risk of cardiovascular events on top of background statin therapy in patients with atherosclerotic cardiovascular disease.[32-34] The results of the ODYSSEY KT trial involving 199 patients with hypercholesterolemia at high risk of a cardiovascular event from South Korea and Taiwan demonstrate that alirocumab changed LDL-C levels by −57.1% (placebo: +6.3%) at 24 weeks and was generally well tolerated during the trial.[35] Therefore, PCSK9 inhibitors would be especially useful in Korean patients with AMI at very high risk of future atherosclerotic cardiovascular disease events, such as those with diabetes, chronic kidney disease, multi-vessel disease, congestive heart failure, and poor tolerance to statin therapy. However, more clinical data regarding the efficacy and safety of PCSK9 inhibitors in Korean patients with AMI is needed.

3. Korean (Asian) versus Caucasian patients concerning statin therapy in AMI

Racial differences in response to statins have been demonstrated, with higher rosuvastatin plasma levels having been seen in Asian patients than in Caucasians.[36] A meta-analysis of twenty trials assessing statin therapy revealed that a >40% reduction in LDL-C required 80 or 40 mg doses of atorvastatin or rosuvastatin for Westerns compared to 18.9 or 14.1 mg for Asians, respectively.[37] In this regard, FDA recommends a lower starting dose in Asian patients (5 mg of rosuvastatin) compared to Caucasians (10 mg of rosuvastatin). Randomized controlled trials of statin therapy have not been designed to compare clinical outcomes as a function of the specific LDL-C level achieved with treatment. However, results from the meta-analysis confirmed the dose-dependent reduction in atherosclerotic cardiovascular disease with LDL-C lowering agents.[38-40] Recent European and American guidelines recommend to reduce LDL-C to a minimum 50% in patients at very high cardiovascular risk.[41,42] Korean guidelines recommend the LDL-C goal to <70 mg/dL or ≥50% reduction from the baseline level in patients with very high risk group.[43] In the KAMIR study, obtaining ≥50% reduction in LDL-C was associated with better clinical outcomes after AMI in real-world practice, whereas achieving <70 mg/dL was not.[16] In this regard, 50% reduction from baseline LDL-C could be the preferential goal

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than <70mgdL in Korean (Asian) population. Further study is warranted to clarify these issues regarding the optimal intensity of statins and the optimal LDL-C goals.

CONCLUSION

From the experience of the KAMIR, statin therapy is effective in Korean patients with AMI, even in patients with very low LDL-C. Early statin therapy is required in patients with AMI, and more than 50% reduction of LDL-C from baseline is associated with better clinical outcomes. Statin therapy has positive effects on clinical outcomes in AMI patients with cardiogenic shock, ischemic heart failure, chronic kidney disease, and vasospasm. Statin withdrawal and low rate of LDL-C target achievement are important issues, and PCSK9 inhibitors would be useful in Korean patients with AMI at very high cardiovascular risk and with poor tolerance to statin therapy. Future researches are warranted to clarify the optimal LDL-C goal and the optimal intensity concerning statin therapy, and the practical role of PCSK9 inhibitors in Korean patients with AMI.

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