Evaluation of the impact of statin therapy on the obesity paradox in patients with acute myocardial infarction

A propensity score matching analysis from the Korea Acute Myocardial Infarction Registry

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Abstract
The phenomenon of obesity paradox after acute myocardial infarction (AMI) has been reported under strong recommendation of statin therapy. However, the impact of statin therapy on this paradox has not been investigated. This study investigated the impact of statin therapy on 1-year mortality according to obesity after AMI. A total of 2745 AMI patients were included from the Korea Acute Myocardial Infarction Registry after 1:4 propensity score matching analysis (n = 549 for nonstatin group and n = 2196 for statin group). Primary and secondary outcomes were all-cause and cardiac death, respectively. During 1-year follow-up, the incidence of all-cause (8.4% vs 3.7%) and cardiac (6.2% vs 2.9%) death was higher in nonstatin group than in statin (P < .001, respectively). In nonstatin group, the incidence of all-cause (7.2% vs 9.0%) and cardiac (5.5% vs 6.5%) death did not differ significantly between obese and nonobese patients. However, in statin group, obese patients had lower 1-year rate of all-cause (1.7% vs 4.8%) and cardiac (1.2% vs 2.9%) death (P < .05, respectively), and lower cumulative rates by Kaplan–Meier analysis of all-cause and cardiac death compared with nonobese patients (log-rank P < .05, respectively). The overall risk of all-cause death was significantly lower in obese than in nonobese patients only in statin group (hazard ratio: 0.35; P = .001). After adjusting for confounding factors, obesity was independently associated with decreased risk of all-cause death in statin group. In conclusion, the greater benefit of statin therapy for survival in obese patients is further confirmation of the obesity paradox after AMI.

Abbreviations: ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers, BMI = body mass index, CKD = chronic kidney disease, CK-MB = creatine kinase-myocardial band, CV = cardiovascular, DBP = diastolic blood pressure, DES = drug-eluting stent, DM = diabetes mellitus, GFR = estimated glomerular filtration rate, HDLC = high-density lipoprotein cholesterol, HIST = high-intensity statin therapy, hs-CRP = high sensitivity C-reactive protein, LAD = left anterior descending coronary artery, LDL = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, STEMI = ST-elevation MI, TIMI = thrombolysis in myocardial infarction.

Keywords: acute myocardial infarction, mortality, obesity, statins

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1. Introduction

Obesity increases the risk of numerous comorbidities, including type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular (CV) disease. High body mass index (BMI) is strongly associated with an increased mortality in the general population. However, the phenomenon known as the “obesity paradox” in which obesity appears to improve survival after acute myocardial infarction (AMI) has been replicated in several studies. Although a number of theories have been proposed, the mechanism by which obesity appears to improve survival after AMI remains uncertain.

The use of statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, reduces mortality and recurrent adverse cardiac events across a wide range of cholesterol levels in patients at high risk of having an atherosclerotic CV event. Thus, statin therapy for secondary prevention is recommended in all high-risk patients. A previous study found that intensive lipid lowering with a statin had a greater impact on the progression of atherosclerotic plaque burden in obese than in nonobese patients with coronary artery disease. However, the effect of statin therapy on mortality according to obesity status has not been evaluated in patients with AMI. Considering that most studies documenting the phenomenon of obesity paradox were performed under the strong recommendation of statin therapy after AMI, this may be a substantial issue in clinical practice. Therefore, this study aimed to evaluate the association between obesity and 1-year mortality according to statin therapy in patients with AMI.

2. Methods

2.1. Subjects and study design

In the present study, we analyzed the baseline data from the Korea AMI Registry (KAMIR), a nationwide, prospective, observational registry in South Korea. Data were collected by a trained study coordinator using a standardized web-based case report form at each site. Of the 12,115 patients from the KAMIR registry between November 2011 and June 2015, 3395 patients were initially excluded from the analysis for the following reasons: BMI was not identified or was <18.5 kg/m² (n = 968), statin therapy was not identified (n = 19), follow-up was not performed (n = 2068), and mortality was not identified or occurred in-hospital (n = 340). After this process, we performed 1:4 propensity score matching between patients on or not on statin therapy using prespecified clinical variables, including age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, and the use of antplatelet agents, beta-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. High-intensity statin therapy (HIST) was defined as atorvastatin 40 or 80 mg/d or rosuvastatin 20 mg/d. Rosuvastatin 40 mg/d was not included in HIST because this dosage was not available in South Korea. Finally, 549 patients without statin therapy and 2196 patients with statin therapy were enrolled in the present study.

The overall design of the KAMIR has been previously described. Briefly, AMI was diagnosed by characteristic clinical presentation, serial changes on the electrocardiogram suggesting infarction or injury, and increase in levels of cardiac enzymes. All patients received a 300-mg loading dose of aspirin, 300 to 600 mg loading dose of clopidogrel, and heparin. The maintenance dose was 100 mg/day for aspirin and 75 mg/day for clopidogrel. Aspirin and clopidogrel were administered to all patients for ≥6 months. Coronary angiography was performed via either the radial or the femoral artery by a standard technique. The use of stent type was at the individual operators’ discretion. During the in-hospital period, patients received essential medical treatment that included beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), if not contraindicated. After discharge, the patients continued to receive the same medications regimen that they had received at the hospital, except for some temporary medications. Clinical follow-up was performed at 1, 6, and 12 months and upon the occurrence of angina-like symptoms.

Coronary lesion morphology was classified using modified American College of Cardiology/ American Heart Association criteria. Multivessel disease was defined as the presence of lesions with ≥50% stenosis in the noninfarct-related coronary artery. Thrombolysis in Myocardial Infarction score was used to determine the degree of coronary flow. Transthoracic echocardiography was performed to assess the left ventricular ejection fraction (LVEF) using the modified Simpson’s biplanar method. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m² calculated by means of the modification of diet in renal disease formula. Body mass index (BMI) was calculated as weight (kg)/height (m²). Obesity was defined as a BMI ≥25 kg/m² based on the criteria for an Asian population. The primary outcome was the occurrence of all-cause death, and the secondary outcome was the occurrence of cardiac death during 1-year follow-up. All death was considered cardiac unless there was a clear noncardiac cause. The study protocol was approved by the Institutional Review Board/Ethical Committees of each clinical site, and written informed consent was obtained from all patients.

2.2. Statistical analysis

Clinical, biochemical, and procedural characteristics are shown according to statin therapy and obesity status. Values are expressed as mean±SD for continuous variables and numbers and percentages for categorical variables. Continuous variables were compared using Student t test or Mann–Whitney rank-sum test, and categorical variables were compared using the χ²-test or Fisher exact test, as appropriate. Kaplan–Meier survival analysis was performed for the cumulative incidence of all-cause and cardiac death, and comparisons between groups were performed with the log-rank test. Subgroup analyses were performed to identify the hazard ratios (HR) of obesity as estimates for clinical outcomes according to statin therapy. Multiple Cox hazards regression models with consecutive adjustment of confounding risk factors were used to identify the effect of statin therapy on 1-year mortality in all participants and to identify the association between obesity and 1-year mortality in participants on statin therapy. The forced entry method was used to enter independent variables into the multiple regression models. MatchIt R-package was used in matching propensity scores. SPSS statistical software version 20.0 (SPSS Inc., Chicago, IL) was used for statistical analyses. Values of P < .05 were considered statistically significant.

3. Results

3.1. Baseline clinical and procedural characteristics

Clinical and procedural characteristics of the 2745 participants (age, 67±11 years; 66% men) in this study are presented in Table 1. Initially, participants were divided into 2 groups according to statin therapy (nonstatin group: n = 549; statin: n = 2196). There...
were significant differences in clinical characteristics between nonstatin and statin groups, with a higher incidence of STElevation MI (STEMI), and higher levels of total cholesterol, low-density lipoproteins (LDL), peak creatine kinase-myocardial band (CK-MB), and peak troponin I in statin group. Among procedural characteristics, the incidence of multivessel disease and type B2/C lesions was significantly higher in statin group than in nonstatin group. Among clinical characteristics according to obesity status in statin and nonstatin group, the prevalence of male sex and dyslipidemia, LVEF, and the levels of total cholesterol and triglyceride were all significantly higher in obese patients than in nonobese patients in both groups. There were no significant differences in procedural characteristics according to obesity status in nonstatin and statin groups except for incidence of type B2/C lesions being significantly higher in obese patients than in nonobese patients in the nonstatin group, and stent diameter being significantly larger in obese patients than in nonobese patients in the statin group. In the statin group, the overall incidence of HIST was 24%, and was significantly higher in obese patients than in nonobese patients (28% vs 22%, P = .002).

3.2. Clinical outcomes according to statin therapy

During 1 year of follow-up, a total of 128 all-cause deaths and 84 cardiac deaths occurred. The occurrence of all-cause and cardiac death was significantly higher in nonstatin group than in statin group (all-cause death: 9.4% vs 3.7%, P < .001; cardiac death: 6.3% vs 2.3%, P < .001) (Table 1). Kaplan–Meier survival analysis showed that the cumulative incidence of all-cause and cardiac death was higher in nonstatin group than in statin group (log-rank P < .001, respectively) (Fig. 1). Statin therapy was associated with decreased risk of all-cause death (HR: 0.44; 95%
confidence interval [CI]: 0.31–0.63; *P* < .001). After adjusting consecutive variables including age, sex, LVEF, previous MI, multivessel disease, STEMI, CKD, stent diameter, stent length, and traditional CV risk factors including hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking, statin therapy was independently associated with decreased risk of all-cause death in all participants (Supplementary file: Table S1, http://links.lww.com/MD/B780).

3.3. Clinical outcomes according to obesity in subjects with and without statin therapy

**Nonstatin group.** In non-statin group, the occurrence of all-cause and cardiac death was not different between obese and nonobese patients (all-cause death: 7.2% vs 9.0%, *P* = .478; cardiac death: 5.5% vs 6.5%, *P* = .649) (Table 1). The cumulative incidence of all-cause and cardiac death did not differ significantly according to obesity status in nonstatin group (Fig. 1). The risk of all-cause (HR: 0.80; 95% CI: 0.42–1.52; *P* = .492) and cardiac death (HR: 0.84; 95% CI: 0.40–1.76; *P* = .650) did not differ significantly according to obesity status in nonstatin group (Fig. 2).

**Statin group.** In contrast to the results in nonstatin group, the occurrence of all-cause and cardiac death was significantly lower in obese patients than in nonobese patients in statin group (all-cause death: 1.7% vs 4.8%, *P* < .001; cardiac death: 1.2% vs 2.9%, *P* < .05) (Table 1). The cumulative incidence of all-cause (log-rank *P* < .001) and cardiac death (log-rank *P* = .012) was significantly lower in obese patients than in nonobese patients.

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**Figure 1.** Estimates of the cumulative rate of (A) all-cause and (B) cardiac death according to statin therapy and obesity.

**Figure 2.** The estimated hazard ratios of obesity for all-cause and cardiac death in (A) nonstatin group and (B) statin group.
The use of statins has reduced the risk of death or CV events in patients with coronary heart disease. In this nationwide study, we could identify that statin therapy was more emphasized in cases of complex coronary and procedural characteristics in current clinical practice after performing propensity score matching using numerous clinical factors. Despite adverse lesional and procedural features in statin group, the cumulative incidence of all-cause and cardiac death was significantly lower in statin group than in nonstatin group in the present study. Moreover, statin therapy was independently associated with the decreased risk of all-cause mortality in patients with AMI.

It is well known that obesity increases CV risk through risk factors such as increased levels of fasting plasma triglycerides, LDL cholesterol, blood glucose, and insulin, elevated blood pressure, and decreased levels of high-density lipoproteins (HDL) cholesterol and accelerates the progression of coronary atherosclerosis in the general population. However, the phenomenon of obesity paradox has been replicated, especially after the event of AMI. Although several hypotheses have been proposed to explain it in patients with AMI, the exact mechanism of this phenomenon remains unknown.

Recently, Nicholls et al reported that an intensive lipid-lowering strategy had greater impact on atherosclerotic burden in patients with higher BMI. According to this study, obese patients had significantly lower plaque progression rates compared with nonobese patients under the intensive lipid-lowering therapy. This result highlighted the potential benefits of statin therapy in obese patients with coronary artery disease. However, there is a paucity of data on the effect of statin therapy on mortality according to obesity status in patients with AMI. In the present study, we focused on the fact that statin is considered the primary lipid-lowering drug for the treatment of dyslipidemia irrespective of obesity status in clinical practice; and the phenomenon of obesity paradox has been observed in AMI patients under the strong recommendation of statin therapy after the event of AMI. Thus, we formulated the hypothesis that statin therapy could be significantly associated with the phenomenon of obesity paradox after the event of AMI. Interestingly, we found that obesity paradox was observed only in patients treated with statin after AMI and that obesity was independently associated with decreased all-cause mortality after adjusting confounding risk factors in these patients. These results might imply that statin therapy significantly contributed to the phenomenon of obesity paradox after AMI in clinical practice.

Considering that intensive pharmacotherapy could play a substantial role in the potential obesity paradox after AMI, it is possible that the use of HIST could influence on 1-year mortality. In the present study, we found that the incidence of HIST was relatively low, about 24%, and that the incidence of HIST was significantly higher in obese patients than in nonobese patients in the present study (28% vs 22%, P < .05). It is noteworthy that the 1-year cumulative incidence of all-cause and cardiac death was not different according to HIST study. Although the baseline levels of LDL cholesterol were significantly higher in obese patients than in nonobese patients in the present study, patients either with or without HIST achieved acceptable mean LDL cholesterol levels at 1-year follow-up according to the recent guidelines of statin therapy for secondary prevention after AMI (Supplementary file: Table S2, http://links.lww.com/MD/ B780). This might imply that statin therapy has a greater beneficial effect on mortality in AMI patients with obesity than in those without obesity regardless of HIST if the acceptable levels of LDL cholesterol are achieved. However, further prospective

### Table 2

| All-cause death | HR     | 95% CI     | P    |
|-----------------|--------|------------|------|
| Model 1         | 0.35   | 0.19–0.63  | .001 |
| Model 2         | 0.42   | 0.23–0.77  | .005 |
| Model 3         | 0.42   | 0.23–0.77  | .005 |
| Model 4         | 0.44   | 0.24–0.82  | .010 |
| Model 5         | 0.36   | 0.18–0.72  | .004 |
| Model 6         | 0.35   | 0.17–0.72  | .004 |
| Model 7         | 0.35   | 0.17–0.72  | .004 |
| Model 8         | 0.29   | 0.11–0.73  | .009 |
| Model 9         | 0.29   | 0.11–0.74  | .010 |
| Model 10        | 0.29   | 0.11–0.75  | .010 |

Model 1: Unadjusted.
Model 2: Adjusted for age.
Model 3: Adjusted for age and gender.
Model 4: Adjusted for age, gender, and LVEF.
Model 5: Adjusted for age, gender, LVEF, previous MI, and multivessel disease.
Model 6: Adjusted for age, gender, LVEF, previous MI, multivessel disease, and CKD.
Model 7: Adjusted for age, gender, LVEF, previous MI, multivessel disease, STEMI, and CKD.
Model 8: Adjusted for age, gender, LVEF, previous MI, multivessel disease, STEMI, CKD, stent diameter, and stent length.
Model 9: Adjusted for age, gender, LVEF, previous MI, multivessel disease, STEMI, CKD, stent diameter, stent length, and traditional CV risk factors except obesity.
Model 10: Adjusted for age, gender, LVEF, previous MI, multivessel disease, STEMI, CKD, stent diameter, stent length, traditional CV risk factors except obesity, and the medication of calcium channel blockers, ACEI or ARB, and HIST.

(Fig. 1). The cumulative incidence of all-cause and cardiac death did not differ significantly according to HIST (Supplementary file: Fig. S1, http://links.lww.com/MD/B780). Obese patients had decreased risk of all-cause (HR: 0.35; 95% CI: 0.19–0.63; P = .001) and cardiac (HR: 0.41; 95% CI: 0.20–0.84; P = .015) death compared with nonobese patients in statin group (Fig. 2).

### 3.4. Impact of obesity on the primary outcome in patients on statin therapy

Multiple Cox hazard regression models were analyzed to identify the association between obesity and 1-year mortality in patients on statin therapy. After adjusting confounding variables including age, sex, LVEF, previous MI, multivessel disease, CKD, stent diameter, stent length, traditional CV risk factors except obesity, and the medication of calcium channel blockers, ACEI or ARB, and HIST, obesity remained independently associated with decreased risk of all-cause death in participants taking a statin (Table 2).

### 4. Discussion

This study confirmed the beneficial effect of statin therapy on mortality in patients with AMI. Despite more complex lesion characteristics in statin group than in nonstatin group, statin group had significantly lower mortality compared with nonstatin group. The major new findings were that 1-year mortality did not differ significantly according to obesity status in statin group, but was significantly lower in obese patients than in nonobese patients in statin group; and this relationship between obesity and 1-year mortality in statin group persisted after adjustment for numerous factors that might impact mortality. The results of this study suggest that the obesity paradox after AMI may be confined to those taking a statin.
studies with larger sample sizes are warranted considering the paucity of data on the definition and efficacy of HIST in patients with AMI in Asian populations.

Although a number of studies have reported the phenomenon of obesity paradox, there remains much debate and uncertainties regarding its validity as a true paradox.34–36 Recently, several studies have emphasized the quality or function of adipose tissue compared with its amount with respect to CV disease and the optimal treatment for atherogenic dyslipidemia in association with obesity.35,36 In addition, the paradoxical preservation of endothelial function in obese patients also has been reported.137 Thus, it should be necessary to evaluate the phenomenon of obesity paradox focusing on these novel issues.

Several limitations should be acknowledged in the present study. First, statin therapy was not randomly administered to patients during hospitalization and follow-up because the KAMIR is an observational study. Second, we could not examine the effects of specific types of statins or dosages on clinical outcomes. Our data seem to be limited only to a standard low dose of statins and this might be influenced by our national medical insurance system. Third, we only used 2 categories (nonobese vs obese) based on the criteria of BMI ≥25.0 kg/m² for Asian populations because the prevalence of BMI ≥30.0 kg/m² was only about 4% in the present study, which is typical of Asian patients with AMI. Fourth, our study did not have adequate sample size or randomization to prove the bene

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