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Original article

# Statin has more protective effects in AMI patients with higher plasma BNP or NT-proBNP level, but not with lower left ventricular ejection fraction

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ABSTRACT

*Background:* The benefit of statin therapy in patients with higher grades of heart failure has yet to be determined. The present study investigated whether statin therapy affects major composite outcomes (MCOs) and all-cause mortality in patients with acute myocardial infarction (AMI) within 1 year after AMI, according to their plasma natriuretic peptide (NP) levels and left ventricular ejection fraction (LVEF).
*Methods:* A total of 11,492 patients with AMI from two nationwide registry databases in Korea were analyzed. AMI patients were divided into quartiles by plasma levels of B-type NP (BNP) or N-terminal pro-BNP (NT-proBNP) at admission. Patients with LVEF <40% on initial echocardiography were also evaluated. Total mortality and MCOs within 12 months of AMI, including death, nonfatal MI, and revascularization, were assessed.
*Results:* Among AMI patients, statin therapy was included in the discharge medications for 9075 (79.0%) patients, but not for the remaining 2417 patients (21.0%), and statin therapy was associated with a 27.8% lower risk of MCOs. After adjusting for risk factors, statin therapy was associated with lower hazard ratios for MCOs and all-cause mortality in only the third and fourth NP quartile subgroups, being effective only with moderate- to high-intensity statin therapy. However, statins did not modify the outcomes in patients with LVEF <40%.
*Conclusions:* Our results show that moderate- to high-intensity statin therapy was associated with a lower risk of major clinical outcomes and all-cause mortality in AMI patients with higher plasma NP, but not in AMI patients with decreased LVEF.


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## Introduction

It has been shown that statin therapy produces a relatively consistent proportional reduction of cardiovascular risk even among different patient types [1,2]. Additionally, a recent guideline from the American College of Cardiology/American Heart Association recommends high-intensity statin therapy for individuals at high risk of atherosclerotic cardiovascular disease, potentially leading to an increase in the use of statins across a broad range of high-risk patients [3]. However, no recommendation was made in the guideline regarding the initiation or continuation of statin therapy in subjects with New York Heart Association class II–IV heart failure, because there was insufficient information on which to base recommendations for or against statin treatment [3].

Two large randomized controlled trials have evaluated the effects of rosuvastatin on major outcomes in patients with chronic heart failure: The Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca-Heart Failure (the GISSI-HF) [4] and the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) [5] trials. Neither trial showed any beneficial effects of statin therapy on major outcomes in patients with chronic heart failure. However, in the CORONA trial, there was a non-significant 8% reduction in the primary composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction (MI), or stroke, with a significant reduction in admission for cardiovascular causes in the rosuvastatin group compared with the placebo group. In the GISSI-HF trial, the cause of heart failure was ischemic in 40% of patients, primary dilated cardiomyopathy in 35% of patients, and hypertension in 18% of patients, while the CORONA study only enrolled patients with ischemic heart failure [5]. Thus, the question of whether statins may be useful in some subgroups of heart failure, including patients with heart failure after acute myocardial infarction (AMI), remains.

The clinical course of heart failure is characterized by progressive deterioration of cardiac performance and sudden death, with coronary artery disease and atrial fibrillation being important precipitating factors [6]. An autopsy study suggested that unrecognized acute coronary events are common underlying causes of sudden death and even death from pump failure [7]. In addition to its well-known anti-atherosclerotic and anti-inflammatory actions [1,8], statin treatment may also reduce the risk of atrial fibrillation in patients with various cardiovascular comorbidities including heart failure [9]. Although the mechanisms of the beneficial effects of statins on this electrical event are not yet clarified, their pleiotropic actions may be an explanation, and they may also work in the failing heart [10]. Thus, we hypothesize that statins could play a salutary role in patients with heart failure, especially heart failure of ischemic origin.

Considering that B-type natriuretic peptide (BNP) and N-terminal pro-B-type NP (NT-proBNP) are valuable markers of cardiac dysfunction and prognosis for both heart failure and AMI [11–14], we aimed to evaluate the effect of statins in AMI patients after risk-stratification by their plasma natriuretic peptide (NP) levels or left ventricular ejection fraction (LVEF), on all-cause mortality and major composite outcomes (MCOs), consisting of cardiac death, non-cardiac death, recurrent MI, and any repeat percutaneous coronary interventions or coronary artery bypass grafting, using nationwide registry data in Korea, the Korea Acute Myocardial Infarction Registry (KAMIR) and the Korea Working Group on Myocardial Infarction registry (KorMI).

## Methods

### *Study population*

We obtained AMI patient data from KAMIR and KorMI studies, prospective multicenter, observational registries designed to study the current epidemiology of hospital management and AMI outcomes in Korea. KAMIR (2005–2008; $n = 14{,}885$) and KorMI (2008–2014; $n = 25{,}977$) contain up to 3 years of clinical follow-up data regarding primary percutaneous coronary interventions in 53 community and university hospitals, as detailed previously [15–17].

Patients who visited emergency departments and were diagnosed with AMI in 53 university/general hospitals were eligible for enrolment in the studies. The web-based registry data contained information on demographics, past medical history, cardiovascular risk profiles, treatment strategies, procedure findings, medications during hospitalization and after discharge, and blood test results. Patients were followed up for their development of total mortality and MCOs at 1 month, 6 months, and 12 months.

Statins included 2–4 mg of pitavastatin, 10–40 mg of atorvastatin, 5–10 mg of rosuvastatin, 50–100 mg of lovastatin, 10–40 mg of simvastatin with or without 10 mg of ezetimibe, 10–40 mg of pravastatin, and 80 mg of fluvastatin, per day, respectively. In all the cases with ezetimibe therapy (10 mg/day), patients were taking the drug in combination with simvastatin, and we considered statin dosage only, when statin users were categorized into low-, moderate-, or high-intensity statin subgroups.

The need for informed consent was waived in the KAMIR study. After the KAMIR registry, there were some protocol amendments to the KorMI registry, including regular laboratory measurements (at 6, 12, 24, and 36 months) and long-term follow-up scheduled for up to 3 years. These study protocols were reviewed and approved by the Institutional Review Board at each participating center. All KorMI participants provided written informed consent. The registries and this study conform to the Declarations of Helsinki. Among the total registered patients from November 2005 to July 2014 ($N = 40{,}862$), we excluded those who died during hospitalization ($N = 1830$), those without follow-up data ($N = 8897$), and those with missing values ($N = 18{,}853$). Finally, 11,492 AMI patients were included in statistical analyses, with a mean follow-up period of 335.3 (standard deviation, 76.3) days. Of these, 11,001 patients underwent echocardiography at baseline evaluations during admission and were considered for subgroup analyses to examine the statin effect on total mortality and MCOs in patients suffering from AMI with reduced LVEF (<40%).

### *Measurements*

Patients who received statin (both with and without ezetimibe) treatment after AMI events, regardless of previous statin therapy before the index events, were considered to be the statin group. All patients were categorized into NP quartile groups according to plasma level of BNP or NT-proBNP, whichever was higher. BNP or NT-proBNP was measured at the emergency room indefinitely before percutaneous coronary intervention by immunoassay [18]. Using body mass index, patients were categorized as underweight (<18.5 kg/m$^2$), normal (18.5–24.9 kg/m$^2$), or obese (≥25.0 kg/m$^2$). Past medical history was taken regarding hypertension, diabetes mellitus, dyslipidemia, heart failure, and stroke. Smoking status was classified as non-smoker, ex-smoker, and current smoker. In addition to statins, we considered other discharge medications such as calcium channel blocker, beta blocker, angiotensin receptor blocker, and angiotensin-converting enzyme inhibitor. Blood samples, except for lipid profiles, were collected at admission or before percutaneous coronary intervention. Overnight fasting blood was drawn for lipid profile measurements. All index transthoracic echocardiographs were recorded during routine clinical practice according to the current guidelines and two-dimensional M-mode echocardiography and Doppler ultrasound examinations were performed within 3 days of

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