ORIGINAL RESEARCH

Hydrophilic Versus Lipophilic Statin Treatments in Patients With Renal Impairment After Acute Myocardial Infarction

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BACKGROUND: Hydrophilic and lipophilic statins have similar efficacies in treating coronary artery disease. However, specific factors relevant to renal impairment and different arterial pathogeneses could modify the clinical effects of statin lipophilicity, and create differences in protective effects between statin types in patients with renal impairment.

METHODS AND RESULTS: A total of 2062 patients with acute myocardial infarction with an estimated glomerular filtration rate <60 mL/min per 1.73 m² were enrolled from the Korea Acute Myocardial Infarction Registry between November 2011 and December 2015. The primary end point was a composite of 2-year major adverse cardiac and cerebrovascular events (MACEs) after acute myocardial infarction occurrence. MACEs were defined as all-cause death, recurrent myocardial infarction, revascularization, and stroke. Propensity-score matching and Cox proportional hazards regression were performed. A total of 529 patients treated with hydrophilic statins were matched to 529 patients treated with lipophilic statins. There was no difference in the statin equivalent dose between the 2 statin groups. The cumulative event rate of MACEs, all-cause mortality, and recurrent myocardial infarction were significantly lower in patients treated with hydrophilic statins in the propensity-score matched population (all \(P<0.05\)). In the multivariable Cox regression analysis, patients treated with hydrophilic statins had a lower risk for composite MACEs (hazard ratio [HR], 0.70 [95% CI, 0.55–0.90]), all-cause mortality (HR, 0.67 [95% CI, 0.49–0.93]), and recurrent myocardial infarction (HR, 0.40 [95% CI, 0.21–0.73]), but not for revascularization and ischemic stroke.

CONCLUSIONS: Hydrophilic statin treatment was associated with lower risk of MACEs and all-cause mortality than lipophilic statin in a propensity-score matched observational cohort of patients with renal impairment following acute myocardial infarction.

Key Words: acute myocardial infarction ■ hydrophilic statin ■ major adverse cardiac and cerebrovascular events ■ renal impairment ■ statin lipophilicity

Acute myocardial infarction (AMI) is a critical cardiovascular complication in patients with renal impairment. Mortality and morbidity rates after AMI are increased even with mild renal impairment and continue to increase rapidly when the estimated glomerular filtration rate (eGFR) is further decreased.\(^1\)\(^-\)\(^3\) To improve clinical outcomes after AMI, statin therapy is highly recommended, because it has significant benefits including reducing major adverse cardiac and cerebrovascular events (MACEs) in patients with renal impairment.\(^4\) Several studies have also demonstrated that statin treatment in patients with renal
Nevertheless, the predominant effect between the 2 statin types was not consistently observed, and no significant differences in the protective effects of statins were reported by prospective randomized trials.\textsuperscript{16–18}

Patients with renal impairment have traditional cardiovascular risk factors as well as specific relevant factors, with lower renal function such as decreased renal excretion, acid-base imbalance, and greater levels of oxidative stress and inflammation, which might modify the clinical benefits of statins.\textsuperscript{19–21} Therefore, the effect of statin lipophilicity could be changed in patients with impaired renal function and affect the protective effects the 2 statin types. In this study, we compared the ability of hydrophilic and lipophilic statins to prevent the occurrence of MACEs after AMI in patients with renal impairment, and attempted to determine which type is preferable for patients with renal impairment.

\section*{METHODS}

This research was supported by the Research of Korea Centers for Disease Control and Prevention (2016-ER6304-02).

\section*{Study Population and Design}

Our study used data from the KAMIR (Korea Acute Myocardial Infarction Registry), a prospective, observational, multicenter, online registry with support from the Korean Society of Cardiology. Patients diagnosed with ST-segment–elevation myocardial infarction or non–ST-segment–elevation myocardial infarction in 20 university hospitals between November 2011 and December 2015 were enrolled in this registry and followed up. The diagnosis of AMI was based on the detection of an increase and/or decrease in cardiac biomarker levels (creatinine kinase-MB and troponin I or T) with at least 1 value above the 99th percentile upper reference limit and with at least 1 of the following: symptoms of ischemia, electrocardiography change (new ST-segment elevation or new left bundle branch block or ST change without ST elevation) and imaging evidence of new loss of viable myocardium or a regional wall motion abnormality.\textsuperscript{22} The present study was performed in compliance with the ethical guidelines of the 1975 Declaration of Helsinki. The authors declare that all supporting data are available within the article and its online supplementary files. The study protocol was approved by the institutional review boards of all centers, and written informed consent was obtained from all participating patients.

A total of 13,104 patients diagnosed with AMI were enrolled in the KAMIR database. Renal impairment was defined as an eGFR of <60 mL/min per 1.73 m\textsuperscript{2}, and 2824 patients with AMI met the criteria. Patients for whom data were missing, with in-hospital MACEs, or who were lost to follow-up within 6 months of being...
diagnosed with an AMI were excluded. Patients not taking statins or taking cholesterol-lowering medications, such as ezetimibe and fenofibrate, were excluded from our study. Finally, 2062 patients with AMI with renal impairment were enrolled in this study. The patients were divided into 2 groups depending on statin type.

Data Collection and Covariates
Data were collected by the attending physician with the assistance of a trained clinical research coordinator, via a web-based case report form in the Clinical Data Management System of the Korean National Institutes of Health. Patients’ baseline demographics, risk factors for coronary artery disease, and laboratory data were collected at admission. Laboratory measurements included hemoglobin, serum creatinine, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Serum creatinine level was measured before percutaneous coronary intervention (PCI) for AMI, and renal function was assessed based on eGFR expressed as milliliters per minute per 1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration equation. Diabetes was defined as patients taking antidiabetic drugs or hemoglobin A1c level ≥6.5%, and hypertension was defined as patients taking antihypertensive drugs, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Medications prescribed at discharge were also recorded. The type of myocardial infarction (MI) (ST-segment-elevation myocardial infarction or non-ST-segment-elevation myocardial infarction) and implementation of PCI were also collected. The left ventricular ejection fraction was measured using the modified Simpson method on 2-dimensional echocardiography.

Exposure
The main predictors of this study were the statin type based on lipophilicity. Atorvastatin, simvastatin, pitavastatin, and fluvastatin were classified as lipophilic statins, whereas rosuvastatin and pravastatin were hydrophilic statins. Because the patients were treated with different statins and doses, we calculated the equivalent dose based on atorvastatin. Prescription doses were compared between the 2 groups by setting atorvastatin 10 mg, rosuvastatin 5 mg, fluvastatin 80 mg, pitavastatin 1 mg, pravastatin 40 mg, and simvastatin 20 mg as equal doses.

Outcomes
The primary end point was a composite of 2-year MACEs after the occurrence of AMI. MACEs were defined as all-cause death, recurrent MI, revascularization, and stroke.

The same AMI criteria were used to diagnose recurrent MI. Revascularization included repeated PCI (target or non-target vessel) and coronary artery bypass grafting. Stroke was defined as focal loss of neurologic function caused by an ischemic event, with residual symptoms lasting at least 24 hours or leading to death. Hemorrhagic stroke was not included in the primary end point.

Statistical Analysis
Continuous variables are described as mean±SD and were analyzed using the Student t test. Categorical data were analyzed using the χ² test. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox regression was used to calculate the corresponding hazard ratios (HRs) with 95% CIs for the combination of MACEs, using lipophilic statin as a reference. Multiple Cox proportional regression analysis determined the association of variables with MACEs after the adjustment for several confounders. Multivariate models included not only parameters that were significantly different between the 2 groups in a univariate testing, but also clinically important parameters.

In addition to the conventional methods for the survival analysis, the propensity-score matched cohort was organized as the main subject of the analysis. Propensity scores were estimated using a multivariable logistic regression model, which represents the probability of receiving a hydrophilic statin. Variables included in the logistic regression model used to estimate the propensity score were as follows: sex, age, body mass index, hypertension, diabetes, history of coronary artery disease, cerebrovascular accident history, smoking, hemoglobin, eGFR, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, Killip class, left ventricular ejection fraction, PCI treatment, MI type, and medication history including aspirin, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. Propensity-score matching between those who had used hydrophilic versus lipophilic statins was performed using nearest-neighbor 1:1 matching. To examine matching quality, we evaluated the balance in the covariates using the standardized differences before and after matching, considering that differences <0.1 were negligible. The propensity-score matched participants were compared using the Kaplan-Meier method and Cox model. An association between eGFR and composite MACEs was demonstrated using multivariate Cox regression analysis. All statistical analyses were performed using SPSS software (version 22.0; IBM, Armonk, NY) and R software (version R 3.6.2; https://cran.r-project.org/). Statistical significance was set at P<0.05.
RESULTS

Patient Characteristics

Among the 2062 patients in this study, 663 (32.2%) were treated with hydrophilic statins. The mean follow-up duration of all patients was 18.6±8.2 months. The baseline characteristics, laboratory findings, MI type, and implementation of PCI and medications are shown in Table 1. Compared with patients receiving lipophilic statins, those receiving hydrophilic statins showed a lower prevalence of diabetes and higher hemoglobin and eGFR levels. The serum levels of total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol did not differ between the 2 groups. The proportion of ST-segment–elevation myocardial infarction was higher, and the Killip class was significantly better in the hydrophilic statin group. Systolic and diastolic blood pressure of the hydrophilic statin group was not different from those of lipophilic statin at admission (127.4±31.6 versus 129.3±32.2; \( P =0.202 \) and 75.3±17.6 versus 76.6±19.1; \( P =0.149 \)) and discharge (117.2±17.1 versus 117.8±16.8; \( P =0.440 \) and 68.2±10.1 versus 68.6±10.3; \( P =0.400 \)). Significant differences in the type of coronary artery related to infarction and number of affected vessels were not observed between the 2 groups (Table S1).

The patients were not randomly assigned to each group, and the data suggested that patients receiving the 2 statin types had different baseline characteristics. Therefore, we used 1:1 propensity-score matching to reduce potential selection bias; therefore, 1058 patients remained as the matched participants. The baseline characteristics of the propensity-score matched cohort were well balanced between the 2 matched groups, including those with significant differences before matching. There was no difference in the statin equivalent dose between the entire cohort and the propensity-matched cohort.

Clinical Outcomes of Hydrophilic Versus Lipophilic Statins

In the propensity-score matched cohort, MACEs occurred in 256 (24.2%) patients. All-cause death was noted in 157 (14.8%), recurrent MI in 50 (4.7%), etc.

Table 1. Baseline Characteristics of the Study Population

| Characteristic               | Whole cohort | Propensity-matched cohort |
|-----------------------------|--------------|----------------------------|
|                             | Hydrophilic, N=663 | Lipophilic, N=1399 | P value | SD | Hydrophilic, N=529 | Lipophilic, N=529 | P value | SD |
| Age, y                      | 71.4±10.6 | 72.2±10.4 | 0.096 | 0.08 | 71.3±10.7 | 71.2±10.8 | 0.889 | 0.01 |
| Men, n (%)                  | 384 (57.9) | 850 (60.8) | 0.238 | 0.06 | 305 (57.7) | 302 (57.1) | 0.901 | 0.01 |
| BMI, kg/m²                  | 23.6±3.5 | 23.4±3.5 | 0.098 | 0.08 | 23.6±3.5 | 23.5±3.5 | 0.753 | 0.02 |
| Hypertension, n (%)         | 486 (73.3) | 1027 (73.4) | 1.000 | 0.00 | 384 (72.6) | 385 (72.8) | 1.000 | 0.00 |
| Diabetes, n (%)             | 286 (43.1) | 712 (50.9) | 0.001 | 0.16 | 229 (43.3) | 224 (42.3) | 0.804 | 0.02 |
| Previous CVD, n (%)         | 216 (32.6) | 484 (34.6) | 0.393 | 0.04 | 168 (31.8) | 162 (30.6) | 0.740 | 0.02 |
| Smoking history, n (%)      | 269 (40.6) | 818 (44.2) | 0.135 | 0.07 | 222 (42.0) | 215 (40.6) | 0.708 | 0.03 |
| Hemoglobin, g/dL            | 12.5±2.4 | 12.1±2.2 | 0.001 | 0.16 | 12.5±2.4 | 12.5±2.3 | 0.795 | 0.02 |
| eGFR, mL/min per 1.73 m²    | 42.1±15.3 | 39.5±16.1 | 0.001 | 0.16 | 42.5±15.0 | 42.5±14.7 | 0.981 | 0.00 |
| Total cholesterol, mg/dL    | 169.5±48.2 | 166.3±47.3 | 0.165 | 0.07 | 169.8±48.8 | 170.4±45.4 | 0.831 | 0.01 |
| Triglycerides, mg/dL        | 125.5±121.0 | 126.1±94.2 | 0.920 | 0.01 | 125.4±125.7 | 124.4±81.6 | 0.873 | 0.01 |
| HDL cholesterol, mg/dL      | 43.2±15.1 | 41.9±15.1 | 0.078 | 0.09 | 42.7±12.4 | 42.8±15.7 | 0.916 | 0.01 |
| LDL cholesterol, mg/dL      | 103.8±39.5 | 100.9±39.9 | 0.131 | 0.07 | 103.9±40.4 | 104.3±38.7 | 0.848 | 0.01 |
| STEMI, n (%)                | 298 (44.9) | 543 (38.8) | 0.009 | 0.12 | 236 (44.6) | 224 (42.3) | 0.335 | 0.05 |
| Killip>1, n (%)             | 202 (30.5) | 612 (43.7) | <0.001 | 0.28 | 167 (31.6) | 169 (31.9) | 0.947 | 0.01 |
| PCI, n (%)                  | 559 (84.3) | 1205 (86.1) | 0.303 | 0.05 | 449 (84.9%) | 451 (85.3%) | 0.931 | 0.01 |
| LVEF, n (%)                 | 48.8±12.1 | 48.9±12.9 | 0.921 | 0.00 | 49.0±12.1 | 48.3±12.7 | 0.335 | 0.08 |
| Aspirin, n (%)              | 661 (99.7) | 1397 (99.9) | 0.819 | 0.03 | 528 (99.8) | 529 (100.0) | 1.000 | 0.06 |
| Clopidogrel, n (%)          | 545 (82.2) | 1265 (80.4) | <0.001 | 0.24 | 449 (84.9) | 451 (85.3) | 0.931 | 0.01 |
| β-blocker, n (%)            | 533 (80.4) | 1157 (82.7) | 0.225 | 0.06 | 433 (81.9) | 441 (83.4) | 0.570 | 0.04 |
| ACEi or ARB, n (%)          | 522 (78.7) | 1068 (77.2) | 0.488 | 0.04 | 417 (78.8) | 415 (78.4) | 0.940 | 0.01 |
| Statin equivalent dose, mg  | 24.4±13.0 | 23.6±13.8 | 0.226 | 0.06 | 24.3±11.4 | 24.6±13.9 | 0.734 | 0.02 |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.
We compared the clinical outcomes of the hydrophilic and lipophilic statins. The cumulative event rate of composite MACEs was significantly lower in hydrophilic statins than in lipophilic statins ($P=0.006$) (Figure [A]). Hydrophilic statin therapy was associated with a lower cumulative event rate of all-cause death ($P=0.017$) (Figure [B]). We also evaluated the cumulative event curve of recurrent MI and observed a significantly lower event rate in the hydrophilic statin group ($P=0.002$) (Figure [C]). There were no significant differences in the revascularization and stroke rates ($P=0.348$ and $P=0.240$, respectively) (Figure [D] and [E]).

In the whole cohort before matching, the cumulative event rate of composite MACEs (Figure [S1]) and individual primary end points were compared between the 2 statin groups. A similar association was observed between statin type and composite MACEs ($P<0.001$), all-cause death ($P<0.001$), and recurrent MI ($P=0.002$).

The observed incidence and HRs of MACEs in the matched cohort are shown in Table 2. Compared with lipophilic statins, hydrophilic statins were significantly associated with a lower risk of MACEs (HR, 0.71 [95% CI, 0.55–0.91]). The observed HR for all-cause mortality (HR, 0.68 [95% CI, 0.50–0.94]) and recurrent MI (HR, 0.42 [95% CI, 0.23–0.76]) were remarkably reduced in the hydrophilic statin group compared with the lipophilic statin group. When we divided all-cause death into cardiac and noncardiac death, the risk of cardiac death was significantly lower with hydrophilic statin use (HR, 0.60 [95% CI, 0.40–0.88]), but the risk of noncardiac death was not reduced. The multivariate Cox regression model also revealed that hydrophilic statin use significantly decreased the risk of composite MACEs (HR, 0.70 [95% CI, 0.55–0.90]), all-cause death (HR, 0.67 [95% CI, 0.49–0.93]), and recurrent MI (HR, 0.40 [95% CI, 0.21–0.73]). Furthermore, when the multiple regression curve between eGFR and HR for MACEs was evaluated in the propensity-score matched cohort, hydrophilic statins showed a lower HR growth rate for MACEs as eGFR decreased than did lipophilic statins (Figure [S2]).

In the whole cohort before matching, the same results were found in the Cox regression analysis after the adjustment for all related variables (Table [S2]). Hydrophilic statin treatment significantly reduced the risk of composite MACEs (HR, 0.70 [95% CI, 0.56–0.87]), all-cause death (HR, 0.62 [95% CI, 0.47–0.82]), and recurrent MI (HR, 0.50 [95% CI, 0.29–0.87]).

A multivariable Cox regression model showing the significance levels of the included covariates in the propensity-matched cohort is described in Table 3. We found that use of hydrophilic statin as well as body mass index (HR, 0.96 [95% CI, 0.92–1.00]), previous cardiovascular disease history (HR, 1.53 [95% CI, 1.18–2.00]), eGFR (HR, 0.98 [95% CI, 0.97–0.99]), ST-segment-elevation myocardial infarction (HR, 0.72 [95% CI, 0.54–0.96]), and left ventricular ejection fraction (HR, 0.98 [95% CI, 0.97–0.99]) were independently associated with risk of MACEs.

## DISCUSSION

Our study clearly demonstrated that hydrophilic statins are more effective than lipophilic statins at reducing the risk of composite MACEs, all-cause mortality, and recurrent MI in patients with AMI with renal impairment. These results were evident in the large prospective cohort, as well as the propensity-score matched cohort that adjusted for variables that could affect the outcome. These findings suggest that the lipophilicity of statins affects their ability to prevent MACEs and that hydrophilic statins have better ability to lipophilic statins in managing cardiovascular risk in patients with renal impairment after AMI treatment.

Earlier studies demonstrated that differences in the risk of MACEs and all-cause mortality rates were insignificant between lipophilic and hydrophilic statins, and that statin lipophilicity did not affect prognosis in patients with AMI without renal impairment.\(^{17,18}\) In contrast, our study showed a positive effect of hydrophilic statins on reducing the risk of MACEs in the patients with renal impairment. These findings indicate that the relationship between statin lipophilicity and clinical benefit depends on renal function. A recent study on patients on dialysis also demonstrated that hydrophilic statins more effectively reduced the risk of cardiovascular events, and its results support our presumption that the clinical effect based on statin lipophilicity is enhanced in patients with renal impairment.\(^{27}\)

Uremic toxins, oxidative stress, inflammation, and lipid disorders that occur in patients with renal impairment aggravate vascular cell senescence and endothelial dysfunction. This exposes patients to the environment, thereby promoting the progression of coronary atherosclerosis. Therefore, effective statin treatment is critical for improving the prognosis of patients with renal impairment following AMI. Our study demonstrated that the risks of MACEs, cardiac death, and recurrent MI were significantly decreased in patients receiving hydrophilic statins compared with those receiving lipophilic statins. These findings suggest that hydrophilic statins are more useful for suppressing the atherosclerotic cardiac events in patients with renal impairment. Although hydrophilic statins cannot easily pass through vascular cells, hydrophilic statins reportedly effectively prohibit intimal proliferation and hyperplasia.\(^{14,28}\) In addition, hydrophilic statins reduce oxidative stress and microinflammation;
moreover, their anti-inflammatory effect is better than those of lipophilic statins in some reports.\textsuperscript{29–31}

The inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reduces cholesterol synthesis in the liver, but the production of fundamental substances, such as coenzyme Q10 is also reduced.\textsuperscript{32,33} Coenzyme Q10 is critical for the production of ATP; consequently, the inhibition of coenzyme Q10 synthesis leads to the impairment of mitochondrial energy generation.\textsuperscript{34} Therefore, lipophilic, but not hydrophilic, statins reduce the coenzyme Q10 and ATP contents in the myocardium, because the higher lipophilicity allows easy penetration into diverse tissues. These adverse effects of lipophilic statins result in the enhancement of myocardial stunning, delay in myocardial recovery, and worsened contractile function after ischemic events.\textsuperscript{35,36}

These different consequences between the 2 statins could increase in patients with renal impairment, because their plasma coenzyme Q10 concentrations are decreased compared with those in the general population.

### Table 2. Incidence and HRs of MACEs Based on Statin Lipophilicity in Propensity-Matched Cohort

| Event                        | No. of events (%) | HR   | 95% CI       | P value |
|------------------------------|------------------|------|--------------|---------|
| Composite of MACEs           | 108 (20.4%)      | 0.70 | 0.55–0.90    | 0.005   |
| All-cause death              | 64 (12.1%)       | 0.67 | 0.49–0.93    | 0.016   |
| Cardiac death                | 40 (7.6%)        | 0.58 | 0.39–0.87    | 0.008   |
| Noncardiac death             | 24 (4.5%)        | 0.86 | 0.49–1.50    | 0.590   |
| Recurrent MI                 | 15 (2.8%)        | 0.80 | 0.21–0.73    | 0.003   |
| Revascularization            | 38 (7.2%)        | 0.77 | 0.50–1.19    | 0.236   |
| Stroke                       | 6 (1.1%)         | 0.40 | 0.15–1.06    | 0.061   |

All analyses are adjusted for the following covariates: age, sex, body mass index, hypertension, diabetes, previous cardiovascular disease history, smoking, estimated glomerular filtration rate, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, MI type, Killip class, percutaneous coronary intervention, left ventricular ejection fraction, aspirin, clopidogrel, β-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and statin equivalent dose. HR indicates hazard ratio; MACEs, major adverse cardiovascular events; and MI, myocardial infarction.
Table 3. Predictors of Major Adverse Cardiovascular Events in Multivariate Cox Regression Analyses in the Propensity-Matched Cohort

| Predictor                        | HR     | 95% CI          | P value |
|----------------------------------|--------|-----------------|---------|
| Age, per 1-\\text{y} increase    | 1.01   | 1.00–1.02       | 0.222   |
| Men vs women                     | 0.97   | 0.69–1.35       | 0.839   |
| BMI, per 1-kg/\\text{m}² increase| 0.96   | 0.92–1.00       | 0.025   |
| Hypertension                     | 1.14   | 0.84–1.56       | 0.408   |
| Diabetes                         | 0.99   | 0.76–1.29       | 0.922   |
| Previous CVD                     | 1.53   | 1.18–2.00       | 0.002   |
| Smoking history                  | 1.05   | 0.77–1.44       | 0.762   |
| Hemoglobin, per 1-g/\\text{dL} increase| 1.01   | 0.94–1.08       | 0.751   |
| eGFR, per 1-\\text{mL/min} per 1.73 m² increase| 0.98   | 0.97–0.99       | <0.0001 |
| Total cholesterol, per 1-mg/\\text{dL} increase| 1.00   | 0.99–1.01       | 0.875   |
| Triglycerides, per 1-mg/\\text{dL} increase| 1.00   | 0.99–1.00       | 0.661   |
| HDL cholesterol, per 1-mg/\\text{dL} increase| 1.00   | 0.99–1.01       | 0.608   |
| LDL cholesterol, per 1-mg/\\text{dL} increase| 1.00   | 0.99–1.01       | 0.884   |
| STEMI vs NSTEMI                   | 0.72   | 0.54–0.96       | 0.025   |
| Killip >1                         | 1.26   | 0.97–1.65       | 0.090   |
| PCI                              | 1.28   | 0.89–1.85       | 0.181   |
| LVEF, per 1% increase            | 0.98   | 0.97–0.99       | <0.0001 |
| Clopidogrel                      | 1.12   | 0.76–1.67       | 0.563   |
| β-Blocker                        | 0.82   | 0.59–1.13       | 0.232   |
| ACEI or ARB                      | 0.96   | 0.71–1.31       | 0.800   |
| Statin equivalent dose, per 10 mg| 0.95   | 0.86–1.06       | 0.337   |
| Hydrophilic statin vs lipophilic statin | 0.70   | 0.55–0.90       | 0.005   |

All analyses are adjusted for the following covariates: age, sex, BMI, hypertension, diabetes, previous CVD history, smoking, eGFR, total cholesterol, triglycerides, HDL, LDL, myocardial infarction type, Killip class, PCI, LVEF, aspirin, clopidogrel, β-blocker, ACEI or ARB, and statin equivalent dose. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation myocardial infarction.
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Supplemental Material
Table S1. Comparison of coronary angiographic findings of the study population.

|                              | Whole cohort |       |       |    |
|------------------------------|--------------|-------|-------|----|
|                              | Hydrophilic  | Lipophilic | P   |    |
| Vessel related to the infarction | 0.135        |       |       |    |
| LAD                          | 265 (44.7%)  | 492 (41.4%) |     |    |
| LCX                          | 102 (17.2%)  | 179 (15.1%) |     |    |
| RCA                          | 212 (35.8%)  | 476 (40.1%) |     |    |
| Left main                    | 14 (2.4%)    | 41 (3.5%)  |     |    |
| No. of affected vessels      | 0.944        |       |       |    |
| One                          | 242 (40.9%)  | 486 (40.2%) |     |    |
| Two                          | 192 (32.4%)  | 393 (32.5%) |     |    |
| Three                        | 158 (26.7%)  | 331 (27.4%) |     |    |

LAD, left anterior descending artery; LCX, left circumflex artery; No., number; RCA, right coronary artery
| Event                        | No. of event (%) | Hydrophilic | Lipophilic | Unadjusted | Adjusted |
|------------------------------|------------------|-------------|------------|------------|----------|
|                              |                  | HR          | 95% CI     | P          | HR       | 95% CI    | P          |
| Composite of MACE            | 144 (21.7%)      | 0.66        | 0.55-0.80  | <0.001     | 0.70     | 0.56-0.87 | 0.001      |
| All-case of death            | 80 (12.1%)       | 0.55        | 0.43-0.70  | <0.001     | 0.62     | 0.47-0.82 | 0.001      |
| Cardiac death                | 52 (7.8%)        | 0.55        | 0.40-0.74  | <0.001     | 0.58     | 0.41-0.82 | 0.002      |
| Non-cardiac death            | 28 (4.2%)        | 0.56        | 0.37-0.85  | 0.006      | 0.68     | 0.43-1.07 | 0.092      |
| Recurrent MI                 | 19 (2.9%)        | 0.46        | 0.28-0.76  | 0.003      | 0.50     | 0.29-0.87 | 0.014      |
| Revascularization            | 54 (8.1%)        | 0.86        | 0.63-1.18  | 0.3        | 0.83     | 0.57-1.20 | 0.314      |
| Stroke                       | 11 (1.7%)        | 0.67        | 0.34-1.32  | 0.2        | 0.44     | 0.18-1.07 | 0.069      |

HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

All analyses are adjusted for the following covariates: age, sex, body mass index, hypertension, diabetes, previous cardiovascular disease history, smoking, estimated glomerular filtration rate, total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, MI type, Killip class, percutaneous coronary intervention, left ventricular ejection fraction, aspirin, clopidogrel, β blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker and statin equivalent dose.
Figure S1. Cumulative event rates of composite major adverse cardiac and cerebrovascular events based on statin lipophilicity in the whole cohort.
Figure S2. Linear associations of statin type and risk of composite major adverse cardiac and cerebrovascular events. The reference of the spline curve was set to eGFR 60 mL/min/1.73 m² in lipophilic statin.