Effect of statin treatment in patients with acute myocardial infarction with prediabetes and type 2 diabetes mellitus

A retrospective observational registry study

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Abstract
Studies comparing long-term clinical outcomes of statin treatment between acute myocardial infarction (AMI) patients with prediabetes and those with type 2 diabetes mellitus (T2DM) after successful percutaneous coronary intervention (PCI) with the newer-generation drug-eluting stents (DESs) are limited. We compared 2-year clinical outcomes between these patients. A total of 11,962 AMI patients were classified as statin users (n=10,243) and statin nonusers (n=1719). Thereafter, statin users and nonusers were further divided into the normoglycemia, prediabetes, and T2DM groups. The major outcome was the occurrence of major adverse cardiac event (MACE) defined as all-cause death, recurrent myocardial infarction (Re-MI), or any repeat coronary revascularization.

After statin treatment, the cumulative incidences of MACE (P=.314), all-cause death, cardiac death (CD), Re-MI, and any repeat revascularization were similar between the prediabetes and T2DM groups. However, the cumulative incidences of MACE (P=.025) and all-cause death (P=.038) in the prediabetes group and those of MACE (P=.001), all-cause death (P=.009), and CD (P=.048) in the T2DM group were significantly higher than those in the normoglycemia group. Moreover, in all the 3 glycemic groups, the cumulative incidences of MACE, all-cause death, and CD were significantly higher among statin nonusers than among statin users.

This study revealed that AMI patients with prediabetes had worse clinical outcomes than those with normoglycemia and comparable to those with T2DM after 2-year statin treatment. However, further studies are warranted to confirm the current findings.

Abbreviations: AMI = acute myocardial infarction, DES = drug-eluting stents, KAMIR = Korea Acute Myocardial Infarction Registry, MACE = major adverse cardiac events, PCI = percutaneous coronary intervention, Re-MI = recurrent myocardial infarction, T2DM = type 2 diabetes mellitus.

Keywords: diabetes, myocardial infarction, outcomes, prediabetes, statin

1. Introduction
Patients with diabetes mellitus (DM) have a two-fold higher risk of cardiovascular death than those without DM.[1,2] Huang et al.[3] reported that compared with normoglycemia, prediabetes was associated with an increased risk of coronary heart disease (relative risk [RR]: 1.10). According to recent reports, the risk profile for major clinical endpoints after contemporary drug-eluting stent (DES) placement may be comparable between prediabetic and DM...
patients. By contrast, some reports [5,6] have demonstrated that the mortality rate is higher in DM patients than in prediabetic patients. However, despite these conflicting findings, approximately two-thirds of acute myocardial infarction (AMI) patients have diabetes or prediabetes. [7] Aspirin, statin, renin-angiotensin system inhibitors (RASIs), and beta-blockers (BBs) have been shown to significantly reduce mortality following AMI in patients with and without DM. [8–11] Moreover, in a large meta-analysis, [12,13] statin treatment showed a 9% proportional reduction in all-cause mortality (P = .02) in patients with established DM. However, in prediabetic patients, intensive lifestyle modifications and metformin therapy are the only universally accepted interventions for DM prevention. [13] In real-world practice, statin is prescribed to all AMI patients without contraindications to statin use regardless of glycemic status to lower the risk of mortality and coronary revascularization requirement based on the recommendations of current guidelines. [8–11] However, limited studies have compared long-term clinical outcomes of statin treatment between AMI patients with prediabetes and those with DM who underwent successful percutaneous coronary intervention (PCI) with newer-generation DES. Here, we aimed to compare the 2-year major clinical outcomes between these 2 groups.

2. Methods

2.1. Study population

This study enrolled patients from the Korea AMI Registry (KAMIR). [14] The KAMIR is a prospective, observational, and on-line registry with a multicenter cohort study in South Korea that was established in November 2005. [14] In the current study, we attempted to confine to type 2 DM (T2DM) patients for diabetes. We considered T2DM based on a previous study, [15] which included patients from the KAMIR. In that study, T2DM was defined by self-reported history (medical treatment, age at DM onset ≥30 years), and absence of a history of ketoacidosis. Hence, we enrolled 23,391 AMI patients aged ≥30 years at the onset of DM who underwent successful PCI with newer-generation DESs from November 2005 to June 2015. Among them, patients with incomplete laboratory results such as unidentified results of blood hemoglobin (Hb) A1c and blood glucose (n = 8432, 36%), patients lost to follow-up (n = 1069, 4.6%), and patients treated with first-generation DES (n = 1928, 8.2%) were excluded. Thus, a total of 11,962 AMI patients who underwent successful PCI with newer-generation DESs were included. The types of newer-generation DESs used are listed in Table 1. The patients were classified as statin users (n = 10,243, 85.6%) and statin nonusers (n = 1719, 14.4%). Thereafter, statin users and nonusers were further divided into the normoglycemia (n = 2708 [26.4%, group A1] and n = 372 [21.6%, group A2], respectively), prediabetes (n = 3201 [31.3%, group B1] and n = 508 [29.6%, group B2], respectively), and T2DM (n = 4334 [42.3%, group C1] and n = 839 [48.8%, group C2], respectively) groups (Fig. 1, Table 1, Supplementary material 1, http://links.lww.com/MD/F664). The main reasons for not using statin among statin nonusers were as follows:

1. expected risk was higher than benefit due to end-stage renal failure, advanced age (≥75 years), or severe heart failure (HF; n = 757, 44%);
2. abnormal liver function (aspartate aminotransferase or alanine aminotransferase level more than three-fold above the upper normal limit; n = 326, 19%); (3) multiorgan failure (n = 50, 2.9%);
4. statin-induced myopathy or arthralgia (n = 61, 3.5%); and
5. unknown (n = 525, 60.5%).

This study protocol was approved by the ethics committee at each participating center and the Chonnam National University Hospital Institutional Review Board (IRB) ethics committee (CNUH-2011-172) according to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all patients prior to their inclusion in the study. We followed up all enrolled patients through face-to-face interview, phone call, and chart review. All 11,962 patients completed a 2-year clinical follow-up. All clinical events were evaluated by an independent event adjudication committee. The processes of event adjudication have been described previously by the KAMIR investigators. [14]

2.2. Percutaneous coronary intervention and medical treatments

Diagnostic coronary angiography and PCI were performed using standard techniques. [16] Before PCI, all patients received loading doses of aspirin (200–300mg) and other antiplatelet agents such as clopidogrel (300–600mg), ticagrelor (180mg), or prasugrel (60mg). After the index PCI, dual antiplatelet therapy (DAPT; a combination of aspirin 100mg/day with clopidogrel 75mg/day, ticagrelor 90mg twice daily, or prasugrel 5–10mg/day) was recommended for at least 1 year. Administration of triple antiplatelet therapy (TAPT; cilostazol [100mg twice daily] combined with DAPT) was based on individual operators' discretion. The types and doses of statins prescribed as discharge medications were as follows: atorvastatin (10–80mg), rosuvastatin (5–40mg), simvastatin (10–40mg), pitavastatin (2–4mg), pravastatin (5–40mg), and fluvastatin (40–80mg). The choice of the type and dose of statin was left at the physicians' discretion.

2.3. Study definitions and endpoints

Inclusion criteria for AMI were defined according to the current guidelines. [8–11] A successful PCI was defined as a residual stenosis of <30% and thrombolysis in myocardial infarction grade 3 flow in the infarct-related artery (IRA) after the procedure. Glycemic categories were determined based on the glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), and random plasma glucose (RPG) levels of the patients at index hospitalization as well as their medical history. T2DM was defined as either known T2DM for which patients received medical treatment (insulin or antidiabetics) or newly diagnosed T2DM defined as an HbA1c level of ≥6.5%, a FPG of ≥126mg/dL (7mmol/L), and/or RPG of ≥200mg/dL (11.1mmol/L) according to the clinical practice recommendations of the American Diabetes Association. [17] Prediabetes was defined as an HbA1c of 5.7% to 6.4% and a FPG of 100 to 125mg/dL (5.6–6.9mmol/L). Additionally, the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation. [18] The major clinical outcome was the occurrence of major adverse cardiac events (MACE), which were defined as all-cause death, recurrent myocardial infarction (Re-MI), any repeat coronary revascularization, all-cause death was classified as cardiac death (CD) or non-CD. Any repeat revascularization comprised target lesion revascularization (TLR), target vessel revascularization (TVR),
# Table 1
Baseline clinical, laboratory, and procedural characteristics in statin users.

| Variables                        | Group A1 Normoglycemia (n = 2708) | Group B1 Prediabetes (n = 3201) | Group C1 T2DM (n = 4334) | Group A1 vs B1 | Group A1 vs C1 | Group B1 vs C1 | Group A1 vs B1 vs C1 |
|----------------------------------|-----------------------------------|---------------------------------|--------------------------|----------------|---------------|---------------|---------------------|
| Age (yr)                         | 60.8 ± 12.9                       | 63.1 ± 12.5                     | 63.9 ± 11.6               | <.001          | <.001         | .003          | .001                |
| Male, n (%)                      | 2196 (81.2)                       | 2428 (75.9)                     | 3073 (70.9)               | <.001          | <.001         | <.001         | <.001               |
| LVEF (%)                         | 53.3 ± 10.3                       | 53.1 ± 10.6                     | 51.5 ± 11.4               | .482           | <.001         | <.001         | <.001               |
| BMI (kg/m²)                      | 23.9 ± 3.0                        | 24.2 ± 3.2                      | 24.4 ± 3.1                | <.001          | <.001         | .029          | <.001               |
| SBP (mm Hg)                      | 132.0 ± 27.6                      | 129.9 ± 26.9                    | 131.6 ± 27.6              | <.001          | <.001         | <.001         | <.001               |
| DBP (mm Hg)                      | 81.0 ± 16.6                       | 79.1 ± 16.2                     | 79.1 ± 16.0               | <.001          | <.001         | .917          | <.001               |
| STEMI, n (%)                     | 1603 (59.2)                       | 1903 (59.5)                     | 2282 (52.7)               | .852           | <.001         | <.001         | <.001               |
| Previous PCI, n (%)              | 1546 (96.4)                       | 1832 (96.3)                     | 2185 (95.7)               | .783           | .275          | .394          | .496                |
| Previous CVA, n (%)              | 1105 (40.8)                       | 1298 (40.5)                     | 2032 (47.3)               | .852           | <.001         | <.001         | <.001               |
| Previous PCI, n (%)              | 979 (88.6)                        | 1123 (86.5)                     | 1752 (85.4)               | .125           | .012          | .358          | .041                |
| LDL cholesterol (mg/L)           | 116.1 ± 74.1                      | 48.1 ± 114.4                    | 47.2 ± 136.9              | .948           | .666          | .749          | .858                |
| Dyslipidemia, n (%)              | 1086 (39.4)                       | 1398 (43.7)                     | 2615 (60.3)               | .001           | <.001         | <.001         | <.001               |
| Hypertension, n (%)              | 79 (2.9)                          | 67 (2.7)                        | 211 (4.9)                 | .693           | <.001         | <.001         | <.001               |
| Previous CABG, n (%)             | 107 (4.0)                         | 153 (4.8)                       | 333 (7.7)                 | .127           | <.001         | <.001         | <.001               |
| Previous CABG, n (%)             | 7 (0.3)                           | 5 (0.2)                         | 34 (0.8)                  | .402           | <.001         | <.001         | <.001               |
| Previous CVA, n (%)              | 114 (4.2)                         | 160 (5.0)                       | 343 (7.9)                 | .154           | <.001         | <.001         | <.001               |
| Previous PCI, n (%)              | 12 (0.4)                          | 27 (0.8)                        | 56 (1.3)                  | .075           | <.074         | <.001         | <.001               |
| Current smokers, n (%)           | 1249 (46.1)                       | 1521 (47.5)                     | 1708 (39.4)               | .285           | <.001         | <.001         | <.001               |
| Normoglycemia (n = 2708)         | 1360.0 ± 174.1                    | 144.6 ± 203.9                   | 104.1 ± 140.8             | .079           | <.001         | <.001         | <.001               |
| Treated vessel                   | –                                 | –                               | –                         | –              | –             | –             | –                   |
| Lipidemic treatment, n (%)       | –                                 | –                               | –                         | –              | –             | –             | –                   |
| Infrarenal AAA                   | –                                 | –                               | –                         | –              | –             | –             | –                   |
| Type B1, n (%)                   | 342 (12.6)                        | 421 (13.2)                      | 527 (12.2)                | .550           | .560          | .199          | .438                |

Note: Values are presented as mean ± standard deviation or n (%). The table continues with additional data.
Table 1 (continued).

| Variables                  | Group A1 Normoglycemia (n = 2708) | Group B1 Prediabetes (n = 3201) | Group C1 T2DM (n = 4334) | Group A1 vs B1 | Group A1 vs C1 | Group B1 vs C1 | Group A1 vs B1 vs C1 |
|----------------------------|-----------------------------------|---------------------------------|--------------------------|----------------|----------------|----------------|---------------------|
| Type B2, n (%)             | 934 (34.5)                        | 1012 (31.6)                     | 1442 (33.3)              | .019           | .293           | .129           | .061                |
| Type C, n (%)              | 1229 (43.9)                       | 1449 (42.7)                     | 2007 (46.3)              | .951           | .431           | .370           | .600                |
| Extent of CAD              |                                    |                                 |                          |                |                |                |                     |
| Single-vessel, n (%)       | 1501 (55.4)                       | 1686 (52.7)                     | 1867 (43.1)              | .137           | <.001          | <.001          | <.001               |
| Two-vessel, n (%)          | 804 (29.7)                        | 981 (30.6)                      | 1449 (33.4)              | .425           | .001           | .011           | .002                |
| ≥ Three-vessel, n (%)      | 403 (14.9)                        | 534 (16.7)                      | 1018 (23.5)              | .059           | <.001          | <.001          | <.001               |
| MUS, n (%)                 | 573 (21.2)                        | 793 (24.5)                      | 938 (21.6)               | .003           | .055           | .004           | .003                |
| OCT, n (%)                 | 21 (0.8)                          | 28 (0.9)                        | 31 (0.7)                 | .774           | .776           | .509           | .739                |
| FFR, n (%)                 | 28 (1.0)                          | 45 (1.4)                        | 60 (1.4)                 | .237           | .225           | .938           | .365                |
| Drug-eluting stents*       |                                   |                                 |                          |                |                |                |                     |
| ZES, n (%)                 | 842 (31.1)                        | 1099 (34.3)                     | 1480 (34.1)              | .008           | .008           | .868           | .012                |
| EES, n (%)                 | 1402 (51.8)                       | 1655 (51.7)                     | 2259 (52.1)              | .957           | .775           | .718           | .906                |
| BES, n (%)                 | 472 (17.4)                        | 449 (14.0)                      | 575 (13.3)               | .001           | <.001          | .341           | <.001               |
| Others, n (%)              | 51 (1.9)                          | 68 (2.1)                        | 108 (2.5)                | .517           | .099           | .316           | .220                |
| Stent diameter (mm)        | 3.15 ± 0.42                       | 3.14 ± 0.41                     | 3.10 ± 0.42              | .003           | <.001          | <.001          | <.001               |
| Stent length (mm)          | 27.4 ± 11.5                       | 27.1 ± 11.5                     | 27.9 ± 11.9              | .294           | .172           | .010           | .033                |
| Number of stent            | 1.43 ± 0.74                       | 1.48 ± 0.79                     | 1.56 ± 0.83              | .004           | <.001          | <.001          | <.001               |

Values are means ± SD or numbers and percentages. The P values for categorical data were obtained from the chi-square or Fisher’s exact test. For continuous variables, differences among the 3 groups were evaluated using the analysis of variance or the Jonckheere Terpineau test, and post-hoc analysis between the 2 groups was carried out using the Hochberg test or Dunnett-T3 test.

ACC/AHA = American College of Cardiology/American Heart Association, ACEIs = angiotensin converting enzyme inhibitors, ARBs = angiotensin receptor blockers, BBs = beta-blockers, BES = biolimus-eluting stent, BMI = body mass index, CABG = coronary artery bypass graft, CAD = coronary artery disease, CBIs = calcium channel blockers, CK-MB = creatine kinase myocardial band, CCR = cardiopulmonary resuscitation, CVA = cerebrovascular events, DBP = diastolic blood pressure, EES = everolimus-eluting stent, eGFR = estimated glomerular filtration rate, FFR = fractional flow reserve, HDL = high-density lipoprotein, IF = insulin failure, IC-CRP = high-sensitivity C-reactive protein, IVUS = intravascular ultrasound, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NG = normoglycemia, NT-ProBNP = N-terminal pro-brain natriuretic peptide, OCT = optical coherence tomography, PCI = percutaneous coronary intervention, RCA = right coronary artery, SBP = systolic blood pressure, STEMI = ST-segment elevation myocardial infarction, T2DM = type 2 diabetes mellitus, ZES = zotarolimus-eluting stent.

*Drug-eluting stents were composed of ZES (Resolute Integrity stent; Medtronic, Inc., Minneapolis, MN), EES (Xience Prime stent; Abbott Vascular, Santa Clara, CA), or BES (BioMatrix Flex stent, Biosensors International, Morges, Switzerland; or Nobori stent, Terumo Corporation, Tokyo, Japan).

A total of 23,391 AMI patients aged ≥ 30 years at the onset of diabetes, who underwent successful DESs implantation from November 2005 to June 2015 in the KAMIR

Exclusion
- Incomplete laboratory results including unidentified results of blood HbA1c and blood glucose (n = 8,432)
- Lost to follow-up (n = 1,069)
- First-generation DESs (n = 1,928)

Finally, a total of 11,962 patients with AMI who underwent successful implantation of newer-generation DESs were included

Figure 1. Flow chart. AMI = acute myocardial infarction, DESs = drug-eluting stents, KAMIR = Korea AMI Registry, NG = normoglycemia, T2DM = type 2 diabetes mellitus.
2.4. Statistical analysis

For continuous variables, differences among the 3 groups were evaluated using analysis of variance or the Jonckheere–Terpstra test, whereas a post-hoc analysis of the 2 groups was performed using the Hochberg test or Dunnett T3 test. Data are expressed as means ± standard deviation. The chi-square test or Fisher’s exact test was performed, as appropriate, to analyze intergroup differences for categorical variables. Data are expressed as numbers and percentages. Various clinical outcomes were analyzed using the Kaplan–Meier method and were compared among the 3 groups using the log-rank test. Because the differences in baseline characteristic could significantly affect major clinical outcomes, sensitivity analyses were performed to adjust for confounders. A multivariate Cox regression model was used. Before multivariate Cox regression analysis, univariate analysis was performed. Covariates included in univariate model were selected if they were significantly different among the 3 groups (P < .001), which are listed in Supplementary material 2, http://links.lww.com/MD/F665 and 3, http://links.lww.com/MD/F666. Any variable with P value of <.001 in univariate analysis and conventional risk factors of poor outcomes in the AMI population were considered potential confounding factors and were entered into the multivariate analysis. Variables included in the multivariate analysis was as follows: age; male sex; left ventricular ejection fraction (LVEF); body mass index; ST-segment elevation myocardial infarction (STEMI); hypertension; dyslipidemia; a previous history of MI, PCI, coronary artery bypass grafting (CABG), and cardiovascular accidents; current smoker; serum creatinine level; eGFR; total cholesterol level; triglyceride level; high-density lipoprotein cholesterol level; low-density lipoprotein cholesterol level; discharge medications (clopidogrel, ticagrelor, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], rosuvastatin, and pitavastatin); IRA (left anterior descending artery [LAD]); treated vessel (right coronary artery [RCA]); single- vessel disease and ≥three-vessel disease; diameter of placed stent; and the number of stents placed. The assumption of proportionality was assessed graphically by the log-minus-log plot, and Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. Moreover, to identify independent predictors of MACE and all-cause death, we used multivariate Cox proportional hazard model. C-statistics with 95% confidence interval (CI) were calculated to validate the discriminant function of the model. All probability values were two-sided and P value of <.05 was considered statistically significant for all analyses. All statistical analyses were performed using Statistical Package for the Social Sciences version 20 (IBM, Armonk, NY).

3. Results

3.1. Baseline characteristics

The mean LVEF value in our study population was >50% (Table 1). The baseline characteristics of Group A1 (normoglycemia and statin users) are as follows: largest number of men and patients with one-vessel disease; highest prescription rate of ticagrelor, prasugrel, and ACEIs; and highest number of cases with LAD as IRA and BES as the deployed stent and deployed stents with the largest diameter. The baseline characteristics of Group B1 (prediabetes and statin users) are as follows: highest number of current smokers and cases with STEMI; highest levels of total and low-density lipoprotein (LDL) cholesterol and peak creatine kinase-MB (CK-MB) level; highest prescription rate of rosuvastatin; and highest use of intravascular ultrasound and zotarolimus-eluting stent (ZES) as the deployed stent. The baseline characteristics of Group C1 (diabetes and statin users) are as follows: patients with the oldest mean age; highest number of cases with non-STEMI (NSTEMI) and patients with multivessel disease and a previous history of hypertension, dyslipidemia, PCI, CABG, and HF; highest levels of N-terminal pro-brain natriuretic peptide, serum creatinine, and triglyceride; highest prescription rate of clopidogrel, ARBs, and atorvastatin; highest number of cases with RCA as IRA and treated vessel; longest length of deployed stents; and highest number of deployed stents. The comparison of baseline characteristics between statin users and nonusers is presented in Supplementary material 1, http://links.lww.com/MD/F664. The baseline characteristics of statin nonusers are presented in Supplementary material 4, http://links.lww.com/MD/F667.

3.2. Clinical outcomes

The comparisons of clinical outcomes among the 3 glycemic groups during the 2-year follow-up period are presented in Tables 2 and 3 and Figure 2. In statin users, the cumulative incidences of MACE (adjusted hazard ratio [aHR]: 1.095; 95% CI: 0.918–1.306; P = .314), all-cause death, CD, and any repeat revascularization were similar between group B1 (prediabetes) and C1 (T2DM) (Table 2). The cumulative incidences of MACE (aHR: 1.288; 95% CI: 1.033–1.606; P = .025) and all-cause death (aHR: 1.525; 95% CI: 1.024–2.271; P = .038) were higher in group B1 than in group A1 (Table 2). The cumulative incidences of MACE (aHR: 1.402; 95% CI: 1.139–1.727; P = .001), all-cause death (aHR: 1.642; 95% CI: 1.130–2.385; P = .009), and CD (aHR: 1.574; 95% CI: 1.004–2.472; P = .048) were significantly higher in group C1 than in group A1 (Table 2). In statin nonusers, the cumulative incidences of MACE, all-cause death, CD, and any repeat revascularization were similar between A2 and B2 as well as between B2 and C2 (Table 2). However, the cumulative incidences of all-cause death (aHR: 1.500; 95% CI: 1.017–2.212; P = .041), CD (aHR: 1.631; 95% CI: 1.052–2.543; P = .030), and any repeat revascularization (aHR: 2.068; 95% CI: 1.066–4.012; P = .040) were higher in group C2 than in group C1 (Table 2). In all the 3 groups (normoglycemia, prediabetes, and T2DM), statin treatment reduced the cumulative incidences of MACE, all-cause death, and CD (Table 3). Additionally, in the T2DM group, the cumulative incidence of any repeat revascularization was lower among statin users than among statin nonusers (aHR: 1.705; 95% CI: 1.218–2.395; P = .002) (Table 3). Kaplan–Meier analyses for major clinical outcomes among statin nonusers are presented in Supplementary material 5, http://links.lww.com/MD/F668. Independent predictors for MACE and all-cause death among statin users at 2 years are listed in Table 4. Male sex, decreased LVEF (<40%), decreased eGFR (<60 mL/minute/1.73 m²), ACEI, and ≥three-vessel disease were found to be meaningful independent predictors for MACE. Moreover, old age (>65 years), decreased LVEF, decreased eGFR, BBS, ACEIs, American College of Cardiology/American Heart Association
Comparison of clinical outcomes among the 3 glycemic status according to the presence or absence of statin treatment at 2yr.

| Statin (+) | Group A1 Normoglycemia | Group B1 Prediabetes | Log-rank | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | P |
|------------|-------------------------|----------------------|----------|------------------------|---|----------------------|---|
| MACE       | 129 (5.6)               | 206 (6.3)            | .015     | 1.314 (1.054–1.637)    | .015 | 1.288 (1.033–1.606)  | .025 |
| All-cause death | 37 (1.5)               | 71 (2.4)            | .023     | 1.580 (1.062–2.352)    | .024 | 1.525 (1.024–2.271)  | .038 |
| Cardiac death | 26 (1.0)               | 51 (1.7)            | .041     | 1.627 (1.014–2.609)    | .043 | 1.540 (0.959–2.473)  | .074 |
| Re-MI      | 37 (1.6)               | 52 (1.7)            | .498     | 1.157 (0.759–1.764)    | .498 | 1.186 (0.776–1.811)  | .430 |
| Any repeat revascularization | 69 (3.0)               | 91 (3.2)            | .668     | 1.071 (0.783–1.464)    | .670 | 1.035 (0.756–1.418)  | .828 |

| Statin (-) | Group A2 Normoglycemia | Group B2 Prediabetes | Log-rank | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | P |
|------------|-------------------------|----------------------|----------|------------------------|---|----------------------|---|
| MACE       | 51 (14.0)               | 79 (15.8)            | .484     | 1.134 (0.797–1.612)    | .485 | 1.242 (0.869–1.775)  | .234 |
| All-cause death | 34 (9.3)               | 57 (11.3)           | .334     | 1.232 (0.806–1.884)    | .336 | 1.391 (0.905–2.140)  | .133 |
| Cardiac death | 26 (7.1)               | 51 (10.1)           | .126     | 1.442 (0.899–2.531)    | .129 | 1.423 (0.892–2.401)  | .142 |
| Re-MI      | 6 (1.8)                | 10 (2.1)             | .697     | 1.222 (0.444–3.363)    | .698 | 1.079 (0.385–3.021)  | .886 |
| Any repeat revascularization | 11 (3.3)               | 22 (4.9)            | .282     | 1.484 (0.720–3.061)    | .285 | 1.561 (0.752–2.323)  | .232 |

| Statin (+) | Group C1 Normoglycemia | Group C1 Prediabetes | Log-rank | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | P |
|------------|-------------------------|----------------------|----------|------------------------|---|----------------------|---|
| MACE       | 129 (5.6)               | 360 (8.1)            | <.001    | 1.704 (1.394–2.084)    | <.001 | 1.402 (1.139–1.727)  | .001 |
| All-cause death | 37 (1.5)               | 144 (3.6)           | <.001    | 2.372 (1.653–3.405)    | <.001 | 1.642 (1.130–2.385)  | .009 |
| Cardiac death | 26 (1.0)               | 96 (2.4)            | <.001    | 2.261 (1.466–3.488)    | <.001 | 1.574 (1.004–2.472)  | .048 |
| Re-MI      | 37 (1.6)               | 99 (2.6)            | .012     | 1.612 (1.105–2.352)    | .013 | 1.473 (0.985–2.189)  | .052 |
| Any repeat revascularization | 69 (3.0)               | 149 (3.8)           | .060     | 1.313 (0.987–1.747)    | .061 | 1.159 (0.862–1.557)  | .292 |

| Statin (-) | Group C2 Normoglycemia | Group C2 Prediabetes | Log-rank | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | P |
|------------|-------------------------|----------------------|----------|------------------------|---|----------------------|---|
| MACE       | 51 (14.0)               | 183 (15.8)           | .063     | 1.349 (0.983–1.852)    | .064 | 1.380 (1.001–1.903)  | .050 |
| All-cause death | 34 (9.3)               | 113 (13.6)          | .038     | 1.495 (1.019–2.194)    | .040 | 1.500 (1.017–2.212)  | .041 |
| Cardiac death | 26 (7.1)               | 94 (11.3)           | .027     | 1.624 (1.052–2.507)    | .029 | 1.631 (1.052–2.543)  | .030 |
| Re-MI      | 6 (1.8)                | 24 (3.2)             | .169     | 1.605 (0.738–3.415)    | .193 | 1.915 (0.775–4.732)  | .159 |
| Any repeat revascularization | 11 (3.3)               | 46 (6.6)            | .035     | 1.985 (1.036–3.842)    | .039 | 2.068 (1.066–4.012)  | .040 |

| Statin (+) | Group B2 Normoglycemia | Group B2 Prediabetes | Log-rank | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | P |
|------------|-------------------------|----------------------|----------|------------------------|---|----------------------|---|
| MACE       | 79 (15.8)               | 153 (18.5)           | .210     | 1.180 (0.906–1.560)    | .211 | 1.051 (0.796–1.388)  | .725 |
| All-cause death | 57 (11.3)               | 113 (13.6)          | .237     | 1.211 (0.881–1.665)    | .239 | 1.006 (0.726–1.394)  | .971 |
| Cardiac death | 51 (10.1)               | 94 (11.3)           | .500     | 1.124 (0.799–1.581)    | .501 | 1.092 (0.894–1.363)  | .163 |
| Re-MI      | 10 (2.1)                | 24 (3.2)             | .295     | 1.479 (0.707–3.093)    | .298 | 1.573 (0.741–3.344)  | .238 |
| Any repeat revascularization | 22 (4.9)               | 46 (6.6)            | .242     | 1.350 (0.615–2.236)    | .244 | 1.269 (0.758–2.124)  | .365 |

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, BMI = body mass index, CABG = coronary artery bypass graft, CI = confidence interval, CVA = cerebrovascular accidents, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HR = hazard ratio, IRA = infarct-related artery, LAD = left anterior descending artery, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MACE = major adverse cardiac events, PCI = percutaneous coronary intervention, RCA = right coronary artery, Re-MI = recurrent myocardial infarction, STEMI = ST-segment elevation myocardial infarction, T2DM = type 2 diabetes mellitus.

4. Discussion

In this study, clinical outcomes of 2-year statin treatment were compared between AMI patients with prediabetes and those with T2DM treated with the newer-generation DES to determine differences in long-term outcomes between both the groups. In this retrospective, observational registry study, analysis of statin treatment outcomes revealed the following:

1. The cumulative incidences of MACE, all-cause death, CD, Re-MI, and any repeat revascularization were similar between the prediabetes and T2DM groups;
Prediabetes and T2DM groups, the higher cumulative incidences of MACE (aHR: 1.402; 95% CI: 1.139–1.727; \( P < .001\)), all-cause death (aHR: 1.642; 95% CI: 1.130–2.385; \( P < .009\)), and CD (aHR: 1.574; 95% CI: 1.004–2.472; \( P = .048\)) were significantly higher in the T2DM group than in the normoglycemia group. Table 2. Hyperglycemia accelerates the formation of advanced glycation end products (AGEs) by nonenzymatic glycation reactions.\(^{[28]}\) These AGEs may play important roles in the development of coronary artery disease both independently and synergistically with DM.\(^{[29]}\) Shimomura et al\(^{[30]}\) demonstrated that the serum level of glyceraldehyde-derived AGEs was significantly (\( P < .05\)) suppressed in AMI patients after 2 weeks of atorvastatin therapy (initial dose of 40 mg at admission followed by a maintenance dose of 10 mg/day) compared with that in the control group. Another report\(^{[31]}\) suggested that statin is one of the most recent promising anti-AGEs agents in DM. However, the effects of statin treatment in terms of long-term clinical outcomes in AMI patients with prediabetes are not well established.

In this study, both in the prediabetes and T2DM groups, the aHRs for major clinical outcomes were not significantly different regardless of the use of statin (Table 2). In the statin users, both in the prediabetes and T2DM groups, the higher cumulative incidence of MACE compared with normoglycemia group may (2) the cumulative incidences of MACE and all-cause death in the prediabetes group and those of MACE, all-cause death, and CD in the T2DM group were higher than those in the normoglycemia group; (3) the cumulative incidences of MACE, all-cause death, and CD in all the 3 glycemic groups (normoglycemia, prediabetes, and T2DM) of statin users were lower than those of statin nonusers; (4) decreased LVEF, decreased eGFR, ACEIs, and ≥-three-vessel disease were common independent predictors of both MACE and all-cause death. Statin can show beneficial effect on primary and secondary prevention of adverse cardiovascular events by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity.\(^{[20,21]}\) These cardioprotective effects of statin are characterized by the prevention of myocardial necrosis, myocardial fibrosis, and cardiac remodeling through the anti-inflammatory, enhanced endothelial nitric oxide production, and antioxidative actions.\(^{[22,23]}\) In this study, decreased cumulative incidences of MACE, all-cause death, and CD were noted among statin users of all the 3 glycemic groups (Table 3). These results are comparable to those of previous reports.\(^{[19,22,23]}\) These results demonstrated obviously positive relationship of statin treatment with longer survival and longer MACE-free survival among AMI patients regardless of glycemic status in the era of newer-generation DES. Early initiation of statin treatment before discharge reduces the rates of MI and total mortality at 1-year in patients with acute coronary syndrome (ACS).\(^{[19,23]}\) Moreover, early statin treatment induces stabilization of atherosclerotic vulnerable plaque and reduces new plaque development after ACS.\(^{[24,25]}\) However, despite statin treatment, the cumulative incidences of MACE (aHR: 1.987; 95% CI: 1.788–2.197; \( P < .001\)) and all-cause death (aHR: 3.207; 95% CI: 2.863–3.572; \( P < .001\)) were significantly reduced in AMI patients after 2 weeks of atorvastatin therapy (initial dose of 40 mg at admission followed by a maintenance dose of 10 mg/day) compared with that in the control group. Another report\(^{[31]}\) suggested that statin is one of the most recent promising anti-AGEs agents in DM. However, the effects of statin treatment in terms of long-term clinical outcomes in AMI patients with prediabetes are not well established.
Figure 2. Kaplan-Meier analysis for the MACE (A), all-cause death (B), cardiac death (C), Re-MI (D), and any repeat revascularization (E) in statin users. MACE = major adverse cardiac events, Re-MI = recurrent myocardial infarction, T2DM = type 2 diabetes mellitus.
be related with higher cumulative incidence of all-cause death (prediabetes) or all-cause death and CD (T2DM group). However, the cumulative incidences of all-cause death or CD were statistically insignificantly different between these 2 groups (Table 2).

Compared with normoglycemia, chronically elevated glucose leads to pan-vascular damage (i.e., macro- and micro-angiopathy through oxidation and vascular inflammation) and therefore, vascular damage is present in the prediabetic state, and its severity is associated with the time of hyperglycemia onset. The time spent waiting for hyperglycemia to reach the currently accepted cut-off levels for the diagnosis of T2DM and to intervene may allow vascular damage to advance and become irreversible.

Although some studies have reported conflicting findings, in the Biodegradable Polymer and Durable Polymer Drug-eluting Stents in an All Comers Population (BIO-RESORT) Silent Diabetes Study, the cumulative incidence of MACE was different between patients with prediabetes (5.5%) and normoglycemia (3%; log-rank, \( P = .07 \)). In our study, \( aHR \) for MACE was significantly higher in the prediabetic group than in the normoglycemia group (\( aHR: 1.288; 95\% CI: 1.033–1.606; P = .025 \); Table 2). In another sub-study of the BIO-RESORT trial, clinical outcomes were similar between patients with prediabetes and those with DM (11.1% vs 10.5%). In addition, other study has suggested that the cumulative incidences of MACE, all-cause death, CD, and any repeat revascularization were similar between AMI patients with prediabetes and those with T2DM after the RASI therapy. In our study, statin reduced the rate of any repeat revascularization in the T2DM group, with an \( aHR \) of 1.159 (group A1 vs C1; 95\% CI: 0.862–1.557; \( P = .329 \)) among statin users compared with 2.068 (group A2 vs C2; 95\% CI: 1.066–4.012; \( P = .040 \)) among statin nonusers (Table 2). This result is comparable with that of the Zhang et al study. In their multicenter, prospective cohort study, after propensity-score matching, post-discharge statin treatment significantly lowered the risk of repeat revascularization (HR: 0.74; 95\% CI: 0.56–1.00; \( P = .005 \)) in 2737 patients who underwent PCI. In Table 2, the occurrence MACE was significantly higher in prediabetes and T2DM groups compared with normoglycemia group who received statin treatment. Therefore, although statin treatment reduced the occurrence of MACE, all-cause death, and CD compared with statin nonusers regardless of glycemic status (Table 3), the beneficial effect of statin treatment could be some different according to glycemic status. Hence, hyperglycemic status may be more related to poor clinical outcomes than with normoglycemia after statin treatment. However, this hypothesis is likely to be proved by further studies.

Despite the beneficial effects of statin, previous studies reported an increased risk of developing new-onset DM after long-term statin treatment. However, because this information was not included in the KAMIR data, we could not present the cumulative events of statin-related new-onset DM during the follow-up period. This point is a major weakness of this study.

Although the study population was insufficient to draw conclusions, more than 50 high-volume university or community hospitals of South Korea participated in this study. Moreover, the population with prediabetes is an important and a common diagnostic accuracy of prediabetes, oral glucose tolerance test.
should be performed. However, we defined prediabetes by the HbA1c and FPG levels, which is an important bias. Third, there may have been some under-reporting and/or missed data due to the non-randomized nature of this study. Fourth, this study was based on discharge medication data and we could not obtain precise information regarding participants’ adherence or non-adherence to antidiabetic drugs during the follow-up period. This might constitute an additional bias. Fifth, statins show their effect in longer duration of use. Even though this study included patients from November 2005 to June 2015, the follow-up duration of the individual patient was strictly confined to 2 years after discharge. Therefore, the 2-year follow-up period of this study was relatively short for determining long-term major clinical outcomes and the sample size was not adequate enough to reach a conclusion. Sixth, although multivariate analysis was performed to strengthen our results, variables not included in the KAMIR may act as a bias. Finally, unfortunately, this registry data did not include complete information concerning the presence or absence of change in any prescription dose of each statin and long-term drug compliance, and drug-related adverse events during the follow-up period. Hence, we could not provide results separately for the different statins, inevitably.

To conclude, in the era of newer-generation DES, this retrospective, observational registry study revealed that AMI patients with prediabetes had worse clinical outcomes than those with normoglycemia and comparable to those with T2DM after 2-year statin treatment. However, further studies are warranted to confirm the current findings.

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