Effects of stent generation on clinical outcomes after acute myocardial infarction compared between prediabetes and diabetes patients

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We investigated the effects of stent generation on 2-year clinical outcomes between prediabetes and diabetes patients after acute myocardial infarction (AMI). A total of 13,895 AMI patients were classified into normoglycemia (group A: 3673), prediabetes (group B: 5205), and diabetes (group C: 5017). Thereafter, all three groups were further divided into first-generation (1G)-drug-eluting stent (DES) and second-generation (2G)-DES groups. Patient-oriented composite outcomes (POCOs) defined as all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization were the primary outcome. Stent thrombosis (ST) was the secondary outcome. In both prediabetes and diabetes groups, the cumulative incidences of POCOs, any repeat revascularization, and ST were higher in the 1G-DES than that in the 2G-DES. In the diabetes group, all-cause death and cardiac death rates were higher in the 1G-DES than that in the 2G-DES. In both stent generations, the cumulative incidence of POCOs was similar between the prediabetes and diabetes groups. However, in the 2G-DES group, the cumulative incidences of Re-MI and all-cause death or MI were significantly higher in the diabetes group than that in the prediabetes group. To conclude, 2G-DES was more effective than 1G-DES in reducing the primary and secondary outcomes for both prediabetes and diabetes groups.

Diabetes mellitus (DM, diabetes) is regarded as a “coronary artery disease (CAD) risk equivalent”1, conferring an approximately twofold increased risk of acute myocardial infarction (AMI)2. Moreover, almost two thirds of those presenting with CAD have either diabetes or prediabetes2. Coronary vessels in patients with diabetes usually present extensive atherosclerosis with a larger number of significant stenosis, longer lesions, and more diffuse disease3,4. Therefore, despite advances in interventional skill, devices, and antiplatelet agents, outcomes of coronary revascularization in patients with diabetes have been poorer than those without5,6. Percutaneous coronary intervention (PCI) in patients with diabetes is associated with increased incidence of restenosis, repeat revascularization, stent thrombosis (ST), and all-cause mortality than those without3,4. Drug-eluting stents (DES) reduce the risk of restenosis as compared with bare-metal stents (BMS). However, ST remains a major concern after the implantation of first-generation (1G)-DES in patients with diabetes7. Relative superiority between the 1G- and 2G-DESs in patients with diabetes remains controversial8–11. Although recent reports revealed that prediabetes is an intergrade between normoglycemia and diabetes12–14, PCI patients with prediabetes were prone to experience adverse clinical events. Individuals with prediabetes are important and common patients who visit interventional cardiologists. However, the main treatment strategies for hyperglycemia are focused on the patients with diabetes rather those with prediabetes15. Moreover, studies regarding the effects of the 1G-DES and 2G-DES

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on clinical outcomes between prediabetes and diabetes patients after AMI were limited. To better understand the characteristic of prediabetes, we compared the 2-year clinical outcomes of the 1G-DES and 2G-DES under two different glycemic states (prediabetes and diabetes).

Results

Baseline characteristics. Table 1 summarizes the baseline clinical, laboratory, and procedural characteristics of the study population. The study population consisted of patients who had a relatively well-preserved left ventricular ejection fraction (LVEF; mean: 52.1 ± 11.4%). The mean value of high-sensitivity C-reactive protein (hs-CRP) and number of patients who received clopidogrel and cilostazole as the discharge medications were significantly higher in 1G-DES group than in 2G-DES group in all three different glycemic groups. In contrast, the number of patients requiring cardiopulmonary resuscitation (CPR) on admission, number of patients who received PCI within 24 h, number of patients who received aspirin, ticagrelor, prasugrel, beta-blockers, and lipid lowering agents as the discharge medications; American College of Cardiology/American Heart Association (ACC/AHA) type C lesion; and mean length of deployed stent were significantly higher in 2G-DES group than in 1G-DES group in all three different glycemic groups. However, the mean value of age, LVEF, body mass index, systolic blood pressure; number of ST-segment-elevation myocardial infarction (STEMI) and dyslipidemia; number of patient with previous history of PCI, coronary artery bypass graft, cerebrovascular accident, and heart failure; number of current smoker and treated vessel; mean value of serum creatinine and diameter of deployed stent; and the use of intravascular ultrasound (IVUS) were similar between the 1G-DES and 2G-DES groups in all three different glycemic groups.

Clinical outcomes. Cumulative incidences of major clinical outcomes during the 2-year follow-up period are summarized in Tables 2, 3, and Fig. 1, and Supplementary information.

Prediabetes group. After the adjustment, the cumulative incidences of POCOs (adjusted hazard ratio [aHR]: 1.369; 95% confidence interval [CI] 1.044–1.720; p = 0.012), any repeat revascularization (aHR: 1.795; 95% CI 1.280–2.518; p = 0.001), and ST (aHR: 2.637; 95% CI 1.370–5.077; p = 0.004) were significantly higher in the 1G-DES than that in the 2G-DES group.

Diabetes group. After the adjustment, the cumulative incidences of POCOs (aHR: 1.331; 95% CI 1.070–1.657; p = 0.010), all-cause death (aHR: 1.354; 95% CI 1.115–2.112; p = 0.009), CD (aHR: 1.700; 95% CI 1.195–2.448; p = 0.003), any repeat revascularization (aHR: 1.673; 95% CI 1.211–2.313; p = 0.002), and ST (aHR: 2.065; 95% CI 1.100–3.876; p = 0.024) were significantly higher in the 1G-DES group than that in the 2G-DES group.

Normoglycemia group. After the adjustment, the cumulative incidences of POCOs, all-cause death, CD, Re-MI, all-cause death or MI, and any repeat revascularization were similar between the 1G-DES and 2G-DES groups. However, the cumulative incidence of ST (aHR: 3.267; 95% CI 1.226–8.678; p = 0.018) was significantly higher in the 1G-DES than that in the 2G-DES group.

1G-DES group. Cumulative incidences of POCOs (aHR: 1.331; 95% CI 0.836–1.535; p = 0.417) and ST (aHR: 1.175; 95% CI 0.551–2.507; p = 0.677) were similar between prediabetes and diabetes groups. The cumulative incidence of any repeat revascularization was significantly higher in the prediabetes than that in the normoglycemia group (aHR: 1.856; 95% CI 1.027–3.359; p = 0.040). Cumulative incidences of POCOs (aHR: 1.667; 95% CI 1.055–2.515; p = 0.015) and any repeat revascularization (aHR: 1.875; 95% CI 1.029–3.215; p = 0.038) were significantly higher in the diabetes than that in the normoglycemia group.

2G-DES group. Cumulative incidences of POCOs (aHR: 1.116; 95% CI 0.962–1.294; p = 0.148) and ST (aHR: 1.546; 95% CI 0.942–2.538; p = 0.085) were similar between prediabetes and diabetes groups. However, cumulative incidences of Re-MI (aHR: 1.393; 95% CI 1.135–2.043; p = 0.032) and all-cause death or MI (aHR: 1.224; 95% CI 1.023–1.524; p = 0.029) in the diabetes group were significantly higher than that in the prediabetes group. Cumulative incidences of POCOs (aHR: 1.294; 95% CI 1.078–1.553; p = 0.006), all-cause death (aHR: 1.353; 95% CI 1.021–1.793; p = 0.035), CD (aHR: 1.392; 95% CI 1.004–1.930; p = 0.047), and all-cause death or MI (aHR: 1.425; 95% CI 1.132–1.794; p = 0.003) were significantly higher in the prediabetes than that in the normoglycemia group. Cumulative incidences of POCOs (aHR: 1.400; 95% CI 1.165–1.683; p < 0.001), all-cause death (aHR: 1.430; 95% CI 1.074–1.955; p = 0.014), CD (aHR: 1.471; 95% CI 1.055–2.052; p = 0.023), Re-MI (aHR: 1.694; 95% CI 1.161–2.472; p = 0.006), all-cause death or MI (aHR: 1.684; 95% CI 1.338–2.120; p < 0.001), any repeat revascularization (aHR: 1.362; 95% CI 1.031–1.769; p = 0.030), and ST (aHR: 2.068; 95% CI 1.125–3.869; p = 0.014) were significantly higher in the diabetes than that in the normoglycemia group.

Table 4 shows independent predictors for POCOs and ST at the 2-year follow-up. Old age (≥ 65 years), male sex, low LVEF (< 40%), cardiogenic shock, cardiopulmonary resuscitation on admission, and multivessel disease were significant independent predictors for POCOs. Low LVEF and < 3 mm diameter of the deployed stent were independent predictors for ST in this study.

Discussion

The primary findings of this study are as follows: (1) in both prediabetes and diabetes groups, the cumulative incidences of POCOs, any repeat revascularization, and ST were higher in the 1G-DES than that in the 2G-DES; (2) in the diabetes group, the cumulative incidences of all-cause death and CD were higher in the 1G-DES than

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| Variables                       | Group A normoglycemia (n = 3673) | Group B prediabetes (n = 5205) | Group C diabetes (n = 5017) | p value |
|--------------------------------|----------------------------------|-------------------------------|-----------------------------|---------|
|                               | Group A1 1G-DES (n = 482)       | Group A2 2G-DES (n = 3191)    | Group B1 1G-DES (n = 676)   | Group B2 2G-DES (n = 4348) |         |
| Age, years                     | 61.6 ± 13.4                     | 61.4 ± 13.0                   | 64.0 ± 12.0                 | 64.3 ± 12.4                   | <0.001 |
| BMI, kg/m²                      | 23.9 ± 2.8                      | 23.8 ± 3.1                    | 24.1 ± 3.1                  | 24.1 ± 3.3                    | <0.001 |
| SBP, mmHg                      | 129.9 ± 26.9                    | 131.2 ± 27.8                  | 130.4 ± 27.9                | 129.5 ± 27.7                  | 0.421 |
| DBP, mmHg                      | 80.3 ± 16.7                     | 80.6 ± 16.7                   | 80.2 ± 16.1                 | 78.7 ± 16.3                   | 0.017 |
| Current smokers, n (%)         | 233 (48.3)                      | 1441 (45.2)                   | 309 (40.3)                  | 1943 (43.8)                   | 0.076 |
| Peak troponin-I, ng/mL          | 39.5 ± 14.0                     | 48.3 ± 20.4                   | 48.3 ± 20.4                 | 55.7 ± 20.4                   | <0.001 |
| Peak troponin-I, mg/mL          | 185 (37.4)                      | 286 (58.5)                    | 180 (38.2)                  | 286 (58.5)                    | <0.001 |

**Discharge medications**

| Variables               | Group A normoglycemia (n = 3673) | Group B prediabetes (n = 5205) | Group C diabetes (n = 5017) | p value |
|-------------------------|----------------------------------|-------------------------------|-----------------------------|---------|
| Aspirin, n (%)          | 454 (94.2)                       | 3092 (96.9)                   | 724 (94.4)                  | 4276 (96.3)                   | <0.001 |
| Clopidogrel, n (%)      | 477 (99.0)                       | 2573 (80.6)                   | 746 (97.3)                  | 3810 (85.8)                   | <0.001 |
| Ticagrelor, n (%)       | 1 (0.2)                          | 382 (12.0)                    | 4 (0.5)                     | 382 (8.6)                     | <0.001 |
| Prasugrel, n (%)        | 0 (0.0)                          | 198 (6.2)                     | 0 (0.5)                     | 203 (4.6)                     | <0.001 |
| Candesartan, n (%)      | 137 (28.4)                       | 449 (14.1)                    | 223 (29.1)                  | 848 (19.1)                    | <0.001 |
| Beta-blocker, n (%)     | 580 (78.8)                       | 2651 (83.1)                   | 608 (79.3)                  | 3680 (82.9)                   | <0.001 |
| ACEI, n (%)             | 603 (69.3)                       | 1843 (57.8)                   | 444 (57.9)                  | 2404 (54.2)                   | 0.012 |
| ARB, n (%)              | 91 (18.9)                        | 765 (24.0)                    | 185 (24.1)                  | 1133 (25.5)                   | 0.004 |
| Lipid lowering agents   | 73 (7.7)                         | 181 (5.7)                     | 55 (7.2)                    | 245 (5.5)                     | 0.248 |

**IRA**

| Variables   | Group A normoglycemia (n = 3673) | Group B prediabetes (n = 5205) | Group C diabetes (n = 5017) | p value |
|-------------|----------------------------------|-------------------------------|-----------------------------|---------|
| Left main, n (%) | 7 (1.5)                        | 54 (1.7)                     | 19 (2.5)                    | 77 (1.7)                     | 0.670 |
| LAD, n (%)     | 257 (53.3)                      | 1603 (50.2)                   | 237 (48.6)                  | 2179 (49.1)                   | 0.275 |
| LCx, n (%)     | 523 (16.4)                      | 136 (17.7)                    | 728 (16.4)                  | 1454 (32.8)                   | 0.140 |
| RCA, n (%)     | 2010 (31.7)                     | 339 (31.2)                    | 239 (28.3)                  | 1144 (25.8)                   | 0.204 |

**Treated vessel**

| Variables   | Group A normoglycemia (n = 3673) | Group B prediabetes (n = 5205) | Group C diabetes (n = 5017) | p value |
|-------------|----------------------------------|-------------------------------|-----------------------------|---------|
| Left main, n (%) | 17 (3.5)                        | 84 (2.6)                     | 27 (3.5)                    | 129 (2.9)                    | 0.239 |
| LAD, n (%)     | 291 (60.4)                      | 1883 (59.0)                   | 460 (60.0)                  | 2591 (58.4)                   | 0.994 |
| LCx, n (%)     | 122 (25.3)                      | 786 (24.6)                    | 217 (28.3)                  | 1144 (25.8)                   | 0.985 |

Continued
that in the 2G-DES; (3) in the normoglycemia group, the cumulative incidence of ST was higher in the 1G-DES than that in the 2G-DES; and (4) in two different stent generations, the cumulative incidence of POCOs was similar between the prediabetes and diabetes groups. However, in the 2G-DES group, the cumulative incidences of Re-MI and all-cause death or MI were higher in the diabetes group than that in the prediabetes group.

Hyperglycemia, elevated free fatty acid level, and increased amount of circulating glycated serum products can accelerate atherosclerosis and vascular injury in patients with diabetes by inducing endothelial dysfunction and vascular inflammation\(^4\). Although previous reports demonstrated that the higher rates of repeat revascularizations and mortality after PCI in patients with diabetes are caused by restenosis and disease progression\(^-4\), comparative clinical outcomes between prediabetes and diabetes were not well illuminated especially, between 1G-DES and 2G-DES. Some recent reports showed that prediabetes is associated with poorer clinical outcomes including cardiovascular mortality and patients with prediabetes and diabetes have similar higher risk profiles compared with normoglycemia\(^3,17\).

Although DES improved outcomes of high-risk patients by reducing the rate of restenosis as compared with BMS\(^8,19\), ST remains a major concern after the DES implantation, especially in diabetes\(^4\). Relative superiority between the 1G-DES and 2G-DES in patients with AMI and diabetes remains controversial, and most previous studies were not performed during the prediabetes stage\(^20,21\). In our study, the cumulative incidence of POCOs was significantly higher in the 1G-DES than that in the 2G-DES in both prediabetes and diabetes groups. Moreover, in two different stent generations, the cumulative incidence of POCOs was similar between the prediabetes and diabetes groups (Table 3). In a substudy of the multicenter BIO-RESORT (BIOdegradable Polymer and DuRable Polymer Drug-eluting Stents in an All COmeRs PopulaTion) trial\(^13\), comparative clinical outcomes were similar between prediabetes and diabetes (11.1% vs. 10.5%). Von Birgelen et al.\(^22\) reported the results of the BIO-RESORT Silent Diabetes Study. In their study, the cumulative incidence of major adverse cardiac events was different between patients with prediabetes (5.5%) and normoglycemia (3.0%) (Log-rank, 0.052).

Table 1. Baseline clinical, laboratory, and procedural characteristics. Values are means±SD or numbers and percentages. The p values for continuous data were obtained from the analysis of variance. The p values for categorical data were obtained from the chi-square or Fisher's exact test. PCI percutaneous coronary intervention, BMS bare-metal stents, 1G first-generation, 2G second-generation, DES drug-eluting stents, LVEF left ventricular ejection fraction, BMI body mass index, CPR cardiopulmonary resuscitation, MI myocardial infarction, CAGB coronary artery bypass graft, CVA cerebrovascular accidents, HF heart failure, CK-MB creatine kinase myocardial band, NT-ProBNP N-terminal pro-brain natriuretic peptide, HS-CRP high-sensitivity-C-reactive protein, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEIs angiotensin converting enzyme inhibitors, ARBs angiotensin receptor blockers, CCBs calcium channel blockers, IRA infarct-related artery, ACC/AHA American College of Cardiology/American Heart Association, CAD coronary artery disease, SES sirolimus-eluting stent, PES paclitaxel-eluting stent, ZES zotarolimus-eluting stent, EES everolimus-eluting stent, IVUS intravascular ultrasound, OCT optical coherence tomography, FFR fractional flow reserve.

| Variables                          | Group A normoglycemia (n = 3673) | Group B prediabetes (n = 5205) | Group C diabetes (n = 5017) |
|-----------------------------------|----------------------------------|--------------------------------|-----------------------------|
|                                   | p value                          | p value                        | p value                     |
| RCA, n (%)                        | 169 (35.1)                       | 1182 (37.0)                    | 292 (38.1)                  |
|                                   | 0.418                            | 1744 (39.3)                    | 0.252                       |
|                                   |                                   | 313 (40.2)                     | 1799 (42.4)                 |
|                                   |                                   | 0.252                          |                             |
| ACC/AHA lesion type                |                                  |                                |                             |
| Type B1, n (%)                    | 82 (17.0)                        | 424 (13.3)                     | 120 (15.6)                  |
|                                   | 0.027                            | 597 (13.5)                     | 0.009                       |
| Type B2, n (%)                    | 153 (31.7)                       | 1064 (33.3)                    | 248 (32.3)                  |
|                                   | 0.500                            | 1425 (32.1)                    | 0.180                       |
| Type C, n (%)                     | 168 (34.9)                       | 1424 (44.6)                    | 284 (37.0)                  |
|                                   | <0.001                           | 1957 (44.1)                    | <0.001                      |
| Extent of CAD                     |                                  |                                |                             |
| 1-vessel, n (%)                   | 229 (47.5)                       | 1744 (54.7)                    | 230 (58.9)                  |
|                                   | 0.003                            | 2234 (50.3)                    | 0.001                       |
| 2-vessel, n (%)                   | 166 (34.4)                       | 962 (30.1)                     | 25 (6.5)                    |
|                                   | 0.057                            | 1398 (31.5)                    | 0.847                       |
| ≥3-vessel, n (%)                  | 87 (18.0)                        | 485 (15.2)                     | 189 (46.4)                  |
|                                   | 0.121                            | 806 (18.2)                     | <0.001                      |
| DESs                              |                                  |                                |                             |
| SES, n (%)                        | 225 (46.7)                       | 330 (43.0)                     | 352 (45.2)                  |
| PES, n (%)                        | 257 (53.3)                       | 437 (57.0)                     | 427 (54.8)                  |
| ZES, n (%)                        | 1015 (31.8)                      | 1529 (34.5)                    | 1478 (34.9)                 |
| EES, n (%)                        | 1625 (50.9)                      | 2278 (51.3)                    | 2194 (51.8)                 |
| BES, n (%)                        | 525 (16.4)                       | 600 (13.5)                     | 536 (12.6)                  |
| Others, n (%)                     | 30 (0.7)                         | 30 (0.7)                       |                             |
| IVUS                              | 119 (24.7)                       | 682 (21.4)                     | 185 (24.1)                  |
| OCT                               | 0 (0.0)                          | 24 (0.8)                       | 1038 (23.4)                 |
| FFR                               | 1 (0.2)                          | 30 (0.9)                       | 60 (1.4)                    |
| Stent diameter, mm                | 3.16±0.42                        | 3.16±0.42                      | 3.14±0.42                   |
| Stent length, mm                  | 25.9±7.8                         | 27.1±11.4                      | 26.0±7.2                   |
| Number of stent                   | 1.50±0.84                        | 1.42±0.75                      | 1.48±0.80                   |
In the SPIRIT V Diabetic Study\(^{10}\), everolimus-eluting stent (EES) was superior to paclitaxel-eluting stent (PES) of these covariates were < 0.05 or having predictive values). \(^a\) Adjusted by male, age, DBP, ACEI, ARB, lipid lowering agent, ACC/AHA type B1/C lesions, 1-vessel disease, stent length (p values of these covariates were < 0.05 or having predictive values). \(^b\) Adjusted by male, age, CPR on admission, primary PCI, PCI within 24 hours, hypertension, peak troponin-I, aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, beta-blocker, lipid lowering agents, ACC/AHA type C lesions, 1-vessel disease, ≥ 3-vessel disease, FFR, stent length, number of stent (p values of these covariates were < 0.05 or having predictive values). \(^c\) Adjusted by male, age, cardiogenic shock, CPR on admission, PCI within 24 hours, previous MI, peak troponin-I, hs-CRP, triglyceride, HDL-cholesterol, aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, beta-blocker, ACEI, ARB, lipid lowering agent, IRA (RCA), ACC/AHA type B1/C lesions, OCT, FFR, stent length (p values of these covariates were < 0.05 or having predictive values).

Table 2. Clinical outcomes between 1G-DES and 2G-DES at 2 years. POCOs patient-oriented composite outcomes defined as a composite of all-cause deaths, Re-MI or any repeat revascularization, Re-MI recurrent myocardial infarction, LVEF left ventricular ejection fraction, DBP diastolic blood pressure, CPR cardiopulmonary resuscitation, PCI percutaneous coronary intervention, hs-CRP high-sensitivity C-reactive protein, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEI angiotensin converting enzyme inhibitor, ARB angiotensin receptor blockers, IRA infarct-related artery, RCA right coronary artery, ACC/AHA American College of Cardiology/American Heart Association, IVUS intravascular ultrasound, OCT optical coherence tomography, FFR fractional flow reserve. \(^a\) Adjusted by male, age, CPR on admission, primary PCI, PCI within 24 hours, hypertension, peak troponin-I, aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, beta-blocker, ACEI, ARB, lipid lowering agent, ACC/AHA type B1/C lesions, 1-vessel disease, stent length (p values of these covariates were < 0.05 or having predictive values). \(^b\) Adjusted by male, age, DBP, cardiogenic shock, CPR on admission, primary PCI, PCI within 24 h, hs-CRP, triglyceride, HDL-cholesterol, aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, beta-blocker, lipid lowering agents, ACC/AHA type C lesions, 1-vessel disease, ≥ 3-vessel disease, FFR, stent length, number of stent (p values of these covariates were < 0.05 or having predictive values). \(^c\) Adjusted by male, age, DBP, cardiogenic shock, CPR on admission, PCI within 24 hours, previous MI, peak troponin-I, hs-CRP, total cholesterol, LDL-cholesterol, aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, beta-blocker, ACEI, ARB, lipid lowering agent, IRA (RCA), ACC/AHA type B1/C lesions, OCT, FFR, stent length (p values of these covariates were < 0.05 or having predictive values).

\(p = 0.07\). As mentioned, despite the combination of new platforms, more biocompatible polymers were utilized in 2G-DES, the relative superiority between 1G- and 2G-DESs in patients with diabetes remains controversial\(^{-31}\). In the SPIRIT V Diabetic Study\(^{10}\), everolimus-eluting stent (EES) was superior to paclitaxel-eluting stent (PES) for in-stent late loss at 9 months. The composite death, MI, and TVR rates were the same in the two groups at 1 year. Bavishi et al.\(^9\) reported that EES showed significantly lower incidence rates of MACEs by 18% and ST by 46% as compared with the 1G-DES. Moreover, the EES showed a trend toward reduced incidence rates of target lesion revascularization (TLR) and TVR \(p = 0.05\). In this study, based on the cumulative incidences of POCOs, any revascularization rate was significantly higher in the 1G-DES than that in the 2G-DES group in
both prediabetes and diabetes group. Therefore, the major clinical outcomes of our study could reflect the meta-analysis results of Bavishi et al.’s study.

The overall rate of ST was also higher in the 1G-DES than in the 2G-DES in all three different glycemic groups (prediabetes: 1.8% vs. 0.7%, log-rank p = 0.001), diabetes: 2.1% vs. 0.9%, log-rank p = 0.007), and normoglycemia (1.5% vs. 0.5%, log-rank p = 0.009). With regard to prediabetes, follow-up data on the comparative long-term effects of 1G-DES and 2G-DES implantation were limited. According to Bavishi et al.’s report, EES reduced the incidence of ST by 46% (RR: 0.54, 95% CI 0.35–0.82) as compared with the 1G-DES in patients with diabetes. The cumulative incidence of ST also higher in the 1G-DES than that in the 2G-DES in patients with normoglycemia. Our result is consistent with the result of Nakatsuma et al. study. This low cumulative incidence of 2G-DES may be related with relatively thin strut struts (50–90 μm) and improved ability for deliverability while maintaining an adequate radial strength and more compatible and thromboresistant than those in the 1G-DES. However, in our study, the occurrence of ST was high within 6 months after index PCI (Supplementary Fig. 1). Therefore, we cannot completely exclude the possibility that ST was associated with PCI procedure. Even though IVUS-guided or functional flow reserve (FFR)-guided PCI could reduce MACE rate, the number of PCI base on these intracoronary image- or functional study-based PCI were less than 30% in our study. Unfortunately, currently under the Korea’s health insurance system, the reimbursement program for the use of IVUS, optical coherence of tomography, or fractional flow reserve during the PCI is very limited or absent.

Interestingly, comparative clinical outcomes of the two different stent generations according to glycemic status showed some different results (Table 3). Different clinical outcomes among three different glycemic states (normoglycemia, prediabetes, and diabetes) were more prominent in the 2G-DES rather 1G-DES. According to advances in interventional skill, devices, and antplatelet agents, 2G-DES showed decreased incidences of all-cause death (aHR: 1.53; 95% CI 1.15–2.12; p = 0.009) and CD (aHR: 1.70; 95% CI 1.19–2.44; p = 0.003) compared with 1G-DES in diabetes group after adjustment (Table 2). Bavishi et al. showed that there was a trend towards reduction in all-cause mortality with zotarolimus compared to 1G-DES (6.3% vs. 7.2%, relative risk: 0.74; 95% CI 0.55–1.00; p = 0.05) in their meta-analysis. However, the cumulative incidences of all clinical outcomes were significantly higher in the diabetes than that in the normoglycemia group. These results may reflect hazardous effects of diabetes are sustained even in the era of 2G-DES.

In our study, in the 1G-DES, the primary and secondary end-points were similar between the prediabetes and diabetes groups. However, in the 2G-DES, the cumulative incidences of Re-MI (aHR: 1.39; 95% CI 1.13–2.04; p = 0.032) and all-cause death or MI (aHR: 1.22; 95% CI 1.023–1.524; p = 0.029) were significantly higher in the diabetes group than that in the prediabetes group. Although the precise mechanisms of the higher incidence of Re-MI in diabetes group are not fully known, one report suggested that the association between diabetes and Re-MI may be related with a direct effect of diabetes. According to recent reports, the cumulative incidence of Re-MI of the diabetes group was significantly higher than that of the prediabetes group (aHR: 1.88; 95% CI 1.201–2.954; p = 0.006 or aHR: 1.660; 95% CI 1.000–2.755; p = 0.020).

More than 50 high-volume university or community hospitals in South Korea participated in this study. The limited reports on the impact of stent generation on long-term clinical outcomes in AMI patients with prediabetes or diabetes were the motivation for the current study. Thus, we believe that our study may provide significant information to interventional cardiologists who perform PCI in patients with AMI with prediabetes or diabetes.

This study has several limitations. First, because the study population was obtained from the Korea AMI registry data, some data might be under-reported and/or missed. Second, it is necessary for diagnosing diabetes to check an HbA1c level ≥ 6.5%, FPG ≥ 126 mg/dL (7.0 mmol/L), and/or RPG ≥ 200 mg/dL (11.1 mmol/L) by repeat testing. If first glycemic status was diabetes and second was prediabetes, or first glycemic status was prediabetes and second was normoglycemia, and this is particularly important in patients with AMI, because such patients reveal hyperglycemia in acute phase. However, in this study, the definitions of prediabetes and diabetes were not based on repeat testing. Moreover, considering the limitation of HbA1c, any other diagnostic tests for diabetes including oral glucose tolerance test are needed for a finer classification. However, detailed information on this variable was not included in the KAMIR. Hence, the results of this study can be altered based on other diagnostic tests and which directly influences the assignment of participants, and this factor may have served as an important bias in this study. Third, the duration and types of antidiabetic treatment are major determinants after PCI in patients with prediabetes or diabetes. However, this study was conducted based on discharge medications, and owing to limitation of registry study, we did not precisely know the adherence or non-adherence of enrolled patients to antidiabetic drugs during the follow-up period. Therefore, this may act as an important bias in this study. Fourth, 2G-DES consisted of durable-polymer-coated DES and biodegradable-polymer-coated DES. The number of biodegradable-polymer DES (BES) was highest in the normoglycemia group (prediabetes: 600/4438 (13.5%); diabetes: 536/4238 (12.6%); normoglycemia: 525/3191 (16.5%); p < 0.001) (Table 1). Although this number was not significantly different between prediabetes and diabetes (p = 0.226), this division may be not reasonable and the composition of 2G-DES could be changed according to other types of utilized newer-generation DES. Therefore, other types of newer-generation DES could influence the outcome of our study. Fifth, although multivariate analysis was performed to strengthen our results, variables not included in the KAMIR may have affected the study outcomes. Sixth, the 2-year follow-up period in this study was relatively short in order to determine the long-term major clinical outcomes; therefore, data from studies with longer follow-up periods are required. Seventh, this study retrospectively enrolled the patients who underwent PCI from 2005–2015. The development of stent platform, potent antplatelet drugs, and use of intracoronary imaging and improvement of procedural skills, all these factors substantially affect the clinical outcomes. Therefore, these factors could be also important bias of this study. Finally, although 2G-DES are considered the safest in the general population, this study confirms that in a select and growing population.
| Outcomes                  | Group A1 normoglycemia (n = 482) | Group B1 prediabetes (n = 767) | Log-rank | Unadjusted HR (95% CI) | p value | Adjusted<sup>b</sup> HR (95% CI) | p value |
|--------------------------|----------------------------------|--------------------------------|----------|------------------------|---------|-------------------------------|---------|
| POCOs                    | 0.072                            | 1.400 (1.968–2.024)           | 0.074    | 1.483 (0.985–2.232)    | 0.059   |
| All-cause death          | 0.422                            | 1.234 (0.738–2.062)           | 0.423    | 1.227 (0.675–2.303)    | 0.502   |
| Cardiac death            | 0.433                            | 1.261 (0.705–2.257)           | 0.435    | 1.455 (0.721–2.935)    | 0.295   |
| Re-MI                     | 0.334                            | 1.498 (0.656–3.422)           | 0.337    | 1.748 (0.685–4.464)    | 0.243   |
| All-cause death or MI    | 0.412                            | 1.215 (0.763–1.933)           | 0.413    | 1.194 (0.707–1.919)    | 0.507   |
| Any repeat revascularization | 0.535                           | 1.719 (0.986–2.999)           | 0.056    | 1.858 (1.027–3.359)    | 0.040   |
| ST (probable or definite) | 0.642                           | 1.259 (0.508–3.119)           | 0.619    | 1.346 (0.511–3.547)    | 0.548   |

| Outcomes                  | Group A2 Normoglycemia (n = 482) | Group B2 prediabetes (n = 4438) | Log-rank | Unadjusted HR (95% CI) | p value | Adjusted<sup>b</sup> HR (95% CI) | p value |
|--------------------------|----------------------------------|---------------------------------|----------|------------------------|---------|-------------------------------|---------|
| POCOs                    | 0.285                            | 1.165 (0.881–1.540)            | 0.285    | 1.135 (0.836–1.535)    | 0.417   |
| All-cause death          | 0.500                            | 1.151 (0.765–1.730)            | 0.500    | 1.166 (0.731–1.860)    | 0.488   |
| Cardiac death            | 0.385                            | 1.221 (0.777–1.919)            | 0.386    | 1.137 (0.678–1.909)    | 0.627   |
| Re-MI                     | 0.462                            | 1.253 (0.688–2.287)            | 0.463    | 1.148 (0.599–2.199)    | 0.678   |
| All-cause death or MI    | 0.283                            | 1.221 (0.847–1.761)            | 0.284    | 1.189 (0.788–1.757)    | 0.410   |
| Any repeat revascularization | 0.663                           | 1.093 (0.733–1.627)            | 0.663    | 1.035 (0.681–1.574)    | 0.872   |
| ST (probable or definite) | 0.969                           | 1.015 (0.484–2.128)            | 0.969    | 1.119 (0.551–2.507)    | 0.677   |

| Outcomes                  | Group A2 Normoglycemia (n = 3191) | Group C2 diabetes (n = 4238) | Log-rank | Unadjusted HR (95% CI) | p value | Adjusted<sup>b</sup> HR (95% CI) | p value |
|--------------------------|----------------------------------|--------------------------------|----------|------------------------|---------|-------------------------------|---------|
| POCOs                    | 193 (6.7)                        | 371 (8.9)                      | <0.001   | 1.388 (1.167–1.650)    | <0.001  | 1.294 (1.078–1.553)           | 0.006   |
| All-cause death          | 80 (2.7)                         | 185 (4.4)                      | <0.001   | 1.642 (1.263–2.134)    | <0.001  | 1.353 (1.021–1.793)           | 0.035   |
| Cardiac death            | 59 (1.9)                         | 140 (3.3)                      | 0.001    | 1.693 (1.249–2.295)    | 0.001   | 1.392 (1.004–1.930)           | 0.047   |
| Re-MI                     | 42 (1.5)                         | 80 (2.0)                       | 0.121    | 1.342 (0.924–1.950)    | 0.122   | 1.288 (0.876–1.894)           | 0.198   |
| All-cause death or MI    | 116 (4.6)                        | 258 (6.1)                      | <0.001   | 1.578 (1.268–1.965)    | <0.001  | 1.425 (1.132–1.794)           | 0.003   |
| Any repeat revascularization | 85 (3.1)                       | 144 (3.6)                      | 0.206    | 1.189 (0.909–1.554)    | 0.206   | 1.223 (0.923–1.619)           | 0.161   |
| ST (probable or definite) | 15 (0.5)                        | 29 (0.7)                       | 0.296    | 1.392 (0.746–2.597)    | 0.298   | 1.520 (0.787–2.937)           | 0.213   |

| Outcomes                  | Group B2 prediabetes (n = 4438) | Group C2 diabetes (n = 4238) | Log-rank | Unadjusted HR (95% CI) | p value | Adjusted<sup>b</sup> HR (95% CI) | p value |
|--------------------------|---------------------------------|--------------------------------|----------|------------------------|---------|-------------------------------|---------|
| POCOs                    | 371 (8.9)                       | 410 (10.3)                     | 0.046    | 1.153 (1.002–1.327)    | 0.046   | 1.116 (0.962–1.294)           | 0.148   |
| All-cause death          | 185 (4.4)                       | 189 (4.7)                      | 0.531    | 1.067 (0.871–1.307)    | 0.531   | 1.109 (0.887–1.386)           | 0.365   |
| Cardiac death            | 140 (3.3)                       | 144 (3.5)                      | 0.543    | 1.075 (0.852–1.356)    | 0.544   | 1.062 (0.822–1.334)           | 0.644   |
| Re-MI                     | 80 (2.0)                        | 105 (2.8)                      | 0.036    | 1.368 (1.022–1.829)    | 0.035   | 1.393 (1.135–2.043)           | 0.032   |

Continued
Table 3. Two-year clinical outcomes according to the different glycemic status. POCOs patient-oriented composite outcomes defined as a composite of all-cause deaths, Re-MI or any repeat revascularization, Re-MI recurrent myocardial infarction, LVEF left ventricular ejection fraction. SRP systolic blood pressure, DBP diastolic blood pressure, MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, HF heart failure, CVA cerebrovascular accidents, CK-MB creatine kinase myocardial band, NT-ProBNP N-terminal pro-brain natriuretic peptide, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEIs angiotensin converting enzyme inhibitors, ARBs angiotensin receptor blockers, CCBs calcium channel blockers, IRA infarct-related artery, RCA right coronary artery, ACC/AHA American College of Cardiology/American Heart Association, FFR fractional flow reserve. a Adjusted by male, age, LVEF, BMI, cardiogenic shock, hypertension, dyslipidemia, previous HF, current smoker, CK-MB, ACEIs, 1-vessel, ≥3-vessel disease, triglyceride, stent diameter (p values of these covariates were <0.005 or having predictive values). b Adjusted by male, age, LVEF, BMI, DBP, STEMI, hypertension, dyslipidemia, previous MI, previous PCI, previous CVA, CK-MB, serum creatinine, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, clopidogrel, ticagrelor, cilostazol, ACEIs, ARBs, CCB, lipid lowering agents, RCA (treated vessel), 1-vessel disease, ≥3-vessel disease, stent diameter, number of stent (p values of these covariates were <0.001 or having predictive values).

| Outcomes                        | Group B2 Prediabetes (n=4438) | Group C2 Diabetes (n=4238) | Log-rank | Unadjusted HR (95% CI) | p value | Adjustedb HR (95% CI) | p value |
|---------------------------------|-------------------------------|----------------------------|----------|------------------------|---------|------------------------|---------|
| All-cause death or MI           | 258 (6.1)                    | 296 (7.4)                  | 0.033    | 1.197 (1.013–1.415)    | 0.034   | 1.224 (1.023–1.524)    | 0.029   |
| Any repeat revascularization    | 144 (3.6)                    | 160 (4.3)                  | 0.203    | 1.157 (0.924–1.449)    | 0.204   | 1.088 (0.863–1.373)    | 0.474   |
| ST (definite or probable)       | 29 (0.7)                     | 40 (0.9)                   | 0.129    | 1.445 (0.896–2.331)    | 0.131   | 1.546 (0.942–2.538)    | 0.085   |

Figure 1. Kaplan–Meier analysis of the incidence of POCOs.
Table 4. Independent predictors for POCOs and stent thrombosis at 2 years. 1G first-generation, 2G second-generation, DES drug-eluting stent, POCOs patient-oriented composite outcomes, HR hazard ratio, LVEF left ventricular ejection fraction, CPR cardiopulmonary resuscitation, ACC/AHA American College of Cardiology/American Heart Association.

| Variables                             | POCOs Univariate | Stent thrombosis Univariate | POCOs Multivariate | Stent thrombosis Multivariate |
|---------------------------------------|------------------|-----------------------------|--------------------|-----------------------------|
|                                       | HR (95% CI)      | p value                     | HR (95% CI)        | p value                     |
| 1G-DES vs. 2G-DES                      | 1.382 (1.200–1.592) | < 0.001                     | 2.451 (1.652–3.636) | < 0.001                     |
| Age (≥ 65 years)                       | 1.631 (1.455–1.828) | < 0.001                     | 1.131 (0.787–1.624) | 0.506                       |
| Male                                  | 1.452 (1.289–1.637) | < 0.001                     | 1.151 (0.773–1.713) | 0.488                       |
| LVEF (< 40%)                           | 2.487 (2.186–2.831) | < 0.001                     | 1.946 (1.188–2.870) | 0.006                       |
| Hypertension                          | 1.291 (1.153–1.447) | < 0.001                     | 1.033 (0.721–1.480) | 0.860                       |
| Dyslipidemia                          | 1.051 (0.885–1.247) | 0.572                       | 1.502 (0.929–2.429) | 0.097                       |
| Cardiogenic shock                     | 1.673 (1.335–2.096) | < 0.001                     | 1.400 (0.652–3.004) | 0.388                       |
| CPR on admission                      | 3.668 (3.079–4.370) | < 0.001                     | 1.687 (0.823–3.457) | 0.153                       |
| Multivessel disease                   | 1.630 (1.449–1.833) | < 0.001                     | 1.256 (0.873–1.808) | 0.219                       |
| ACC/AHA type B2/C lesion              | 1.171 (1.023–1.341) | 0.022                       | 1.582 (0.979–2.558) | 0.061                       |
| Stent diameter ≥ 3.0 mm               | 1.195 (1.060–1.347) | 0.004                       | 2.537 (1.721–3.634) | < 0.001                     |
| Stent length ≥ 28 mm                  | 1.202 (1.073–1.345) | 0.001                       | 1.335 (0.932–1.913) | 0.115                       |

A total of 45,322 patients with AMI, including patients with diabetes aged ≥ 30 years at the onset of diabetes, from November 2005 to June 2015 in the KAMIR, were evaluated.

Exclusion:
- Incomplete laboratory results (n = 9081)
- Lost to follow-up (n = 2175)
- Unidentified blood HbA1c and blood glucose results (n = 13,931)
- Different generation of stents were deployed in the same patients (n = 40)
- Duration of DAPT < 12months (n = 5438)
- Bare-metal stents (n = 762)

Finally, a total of 13,895 AMI patients were included.

Figure 2. Study flow chart. AMI, acute myocardial infarction; KAMIR, Korea AMI Registry; HbA1c, hemoglobin A1c; 1G, first-generation; 2G, second-generation; DES, drug-eluting stent; DAPT, dual antiplatelet therapy.
Percutaneous coronary intervention and medical treatment. Before PCI, all patients were administered loading doses of aspirin 200–300 mg and clopidogrel 300–600 mg; alternatively, ticagrelor 180 mg or prasugrel 60 mg was administered. PCI was performed via the femoral or radial approach after an intravenous bolus dose of heparin (50–100 U/kg) to achieve an activated clotting time of > 250 s. DAPT (a combination of aspirin 100 mg/day with clopidogrel 75 mg/day or ticagrelor 90 mg twice daily or prasugrel 5–10 mg/day) was recommended for > 12 months for patients who underwent PCI. Triple antiplatelet therapy (TAPT: cilostazol 100 mg twice daily in addition to DAPT) was left to the discretion of the individual operators. Diagnostic coronary angiography and PCI were performed using standard guideline.

Study definitions and clinical outcomes. Glycemic status was determined based on medical history and glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and random plasma glucose (RPG) levels at the index hospitalization. According to the American Diabetes Association clinical practice recommendation, prediabetes was defined as an HbA1c of 5.7–6.4% and an FPG of 100–125 mg/dL (5.6–6.9 mmol/L). Diabetes was categorized as either known diabetes defined as ongoing medical treatment for diabetes (insulin or antidiabetics), or newly diagnosed diabetes, defined as an HbA1c level ≥ 6.5%, FPG ≥ 126 mg/dL (7.0 mmol/L), and/or RPG ≥ 200 mg/dL (11.1 mmol/L). If the admission electrocardiogram of patients who complained of chest pain showed ST-segment elevations in at least two contiguous leads of ≥ 2 mm (0.2 mV) in men, or ≥ 1.5 mm (0.15 mV) in women in leads V2–V3 and/or ≥ 1 mm (0.1 mV) in other contiguous chest leads or limb leads or new-onset left bundle branch block, the patients were considered to have STEMI, whereas patients who did not present persistent ST-segment elevation with increased cardiac biomarkers and with appropriate clinical context were considered to have non-STEMI (NSTEMI). In cases of NSTEMI, an early invasive treatment strategy was defined as PCI within 24 h after admission. A successful PCI was defined as a residual stenosis of < 30% and more than grade 3 flow in Thrombolysis In Myocardial Infarction flow for the infarct-related artery (IRA) after the procedure. The primary outcome of this study was the occurrence of POCOs, defined as cause death, Re-MI, or any coronary repeat revascularization. The secondary outcome was definite or probable ST during the 2-year follow-up period. All-cause death was classified as CD or non-CD. Any repeat revascularization comprised target lesion revascularization, target vessel revascularization, and non-TVR. Re-MI, TLR, TVR, and non-TVR definitions have already been published previously. The cumulative incidence of ST was defined by the current consensus.

Statistical analyses. For continuous variables, differences between the two groups were evaluated with the unpaired t-test. Additionally, differences among the three glycemic groups were evaluated using analysis of variance or the Jonckheere–Terpstra test, whereas a post-hoc analysis of the two groups was performed using the Hochberg test or Dunnett T3 test; data were expressed as mean ± standard deviation. For categorical variables, intergroup differences were analyzed using chi-squared test or Fisher’s exact test, as appropriate. Data were expressed as numbers and percentages. The Kaplan–Meier method was used to estimate various clinical outcomes, and the log-rank test was used to compare intergroup differences (Fig. 1 and Supplementary information). Variables with a p value of < 0.001 or < 0.05 in the 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. These included variables shown in Tables 2 and 3. For all analyses, two-sided values of p < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS software version 20 (IBM; Armonk, NY, USA).

Data availability Data is contained with the article or supplementary information.

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Author contributions
Y.H.K. and A.-Y.H. researched data and wrote the manuscript. Y.H.K., A.-Y.H., M.H.J., B.-K.K., J.-S.K., and M.-K.H. contributed to study design. M.H.J., S.-J.H., S.K., C.-M.A., J.-S.K., Y.-G.K., D.C., M.-K.H., and Y.J. contributed to the collection research data. M.H.J., B.-K.K., J.-S.K., Y.-G.K., D.C., M.-K.H., and Y.J. contributed to provide intellectual inputs for the discussion. Y.H.K., A.-Y.H., S.-J.H., S.K. contributed to data analysis and edited the manuscript. M.H.J., D.C., M.-K.H., and Y.J. contributed to provide supervisor role during the full processes of manuscript submitting and editing. All authors take full responsibility for this work.

Competing interests
The authors declare no competing interests.

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