Comparison of First- and Second-Generation Drug-Eluting Stents in Patients with Acute Myocardial Infarction and Prediabetes Based on the Hemoglobin A1c Level

Yong Hoon Kim,1 Ae-Young Her,1 Myung Ho Jeong,2 Byeong-Keuk Kim,3 Sung-Jin Hong,3 Seunghwan Kim,4 Chul-Min Ahn,3 Jung-Sun Kim,3 Young-Guk Ko,3 Donghoon Choi,3 Myeong-Ki Hong,3 and Yangsoo Jang

1Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Republic of Korea
2Department of Cardiology, Chonnam National University Hospital, Gwangju, Republic of Korea
3Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
4Division of Cardiology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, Republic of Korea

Correspondence should be addressed to Yong Hoon Kim; yhkim02@kangwon.ac.kr

Received 19 December 2019; Revised 27 February 2020; Accepted 20 June 2020; Published 18 July 2020

Objective. To compare major clinical outcomes after successful percutaneous coronary intervention (PCI) with first-generation (1G) drug-eluting stents (DES) and second-generation (2G) DES in patients with acute myocardial infarction (AMI) and prediabetes. Background. Patients with prediabetes are associated with an increased incidence of coronary artery disease. The relative superiority of 1G- and 2G-DES in these patients is not well established. Methods. A total of 4997 patients with AMI and prediabetes were divided into two groups: the 1D-DES group (n = 726) and the 2G-DES group (n = 4271). The primary outcomes were the patient-oriented composite outcomes (POCOs) defined as all-cause death, recurrent myocardial infarction (Re-MI), and any disease revascularization at 2-year follow-up. The secondary outcome was probable or definite stent thrombosis (ST). Results. After propensity score-matching (PSM) analysis, two PSM groups (698 pairs, n = 1396, C-statistics = 0.725) were generated. The cumulative incidence rates of POCOs (hazard ratio (HR): 1.467; 95% confidence interval (CI): 1.068–2.015; p = 0.018), any disease revascularization (HR: 2.259; 95% CI: 1.397–3.654; p = 0.001), and ST (HR: 4.361; 95% CI: 1.243–15.30; p = 0.021) in the 1G-DES group were significantly higher than those in the 2G-DES group. However, the cumulative incidence rates of all-cause death, cardiac death, and Re-MI were similar between the two groups. Conclusions. In patients with AMI and prediabetes, 2G-DES implantation was more efficacious than 1G-DES implantation over a 2-year follow-up period. However, further studies are needed to confirm these results.

1. Introduction

In the fibrinolytic era, hyperglycemia, rather than normoglycemia, was a major independent prognostic factor of adverse clinical outcomes in patients with acute myocardial infarction (AMI) [1, 2]. Similarly, in the drug-eluting stent (DES) era, hyperglycemia is an independent predictor of early and late mortality in patients with ST-segment elevation myocardial infarction (STEMI) regardless of the presence or absence of known diabetes [3, 4]. The exact mechanisms by which hyperglycemia is associated with adverse major clinical outcomes in AMI have not been fully elucidated yet. With regard to diabetes mellitus (DM), many studies have shown its association with higher long-term risk of death, myocardial infarction (MI), and repeat revascularization in patients undergoing percutaneous coronary
intervention (PCI) [5–7]. Patients with prediabetes are at an increased risk of cardiovascular disease (CVD), and prediabetes is associated with an increased incidence of coronary artery disease (CAD) [8, 9]. Even though the relative superiority between the first-generation (1G) and second-generation (2G) DESs in patients with AMI is controversial [10–12], most previous studies were not performed under the circumstance of prediabetes. Therefore, the comparative long-term clinical outcomes between the two DES generations were limited. Hence, we investigated and compared the major clinical outcomes after successful PCI with 1G-DES and 2G-DES in patients with AMI and prediabetes over a 2-year follow-up period.

2. Methods

2.1. Study Population. This study was a nonrandomized, multicenter, observational, and retrospective cohort study. A total of 45863 patients from the Korea AMI Registry (KAMIR) who had AMI and underwent successful stent implantation between November 2005 and June 2015 were evaluated. KAMIR is the first nationwide and multicenter registry that included >50 community and teaching hospitals in South Korea since November 2005 [13]. Eligible patients were aged ≥18 years at the time of hospital admission. Among the patients, those with incomplete laboratory results, including unidentified blood hemoglobin (Hb) A1c and blood glucose test results (n = 27737, 60.5%), those who were lost to follow-up (n = 3275, 7.1%), those who received a bare-metal stent (n = 297, 0.6%), those with concomitant use of 1G-DES and 2G-DES (n = 174, 0.4%), those with normoglycemia (n = 3845, 8.4%), those with DM (n = 5291, 11.5%), and those with cardiogenic shock (n = 247, 0.5%) were excluded. Finally, 4997 patients with AMI and prediabetes who underwent successful DES implantation were included in the study. The patients were divided into two groups: the 1G-DES group (n = 726, 14.5%); sirolimus-eluting stent (SES; Cypher, Cordis Corp., Miami Lakes, Florida; n = 313, 43.1%) and paclitaxel-eluting stent (PES, Taxus, Boston Scientific, Natick, Massachusetts; n = 413, 56.9%)) and the 2G-DES group (n = 4271, 85.5%; zotarolimus-eluting stent (ZES; Resolute Integrity, Medtronic, Inc., Minneapolis, MN; n = 1466, 34.3%), everolimus-eluting stent (EES; Xience Prime, Abbott Vascular, Santa Clara, CA; or Promus Element, Boston Scientific, Natick, MA; n = 2132, 49.9%), biolimus-eluting stent (BES; BioMatrix Flex, Biosensors International, Morges, Switzerland; or Nobori, Terumo Corporation, Tokyo, Japan; n = 577, 13.5%), and other stents (n = 96, 2.2%; Figure 1). The study protocol was approved by the institutional review board of each participating center, and the study was conducted in accordance with the principles of the 1975 Declaration of Helsinki. In this retrospective study, we evaluated patients who had provided written informed consent prior to participation in the KAMIR study. Therefore, any information concerning adverse events of these 4997 participants with AMI and prediabetes including the time intervals and the types of events after the index PCI, which occurred during a 2-year follow-up period, was monitored at the outpatient clinic, by phone calls, or by reviewing their charts at each participating center in those days.

2.2. Percutaneous Coronary Intervention and Medical Treatment. Coronary angiography and PCI were performed in accordance with the general guideline [14]. Before PCI, all the patients received loading doses of aspirin 200–300 mg and clopidogrel 300–600 mg; alternatively, ticagrelor 180 mg or prasugrel 60 mg was administered. Dual antiplatelet therapy (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) for >12 months was recommended for patients who underwent PCI. Administration of triple antiplatelet therapy (cilostazol (Pletal®, Otsuka Pharmaceutical Co., Tokyo, Japan) 100 mg twice daily added to DAPT) was left to the discretion of the individual physicians.

2.3. Study Definitions and Clinical Outcomes. Prediabetes was determined based on the medical history and glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels at the index hospitalization and defined as an HbA1c level of 5.7%–6.4% and an FPG level of 100–125 mg/dL (5.6–6.9 mmol/L) [15]. ST-segment elevation myocardial infarction (STEMI) and non-STEMI were defined in accordance with the current guidelines [16, 17]. In NSTEMI cases, an early invasive treatment strategy was defined as performing PCI within 24 hours after admission [17]. A successful PCI was defined as a residual stenosis of <30% and thrombolysis in myocardial infarction (TIMI) with grade III flow for the infarct-related artery (IRA) after the procedure. The primary clinical outcome of this study was the occurrence of patient-oriented composite outcomes (POCOs) defined as all-cause death, recurrent myocardial infarction (Re-MI), or any disease revascularization (ADR) at 2-year follow-up. The secondary outcome was definite or probable stent thrombosis (ST) at 2-year follow-up. All-cause death was classified as cardiac death (CD) or non-CD. ADR was composed of target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR. The definitions of Re-MI, TLR, TVR, and non-TVR were previously published [18]. The cumulative incidence of ST was defined by current consensus as acute (0 to 24 h), subacute (24 h to 30 days), late (30 days to 1 year), and very late (>1 year) [19].

2.4. Statistical Analyses. For continuous variables, in this study, the normality test was performed using the Kolmogorov–Smirnov normality test. According to the normality results, the independent samples t-test was applied to examine the difference of continuous variables means of the two groups, and the data were expressed as the mean ± standard deviations. For categorical variables, the differences between the two groups were analyzed using the chi-squared test or, if not applicable, Fisher’s exact test, and the data were expressed as counts and percentages. To adjust for potential confounders, a propensity score-matching (PSM) analysis was performed using a logistic regression model. We tested all available variables listed in Table 1 that could be of potential relevance. The C-statistics for PSM was 0.725 in the current study. Patients in the 1G-DES group were then one-to-one matched to those in the
A total of 45863 AMI patients who underwent successful stent implantation from November 2005 to June 2015 in the KAMIR were eligible

Exclusion
(i) Incomplete laboratory results including unidentified blood HbA1c and blood glucose test results (n = 27737)
(ii) Lost to follow-up (n = 3275)
(iii) BMS (n = 297)
(iv) Concomitant use of 1G-DES and 2G-DES (n = 174)
(v) Normoglycemia (n = 3845)
(vi) Diabetes mellitus (n = 5291)
(vii) Cardiogenic shock (n = 247)

Finally, a total of 4997 patients with AMI and prediabetes who underwent successful DES implantation were included

Figure 1: Study flowchart. AMI: acute myocardial infarction; KAMIR: Korea AMI Registry; HbA1c: hemoglobin A1c; BMS: bare-metal stent; 1G: first-generation; 2G: second-generation; DES: drug-eluting stent; PSM: propensity score-matching analysis.

Table 1: Baseline clinical, laboratory, and procedural characteristics.

| Variables                        | All patients | 1G-DES (n = 726) | 2G-DES (n = 4271) | p value | 1G-DES (n = 698) | 2G-DES (n = 698) | p value |
|----------------------------------|--------------|------------------|------------------|---------|------------------|------------------|---------|
| Age (years)                      |              | 63.8 ± 12.1      | 64.2 ± 12.4      | 0.464   | 63.9 ± 12.0      | 63.7 ± 12.8      | 0.814   |
| Men, n (%)                       |              | 535 (73.7)       | 316 (74.2)       | 0.773   | 516 (73.9)       | 520 (74.5)       | 0.854   |
| LVEF (%)                         |              | 52.6 ± 12.4      | 52.4 ± 11.2      | 0.798   | 52.7 ± 12.5      | 52.4 ± 11.5      | 0.618   |
| BMI (kg/m²)                      |              | 24.1 ± 3.1       | 24.1 ± 3.3       | 0.854   | 24.1 ± 2.9       | 24.1 ± 3.1       | 0.927   |
| SBP (mmHg)                       |              | 133.7 ± 24.8     | 132.3 ± 25.2     | 0.150   | 133.2 ± 24.2     | 134.1 ± 25.5     | 0.502   |
| DBP (mmHg)                       |              | 82.0 ± 14.5      | 80.1 ± 15.0      | 0.003   | 81.5 ± 13.9      | 81.6 ± 15.7      | 0.866   |
| STEMI, n (%)                     |              | 405 (55.8)       | 2442 (57.2)      | 0.484   | 391 (56.0)       | 394 (56.4)       | 0.871   |
| Primary PCI, n (%)               |              | 376/405 (92.8)   | 2346/2442 (96.1) | 0.003   | 363/391 (92.8)   | 371/394 (94.2)   | 0.452   |
| NT-proBNP (pg/mL)                |              | 4271 (97.4)      | 3674 (86.0)      | <0.001  | 239/307 (77.9)   | 239/304 (78.6)   | <0.001  |
| CPR on admission                 |              | 17 (2.3)         | 181 (4.2)        | 0.013   | 17 (2.4)         | 16 (2.3)         | 0.860   |
| Hypertension, n (%)              |              | 362 (49.9)       | 2087 (48.9)      | 0.619   | 351 (50.3)       | 346 (49.6)       | 0.789   |
| Dyslipidemia, n (%)              |              | 70 (9.6)         | 503 (11.8)       | 0.095   | 70 (10.0)        | 72 (10.3)        | 0.859   |
| Previous MI, n (%)               |              | 20 (2.8)         | 131 (3.1)        | 0.649   | 19 (2.7)         | 15 (2.1)         | 0.603   |
| Previous PCI, n (%)              |              | 41 (5.6)         | 228 (5.3)        | 0.733   | 40 (5.7)         | 33 (4.7)         | 0.471   |
| Previous CABG, n (%)             |              | 3 (0.4)          | 13 (0.3)         | 0.631   | 3 (0.4)          | 2 (0.3)          | 0.654   |
| Previous CVA, n (%)              |              | 45 (6.2)         | 253 (5.9)        | 0.773   | 43 (6.2)         | 37 (5.3)         | 0.565   |
| Previous HF, n (%)               |              | 8 (1.1)          | 48 (1.1)         | 0.959   | 8 (1.1)          | 5 (0.7)          | 0.579   |
| Current smokers, n (%)           |              | 293 (40.4)       | 1875 (43.9)      | 0.075   | 280 (40.1)       | 307 (44.0)       | 0.143   |
| Peak CK-MB (mg/dL)               |              | 127.8 ± 208.2    | 136.4 ± 196.5    | 0.278   | 129.4 ± 210.2    | 119.5 ± 141.6    | 0.301   |
| Peak troponin-I (ng/mL)          |              | 39.3 ± 88.9      | 46.1 ± 120.4     | 0.178   | 40.4 ± 83.0      | 39.7 ± 59.3      | 0.869   |
| NT-proBNP (pg/mL)                |              | 2141.2 ± 5100.7  | 1852.1 ± 4784.8  | 0.232   | 2044.5 ± 4062.4  | 1997.2 ± 3788.8  | 0.821   |
| hs-CRP (mg/dL)                   |              | 12.9 ± 36.8      | 9.7 ± 53.4       | 0.145   | 12.1 ± 31.3      | 14.1 ± 85.9      | 0.550   |
| Serum creatinine (mg/L)          |              | 1.11 ± 1.03      | 1.10 ± 1.52      | 0.935   | 1.11 ± 1.03      | 1.22 ± 2.77      | 0.314   |
| Serum glucose (mg/dL)            |              | 149.3 ± 48.9     | 150.4 ± 50.8     | 0.590   | 149.1 ± 47.6     | 151.4 ± 49.9     | 0.381   |
| Total cholesterol (mg/dL)        |              | 188.1 ± 43.4     | 186.9 ± 44.4     | 0.494   | 187.9 ± 43.3     | 185.8 ± 42.0     | 0.360   |
| Triglyceride (mg/L)              |              | 117.9 ± 75.6     | 131.9 ± 102.2    | <0.001  | 118.8 ± 75.7     | 120.3 ± 67.1     | 0.698   |
| HDL cholesterol (mg/L)           |              | 45.0 ± 12.8      | 43.6 ± 15.4      | 0.020   | 44.8 ± 12.3      | 44.1 ± 15.4      | 0.380   |
| LDL cholesterol (mg/L)           |              | 121.0 ± 36.7     | 119.5 ± 43.3     | 0.361   | 120.7 ± 38.6     | 118.7 ± 36.1     | 0.300   |
| Discharge medications            |              |                  |                  |         |                  |                  |         |
| Aspirin, n (%)                   |              | 684 (94.2)       | 4119 (96.4)      | 0.004   | 658 (94.3)       | 654 (93.7)       | 0.653   |
| Clopidogel, n (%)                |              | 707 (97.4)       | 3674 (86.0)      | <0.001  | 680 (97.4)       | 680 (97.4)       | 1.000   |
2G-DES group according to propensity scores with the nearest available pair-matching method. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 698 matched pairs. Various clinical outcomes were estimated using the Kaplan–Meier method, and differences between the two groups were compared using the log-rank test. For all analyses, two-sided values of \( p < 0.05 \) were considered statistically significant. All statistical analyses were performed using the SPSS version 20 software (IBM; Armonk, NY, USA).

### 3. Results

#### 3.1. Baseline Characteristics

The baseline clinical, laboratory, and procedural characteristics of the study population are summarized in Table 1. The mean age (63.8 ± 12.1 years) of the study population was similar between the two groups. The proportion of patients with diabetes, hypertension, hyperlipidemia, and current smoking was similar between the two groups. The mean body mass index and left ventricular ejection fraction were also similar between the two groups. The proportion of patients with prior PCI and prior CABG was similar between the two groups. The proportion of patients with prior PCI was higher in the 1G-DES group than in the 2G-DES group, whereas the proportion of patients with prior CABG was higher in the 2G-DES group than in the 1G-DES group. The proportion of patients with prior PCI and prior CABG was similar between the two groups.

### Table 1: Continued.

| Variables | All patients | Propensity score-matched patients |
|-----------|--------------|----------------------------------|
|           | 1G-DES (n = 726) | 2G-DES (n = 4271) | p value | 1G-DES (n = 698) | 2G-DES (n = 698) | p value |
| Ticagrelor, n (%) | 3 (0.4) | 363 (8.5) | <0.001 | 3 (0.4) | 4 (0.6) | 0.705 |
| Prasugrel, n (%) | 2 (0.3) | 194 (4.5) | <0.001 | 2 (0.3) | 2 (0.3) | 1.000 |
| Cilostazol, n (%) | 217 (29.9) | 812 (19.0) | <0.001 | 197 (28.2) | 213 (30.5) | 0.378 |
| BB, n (%) | 573 (78.9) | 3552 (83.2) | 0.005 | 552 (79.1) | 571 (81.8) | 0.200 |
| ACEI, n (%) | 419 (57.7) | 2311 (54.1) | 0.071 | 396 (56.7) | 393 (56.3) | 0.871 |
| ARB, n (%) | 178 (24.5) | 1101 (25.8) | 0.472 | 174 (24.9) | 171 (24.5) | 0.901 |
| CCB, n (%) | 54 (7.4) | 240 (5.6) | 0.054 | 48 (6.9) | 50 (7.2) | 0.917 |
| Lipid-lowering agents, n (%) | 535 (73.7) | 3673 (86.0) | <0.001 | 530 (75.9) | 542 (77.7) | 0.447 |

### Infarct-related artery

| Treated vessel | 1G-DES | 2G-DES | p value |
|----------------|--------|--------|---------|
| Left main, n (%) | 18 (2.5) | 77 (1.8) | 0.217 |
| LAD, n (%) | 363 (50.0) | 2147 (50.3) | 0.878 |
| LCx, n (%) | 134 (18.5) | 706 (16.5) | 0.199 |
| RCA, n (%) | 211 (29.1) | 1341 (31.4) | 0.209 |

### ACC/AHA lesion type

| Extent of CAD | 1G-DES | 2G-DES | p value |
|---------------|--------|--------|---------|
| 1-vessel, n (%) | 321 (44.2) | 2165 (50.7) | <0.001 |
| 2-vessel, n (%) | 224 (30.9) | 1326 (31.0) | 0.917 |
| ≥3-vessel, n (%) | 181 (24.9) | 780 (18.3) | <0.001 |

### IVUS

| OCT | 177 (24.4) | 1007 (23.6) | 0.638 |
| FFR | 0 (0.0) | 33 (0.8) | 0.017 |

### Stents

| SES, n (%) | 313 (43.1) | 303 (43.4) |
| PES, n (%) | 413 (56.9) | 395 (56.6) |
| ZES, n (%) | 1466 (34.3) | 237 (34.0) |
| EES, n (%) | 2132 (49.9) | 366 (52.4) |
| BES, n (%) | 577 (13.5) | 73 (10.5) |
| Others, n (%) | 96 (2.2) | 22 (3.1) |

### Stent diameter (mm)

| Stent length (mm) | 25.9 ± 7.15 | 26.9 ± 11.5 | 0.031 |
| Number of stents | 1.54 ± 0.84 | 1.48 ± 0.80 | 0.051 |

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 between the two groups were evaluated with independent samples t-test. LVEF: left ventricular ejection fraction; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CPR: cardiopulmonary resuscitation; CAGB: coronary artery bypass graft; CVA: cerebrovascular events; 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; BB: beta-blocker; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blockers; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery; ACC/AHA: American College of Cardiology/American Heart Association; CAD: coronary artery disease; IVUS: intravascular ultrasound; OCT: optical coherence tomography; FFR: fractional flow reserve; SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent; ZES: zotarolimus-eluting stent; EES: everolimus-eluting stent; BES: biolimus-eluting stent.
Multivessel disease was a common independent predictor of pre-death, CD, and Re-MI were similar between the two groups; the cumulative incidence rates of all-cause death, CD, and Re-MI were similar between the two groups; the proportion of patients who underwent primary PCI (92.8% vs. 96.1%, p = 0.003) or PCI within 24 hours (76.6% vs. 85.5%, p < 0.001) was significantly higher in the 2G-DES group than in the 1G-DES group. The proportion of patients with cardiopulmonary resuscitation (CPR) on admission (4.2% vs. 2.3%, p = 0.013) and the prescription rates of aspirin, ticagrelor, prasugrel, and lipid-lowering agents as discharge medications; the number of American College of Cardiology/American Heart Association (ACC/AHA) type C lesions; the incidence of single-vessel disease; the use frequency of optical coherence tomography and fractional flow reserve; and the mean total length of the deployed stents were significantly greater in the 2G-DES group than in the 1G-DES group. By contrast, the prescription rates of clopidogrel and cilostazol as discharge medications and the incidence of ≥ 3-vessel disease were significantly higher in the 1G-DES group than in the 2G-DES group. However, these intergroup differences in baseline characteristics were well balanced after PSM adjustment.

3.2. Clinical Outcomes. The cumulative incidences of major clinical outcomes at 2 years are listed in Table 2 and Figure 2. After PSM analysis, the cumulative incidence rates of POCOs (hazard ratio (HR): 1.467; 95% confidence interval (CI): 1.068–2.015; p = 0.018), ADR (HR: 2.259; 95% CI: 1.397–3.654; p = 0.001), and ST (HR: 4.361; 95% CI: 1.243–15.30; p = 0.021) were significantly higher in the 1G-DES group than in the 2G-DES group. However, the cumulative incidence rates of all-cause death, CD, and Re-MI were similar between the two groups. Table 3 shows the independent predictors of POCOs and ADR at 2 years. Old age (≥ 65 years), LVEF of ≤ 50%, CPR on admission, use of a lipid-lowering agent, and multivessel disease were significant independent predictors of POCOs. In addition, multivessel disease was a significant independent predictor of ADR in this study.

4. Discussion

The main findings of this study are as follows: (1) the cumulative incidence rates of POCOs, ADR, and ST were significantly higher in the 1G-DES group than in the 2G-DES group; (2) the cumulative incidence rates of all-cause death, CD, and Re-MI were similar between the two groups; (3) Multivessel disease was a common independent predictor of both POCOs and ADR.

1G-DES is made of stainless steel with a closed-cell design and has a relatively thick inner diameter (130–150 μm), making them difficult to maneuver through significantly diseased and calcified vessels. In addition, the major serious problem of the 1G-DES was the occurrence of (very) late ST, induced by the polymer or even by the stent material itself [20]. By contrast, the 2G-DES is made of cobalt-chromium (CoCr) and has thinner stent struts (50–90 μm) and showed improved ability for deliverability while maintaining an adequate radial strength [21]. The polymers in the 2G-DES were more biocompatible and thromboresistant than those in the 1G-DES [22]. One meta-analysis revealed that CoCr-EESs were associated with significantly lower rates of definite ST than PESs (odds ratio (OR): 0.34, 95% CI: 0.19–0.62) [23]. With regard to diabetes, Bavishi et al. [24] performed a meta-analysis of randomized trials to compare the efficacy and safety between the 1G-DES and the 2G-DES. In their study, the EES showed significantly decreased incidence rates of major adverse cardiac events by 18% (relative risk (RR)): 0.82, 95% CI: 0.70–0.96) and ST by 46% (RR: 0.54, 95% CI: 0.35–0.82) as compared with the 1G-DES. Moreover, the EES showed a trend toward reduced incidence rates of TLR and TVR (p = 0.05). The ZES was associated with 89% increased risk of TLR (RR: 1.89, 95% CI: 1.10–3.22) as compared with the 1G-DES in their study. The results of our study may be similar to those of their study. However, their study population was not confined to patients with AMI.

Higher blood glucose level was an important factor of increased risk of death and poor clinical outcome after AMI [25–27]. Kowalczyk et al. [28] reported that patients with HbA1c levels of ≤ 5.9% had significantly lower posthospital mortality (4.5%) than those with HbA1c levels of > 5.9% (25.0%; p < 0.001) in 2146 AMI survivors. However, the evident underlying pathological mechanisms related to the adverse clinical outcomes in hyperglycemia status remain unclear. Liu et al. [29] suggested that elevated glucose level is associated with the development of endothelial dysfunction. Moreover, this endothelial dysfunction is the leading cause of platelet activation [30]. In addition, hyperglycemia plays an important role in the development of diabetic macrovascular complications, including atherosclerosis and restenosis [31]. Patients with diabetes have more diffuse disease that often rapidly progresses and tend to have exaggerated neointimal hyperplasia and increased need for repeat revascularization [32]. Moreover, glycosylation of vascular collagen and elastin is thought to lead to a more diffuse pattern of restenosis [33].

Even though the 2G-DES uses an evolved stent platform and a more biocompatible polymer than that in the 1G-DES, data concerning the outcomes between the two DESs in patients with AMI are conflicting [10, 34]. With regard to diabetes, the relative superiority between the 1G-DES and the 2G-DES in patients with diabetes is controversial [35–37]. Furthermore, in patients with prediabetes, limited follow-up data are available regarding the comparative long-term effects of 1G-DES and 2G-DES implantation. Even though the study population, follow-up duration, and definition of prediabetes were different between in our study and that of Kok et al. [38], clinical outcomes were compared between prediabetes and diabetes (11.1% vs. 10.5%). Therefore, the major clinical outcomes of our study could reflect the meta-analysis results of the study of Bavishi et al. [24].
Table 2: Clinical outcomes by Kaplan–Meier analysis and Cox proportional hazard ratio analysis at 2 years.

| Outcomes                          | 1G-DES | 2G-DES | Log-rank | Hazard ratio (95% CI) | p value |
|-----------------------------------|--------|--------|----------|-----------------------|---------|
| **All patients**                  |        |        |          |                       |         |
| POCOs                             | 100 (13.9) | 353 (8.8) | <0.001 | 1.616 (1.294–2.017) | <0.001 |
| All-cause death                   | 43 (5.9) | 171 (4.2) | 0.035 | 1.431 (1.024–1.999) | 0.036 |
| Cardiac death                     | 34 (4.7) | 129 (3.1) | 0.030 | 1.514 (1.037–2.209) | 0.032 |
| Re-MI                             | 9 (1.3)  | 79 (2.0)  | 0.192 | 1.576 (0.791–3.141) | 0.196 |
| Death or MI                       | 52 (7.2) | 244 (6.0) | 0.224 | 1.204 (0.892–1.624) | 0.225 |
| *Any disease revascularization    | 58 (8.4) | 138 (3.6) | <0.001 | 2.383 (1.752–3.238) | <0.001 |
| Stent thrombosis (probable or definite) | 14 (1.9) | 28 (0.7)  | 0.001 | 2.956 (1.556–5.615) | 0.001 |
| Acute                             | 1 (0.1)  | 2 (0.0)   | 0.355 | 2.941 (0.267–32.44) | 0.378 |
| Subacute                          | 4 (0.6)  | 13 (0.3)  | 0.290 | 1.814 (0.591–5.63)  | 0.298 |
| Late                              | 7 (1.0)  | 10 (0.2)  | 0.002 | 4.146 (1.578–10.89) | 0.004 |
| Very late                         | 2 (0.3)  | 3 (0.1)   | 0.103 | 3.967 (0.663–23.74) | 0.131 |
| **Propensity score-matched patients** |       |        |          |                       |         |
| POCOs                             | 94 (13.5) | 64 (9.5)  | 0.017 | 1.467 (1.068–2.015) | 0.018 |
| All-cause death                   | 42 (6.0) | 36 (5.3)  | 0.541 | 1.149 (0.736–1.793) | 0.541 |
| Cardiac death                     | 33 (4.8) | 25 (3.7)  | 0.317 | 1.303 (0.775–2.191) | 0.319 |
| Re-MI                             | 8 (1.2)  | 8 (1.2)   | 0.971 | 1.019 (0.382–2.714) | 0.971 |
| Death or MI                       | 50 (7.2) | 44 (6.5)  | 0.588 | 1.118 (0.746–1.667) | 0.588 |
| *Any disease revascularization    | 54 (8.2) | 24 (3.6)  | 0.001 | 2.259 (1.397–3.654) | 0.001 |
| Stent thrombosis (probable or definite) | 13 (1.9) | 3 (0.4)   | 0.012 | 1.019 (0.382–2.714) | 0.012 |
| Acute                             | 1 (0.1)  | 0 (0.0)   | —     | —                     | —       |
| Subacute                          | 3 (0.4)  | 1 (0.1)   | 0.316 | 3.006 (0.313–28.90) | 0.340 |
| Late                              | 7 (1.0)  | 2 (0.3)   | 0.093 | 3.526 (0.733–16.98) | 0.116 |
| Very late                         | 2 (0.3)  | 0 (0.0)   | 0.155 | —                     | —       |

Table 3: Independent predictors for POCOs and any disease revascularization at 2 years in all patients.

| Variables                          | POCOs | Any disease revascularization |
|-----------------------------------|-------|------------------------------|
|                                   | Univariate | Multivariate | Univariate | Multivariate |
| 1G-DES vs. 2G-DES                 | 1.616 (1.294–2.017) | <0.001 | 1.520 (1.213–1.905) | <0.001 |
| Age (≥65 years)                   | 1.548 (1.282–1.867) | <0.001 | 1.318 (1.072–1.620) | 0.009 |
| Men                               | 1.269 (1.039–1.550) | 0.020 | 1.030 (0.828–1.282) | 0.789 |
| LVEF (<50%)                       | 1.652 (1.374–1.986) | <0.001 | 1.437 (1.191–1.733) | <0.001 |
| Hypertension                      | 1.333 (1.107–1.605) | 0.002 | 1.187 (0.977–1.441) | 0.084 |
| Dyslipidemia                      | 1.075 (0.811–1.425) | 0.617 | 1.182 (0.887–1.575) | 0.252 |
| CPR on admission                  | 4.004 (3.020–5.309) | <0.001 | 3.722 (2.799–4.950) | <0.001 |
| Lipid-lowering agent              | 2.487 (2.038–3.035) | <0.001 | 2.355 (1.908–2.857) | <0.001 |
| MVD                               | 1.733 (1.430–2.102) | <0.001 | 1.585 (1.303–1.928) | <0.001 |
| ACC/AHA type B2/C lesion          | 1.141 (0.918–1.419) | 0.234 | 1.131 (0.905–1.413) | 0.278 |
| Stent diameter (<3.0 mm)          | 1.176 (0.967–1.431) | 0.104 | 1.088 (0.891–1.328) | 0.407 |
| Stent length (≥28 mm)             | 1.174 (0.975–1.413) | 0.091 | 1.060 (0.877–1.281) | 0.546 |

1G: first-generation; 2G: second-generation; DES: drug-eluting stent; HR: hazard ratio; CI: confidence interval; POCOs: patient-oriented composite outcomes; Re-MI: recurrent myocardial infarction. *Any disease revascularization was composed of target lesion revascularization, target vessel revascularization, and nontarget vessel revascularization.
All patients
POCOs
HR: 1.616; 95% CI: 1.294 – 2.017; p < 0.001

PSM patients
POCOs
HR: 1.467; 95% CI: 1.068 – 2.015; p = 0.018

All patients
All-cause death
HR: 1.431; 95% CI: 1.024 – 1.999; p = 0.036

PSM patients
All-cause death
HR: 1.149; 95% CI: 0.736 – 1.793; p = 0.541

Figure 2: Continued.
All patients Cardiac death
4.7%
3.1%
HR: 1.514; 95% CI: 1.037 – 2.209; p = 0.032

PSM patients Cardiac death
4.8%
3.7%
HR: 1.303; 95% CI: 0.775 – 2.191; p = 0.319

All patients Re-MI
2.0%
1.3%
HR: 1.576; 95% CI: 0.791 – 3.141; p = 0.196

PSM patients Re-MI
1.2%
1.2%
HR: 1.019; 95% CI: 0.382 – 2.714; p = 0.971

Figure 2: Continued.
was similar between the two DES generations. By contrast, late ST was significantly different between the two groups. The main cause of these results may be related to the relatively higher numbers of patients who received EES (n = 2132/4271, 49.9%) in this study population. In the study of Bangalore et al. [39], EES was associated with the lowest...
incidence rates of TVR, Re-MI, and ST as compared with ZES and PES. In the study of Kedhi et al. [35], the difference in the risk of ST was already observed in the early phase and was maintained during the 1-year follow-up. Similarly, in our study, the risk of ST was already determined within 1 year after the index PCI.

Although oral glucose tolerance test (OGTT) is considered more sensitive than measurement of HbA1c level for defining diabetes [15], in this study, prediabetes was determined on the basis of patients’ medical history and HbA1c and FPG levels at the index hospitalization. One of the main advantages of measuring HbA1c level is that it can be performed at any time because it does not require fasting. This is especially convenient in circumstances in which performing the test and interpreting the result may be difficult in the milieu of an acute illness such as AMI [38, 40]. Therefore, despite that measurement of HbA1c level may not be ideal, it can be used as an alternative diagnostic tool for making these important assessments.

In this KAMIR study, >50 high-volume university or community hospitals in South Korea participated, but the study population was insufficient to provide meaningful results. Taken together, the results of this study may provide a meaningful message to the interventional cardiologist during PCI to help select the appropriate DES, especially in patients with AMI and prediabetes.

This study has several limitations. First, some data may have been underreported and/or missing owing to the non-randomized nature of this study. Second, a proportion of the patients with prediabetes (based on HbA1c level) may be diagnosed with overt diabetes if retested using a more sensitive diagnostic test (e.g., OGTT). This may be a source of bias in the study. Third, the study was based on discharge medications, as we could not confirm the participants’ adherence or non-adherence to their antidiabetic drugs. Therefore, we could not discern the degree of glycemic control of the participants during the follow-up period, which might constitute an additional bias in this study. Fourth, the 2-year follow-up period was relatively short for determining the long-term major clinical outcomes; thus, longer follow-up period data are required. Fifth, we performed a PSM analysis to strengthen our results, but variables not included in the KAMIR study may have affected the study outcomes.

In conclusion, with regard to the beneficial effects on POCOs, ADR, and ST reduction capacity, in patient with AMI and prediabetes, 2G-DES implantation was more efficacious than 1G-DES implantation during the 2-year follow-up period. However, further randomized trials are needed to more precisely confirm the superior efficacy of 2G-DES over 1G-DES.

Data Availability
The data used to support the findings of this study are included within the article and supplementary tables.

Conflicts of Interest
The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions
Yong Hoon Kim and Ae-Young Her contributed equally to this work.

Acknowledgments
The authors thank all of the clinical investigators who contributed time and effort to this study, as well as the Korea Acute Myocardial Infarction (KAMIR) Investigators. This research was supported by a fund (2016-ER6304-02) by Research of Korea Centers for Disease Control and Prevention.

References
[1] N. N. Wahab, E. A. Cowden, N. J. Pearce, M. J. Gardner, H. Merry, and J. L. Cox, “Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era?” Journal of the American College of Cardiology, vol. 40, no. 10, pp. 1748–1754, 2002.
[2] M. S. Sabatine, C. P. Cannon, C. M. Gibson et al., “Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation,” New England Journal of Medicine, vol. 352, no. 12, pp. 1179–1189, 2005.
[3] D. Planer, B. Witzenbichler, G. Guagliumi et al., “Impact of hyperglycemia in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: the HORIZONS-AMI trial,” International Journal of Cardiology, vol. 167, no. 6, pp. 2572–2579, 2013.
[4] C. K. Naber, R. H. Mehta, C. Jünger et al., “Impact of admission blood glucose on outcomes of nondiabetic patients with acute ST-elevation myocardial infarction (from the German Acute Coronary Syndromes [ACOS] Registry),” The American Journal of Cardiology, vol. 103, no. 5, pp. 583–587, 2009.
[5] D. E. Cutlip, A. G. Chhabra, D. S. Baim et al., “Beyond restenosis,” Circulation, vol. 110, no. 10, pp. 1226–1230, 2004.
[6] I. Iakovou, T. Schmidt, E. Bonizzoni et al., “Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents,” JAMA, vol. 293, no. 17, pp. 2126–2130, 2005.
[7] T. T. Lee, L. Feinberg, D. S. Baim et al., “Effect of diabetes mellitus on five-year clinical outcomes after single-vessel coronary stenting (a pooled analysis of coronary stent clinical trials),” The American Journal of Cardiology, vol. 98, no. 6, pp. 718–721, 2006.
[8] M. K. Ali, K. M. Bullard, S. Saydah, G. Imperatore, and E. W. Gregg, “Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988–2014,” The Lancet Diabetes & Endocrinology, vol. 6, no. 5, pp. 392–403, 2018.
[9] M. Coutinho, H. C. Gerstein, Y. Wang, and S. Yusuf, “The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years,” Diabetes Care, vol. 22, no. 2, pp. 233–240, 1999.
[10] S. H. Hofma, P. C. Smits, J. Brouwer et al., “Long-term follow-up of second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction: three-year results of the XAMI trial,” Euro-Intervention, vol. 10, no. 11, pp. 1280–1283, 2015.
[11] E. Di Lorenzo, R. Sauro, M. Capasso et al., “Long-term results of the randomized comparison of everolimus-eluting stents and sirolimus-eluting stent in patients with ST elevation
myocardial infarction (RACES-MI trial),” *International Journal of Cardiology,* vol. 202, pp. 177–182, 2016.

[12] G. De Luca, P. Smits, S. H. Hofma et al., “Everolimus eluting stent vs first generation drug-eluting stent in primary angioplasty: a pooled patient-level meta-analysis of randomized trials,” *International Journal of Cardiology,* vol. 244, pp. 121–127, 2017.

[13] D. S. Sim and M. H. Jeong, “Differences in the Korean acute myocardial infarction registry compared with western registries,” *Korean Circulation Journal,* vol. 47, no. 6, pp. 811–822, 2017.

[14] E. D. Grech, “Percutaneous coronary intervention. II: the procedure,” *BMJ,* vol. 326, no. 7399, pp. 1137–1140, 2003.

[15] E. D. Grech, “Standards of medical care in diabetes-2010,” *Diabetes Care,* vol. 33, no. 1, 2010.

[16] P. T. O’Gara, F. G. Kushner, D. D. Ascheim et al., “ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology foundation/American heart association task force on practice guidelines,” *Diabetes Care,* vol. 61, no. 4, pp. e78–e140, 2013.

[17] E. A. Amsterdam, N. K. Wenger, R. G. Brindis et al., “2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes,” *Journal of the American College of Cardiology,* vol. 64, no. 24, pp. e139–e228, 2014.

[18] Y. H. Kim, A.-Y. Her, M. H. Jeong et al., “Impact of renin-angiotensin system inhibitors on long-term clinical outcomes in patients with acute myocardial infarction treated with successful percutaneous coronary intervention with drug-eluting stents: comparison between STEMI and NSTEMI,” *Atherosclerosis,* vol. 280, pp. 166–173, 2019.

[19] P. K. Bundhun, Z. J. Wu, and M. H. Chen, “Is there any significant difference in stent thrombosis between sirolimus and paclitaxel eluting stents?: a systematic review and meta-analysis of randomized controlled trials,” *Medicine (Baltimore),* vol. 95, no. 5, 2016.

[20] A. M. Galloe, H. Kelbak, L. Thuesen et al., “SORT OUT II investigators. 10-Year clinical outcome after randomization to treatment by sirolimus- or paclitaxel-eluting coronary stents,” *Nature Reviews Cardiology,* vol. 69, no. 6, pp. 616–624, 2017.

[21] S. Torii, H. Jinnouchi, A. Sakamoto et al., “Drug-eluting coronary stents: insights from preclinical and pathology studies,” *Nature Reviews Cardiology,* vol. 17, no. 1, pp. 37–51, 2019.

[22] G. Sarno, B. Lagerqvist, O. Fröbert et al., “Lower risk of stent thrombosis and restenosis with unrestricted use of ‘new-generation’ drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR),” *European Heart Journal,* vol. 33, no. 5, pp. 606–613, 2012.

[23] T. Palmerini, G. Biondi-Zoccai, D. D. Riva et al., “Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis,” *The Lancet,* vol. 379, no. 9824, pp. 1393–1402, 2012.

[24] C. Bavishi, U. Baber, S. Panwar et al., “Efficacy and safety of everolimus and zotarolimus-eluting stents versus first-generation drug-eluting stents in patients with diabetes: a meta-analysis of randomized trials,” *International Journal of Cardiology,* vol. 230, pp. 310–318, 2017.

[25] S. E. Capes, D. Hunt, K. Malmberg, and H. C. Gerstein, “Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview,” *The Lancet,* vol. 355, no. 9206, pp. 773–778, 2000.

[26] C. Berry, S. Noble, J. C. Grégoire et al., “Glycaemic status influences the nature and severity of coronary artery disease,” *Diabetologia,* vol. 53, no. 4, pp. 652–658, 2010.