Outcomes between prediabetes and type 2 diabetes mellitus in older adults with acute myocardial infarction in the era of newer-generation drug-eluting stents: a retrospective observational study

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Abstract

Background: The comparative clinical outcomes between prediabetes and type 2 diabetes mellitus (T2DM) in older adults with AMI in the era of newer-generation drug-eluting stents (DES) are limited. We investigated the 2-year clinical outcomes of these patients.

Methods: A total of 5492 AMI patients aged ≥65 years were classified into three groups according to their glycemic status: normoglycemia (group A: 1193), prediabetes (group B: 1696), and T2DM (group C: 2603). The primary outcome was the occurrence of major adverse cardiac events (MACE), defined as all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization. The secondary outcome was stent thrombosis (ST).

Results: The primary and secondary outcomes cumulative incidences were similar between the prediabetes and T2DM groups. In both the prediabetes and T2DM groups, the cumulative incidences of MACE (adjusted hazard ratio [aHR]: 1.373; p = 0.020 and aHR: 1.479; p = 0.002, respectively) and all-cause death or MI (aHR: 1.436; p = 0.022 and aHR: 1.647; p = 0.001, respectively) were significantly higher than those in the normoglycemia group. Additionally, the cumulative incidence of all-cause death in the T2DM group was significantly higher than that in the normoglycemia group (aHR, 1.666; p = 0.003).

Conclusions: In this retrospective study, despite the 2-year clinical outcomes of the patients with prediabetes and T2DM in the older adults were worse than those in the normoglycemia group; they were similar between the prediabetes and T2DM groups. Hence, comparable treatment strategies should be strengthened between prediabetes and T2DM in older adults with AMI.

Trial registration: Retrospectively registered.

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Background
The prevalence of diabetes mellitus (DM) is growing rapidly. The number of DM cases is expected to reach 642 million by 2040 worldwide [1]. Of those aged 65 years and above, an estimated 22–33% had diabetes [2–4] or more than 20% had impaired glucose regulation [5]. There are numerous complex factors involved in diabetes in older adults, including decreased physical activity [6], defective beta-cell adaptation to insulin resistance [7], and decrease in endogenous estrogen and testosterone concentrations, which are believed to negatively affect glucose hemostasis [8]. Diabetes in older adults is associated with higher mortality [4], which is known to be associated with a higher risk of myocardial infarction (MI) [4, 9]. However, the prognostic implications of prediabetes in older adults remain incompletely characterized. Prediabetes comprises impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), as determined by oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c) [10]. George et al. [11] showed that IGT (hazard ratio [HR]: 1.54, 95% CI: 1.06–2.24; P = 0.024) independently predicted major adverse cardiac event (MACE)-free survival in 768 patients with acute MI (AMI). Yang et al. [12] demonstrated that fasting plasma glucose (FPG) levels were associated with a higher risk of in-hospital mortality in 1854 elderly (aged ≥65 years) patients with AMI. According to more recent reports [13, 14], patients with prediabetes had worse outcomes compared to those with normoglycemia and comparable to those with type 2 DM (T2DM). In the study by Kim et al. [14], old age (≥ 65 years) was a significant independent predictor of all-cause death (P < 0.001). However, in the Preiss et al. study [15], glycemic measures were not predictive of cardiovascular events. Another study suggested that patients with prediabetes and normoglycemia had similar 1-year mortality rates (adjusted odds ratio: 0.90; 95% CI: 0.66–1.24) in their 8795 high-risk non-ST-segment elevation myocardial infarction (NSTEMI) patients [16]. Kim et al. [17] showed that stent generation could be regarded as an important determinant of MACE. Hence, to clarify the comparative clinical outcomes between prediabetes and T2DM in older adults and to reflect contemporary trends of percutaneous coronary intervention (PCI), we compared the 2-year clinical outcomes between prediabetes and T2DM in older adults with AMI who underwent successful implantation of newer-generation drug-eluting stents (DES).

Methods
Study design and population
In this retrospective cohort study, patients with diabetes were confined to T2DM based on a previous study [18] that also included patients from the Korea AMI Registry (KAMIR) [19]. KAMIR is a nationwide, prospective, observational online registry in South Korea since November 2005 to evaluate the current epidemiology and major clinical outcomes of patients with AMI. Eligible patients were aged ≥18 years at the time of hospital admission, a more than 50 high-volume university or teaching hospitals for primary PCI and onsite cardiac surgery participated in this registry. Details of the registry can be found on the KAMIR website (http://www.kamir.or.kr). The definition of older adults is controversial. In general, a person is considered old if his or her civil age is ≥60 or ≥65 years [20]. Additionally, based on the Consensus Development Conference on Diabetes and Older Adults (defined as those aged ≥65years) in February 2012 convened by the American Diabetes Association (ADA) [4], we defined the cut-off value of older adults aged ≥65 years in our study. Hence, a total of 10,138 AMI patients aged ≥65 years who were aged ≥30 years at the onset of diabetes, and who underwent successful newer-generation DES implantation from January 2006 to June 2015 in the KAMIR were evaluated. Patients who had the following conditions were excluded: (1) incomplete laboratory results including unidentified results of blood hemoglobin (Hb) A1c and blood glucose (n = 4109; 40.5%); or (2) lost to follow-up (n = 537; 5.3%). After exclusion, 5492 AMI patients who underwent successful newer-generation DESs were included. The types of newer-generation DESs used are listed in Table 1. The patients were classified into normoglycemia (group A, n = 1193 [21.7%]), prediabetes (group B, n = 1696 [30.9%]), and T2DM (group C, n = 2603 [47.4%]) groups (Fig. 1). The study protocol was approved by the ethics committee at each participating center and the Chonnam National University Hospital Institutional Review Board (IRB) ethics committee (CNUH-2011-172), according to the ethical guidelines of the 1975 Declaration of Helsinki. Informed written consent was obtained from all patients prior to inclusion in the study. All 5492 patients completed a 2-year clinical follow-up, and any information concerning adverse events that occurred during the follow-up period was monitored at the outpatient clinic, by phone calls, or by reviewing their charts at each participating center. Moreover, all clinical events were evaluated by an independent event adjudication committee [19].

Keywords: Diabetes, Elderly, Myocardial infarction, Prediabetes
Table 1  Baseline characteristics

|                        | Normoglycemia | Prediabetes | T2DM | p value                      |
|------------------------|---------------|-------------|------|------------------------------|
|                        | Group A       | Group B     | Group C | Group A vs. B | Group A vs. C | Group B vs. C | Group A vs. B vs. C |
| Age (years)            | 74.7 ± 6.1    | 74.5 ± 6.2  | 73.8 ± 5.6 | 0.488          | < 0.001       | < 0.001       | < 0.001               |
| Male, n (%)            | 764 (64.0)    | 987 (58.2)  | 1428 (54.9) | 0.002          | < 0.001       | 0.032         | < 0.001               |
| LVEF (%)               | 51.3 ± 11.0   | 51.9 ± 11.5 | 50.3 ± 12.2 | 0.139          | 0.015         | < 0.001       | < 0.001               |
| BMI (kg/m²)            | 22.9 ± 2.9    | 23.3 ± 3.0  | 23.7 ± 3.0  | 0.001          | < 0.001       | < 0.001       | < 0.001               |
| SBP (mmHg)             | 127.6 ± 28.4  | 129.1 ± 27.0| 130.2 ± 28.1| 0.165          | 0.011         | 0.211         | 0.032                 |
| DBP (mmHg)             | 76.7 ± 16.0   | 77.6 ± 15.4 | 76.7 ± 15.4 | 0.100          | 0.880         | 0.062         | 0.126                 |
| STEMI, n (%)           | 652 (54.7)    | 958 (56.5)  | 1272 (48.9) | 0.329          | 0.001         | < 0.001       | < 0.001               |
| Primary PCI, n (%)     | 622 (95.4)    | 915 (95.5)  | 1225 (96.3) | 0.915          | 0.295         | 0.299         | 0.469                 |
| Discharge medications  | 1193          | 1696        | 2603        |                |               |               |                      |
| Blood glucose (mg/dL)  | 139.9         | 137.0       | 138.9       | 0.048          | 0.003         | 0.370         | 0.014                 |
| CPR on admission, n (%)| 69 (5.8)      | 82 (4.8)    | 118 (4.5)   | 0.270          | 0.002         | 0.089         | 0.031                 |
| Admission Killip class | I             | II          | III         | IV             |               |               |                       |
|                        | 909 (76.2)    | 1269 (74.8) | 1828 (70.2) | 0.399          | < 0.001       | < 0.001       | < 0.001               |
|                        | 134 (11.2)    | 216 (12.7)  | 336 (12.9)  | 0.247          | 0.159         | 0.889         | 0.327                 |
|                        | 82 (6.9)      | 135 (8.0)   | 298 (11.4)  | 0.275          | < 0.001       | < 0.001       | < 0.001               |
|                        | 68 (5.7)      | 76 (4.5)    | 141 (5.4)   | 0.138          | 0.723         | 0.176         | 0.268                 |
| Dyslipidemia, n (%)    | 87 (7.3)      | 166 (9.8)   | 337 (12.9)  | 0.019          | < 0.001       | 0.002         | < 0.001               |
| Previous MI, n (%)     | 30 (2.5)      | 46 (2.7)    | 152 (5.8)   | 0.814          | < 0.001       | < 0.001       | < 0.001               |
| Previous PCI, n (%)    | 57 (4.8)      | 103 (6.1)   | 238 (9.1)   | 0.138          | < 0.001       | < 0.001       | < 0.001               |
| Previous CABG, n (%)   | 2 (0.2)       | 2 (0.1)     | 27 (1.0)    | 0.723          | 0.002         | < 0.001       | < 0.001               |
| Previous HF, n (%)     | 95 (8.0)      | 133 (7.8)   | 277 (10.6)  | 0.944          | 0.010         | 0.002         | 0.002                 |
| Previous CVA, n (%)    | 95 (8.0)      | 133 (7.8)   | 277 (10.6)  | 0.944          | 0.010         | 0.002         | 0.002                 |
| Current smokers, n (%) | 280 (23.5)    | 455 (26.8)  | 549 (21.1)  | 0.041          | 0.108         | < 0.001       | < 0.001               |
| Peak CK-MB (mg/dL)     | 1304 ± 194.4  | 135.3 ± 214.5| 940.0 ± 128.5| 0.524          | < 0.001       | < 0.001       | < 0.001               |
| Peak troponin-I (ng/mL)| 47.5 ± 76.6   | 46.0 ± 88.6 | 45.4 ± 98.6 | 0.616          | 0.588         | 0.882         | 0.895                 |
| NT-ProBNP (pg/mL)      | 24986 ± 4563.2| 21205 ± 3221.8| 32007.5 ± 5819.2| 0.014          | < 0.001       | < 0.001       | < 0.001               |
| hs-CRP (mg/dL)         | 9.4 ± 35.5    | 11.5 ± 60.6 | 12.3 ± 46.0 | 0.241          | 0.034         | 0.644         | 0.238                 |
| Serum creatinine (mg/L)| 1.06 ± 0.93   | 1.04 ± 1.03 | 1.24 ± 1.08 | 0.648          | < 0.001       | < 0.001       | < 0.001               |
| eGFR (mL/min/1.73m²)   | 87.7 ± 46.1   | 86.2 ± 47.7 | 78.2 ± 42.2 | 0.783          | < 0.001       | < 0.001       | < 0.001               |
| Blood glucose (mg/dL)  | 139.9 ± 55.3  | 150.3 ± 52.1| 219.1 ± 97.7| < 0.001        | 0.143         | < 0.001       | < 0.001               |
| Hemoglobin A1C (%)     | 5.3 ± 0.5     | 6.0 ± 0.2   | 7.5 ± 2.8   | < 0.001        | < 0.001       | < 0.001       | < 0.001               |
| Total cholesterol (mg/dL)| 172.9 ± 39.4 | 182.1 ± 42.8| 170.8 ± 44.4| < 0.001        | 0.143         | < 0.001       | < 0.001               |
| Triglyceride (mg/L)    | 97.2 ± 69.6   | 108.3 ± 70.2| 123.7 ± 90.2| < 0.001        | < 0.001       | < 0.001       | < 0.001               |
| HDL-cholesterol (mg/L) | 45.5 ± 16.6   | 44.9 ± 17.5 | 41.9 ± 14.0 | 0.386          | < 0.001       | < 0.001       | < 0.001               |
| LDL-cholesterol (mg/L) | 109.3 ± 35.5  | 116.3 ± 46.4| 105.9 ± 36.8| < 0.001        | 0.007         | < 0.001       | < 0.001               |
| Glucose management     |                |             |             |                |               |               |                       |
| Diet, n (%)            | 139 (5.3)     | –           | –           | –              |               |               |                       |
Table 1 (continued)

|                                      | Normoglycemia Group A (n = 1193) | Prediabetes Group B (n = 1696) | T2DM Group C (n = 2603) | p value Group A vs. B | Group A vs. C | Group B vs. C | Group A vs. B vs.C |
|--------------------------------------|----------------------------------|--------------------------------|-------------------------|-----------------------|--------------|---------------|-------------------|
| Oral agent, n (%)                   |                                  |                                |                         |                       |              |               |                   |
| Insulin, n (%)                       |                                  |                                |                         |                       |              |               |                   |
| Untreated, n (%)                     |                                  |                                |                         |                       |              |               |                   |
| IRA                                  |                                  |                                |                         |                       |              |               |                   |
| Left main, n (%)                     | 28 (2.2)                         | 33 (1.9)                       | 52 (2.0)                | 0.690                 | 0.713        | 0.905         | 0.902             |
| LAD, n (%)                           | 569 (47.7)                       | 810 (47.8)                     | 1203 (46.2)             | 0.970                 | 0.362        | 0.335         | 0.511             |
| LCx, n (%)                           | 191 (16.0)                       | 266 (15.7)                     | 422 (16.2)              | 0.813                 | 0.887        | 0.670         | 0.899             |
| RCA, n (%)                           | 405 (33.9)                       | 587 (34.6)                     | 926 (35.6)              | 0.712                 | 0.341        | 0.535         | 0.589             |
| Treated vessel                       |                                  |                                |                         |                       |              |               |                   |
| Left main, n (%)                     | 39 (3.3)                         | 65 (3.8)                       | 86 (3.3)                | 0.478                 | 0.956        | 0.397         | 0.599             |
| LAD, n (%)                           | 684 (57.3)                       | 990 (58.4)                     | 1525 (58.6)             | 0.578                 | 0.468        | 0.899         | 0.762             |
| LCx, n (%)                           | 314 (26.3)                       | 436 (25.7)                     | 738 (28.4)              | 0.730                 | 0.198        | 0.059         | 0.129             |
| RCA, n (%)                           | 476 (39.9)                       | 692 (40.8)                     | 1129 (43.4)             | 0.626                 | 0.047        | 0.101         | 0.078             |
| Extent of CAD                         |                                  |                                |                         |                       |              |               |                   |
| Single-vessel disease, n (%)         | 574 (48.1)                       | 812 (47.9)                     | 1009 (38.8)             | 0.900                 | < 0.001      | < 0.001       | < 0.001           |
| Two-vessel disease, n (%)            | 384 (32.2)                       | 531 (31.3)                     | 885 (34.0)              | 0.626                 | 0.283        | 0.068         | 0.164             |
| ≥ Three-vessel disease, n (%)        | 235 (19.7)                       | 353 (20.8)                     | 709 (27.2)              | 0.482                 | < 0.001      | < 0.001       | < 0.001           |
| Vascular access                      |                                  |                                |                         |                       |              |               |                   |
| Transradial, n (%)                   | 358 (30.0)                       | 500 (29.5)                     | 725 (27.9)              | 0.760                 | 0.248        | 0.306         |                   |
| Transfemoral, n (%)                  | 835 (70.0)                       | 1196 (70.5)                    | 1878 (72.1)             | 0.760                 | 0.172        | 0.248         | 0.306             |
| ACC/AHA lesion type                  |                                  |                                |                         |                       |              |               |                   |
| Type B1, n (%)                       | 133 (11.1)                       | 221 (13.0)                     | 331 (12.7)              | 0.134                 | 0.182        | 0.780         | 0.281             |
| Type B2, n (%)                       | 413 (34.6)                       | 517 (30.5)                     | 841 (32.3)              | 0.019                 | 0.169        | 0.214         | 0.064             |
| Type C, n (%)                        | 560 (46.9)                       | 776 (45.8)                     | 1174 (45.1)             | 0.529                 | 0.293        | 0.684         | 0.572             |
| Pre-PCI TIMI flow grade              |                                  |                                |                         |                       |              |               |                   |
| 0/1, n (%)                           | 671 (56.2)                       | 987 (58.2)                     | 1328 (51.0)             | 0.296                 | 0.003        | < 0.001       | < 0.001           |
| 2/3, n (%)                           | 522 (43.8)                       | 709 (41.8)                     | 1275 (49.0)             | 0.296                 | 0.003        | < 0.001       | < 0.001           |
| IVUS, n (%)                          | 223 (18.7)                       | 391 (23.1)                     | 529 (20.3)              | 0.005                 | 0.254        | 0.033         | 0.012             |
| OCT, n (%)                           | 6 (0.5)                          | 12 (0.7)                       | 16 (0.6)                | 0.633                 | 0.819        | 0.703         | 0.787             |
| FFR, n (%)                           | 10 (0.8)                         | 19 (1.1)                       | 24 (0.9)                | 0.571                 | 0.855        | 0.534         | 0.712             |
| Drug-eluting stents*                 |                                  |                                |                         |                       |              |               |                   |
| ZES, n (%)                           | 364 (30.5)                       | 608 (35.8)                     | 914 (35.1)              | 0.003                 | 0.006        | 0.625         | 0.006             |
| EES, n (%)                           | 604 (50.6)                       | 819 (48.3)                     | 1292 (49.6)             | 0.216                 | 0.570        | 0.399         | 0.447             |
| BESt, n (%)                          | 204 (17.1)                       | 238 (14.0)                     | 342 (13.1)              | 0.024                 | 0.001        | 0.411         | 0.005             |
| Others, n (%)                        | 21 (1.8)                         | 31 (1.8)                       | 55 (2.1)                | 0.893                 | 0.534        | 0.578         | 0.698             |
| Stent diameter (mm)                  | 3.10 ± 0.40                      | 3.07 ± 0.40                    | 3.05 ± 0.40             | 0.075                 | 0.002        | 0.173         | 0.007             |
| Stent length (mm)                    | 27.9 ± 11.9                      | 27.6 ± 12.0                    | 27.6 ± 12.1             | 0.435                 | 0.519        | 0.826         | 0.726             |
| Number of stent                      | 1.47 ± 0.76                      | 1.53 ± 0.84                    | 1.58 ± 0.84             | 0.041                 | < 0.001      | 0.047         | < 0.001           |

Values are means ± SD or numbers (percentages). The p values for continuous data obtained from the analysis of variance. The p values for categorical data from chi-square or Fisher’s exact test. LVEF left ventricular ejection fraction, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, STEMI ST-elevation myocardial infarction, NSTEMI non-STEMI, CPR cardiopulmonary resuscitation, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, HF heart failure, CVA cerebrovascular accident, CK-MB creatine kinase myocardial band, NT-ProBNP N-terminal pro-brain natriuretic peptide, hs-CRP high sensitivity C-reactive protein, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, BBs beta-blockers, ACEs angiotensin converting enzyme inhibitors, ARBs angiotensin receptor blockers, CCBs calcium channel blockers, IRA infarct-related artery, 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., ZES zotarolimus-eluting stent, EES everolimus-eluting stent, BESt: biolimus-eluting stents

* Drug-eluting stents were composed of ZES (Resolute Integrity stent; Medtronic, Inc., Minneapolis, MN), EES (Xience Prime stent, Abbott Vascular, Santa Clara, CA; or Promus Element stent, Boston Scientific, Natick, MA), BESt (BioMatrix Flex stent, Biosensors International, Morges, Switzerland; or Nobori stent, Terumo Corporation, Tokyo, Japan), and others include any other newer-generation drug-eluting stents except for ZES, EES, and BESt.
Percutaneous coronary intervention procedure and medical treatment

Based on the known standard techniques [21], diagnostic coronary angiography and percutaneous coronary intervention (PCI) were performed. The loading doses of antiplatelet agents were as follows: aspirin 200–300 mg with clopidogrel 300–600 mg, ticagrelor 180 mg, or prasugrel 60 mg. All patients were asked to take dual antiplatelet therapy (DAPT) for at least 12 months after PCI. Based on previous reports [22, 23], triple antiplatelet therapy (aspirin + clopidogrel + cilostazol [100 mg twice daily]) was used. The use of DAPT or TAPT was left at the discretion of individual operators.

Study definitions and clinical outcomes

Glycemic levels of the included patients were determined based on glycosylated hemoglobin (HbA1c), FPG, and random plasma glucose (RPG) levels of the patients at the index hospitalization, as well as their medical history. According to the ADA clinical practice recommendations [10], normoglycemia was defined as HbA1c < 5.7% and FPG < 100 mg/dL (5.6 mmol/L), prediabetes as HbA1c 5.7–6.4%, and FPG 100–125 mg/dL (5.6–6.9 mmol/L), and T2DM was defined as either known diabetes for which patients received insulin or antidiabetic treatment, or newly diagnosed diabetes defined as a HbA1c level ≥ 6.5%, FPG ≥ 126 mg/dL (7.0 mmol/L), and/or RPG ≥ 200 mg/dL (11.1 mmol/L). Additionally, if there were some discrepancies between the HbA1c levels and those of FPG or RPG, we prioritized the level of HbA1c. AMI was defined according to the current guidelines [24–27]. A successful PCI was defined as residual stenosis < 30% and thrombolysis in myocardial infarction (TIMI) grade 3 flow for the infarct-related artery (IRA) after the procedure. The primary PCI strategy was performed based on the current guidelines [24, 26]. Early invasive treatment strategy of the patients with non-ST-segment elevation MI (NSTEMI) was defined as a PCI within 24 h after admission [27]. In this study, the primary outcome was the occurrence of major adverse cardiac events (MACE). All-cause death, recurrent myocardial infarction (Re-MI), or any coronary repeat revascularization were included in the MACE. All-cause death was defined as cardiac death (CD) or non-CD. Composites of target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR were included in any repeat revascularization. The definitions of Re-MI, TLR, TVR, and non-TVR were included in our previous publication [28]. The secondary outcome was the occurrence of definite or probable stent thrombosis (ST) [29].

Statistical analysis

For continuous variables, the data were expressed as the mean ± standard deviation. The differences among the three groups were evaluated using analysis of variance or the Jonckheere-Terpstra test, while a post-hoc analysis of the two groups was performed using the Hochberg test or the Dunnett T3 test. For categorical variables, intergroup differences were analyzed using the χ² test or Fisher’s exact test, as appropriate, and data were expressed
as counts and percentages. We tested all variables with 
\( p < 0.1 \), among the three glycemic groups, which were 
included in the univariate analysis. After univariate 
analysis, all variables in the univariate analysis \( (p < 0.05) \) 
were entered into the multivariate Cox regression anal-
ysis. These variables included the following: age, male sex, 
left ventricular ejection fraction (LVEF), systolic blood 
pressure (SBP), STEMI, cardiogenic shock, cardio-
pulmonary resuscitation (CPR) on admission, Killip class 
III/IV, dyslipidemia, previous MI, previous cerebrovascu-
lar accidents (CVA), peak creatine kinase myocardial 
band (CK-MB), N-terminal pro-brain natriuretic peptide 
(NT-ProBNP), serum creatinine, estimated glomeru-
lar filtration rate (eGFR), total cholesterol, high-density 
lipoprotein (HDL)-cholesterol, low-density lipoprotein 
(LDL)-cholesterol, clopidogrel, ticagrelor, beta-blocker, 
angiotensin-converting enzyme inhibitor (ACEI), angio-
tensin receptor blocker (ARB), lipid-lowering agent, 
single-vessel disease, more than three diseased vessels, 
American College of Cardiology/American Heart Associ-
ation (ACC/AHA) type B2/C lesions, pre-PCI TIMI flow 
grade 2/3, and mean the number of deployed stents per 
patient. Various clinical outcomes were estimated using 
the Kaplan-Meier method, and intergroup differences 
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 
SPSS version 20 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

Baseline characteristics of the study population are 
shown in Table 1. The mean value of the LVEF was more 
than 50%, which was the highest in the prediabetes group 
group B). The normoglycemia group (group A) included 
the oldest mean patient age of all groups and most men. 
Group A had the highest number of PCI within 24 h, Kil-
lip class I, single-vessel disease, and the highest prescrip-
tion rates of ticagrelor, prasugrel, and ACEI. Moreover, 
the mean blood levels of HDL-cholesterol and eGFR were 
the highest in group A. Group B had the highest number of 
NSTEMI, current smokers, pre-PCI TIMI flow grade 
0/1, and the use of intravascular ultrasound; the high-
est peak CK-MB, total cholesterol, and LDL-cholesterol. 
The T2DM group (group C) had the highest number of 
NSTEMI, Killip class III, dyslipidemia, previous MI, PCI, 
CABG, heart failure, and CVA; more than three diseased 
vessels; and pre-PCI TIMI flow grade 2/3; the highest 
mean values of BMI, SBP, NT-ProBNP, serum creatinine, 
and triglycerides; the highest prescription rates of clopi-
dogrel, cilostazole, ARB, and calcium channel blocker. 
However, the types of IRA and the number of treated 
vessels were not significantly different among the three 
groups (group A vs. B vs. C).

Clinical outcomes

Table 2 and Fig. 2 a-2g show the cumulative incidences 
of major clinical outcomes during the 2-year follow-
up period. After adjustment, the cumulative incidence of 
MACE (Fig. 2a) was significantly higher in group B 
(adjusted HR [aHR], 1.373; 95% confidence interval [CI], 
1.051–1.795; \( p = 0.020 \)) and in group C (aHR, 1.479; 95% 
CI, 1.149–1.904; \( p = 0.002 \)) than in group A (Fig. 2a). 
However, the cumulative incidence of MACE between 
groups B and C were similar (aHR: 1.112, 95% CI: 0.911– 
1.259; \( p = 0.297 \)). The cumulative incidence of all-cause 
death or MI (Fig. 2e) was also significantly higher in 
group B (aHR: 1.436, 95% CI: 1.052–1.961; \( p = 0.022 \)) and 
in group C (aHR: 1.647, 95% CI: 1.231–2.105; \( p = 0.001 \)) 
than in group A. However, the cumulative incidence of 
all-cause death or MI between groups B and C was simi-
lar (aHR: 1.170; 95% CI; 0.932–1.470; \( p = 0.176 \)). Addi-
tionally, the cumulative incidence of all-cause death 
(Fig. 2b, aHR: 1.666; 95% CI: 1.193–2.327; \( p = 0.003 \) was 
significantly higher in group C than in group A. However, 
the cumulative incidence of ST (Fig. 2g, was not signifi-
cantly different among the three glycemic groups. More-
over, the cumulative incidences of all-cause death (Fig. 2b, 
aHR: 1.232, 95% CI: 0.945–1.608; \( p = 0.124 \)), CD (Fig. 2c, 
aHR: 1.108, 95% CI: 0.813–1.510; \( p = 0.518 \)), Re-MI 
(Fig. 2d, aHR: 1.127, 95% CI: 0.730–1.737; \( p = 0.590 \)), 
and repeat revascularization (Fig. 2f, aHR: 1.018; 95% 
CI: 0.716–1.449; \( p = 0.920 \) were not significantly differ-
ent between groups B and C. Table 3 shows independent 
predictors for MACE at 2years. Age, male sex, decreased 
LVEF (<40%), STEMI, cardiogenic shock, CPR on ad-
mission, Killip class III/IV, NT-ProBNP, decreased eGFR 
(<60 mL/min/1.73m²), ticagrelor, β-blocker, ACEI, ARB, 
lipid-lowering agent, multivessel disease, and ACC/AHA 
type B2/C lesions were significant independent predic-
tors of MACE in our study.

Discussion

The main findings of this study are as follows: (1) The 
cumulative incidences of MACE, all-cause death, CD, 
Re-MI, all-cause death or MI, and any repeat revascu-
larization between groups B (prediabetes) and C (T2DM) 
were not significantly different. (2) The cumulative inci-
dence of ST was not significantly different among the 
three glycemic groups; (3) The cumulative incidences 
of MACE and all-cause death or MI in groups B and C 
were significantly higher than those in group A (normo-
glycemia); (4) The cumulative incidence of all-cause death 
in group C was significantly higher than that in group A; 
(5) Age, male sex, decreased LVEF, STEMI, cardiogenic
Table 2  Comparison of clinical outcomes at 2 years

| Outcomes                        | Group A Normoglycemia (n = 1193) | Group B Prediabetes (n = 1696) | Log-Rank                      | Unadjusted HR (95% CI) | p value | Adjusted* HR (95% CI) | p value |
|---------------------------------|----------------------------------|--------------------------------|--------------------------------|------------------------|---------|-----------------------|---------|
| MACE                            | 85 (8.0)                         | 163 (10.2)                     | 0.038                          | 1.319 (1.015–1.714)    | 0.039   | 1.373 (1.051–1.795)   | 0.020   |
| All-cause death                 | 49 (4.4)                         | 90 (5.6)                       | 0.191                          | 1.260 (0.890–1.785)    | 0.192   | 1.364 (0.952–1.955)   | 0.091   |
| Cardiac death                   | 37 (3.3)                         | 68 (4.2)                       | 0.240                          | 1.270 (0.851–1.896)    | 0.242   | 1.285 (0.847–1.949)   | 0.238   |
| Re-MI                           | 19 (2.0)                         | 34 (2.2)                       | 0.493                          | 1.217 (0.694–2.133)    | 0.494   | 1.262 (0.708–2.247)   | 0.430   |
| All-cause death or MI           | 63 (5.9)                         | 124 (7.7)                      | 0.050                          | 1.352 (0.998–1.831)    | 0.051   | 1.436 (1.052–1.961)   | 0.022   |
| Any repeat revascularization    | 26 (2.7)                         | 53 (3.5)                       | 0.190                          | 1.367 (0.855–2.186)    | 0.191   | 1.381 (0.857–2.225)   | 0.184   |
| Stent thrombosis (probable or definite) | 3 (0.3)                     | 9 (0.5)                        | 0.250                          | 2.114 (0.572–7.809)    | 0.261   | 2.257 (0.600–8.487)   | 0.228   |
| Any repeat revascularization    | 26 (2.7)                         | 94 (4.2)                       | 0.031                          | 1.605 (1.040–2.479)    | 0.033   | 1.269 (0.805–2.002)   | 0.305   |
| Stent thrombosis (probable or definite) | 85 (8.0)                     | 306 (12.5)                     | <0.001                         | 1.620 (1.274–2.061)    | <0.001  | 1.479 (1.149–1.904)   | 0.002   |
| All-cause death                 | 49 (4.4)                         | 186 (7.5)                      | 0.001                          | 1.710 (1.248–2.342)    | 0.001   | 1.666 (1.193–2.327)   | 0.003   |
| Cardiac death                   | 37 (3.3)                         | 130 (5.2)                      | 0.012                          | 1.592 (1.105–2.293)    | 0.013   | 1.474 (0.998–2.178)   | 0.051   |
| Re-MI                           | 19 (2.0)                         | 66 (2.9)                       | 0.091                          | 1.547 (0.929–2.577)    | 0.094   | 1.330 (0.781–2.265)   | 0.294   |
| All-cause death or MI           | 63 (5.9)                         | 243 (9.9)                      | <0.001                         | 1.740 (1.319–2.296)    | <0.001  | 1.647 (1.231–2.205)   | 0.001   |
| Any repeat revascularization    | 26 (2.7)                         | 94 (4.2)                       | 0.031                          | 1.605 (1.040–2.479)    | 0.033   | 1.269 (0.805–2.002)   | 0.305   |
| Stent thrombosis (probable or definite) | 3 (0.3)                     | 20 (0.8)                        | 0.057                          | 3.063 (0.910–10.31)    | 0.071   | 2.185 (0.618–7.727)   | 0.225   |

* Adjusted by age, male, LVEF, SBP, STEMI, cardiogenic shock, CPR on admission, Killip class III/IV, dyslipidemia, previous MI and CVA, peak CK-MB, NT-ProBNP, serum creatinine, eGFR, total cholesterol, HDL-cholesterol, LDL-cholesterol, clopidogrel, ticagrelor, BB, ACEI, ARB, lipid lowering agents, single-vessel disease, ≥ three-vessel disease ACC/AHA type B2/C lesions, pre-PCI TIMI flow grade 2/3, and number of stent

MACE major adverse cardiac events, Re-MI recurrent myocardial infarction, LVEF left ventricular ejection fraction, SBP systolic blood pressure, STEMI ST-segment elevation myocardial infarction, CPR cardiopulmonary resuscitation, MI myocardial infarction, CVA cerebrovascular events, CK-MB creatine kinase myocardial band, NT-ProBNP N-terminal pro-brain natriuretic peptide, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, BB beta-blocker, ACEI angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, PCI percutaneous coronary intervention, TIMI Thrombolysis In Myocardial Infarction

shock, CPR on admission, Killip class III/IV, NT-ProBNP, decreased eGFR, ticagrelor, β-blocker, ACEI, ARB, lipid-lowering agent, multivessel disease, and ACC/AHA type B2/C lesions were significant independent predictors for MACE.

In normal aging, there is a 2 mg/dL/decade rise in FPG [30], older adults have a higher chance of developing diabetes than younger adults [31, 32]. A meta-analysis reported that the pooled incidence of diabetes was 47.4, 45.5, and 70.4 per 1000 person-years among subjects with IFG, IGT, and IGT+IGT respectively [33]. Moreover, although prediabetes is regarded as an intermediate metabolic state from normoglycemia to DM [34], a higher absolute risk of complications was reported in older adults with diabetes than in younger adults [4, 35], and prediabetes is related to macrovascular complications that are recognized in individuals with overt DM [34, 36]. Therefore, without any intervention, prediabetes often progresses to DM and is associated with an increased risk of cardiovascular mortality [37]. However, the prognostic implications of prediabetes in older adults are less well understood. Hence, in this study, we compared the 2-year major clinical outcomes between the prediabetes and T2DM groups in older adults with AMI. In our study, the cumulative incidences of primary and secondary outcomes were not significantly different between the prediabetes and T2DM groups. Both the prediabetes and T2DM groups showed worse clinical
Fig. 2 Kaplan-Meier analysis for the MACE (a), all-cause death (b), cardiac death (c), Re-MI (d), All-cause death or MI (e), any repeat revascularization (f), and stent thrombosis (g) during a 2-year follow-up period. MACE major adverse cardiac events, Re-MI recurrent myocardial infarction, T2DM type 2 diabetes mellitus.
outcomes than those in the normoglycemia group. Our results are consistent with the findings from recent reports [13, 14, 38]. In our study, MACE occurred in 8.0 and 10.2% of patients with normoglycemia and with prediabetes (aHR: 1.373, 95% CI: 1.051–1.795; \( p = 0.020 \)), and this result was similar to that reported by Chatto-
padhyay et al. [39] In their 1056 MI survivals [39], the HR for MACE between patients with or without prediabetes was 1.43 (95% CI: 1.03–1.98; \( p = 0.001 \)). In our study, the cumulative incidences of all-cause death, CD, and Re-MI were not significantly different between normoglycemia and prediabetes. However, the net outcome (the cumulative incidence of all-cause death or MI) was significantly higher in the prediabetes group than in the normoglycemia group (aHR: 1.436; 95% CI: 1.052–1.961; \( p = 0.022 \)) (Table 2). This higher cumulative incidence of all-cause death or MI in the prediabetes group was related to a higher cumulative incidence of MACEs in this group. A possible explanation for these results may be related to hyperglycemia itself [40]. Patients with T2DM have a risk of death two times that of individuals without diabetes [41]. In our study, although the aHR for all-cause death was less than two times, the aHR for all-cause death was significantly higher in the T2DM group than in the normoglycemia group (aHR: 1.666; 95% CI: 1.193–2.327; \( p = 0.003 \)). Other possible pathological mechanisms related to the worse clinical outcomes of hyperglycemia in patients with AMI include elevated levels of free fatty acids (which may cause cardiac arrhythmia), insulin resistance, impaired myocardial glucose utilization, microvascular dysfunction, and vascular inflammation [42, 43].

Chronically elevated blood glucose leads to pan-vascular damage, which could present in the prediabetes state, and its severity is associated with the onset of hyperglycemia [44, 45]. As a result, the time delay for hyperglycemia to reach the currently defined cut-off levels for the diagnosis of DM and intervention may cause vascular damage to advance and become irreversible [46]. Hence, in the case of older adults with

### Table 3: Independent predictors for MACE

| Variables | Unadjusted HR (95% CI) | p value | Adjusted HR (95% CI) | p value |
|-----------|-------------------------|---------|----------------------|---------|
| Group A vs. Group B | 1.319 (1.015–1.714) | 0.039 | 1.363 (1.102–1.815) | 0.016 |
| Group A vs. Group C | 1.620 (1.274–2.061) | <0.001 | 1.455 (1.135–1.864) | 0.003 |
| Group B vs. Group C | 1.231 (1.018–1.488) | 0.032 | 1.099 (0.902–1.339) | 0.349 |
| Age | 1.019 (1.005–1.033) | 0.007 | 1.315 (1.109–1.666) | <0.001 |
| Male | 1.175 (0.994–1.389) | 0.058 | 1.198 (1.032–1.390) | 0.017 |
| LVEF < 40% | 2.396 (1.994–2.880) | <0.001 | 1.926 (1.592–2.330) | <0.001 |
| STEMI | 1.182 (1.001–1.397) | 0.049 | 1.289 (1.083–1.534) | 0.004 |
| Cardiogenic shock | 1.853 (1.378–2.491) | <0.001 | 1.626 (1.025–2.031) | 0.005 |
| CPR on admission | 4.681 (3.726–5.881) | <0.001 | 3.746 (2.948–4.760) | <0.001 |
| Killip class III/IV | 2.840 (2.459–3.280) | <0.001 | 1.550 (1.312–1.830) | <0.001 |
| Hypertension | 1.097 (0.922–1.306) | 0.295 | 1.002 (0.837–1.199) | 0.984 |
| NT-ProBNP | 1.000 (0.999–1.001) | <0.001 | 1.002 (1.000–1.003) | 0.011 |
| eGFR < 60 mL/min/1.73m² | 1.783 (1.501–2.117) | <0.001 | 1.415 (1.319–1.766) | <0.001 |
| Clopidogrel | 1.037 (0.858–1.254) | 0.705 | 1.195 (0.993–1.532) | 0.159 |
| Ticagrelor | 1.366 (1.035–1.804) | 0.028 | 1.562 (1.095–2.282) | 0.014 |
| Cilostazol | 1.275 (1.016–1.600) | 0.036 | 1.157 (0.919–1.457) | 0.215 |
| Beta-blocker | 2.599 (2.189–3.087) | <0.001 | 1.676 (1.379–2.037) | <0.001 |
| ACEI | 2.154 (1.808–2.566) | <0.001 | 1.853 (1.550–2.151) | <0.001 |
| ARB | 1.020 (0.884–1.176) | 0.788 | 1.195 (1.003–1.423) | 0.046 |
| Lipid lowering agent | 2.588 (2.167–3.089) | <0.001 | 1.851 (1.525–2.246) | <0.001 |
| Single-vessel disease | 1.426 (1.196–1.699) | <0.001 | 1.087 (0.881–1.343) | 0.436 |
| Multivessel disease | 1.434 (1.202–1.710) | <0.001 | 1.249 (1.032–1.510) | 0.022 |
| ACC/AHA type B2/C | 1.274 (1.031–1.575) | 0.025 | 1.363 (1.101–1.688) | 0.005 |
| Pre-PCI TIMI flow grade 2/3 | 1.023 (0.901–1.162) | 0.725 | 1.071 (0.936–1.225) | 0.319 |
| Number of stent | 1.155 (1.054–1.266) | 0.002 | 1.089 (0.982–1.207) | 0.105 |

HR: hazard ratio, CI: confidence interval, Group A: normoglycemia, Group B: prediabetes, Group C: T2DM, LVEF: left ventricular ejection fraction, STEMI: ST-segment elevation myocardial infarction, eGFR: estimated glomerular filtration rate, CPR: cardiopulmonary resuscitation, ACC/AHA: American College of Cardiology/American Heart Association, IVUS: intravascular ultrasound
prediabetes, the more intensive treatment of significant risk factors for MACE follows the same or similar guidelines established for patients with T2DM, and a diabetes screening for these patients (≥ 65 years) to identify those with prediabetes or T2DM may be beneficial. In the Steno-2 trial, intensified intervention including multiple risk factors reduced the risk of cardiovascular events by 50% among patients with T2DM [47]. From these points of view, our findings emphasize that the long-term prognosis of older adults with prediabetes is worse than that of normoglycemia, and a prediabetes group is an important group for cardiologists [48]. However, in this retrospective cohort, patients in the normoglycemia group had a relatively low-risk (e.g., highest number of PCI within 24 h, Killip class I, and single-vessel disease, and the largest diameter of a deployed stent) than those included in the prediabetes or T2DM groups. Therefore, although we attempted to adjust the various variables through multivariate analysis, we speculate that these different baseline characteristics may play an important role in explaining the relatively low MACE and all-cause death or MI rate in the normoglycemia group. There has been some data as to clinical outcomes between prediabetes and T2DM [49]. Moreover, it is well known about older age is a strong predictor of mortality in AMI patients receiving newer generation DES [50]. Importantly, hyperglycemia including prediabetes and T2DM in older AMI patients showed worse 2-year clinical outcomes than those in the normoglycemia group in this study. Moreover, the primary outcome between the prediabetes and T2DM groups was not significantly different. Hence, prediabetes in older AMI patients is not a benign condition. Our results suggest that it is important for interventional cardiologists to screen for and manage prediabetes in order to reduce the incidence of MACE in older AMI patients. In addition to lifestyle modifications, closer follow-ups and intensified medical treatment are needed to reduce the risk of developing DM and secondarily prevent clinically apparent coronary artery disease [13].

Despite the relatively higher prevalence of prediabetes and DM in older adults, older individuals and/or those with multiple comorbidities have often been excluded from randomized controlled trials [51, 52]. Even though the size of the study population may be insufficient to provide a firm conclusion, more than 50 community and teaching hospitals in South Korea participated in this nationwide registry analysis. Moreover, previous studies [31, 34, 37, 39–42, 46, 47] were not confined to patients with AMI who received newer-generation DESs. Hence, our findings that the long-term prognosis of older adults with prediabetes is worse than that of normoglycemia, and individuals at prediabetes state are an important group to cardiologists [48] in the era of newer-generation DES.

This study has some limitations. First, because our study was performed based on registry data, there may have been some under-reporting and/or missing data. Second, in the study, glycemic status was determined by the HbA1c, FPG, and RPG levels of the patients at the index hospitalization, as well as their medical history. To determine glycemic status more accurately, other diagnostic tests for diabetes, including OGTTs, are needed for a finer classification. However, this information was not included in the registry data. Therefore, this is a major shortcoming of this study. Third, the duration and type of antidiabetic treatment are major determinants of PCI in patients with prediabetes or diabetes. However, we did not precisely know the adherence or non-adherence rate of enrolled patients to antidiabetic drugs during the follow-up period, owing to the limitations of the registry study. Moreover, the lack of information concerning the duration of T2DM before enrollment and the degree of glycemic control of the participants during the follow-up period might constitute an additional bias in this study. Fourth, the 2-year follow-up period of this study was relatively short for determining the long-term major clinical outcomes, and multivariable analysis was performed to strengthen our results, and some variables not included in the KAMIR may have affected the study outcomes. Finally, in this study, South Korean patients alone were enrolled; careful caution is needed to interpret the current results, especially among other ethnicities in different parts of the world.

Conclusions

In conclusion, in this retrospective study, regarding the cumulative incidences of MACE and all-cause death or MI, the 2-year clinical outcomes of the patients with prediabetes and T2DM in older adults were worse than those in normoglycemia patients in the era of newer-generation DES. However, the primary and secondary clinical outcomes were similar between the prediabetes and T2DM groups in older adults. Hence, more aggressive efforts should be made to reduce MACE and all-cause death or MI in older adults with diabetes. However, to confirm these results, further large-scale and long-term follow-up studies are needed.

Abbreviations

AMI: Acute myocardial infarction; KAMIR: Korea AMI registry; PCI: Percutaneous coronary intervention; T2DM: Type 2 diabetes mellitus; MACE: Major adverse cardiac events; DES: Drug-eluting stent; Re-MI: Recurrent myocardial infarction; LVEF: Left ventricular ejection fraction; eGFR: Estimated glomerular filtration rate; Hba1c: Hemoglobin A1c.
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Authors’ contributions
Y.H.K. and A.-Y.H. researched data and wrote the manuscript. Y.H.K., A.-Y.H., B.-K.K., J.-S.K., S.-H.P., B.G.K., S.K., M.-K.H., and Y.J. contributed to study design. M.H.J., B.-K.K., S.-H.J., S.K., C.-A.M., J.-Y.K., G.-D.C., M.-K.H., and Y.J. contributed to the collection research data. Y.H.K., A.-Y.H., S.-H.J., and S.K. contributed to data analysis and edited the manuscript. Y.H.K., M.H.J., D.C., M.-K.H., and Y.J. contributed to provide intellectual inputs for the discussion. Y.H.K., A.-Y.H., S.-H.J., and S.K. contributed to data analysis and writing the manuscript.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Declarations
Ethics approval and consent to participate
This study was approved by the ethics committee of each participating center and the Chonnam National University Hospital Institutional Review Board ethics committee (CNUH-2011-172) according to the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to inclusion in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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