ABSTRACT

BACKGROUND Diabetes is a well-known risk factor for adverse outcomes after coronary revascularization.

OBJECTIVES This study sought to determine high-risk subgroups in whom the excess risks of diabetes relative to nondiabetes are particularly prominent and thus may benefit from more aggressive interventions.

METHODS The study population consisted of 39,427 patients (diabetes: n = 15,561; nondiabetes: n = 23,866) who underwent first percutaneous coronary intervention (n = 33,144) or coronary artery bypass graft (n = 6,283) in the pooled CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Graft) registry. The primary outcome measure was major adverse cardiovascular and cerebral endpoints (MACCE), which was defined as a composite of all-cause death, myocardial infarction, and stroke.

RESULTS With median follow-up of 5.6 years, diabetes was associated with significantly higher adjusted risks for MACCE. The excess adjusted risks of diabetes relative to nondiabetes for MACCE increased with younger age (64 years: adjusted HR: 1.30; 95% CI: 1.19-1.41; P < 0.001; 64-73 years: adjusted HR: 1.24; 95% CI: 1.16-1.33; P < 0.001; >73 years: adjusted HR: 1.17; 95% CI: 1.10-1.23; P < 0.001; Pinteraction < 0.001), mainly driven by greater excess adjusted mortality risk of diabetes relative to nondiabetes in younger tertile. No significant interaction was observed between adjusted risk of diabetes relative to nondiabetes for MACCE and other subgroups such as sex, mode of revascularization, and clinical presentation of acute myocardial infarction.

CONCLUSIONS The excess risk of diabetes relative to nondiabetes for MACCE was profound in the younger population. This observation suggests more aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in younger patients. (JACC: Asia 2022;2:294–308) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Despite recent advances in the treatment of diabetes, diabetes remains an established risk factor for adverse macrovascular and microvascular events in the general population, as well as in patients with either established atherosclerosis or significant risk factors for atherosclerosis. Cardiovascular disease is a leading cause of death in patients with diabetes, reinforcing the need for aggressive cardiovascular risk reduction in this population, especially among those who already have atherosclerotic cardiovascular disease. Coronary revascularization is often needed in patients with diabetes, and it is well known that patients with diabetes, compared with those without, have higher risk for adverse cardiovascular events after coronary revascularization. However, it remains unclear whether there are some patient subgroups in whom the excess risks of diabetes relative to nondiabetes are particularly prominent for adverse clinical outcomes after coronary revascularization and thus may benefit from more aggressive interventions for secondary prevention. Therefore, we aimed to identify the factors that modify the cardiovascular and noncardiovascular risk of diabetes relative to nondiabetes after coronary revascularization with percutaneous coronary intervention (PCI) or with coronary artery bypass graft (CABG) in a large-scale Japanese pooled population.

METHODS

STUDY POPULATION. The CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) PCI/CABG registry cohorts 1, 2, and 3 are a series of physician-initiated, non-company-sponsored, multicenter registries enrolling consecutive patients who underwent first coronary revascularization with PCI or CABG in Japan. We enrolled only patients with stable coronary artery disease in cohort 1, excluding those with acute myocardial infarction (AMI) within a week before the index procedure. Cohort 1 enrolled 9,877 patients from 21 centers between January 1, 2000, and December 31, 2002, in the bare-metal stent era. Cohort 2 enrolled 15,939 patients from 26 centers between January 1, 2005, and December 31, 2007, after the introduction of drug-eluting stents in 2004. Cohort 3 enrolled 14,927 patients from 22 centers between January 1, 2011, and December 31, 2013, after the approval of new-generation drug-eluting stents in 2010.
We pooled the 3 cohorts with a total of 40,743 patients. From the pooled population, we excluded 1,093 who had undergone combined non-coronary surgery, 207 patients who refused to participate in the registry, and 4 patients in cohort 1 who presented with AMI (violation for the inclusion criteria). After further excluding 12 patients with unknown diabetes status, the final study population consisted of 39,427 patients (15,561 patients with diabetes and 23,866 patients without diabetes) of whom 33,144 patients underwent PCI and 6,283 patients underwent CABG (Figure 1). For the subgroup

(Supplemental Appendix A).
analysis stratified by the clinical presentation of AMI and non-AMI, we excluded 9,329 patients from cohort 1 and obtained the data set of 30,098 patients (11,909 patients with diabetes and 18,189 patients without diabetes) (Figure 1).

The relevant ethics committees in all the participating centers approved the study protocol. Because enrollment was retrospective, written informed consent from the patients was waived; however, we excluded the 207 patients who refused to participate in the study when contacted for follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

DEFINITIONS AND OUTCOME MEASURES. The definitions for baseline characteristics were consistent across the 3 cohorts. Patients with diabetes were defined as those receiving treatment with oral hypoglycemic agents or insulin, those with prior clinical diagnosis of diabetes, those with hemoglobin A1c levels of ≥6.5%, and those with nonfasting blood glucose levels of ≥200 mg/dL. Hemoglobin A1c levels were expressed in National Glycohemoglobin Standardization Program percentages. Left ventricular ejection fraction was measured either by left ventriculography or echocardiography. Prior stroke was defined as an ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours. Peripheral vascular disease was regarded as present when carotid, aortic, or other peripheral vascular diseases were being treated or when affected patients were scheduled for surgical or endovascular interventions. Renal function was expressed as estimated glomerular filtration rate and calculated according to the Modification of Diet in Renal Disease formula modified for Japanese patients. High-intensity statin therapy was defined as atorvastatin doses of ≥20 mg, fluvastatin doses of ≥40 mg, pitavastatin doses of ≥4 mg, rosuvastatin doses of ≥10 mg, or simvastatin doses of ≥20 mg.

The primary outcome measure in the present study were major adverse cardiovascular and cerebral endpoints (MACCE), defined as a composite of all-cause death, myocardial infarction (MI), and stroke. We also assessed a respective endpoint of all-cause death, cardiovascular death, noncardiovascular death, MI, stroke, target vessel revascularization (TVR), any coronary revascularization, and heart failure hospitalization. The definitions for outcome measures were consistent across the 3 cohorts. Death was regarded as cardiac in origin, unless obvious noncardiac causes could be identified; thus, death from an unknown cause and any death during the index hospitalization for coronary revascularization were regarded as cardiac death. Cardiovascular death included cardiac death and other death related to stroke, renal disease, and vascular disease. MI was adjudicated according to the ARTS (Arterial Revascularization Therapies Study) definition in which only Q-wave MI was regarded as myocardial infarction.

| TABLE 1 Baseline Characteristics: Diabetes Versus Nondiabetes |
|---------------------------------|-----------------|-----------------|---------|
|                                  | Diabetes (n = 15,561) | Nondiabetes (n = 23,866) | P Value |
|---------------------------------|-----------------|-----------------|---------|
| **Clinical characteristics**     |                 |                 |         |
| Age, y                          | 67.9 ± 10.0     | 68.8 ± 11.2     | <0.001  |
| Age, tertiles<sup>1</sup>        |                 |                 | <0.001  |
| ≥64 y                           | 5,419 (34.8)    | 7,835 (32.8)    |         |
| 64-73 y                         | 5,377 (34.6)    | 7,194 (30.1)    |         |
| >73 y                           | 4,765 (30.6)    | 8,837 (37.0)    |         |
| Men<sup>2</sup>                 | 11,163 (71.7)   | 17,387 (72.9)   | 0.02    |
| Body mass index, kg/m<sup>2</sup> | 24.1 ± 3.6     | 23.5 ± 3.4      | <0.001  |
| Body mass index ≥25.0 kg/m<sup>2</sup> | 5,451 (35.7) | 7,010 (30.1) | <0.001  |
| Acute myocardial infarction<sup>3</sup> | 3,579 (23.0) | 6,823 (28.6)   | <0.001  |
| ST-segment elevation myocardial infarction | 2,791 (17.9) | 5,521 (23.1) | <0.001  |
| Hypertension<sup>4</sup>        | 12,666 (81.4)   | 18,548 (77.7)   | <0.001  |
| Diastolic hypertension<sup>4</sup> | 7.5 ± 1.5    | 5.7 ± 0.4       | <0.001  |
| Diabetes mellitus on oral antidiabetes | 9,501 (61.1) | 0 (0)          |         |
| Diabetes mellitus on insulin therapy | 3,519 (22.7) | 0 (0)          |         |
| Current smoking<sup>5</sup>     | 4,331 (28.0)    | 6,903 (29.1)    | 0.02    |
| eGFR, mL/min/1.73 m<sup>2</sup> | 62.9 ± 28.8     | 66.1 ± 26.2     | <0.001  |
| eGFR <30 mL/min/1.73 m<sup>2</sup> without dialysis<sup>6</sup> | 952 (6.1) | 831 (3.5) | <0.001  |
| Dialysis<sup>7</sup>            | 1,027 (6.6)     | 684 (2.9)       | <0.001  |
| Left ventricular ejection fraction, % | 58.2 ± 13.9 | 60.0 ± 13.0     | <0.001  |
| Mitral regurgitation grade ≥3/4 | 663 (5.1)       | 1,007 (5.1)     | 1.00    |
| Prior myocardial infarction<sup>8</sup> | 2,712 (17.4) | 3,284 (13.8) | <0.001  |
| Prior stroke<sup>9</sup>        | 2,308 (14.8)    | 2,772 (11.6)    | <0.001  |
| Peripheral vascular disease<sup>10</sup> | 1,701 (10.9) | 1,971 (8.3) | <0.001  |
| Atrial fibrillation<sup>11</sup> | 1,328 (8.5) | 2,175 (9.1) | 0.0503  |
| Anemia (hemoglobin <11.0 g/dL)<sup>12</sup> | 2,493 (16.0) | 2,608 (10.9) | <0.001  |
| Chronic obstructive pulmonary disease<sup>13</sup> | 434 (2.8) | 922 (3.9) | <0.001  |
| Liver cirrhosis<sup>14</sup>    | 508 (3.3)       | 590 (2.5)       | <0.001  |
| Malignancy<sup>15</sup>        | 1,571 (10.1)    | 2,345 (9.8)     | 0.39    |
| **Procedural characteristics**  |                 |                 |         |
| Number of target lesions or anastomoses | 1.8 ± 1.1 | 1.6 ± 0.9       | <0.001  |
| Target of left main coronary artery | 1,500 (9.6) | 1,966 (8.2) | <0.001  |
| Target of proximal LAD | 9,756 (67.7) | 14,281 (63.4) | <0.001  |
| Target of left main coronary artery | 2,988 (20.7) | 3,835 (17.0) | <0.001  |
| Multivessel disease<sup>16</sup> | 1,500 (9.6) | 1,966 (8.2) | <0.001  |
| Percutaneous coronary intervention | 12,481 (80.2) | 20,663 (86.6) | <0.001  |
| Total number of stents | 1.8 ± 1.4 | 1.6 ± 1.2 | <0.001  |
| Total stent length, mm | 41.5 ± 32.3 | 36.0 ± 28.0 | <0.001  |
| Stent use | 11,531 (92.4) | 18,926 (91.6) | 0.01 |
| Drug-eluting stent use | 6,924 (60.0) | 10,198 (53.9) | <0.001  |
| New-generation drug-eluting stent use | 4,048 (35.1) | 6,135 (32.4) | <0.001  |
| Coronary artery bypass graft | 3,080 (23.3) | 3,023 (14.3) | <0.001  |
| Internal thoracic artery use | 2,970 (96.4) | 3,031 (94.6) | <0.001  |
| Off-pump surgery | 1,428 (46.4) | 1,463 (45.7) | 0.61 |

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when it occurred within 7 days of the index procedure.\textsuperscript{11} Stroke was defined as an ischemic or hemorrhagic stroke with neurological symptoms lasting $\geq$24 hours. TVR was defined as either PCI or CABG performed for restenosis, thrombosis, de novo disease progression of the target vessel, or graft failure. Any coronary revascularization was defined as either PCI or CABG for any reasons. Heart failure hospitalization was defined as hospitalization for worsening heart failure requiring intravenous drug therapy.

**DATA COLLECTION FOR BASELINE CHARACTERISTICS AND FOLLOW-UP EVENTS.** Clinical, angiographic, and procedural data were collected from the hospital charts or hospital databases according to the predefined definitions by experienced clinical research coordinators from the Research Institute for Production Development (Kyoto, Japan) (Supplemental Appendix B). Follow-up data were collected from the hospital charts or obtained through contact with patients, their relatives, or the referring physicians. Clinical events after the index procedure were assessed as follow-up events, except for scheduled staged coronary revascularization procedures performed within 3 months of the index procedure, which were regarded as part of the index procedure. The clinical event committee determined whether any incidents were clinical events (Supplemental Appendix C).

**STATISTICAL ANALYSIS.** Data for categorical variables were calculated as numbers and percentages and were compared using chi-square test with Yates’ continuity correction. Data for continuous variables were expressed as mean $\pm$ SD or as median (IQR) and were compared using Student’s $t$-test or the Wilcoxon rank-sum test. HRs and their 95% CIs were calculated using univariate or multivariable Cox proportional hazard models to estimate the risk of diabetes relative to nondiabetes on the clinical outcome measures. Clinically relevant variables listed in Table 1 were simultaneously included in the multivariable models as the explanatory variables to adjust for the baseline characteristics. The enrollment periods of cohorts 1, 2, and 3 were also included as a stratification variable to fit separate baseline hazard functions. We explored the 4 potential modifiers of the risk of diabetes relative to nondiabetes for clinical outcome measures in the subgroup analyses (age tertiles, sex, mode of revascularization of PCI or CABG, and clinical presentation of AMI or non-AMI). The potential risk modifiers were arbitrarily selected based on clinical relevance. In the subgroup analyses, we added the interaction variables in the multivariable models. We calculated a type III sum of squares to estimate the effect of interactions. Because we did not enroll patients with AMI in cohort 1, we excluded those who were included in cohort 1 from subgroup analysis of clinical presentation of AMI or non-AMI. To confirm the interaction between diabetes status and mode of revascularization in patients with complex coronary artery disease, the subgroup analysis for the mode of revascularization was also conducted in patients with complex coronary artery disease (defined as either multivessel disease or left main coronary artery disease) as a sensitivity analysis. As another sensitivity analysis, we stratified the patients according to the enrollment periods of cohorts 1, 2, and 3. The explanatory variable of AMI was removed in the models for patients enrolled in cohort 1.

Two-sided $P$ values of $<0.05$ indicated statistical significance. We used the R statistical software (version 4.0.2, R Foundation for Statistical Computing) to analyze all the data.

**RESULTS**

**BASELINE CHARACTERISTICS.** In comparison with patients without diabetes, patients with diabetes were younger (age $67.9 \pm 10.0$ years vs $68.8 \pm 11.2$ years; $P < 0.001$), less likely to be men (71.9% vs 72.9%; $P = 0.02$), and less often presented with AMI.
FIGURE 2 Kaplan-Meier Curves for the Clinical Outcome Measures: Diabetes Versus Nondiabetes

A. Major adverse cardiovascular and cerebral endpoints

B. All-cause death

C. Cardiovascular death

D. Noncardiovascular death

E. Myocardial infarction

F. Stroke

G. Target vessel revascularization

H. Any coronary revascularization

I. Heart failure hospitalization

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(23.0% vs 28.6%; *P* < 0.001). Patients with diabetes more often had comorbidities such as hypertension (81.4% vs 77.7%; *P* < 0.001), chronic renal failure (estimated glomerular filtration rate of <30 mL/min/1.73 m² without dialysis: 6.1% vs 3.5%; dialysis: 6.6% vs 2.9%; *P* < 0.001), heart failure (19.6% vs 15.7%; *P* < 0.001), and anemia (16.0% vs 10.9%; *P* < 0.001). The previous history of cardiovascular events such as MI (17.4% vs 13.8%; *P* < 0.001) and stroke (14.8% vs 11.6%; *P* < 0.001) were more prevalent in patients with diabetes than in those without diabetes (Table 1). Regarding procedural characteristics, multivessel disease was present in 69.5% of patients with diabetes and in 55.8% of patients without diabetes (*P* < 0.001). PCI was performed in 80.2% of patients with diabetes and in 86.6% of patients without diabetes (*P* < 0.001). Among 33,144 patients who underwent PCI, 6,335 patients (19.1%) underwent staged PCI within 3 months after the index procedure.

Baseline characteristics were substantially different according to age tertiles, sex, mode of revascularization, and clinical presentation, whereas the differences between patients with versus without diabetes in each subgroup were mostly consistent with those in the entire study population (Supplemental Tables 1 to 4). Younger patients were more likely to be men and had greater body mass index. Current smoking habit was present in 45.5% of patients ≤64 years of age, but only in 15.2% of patients >73 years of age. Older patients more often had the previous history of stroke and had comorbidities such as peripheral vascular disease, atrial fibrillation, anemia, and malignancy. Men, compared with women, less often had anemia and renal failure without dialysis and more often had current smoking habits. Regarding mode of revascularization, patients who underwent PCI more often had AMI presentation, heart failure, and malignancy and less often had prior MI, prior stroke, peripheral vascular disease, and anemia than those who underwent CABG (Supplemental Tables 1 to 4).

Complex coronary artery disease was present in 25,005 patients. Patients with complex coronary artery disease less often presented with AMI, but they were older and more often had comorbidities such as hypertension, diabetes, heart failure, prior MI, prior stroke, and peripheral vascular disease. The vast majority of patients without complex coronary artery disease underwent PCI (Supplemental Table 5).

Baseline characteristics were substantially different across the 3 cohorts. Patients in cohort 3 compared with those in cohort 1 were older and more often had comorbidities such as hypertension, heart failure, mitral regurgitation, and malignancy, but less often had prior histories of MI and stroke (Supplemental Table 6).

**CLINICAL OUTCOMES IN THE ENTIRE STUDY POPULATION.** Median follow-up duration was 5.6 (IQR: 4.4-6.9) years in the entire study population; 10.6 (IQR: 5.0-11.8) years in cohort 1, 5.1 (IQR: 4.2-5.9) years in cohort 2, and 5.7 (IQR: 4.4-6.7) years in cohort 3. Clinical follow-up information was obtained in 97.9% of patients (cohort 1: 98.8%, cohort 2: 98.4%, and cohort 3: 96.9%) at 1 year, 95.2% (cohort 1: 94.7%, cohort 2: 96.3%, and cohort 3: 94.2%) at 3 years, and 79.1% (cohort 1: 88.1%, cohort 2: 70.0%, and cohort 3: 82.7%) at 5 years after the index procedure. Diabetes as compared with nondiabetes was associated with significantly higher crude and adjusted risk for all the outcome measures. The magnitude of excess adjusted mortality risk of diabetes relative to nondiabetes was modest, which was mainly driven by the excess risk for cardiovascular death. Nevertheless, diabetes, compared with nondiabetes, also had significant excess risk for noncardiovascular death. The magnitude of excess adjusted risk of diabetes relative to nondiabetes was moderate for heart failure hospitalization, while it was modest for MI, stroke, TVR, and any coronary revascularization (Figure 2).

**SUBGROUP ANALYSES STRATIFIED BY THE MODIFIERS FOR THE RISK OF DIABETES.** With regard to primary outcome measure of MACCE, there was a significant interaction between adjusted risk of diabetes relative to nondiabetes and age tertiles, while no significant interaction was observed between diabetes status and other subgroups such as sex, mode of revascularization, and clinical presentation of AMI. The magnitude of the excess risk of diabetes relative to nondiabetes increased in younger patients for MACCE (Figure 3, Supplemental Figure 1).

![FIGURE 2 Continued](image-url)

Kaplan-Meier curves for (A) major adverse cardiovascular and cerebral endpoints, (B) all-cause death, (C) cardiovascular death, (D) noncardiovascular death, (E) myocardial infarction, (F) stroke, (G) target vessel revascularization, (H) any coronary revascularization, and (I) heart failure hospitalization. The Kaplan-Meier curves were truncated at 5 years.
FIGURE 3  Forest Plots for the Adjusted HRs of Diabetes

A  Age tertiles

| Major adverse cardiovascular and cerebral endpoints | N of patients with event (cumulative 5-year incidence) / N of patients at risk | Adjusted HR (95%CI) | P value |
|----------------------------------------------------|----------------------------------------------------------------------------------|----------------------|---------|
| ≤ 64 years                                         | 1244 (17.9%) / 5419                                                              | 1.30 (1.19-1.41)     | <0.001  |
| 64-73 years                                        | 1786 (25.7%) / 5377                                                              | 1.24 (1.16-1.33)     | <0.001  |
| >73 years                                          | 2217 (39.8%) / 4765                                                              | 1.17 (1.10-1.23)     | <0.001  |

All-cause death

| P for interaction | 1.41 (1.25-1.59) <0.001 |
|-------------------|--------------------------|
| ≤ 64 years        | 732 (9.9%) / 5419         |
| 64-73 years       | 1276 (16.7%) / 5377       |
| >73 years         | 1826 (31.6%) / 4765       |

Cardiovascular death

| P for interaction | 1.59 (1.36-1.86) <0.001 |
|-------------------|--------------------------|
| ≤ 64 years        | 485 (6.8%) / 5419         |
| 64-73 years       | 684 (9.4%) / 5377         |
| >73 years         | 1026 (19.5%) / 4765       |

Noncardiovascular death

| P for interaction | 1.21 (1.08-1.36) 0.001 |
|-------------------|------------------------|
| ≤ 64 years        | 247 (3.4%) / 5419       |
| 64-73 years       | 592 (8.1%) / 5377       |
| >73 years         | 800 (15.0%) / 4765      |

Myocardial infarction

| P for interaction | 1.19 (1.03-1.37) 0.02 |
|-------------------|------------------------|
| ≤ 64 years        | 394 (6.2%) / 5419       |
| 64-73 years       | 368 (5.9%) / 5377       |
| >73 years         | 354 (7.7%) / 4765       |

Stroke

| P for interaction | 1.21 (1.08-1.36) 0.001 |
|-------------------|------------------------|
| ≤ 64 years        | 364 (5.2%) / 5419       |
| 64-73 years       | 511 (8.2%) / 5377       |
| >73 years         | 511 (11.0%) / 4765      |

Target vessel revascularization

| P for interaction | 1.41 (1.20-1.65) <0.001 |
|-------------------|--------------------------|
| ≤ 64 years        | 1692 (30.0%) / 5419      |
| 64-73 years       | 1554 (28.7%) / 5377      |
| >73 years         | 1034 (24.1%) / 4765      |

Any coronary revascularization

| P for interaction | 1.33 (1.23-1.44) <0.001 |
|-------------------|--------------------------|
| ≤ 64 years        | 2071 (36.0%) / 5419      |
| 64-73 years       | 1961 (36.1%) / 5377      |
| >73 years         | 1341 (31.2%) / 4765      |

Heart failure hospitalization

| P for interaction | 2.23 (1.89-2.63) <0.001 |
|-------------------|--------------------------|
| ≤ 64 years        | 466 (7.1%) / 5419        |
| 64-73 years       | 606 (9.3%) / 5377        |
| >73 years         | 768 (16.8%) / 4765       |

0.5  Better in diabetes   1.0  Worse in diabetes  2.0  Adjusted HR of diabetes relative to non-diabetes

Forest plots for (A) age tertiles, (B) sex, (C) mode of revascularization, and (D) clinical presentation. Cumulative incidence was represented by the values at 5 years. Number of patients with event and the HRs were estimated through the entire follow-up period. To calculate HRs and interactions, we incorporated the risk-adjusting variables listed in Table 1. Abbreviations as in Figure 1.
As for respective outcome measures, there was a significant interaction between age tertiles and the adjusted risk of diabetes relative to nondiabetes for all-cause death, cardiovascular death, and heart failure hospitalization. In terms of TVR and any coronary revascularization, there was a significant diabetes-by-subgroup interaction in the sex and mode of revascularization subgroups (Figure 3, Supplemental Figures 2 and 3). The magnitude of the excess risk of diabetes relative to nondiabetes for these outcome measures was greater in women and in those who underwent PCI. Regarding clinical presentation, there was no significant diabetes-by-subgroup interaction in the AMI/non-AMI subgroups for MACCE and respective outcome measures. There was a consistent trend toward higher risk of diabetes relative to nondiabetes for all the outcome measures regardless of clinical presentation of AMI except for non-cardiovascular death in patients who presented with AMI (Figure 3, Supplemental Figure 4).

In the sensitivity analysis in patients who had a complex coronary artery disease, the results in the subgroup analysis stratified by mode of revascularization were consistent with those in the main results.

### FIGURE 3 Continued

| Outcome Measure                        | Men (cumulative 5-year incidence) | Adjusted HR (95% CI) | P value |
|---------------------------------------|-----------------------------------|----------------------|---------|
| Major adverse cardiovascular and cerebral endpoints | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| N of patients with events | N of patients at risk | P for interaction | | | | | | | |
| All-cause death | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| Cardiovascular death | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| Noncardiovascular death | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| Myocardial infarction | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| Stroke | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| Target vessel revascularization | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| Any coronary revascularization | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
| Heart failure hospitalization | | | | | | | | | |
| Diabetes | Non-diabetes | Men | Women | Men | Women | | 0.5 | 1.0 | 2.0 | Adjusted HR of diabetes relative to non-diabetes |
The results of the sensitivity analysis in cohorts 1, 2, and 3, separately, were largely in line with those observed in the entire study population (Supplemental Figures 6 to 8).

**DISCUSSION**

Diabetes compared with nondiabetes was independently associated with worse cardiovascular outcomes up to 5 years after coronary revascularization in our large-scale pooled registry including 15,561 patients with diabetes and 23,866 patients without diabetes. We found a few modifiers of the excess risk of diabetes relative to nondiabetes for clinical outcome measures. In terms of primary endpoint of MACCE, there was a significant interaction between diabetes status and age tertiles, while no significant interaction was observed between diabetes status and sex, mode of revascularization, or clinical presentation of AMI (Central Illustration). The excess adjusted risk of diabetes relative to nondiabetes for all-cause death varied widely from a 41% increase in younger patients to a 15% increase in older patients. Our findings of the greater excess mortality risk in younger patients with diabetes were largely consistent with those observed in the general population.
However, the absolute mortality risk in the younger patients with diabetes were extremely low in the general population, whereas in the present study, the observed absolute difference in all-cause death between diabetes and non-diabetes in the younger tertile was substantial (9.9% vs 5.5% at 5 years after coronary revascularization). The observed interaction between age tertiles and the effect of diabetes status on all-cause death was driven mainly by the higher excess risk for cardiovascular death in younger patients with diabetes. Moreover, we might assume the higher excess mortality risk of diabetes relative to nondiabetes among younger patients might be related to the higher excess risk for heart failure hospitalization. More aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in a patient population with greater excess mortality risk of diabetes relative to nondiabetes. Our results might suggest that more aggressive interventions for secondary prevention including liberal use of sodium-glucose cotransporter-2 inhibitors with a specific effect for heart failure might reduce the mortality risk in younger patients who underwent coronary revascularization. Alternatively, therapeutic interventions for secondary prevention in patients with diabetes might be
From the pooled CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Graft) registry, we found the excess risk of diabetes relative to nondiabetes for major adverse cardiovascular and cerebral endpoints MACCE was profound in the younger population, whereas no significant interaction was observed between adjusted risk of diabetes relative to nondiabetes for MACCE and other subgroups such as sex, mode of revascularization, and clinical presentation of acute myocardial infarction.
attenuated in older patients with smaller excess mortality risk of diabetes relative to nondiabetes. The higher risk of diabetes relative to nondiabetes in women has been underscored in the patient-level pooled analysis including 10,448 women who underwent PCI with drug-eluting stents in 26 randomized controlled trials (RCTs), in which 3-year adjusted risks for all-cause death, MI, target lesion revascularization, and definite or probable stent thrombosis in women with diabetes were significantly higher compared with in women without diabetes. Despite the lower absolute risks of cardiovascular events in women, the excess risks of diabetes relative to nondiabetes for cardiovascular events were greater in women than in men in the general population. In line with these studies, women, compared with men, were associated with greater excess risks of diabetes relative to nondiabetes for TVR and any coronary revascularization in our study. In contrast, in the prespecified subgroup analysis of patient-level pooled analysis including 32,877 patients undergoing PCI in 23 RCTs, no significant interaction between sex and clinical outcomes based on diabetes status was observed for 5-year risk of ischemia-driven target lesion revascularization (men vs women; diabetes: 12.6% vs 13.5%; nondiabetes: 9.5% vs 9.7%; \( P_{\text{interaction}} = 0.70 \)). This discrepancy could at least in part be explained by the difference in the lesion complexity between our all-comers registry and RCTs (eg, mean number of treated lesions: 1.7 vs 1.3 lesions); however, further studies are needed to clarify the sex difference in the effect of diabetes on clinical outcomes after coronary revascularization.

Dedicated RCTs have shown that CABG is more beneficial than PCI in patients with diabetes. However, no clear interactions between diabetes status and effects of mode of revascularization on long-term clinical outcomes were reported in the recent RCTs. According to the collaborative analysis of 22 RCTs, the rate of 5-year mortality among patients with diabetes was significantly higher in the PCI arm than in the CABG arm (HR: 1.44; 95% CI: 1.20-1.74; \( P < 0.001 \)), whereas no significant difference was observed between PCI and CABG among patients without diabetes (HR: 1.02; 95% CI: 0.86-1.21; \( P = 0.81, P_{\text{interaction}} = 0.008 \)). The intention of the collaborative analysis was not to explore difference in the magnitude of excess risk of diabetes relative to nondiabetes by mode of revascularization; nevertheless, we could infer that the magnitude of excess mortality risk of diabetes relative to nondiabetes was greater among patients who underwent PCI than in those who underwent CABG. However, in the present study, there was no significant interaction between mode of revascularization (PCI/CABG) and mortality risk of diabetes relative to nondiabetes. This discrepancy might be explained, at least in part, by the older population in our registry (mean patient’s age: 68.4 years) compared with the collaborative analysis of RCTs (mean patient’s age: 63.6 years), because survival benefit with CABG over PCI in patients with diabetes was profound in younger patients. Meanwhile, there was significant interaction between mode of revascularization and risks of diabetes relative to nondiabetes for coronary events such as MI, TVR, and any coronary revascularization. In patients who underwent CABG, there was virtually no excess risk of diabetes relative to nondiabetes for coronary events. Our results not only support the benefit of CABG in relation to PCI in patients with diabetes, but also highlight the need for more aggressive secondary prevention measures to reduce the risk of cardiovascular events in patients with diabetes who underwent PCI.

In the stratified analysis for clinical presentation, there was no previous study comparing the risks of diabetes relative to nondiabetes for cardiovascular events between patients with AMI and non-AMI. In the present study, there were no significant interactions between clinical presentation and the risks of diabetes relative to nondiabetes for cardiovascular events. More aggressive interventions for patients with diabetes might be relevant not only in patients with AMI, but also in patients with non-AMI.

**Study Limitations.** First, selection of potential modifiers of the risk of diabetes for adverse events was arbitrary. We could not deny the presence of other important risk modifiers. Second, there might be residual confounders affecting the risk of diabetes relative to nondiabetes for adverse events, although we conducted extensive multivariable adjustment. Third, diabetes therapy might have been changed during the inclusion period, which began with the use of bare-metal stents and ended with the use of new-generation drug-eluting stents. Moreover, recently developed glucose-lowering drugs, such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, might further reduce the risk of cardiovascular events in patients with diabetes. Fourth, while we sought to assess the impact of baseline diabetes status on clinical outcomes, we did not take into account changes in diabetes status during the follow-up period. Fifth, because of the long inclusion period, MI was adjudicated according to the classical definition of Q-wave MI, not the current universal definition of MI. Sixth, whereas 69.5% of patients with
diabetes had multivessel disease, more than four-fifths of patients underwent PCI. Moreover, the proportion of PCI significantly increased from 2000 to 2013 in Japan, particularly in patients with multivessel disease.\(^5\) The observed interaction between diabetes status and mode of revascularization might not be applicable in patients outside Japan. Finally, follow-up rates were far from complete to enable us to evaluate the effect of diabetes on long-term outcomes for up to 5 years; however, median follow-up duration for survivors were comparable between patients with diabetes (5.9; IQR: 4.9-7.0) and those without diabetes (5.9; IQR: 4.9-7.1).

**CONCLUSIONS**

The excess risk of diabetes relative to nondiabetes for MACCE was profound in the younger population. Our observation suggests more aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in younger patients.

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**ADDRESS FOR CORRESPONDENCE:** Dr Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: taketaka@kuhp.kyoto-u.ac.jp.

**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** The excess adjusted risks of diabetes relative to nondiabetes for MACCE increased with younger age, mainly driven by greater excess adjusted mortality risk of diabetes relative to nondiabetes in younger tertile. No significant interaction was observed between adjusted risk of diabetes relative to nondiabetes for MACCE and other subgroups such as sex, mode of revascularization, and clinical presentation of acute myocardial infarction.

**TRANSLATIONAL OUTLOOK:** More aggressive interventions for secondary prevention in patients with diabetes might be particularly relevant in younger patients.

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**ADDRESS FOR CORRESPONDENCE:** Dr Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: taketaka@kuhp.kyoto-u.ac.jp.

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KEY WORDS coronary artery bypass graft, diabetes, percutaneous coronary intervention

APPENDIX For supplemental figures and tables and lists of participants, please see the online version of this paper.