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# "Silent" Diabetes and Clinical Outcome After Treatment With Contemporary Drug-Eluting Stents

## The BIO-RESORT Silent Diabetes Study

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## ABSTRACT

**OBJECTIVES** This study sought to assess the prevalence and clinical impact of silent diabetes and pre-diabetes in "nondiabetic" percutaneous coronary intervention (PCI) all-comers.

**BACKGROUND** Patients with undetected and thus untreated (silent) diabetes may have higher event risks after PCI with contemporary drug-eluting stents (DES).

**METHODS** The BIO-RESORT Silent Diabetes study, performed at Thoraxcentrum Twente, is a substudy of the randomized multicenter BIO-RESORT (BIOdegradable Polymer and DuRable Polymer Drug-eluting Stents in an All COmeRs PopulaTion) trial (NCT01674803). Patients underwent oral glucose tolerance testing (OGTT), and assessment of glycosylated hemoglobin with fasting plasma glucose. Primary endpoint was a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization at 1 year.

**RESULTS** Of the 988 participants, OGTT detected silent diabetes in 68 (6.9%), pre-diabetes in 133 (13.3%), and normal glucose metabolism in 788 (79.8%). Patients with silent diabetes had higher primary endpoint rates (13.2% vs. 7.6% vs. 4.8%; $p < 0.001$; silent diabetes vs. normal: hazard ratio: 4.2; 95% confidence interval: 1.9 to 9.2). Differences were driven by myocardial infarction ($p < 0.001$) which occurred mostly <48 h. Based on glycosylated hemoglobin and fasting plasma glucose, silent diabetes was found in 33 (3.3%) patients, pre-diabetes in 217 (22.0%) patients, and normal glucose metabolism in 738 (74.7%) patients; primary endpoint rates were similar to OGTT-based analyses (12.1% vs. 5.5% vs. 3.1%; $p = 0.01$). Multivariate analyses demonstrated that abnormal glucose metabolism by either diagnostic approach, present in 330 (33.4%) patients, independently predicted adverse event risk (hazard ratio: 2.2; 95% confidence interval: 1.2 to 4.2).

**CONCLUSIONS** Abnormal glucose metabolism was detected in 1 of 3 "nondiabetic" PCI patients and was independently associated with up to 4-fold higher event risks. Future intervention trials should determine whether meaningful benefits accrue from routine glycemia testing in such patients. (J Am Coll Cardiol Intv 2018;11:448–59)


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Diabetes mellitus (DM) is associated with adverse outcome in the general population and even more so in patients with cardiovascular disease (1). Many patients with coronary artery disease share risk factors with the metabolic syndrome and are for that reason at risk of developing diabetes (2). Diabetic patients, who represent an increasing proportion of all patients referred for percutaneous coronary intervention (PCI), are at a higher adverse events risk (3,4) and continue to show a higher mortality despite the development of newer-generation drug-eluting stents (DES) with improved biocompatibility (4–7). Traditionally, the diagnosis of diabetes or pre-diabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG])—an early stage of diabetes—is made based on increased fasting plasma glucose (FPG) levels or oral glucose tolerance testing (OGTT) or elevated glycosylated hemoglobin ($HbA_{1c}$) (8–10).

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A substantial proportion of patients have undetected and thus untreated (silent) diabetes, which may lead to more cardiovascular complications. Abnormal glucose metabolism with its chronic hyperglycemic state leads to dyslipidemia, hypercoagulability, increased atheroma burden, vessel wall inflammation, and vulnerable plaques (7,11). Previous post hoc analyses of data from the TWENTE (The Real-World Endeavor Resolute versus Xience V Drug-Eluting Stent Study in Twente) trial, which assessed PCI with newer-generation DES in a broad patient population (12), suggested a relation between undetected diabetes and outcome following PCI (13). In addition, based on data from the EUROASPIRE IV (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) study (14), it was recently recommended that all patients with cardiovascular disease should undergo OGTT, which is considered by some, but not all (15), a standard for detecting diabetes (8,9,14,16).

Therefore, in the present BIO-RESORT (BIOdegradable Polymer and DuRable Polymer Drug-eluting Stents in an All COmeRs PopulaTion) Silent Diabetes study, we used OGTT and $HbA_{1c}$ with FPG to prospectively assess the prevalence of silent diabetes and pre-diabetes in a population of PCI all-comer patients. In addition, we investigated the potential impact of abnormal glucose metabolism on 1-year clinical outcome.

## METHODS

**STUDY DESIGN, PATIENTS, AND PROCEDURES.** The BIO-RESORT Silent Diabetes study, performed at Thoraxcentrum Twente, is a pre-specified, prospective substudy of the randomized multicenter BIO-RESORT trial (17), registered with ClinicalTrials.gov (NCT01674803). The randomized trial enrolled all-comer patients undergoing PCI procedures that reflected daily clinical practice. Patients were treated with 1 of 3 contemporary DES: Synergy everolimus-eluting stent (Boston Scientific, Natick, Massachusetts), Orsiro sirolimus-eluting stent (Biotronik, Bülach, Switzerland), or Resolute Integrity zotarolimus-eluting stent (Medtronic, Santa Rosa, California). As recently reported, 1-year clinical outcome did not differ significantly between the 3 stents (17).

Patients without known diabetes, treated at Thoraxcentrum Twente in Enschede, the Netherlands, were invited to participate in the substudy. A total of 988 of 1,889 invited patients agreed to participate. Four to 6 weeks after the index procedure, OGTT was done at an outpatient setting by experienced staff from the central laboratory department. After 8 h of fasting, blood samples were taken to measure baseline FPG and $HbA_{1c}$; patients then drank 75 g glucose dissolved in 300 ml water within 5 min (18). To ensure optimal accuracy of the test, patients remained at the clinic and were instructed not to perform any energy-consuming activities during the next 2 h. Subsequently, an additional blood sample was taken to measure the 2-h glucose level (Hexokinase, Roche Diagnostics, Almere, the Netherlands). $HbA_{1c}$ levels were measured with a Tina-quant third-generation assay on Cobas 6000 analyzer (Roche Diagnostics). Patients and their general practitioners received a letter that contained the exact laboratory results and advice on how to proceed further, based on current guidelines.

The BIO-RESORT trial complied with the CONSORT 2010 Statement and Declaration of

**ABBREVIATIONS AND ACRONYMS**

**DES** = drug-eluting stent(s)
**DM** = diabetes mellitus
**FPG** = fasting plasma glucose
**IFG** = impaired fasting glucose
**IGT** = impaired glucose tolerance
**MI** = myocardial infarction
**OGTT** = oral glucose tolerance testing
**PCI** = percutaneous coronary intervention

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**TABLE 1 Definitions of Different Metabolic States**

| | OGTT* | $HbA_{1c}$ and FPG† |
|---|---|---|
| ("Silent") diabetes | FPG ≥7.0 mmol/l<br>OR<br>2-h G ≥11.1 mmol/l | FPG ≥7.0 mmol/l<br>OR<br>$HbA_{1c}$ ≥48 mmol/mol |
| Pre-diabetes | | |
| Impaired glucose tolerance | FPG <7.0 mmol/l<br>AND<br>2-h G 7.8–11.1 mmol/l | |
| Impaired fasting glucose | | FPG 6.1–6.9 mmol/l<br>AND<br>$HbA_{1c}$ 42–47 mmol/mol |
| Normal G metabolism | FPG <6.1 mmol/l AND<br>2-h G <7.8 mmol/l | FPG <6.1 mmol/l<br>AND<br>$HbA_{1c}$ ≤41 mmol/mol |

*Based on the World Health Organization 1999 criteria. †Based on the International Expert Committee 2009 criteria.

FPG = fasting plasma glucose; G = glucose; $HBA_{1c}$ = glycosylated hemoglobin; OGTT = oral glucose tolerance testing.

Helsinki and was approved by the Medical Ethics Committee Twente (17). All patients provided written informed consent.

**DEFINITIONS OF METABOLIC STATES AND STUDY ENDPOINTS.** Definitions of metabolic states were based on the World Health Association 1999 criteria for OGTT and the International Expert Committee 2009 criteria for $HbA_{1c}$ with FPG (19,20). Patients were considered to have normal glucose metabolism if FPG was <6.1 mmol/l and 2-h glucose levels were <7.8 mmol/l, or $HbA_{1c}$ levels were ≤41 mmol/mol (**Table 1**). Pre-diabetes was defined as either IGT by OGTT or IFG: FPG level <7.0 mmol/l and 2-h glucose level of 7.8 to 11.0 mmol/l; or FPG level of 6.1 to 6.9 mmol/l and $HbA_{1c}$ level of 42 to 47 mmol/mol. Patients were considered diabetics if FPG levels were ≥7.0 mmol/l or 2-h glucose levels were ≥11.1 mmol/l, or if $HbA_{1c}$ levels were ≥48 mmol/mol (8,9,19,20).

Of note, $HbA_{1c}$ has been endorsed for DM diagnosis and screening. In 2009, the International Expert Committee jointly organized by the American Diabetes Association, the International Diabetes Federation, and the European Association for the Study of Diabetes recommended $HbA_{1c}$ to be added to the diagnostic instruments for detecting DM, with the recommended $HbA_{1c}$ cutoff point of ≥48 mmol/mol (≥6.5%) (19,20).

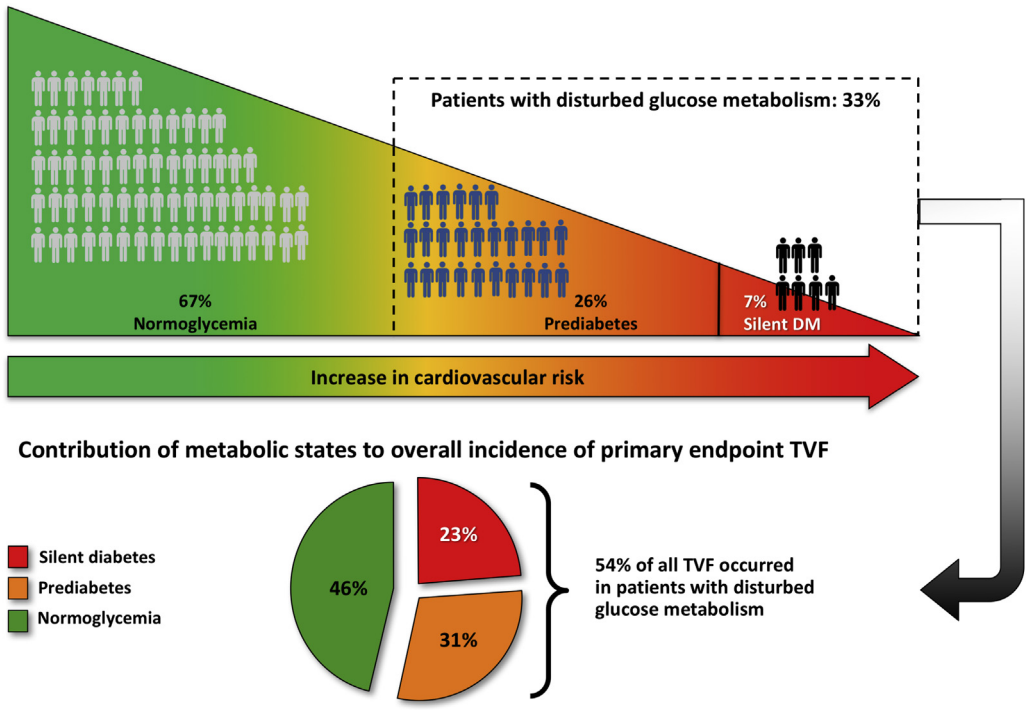
The pre-specified endpoints of the BIO-RESORT Silent Diabetes study are based on the Academic Research Consortium (21) and have been described previously (17). In brief, the primary endpoint target vessel failure is a composite of cardiac death, target vessel-related myocardial infarction (MI), or repeated target vessel revascularization (components in hierarchical order). Death was considered cardiac, unless an unequivocal noncardiac cause could be established. MI was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated confirmatory cardiac biomarkers (i.e., troponin or myocardial band fraction of creatine kinase). Periprocedural MI occurred within 48 h of the PCI procedure. The more global major adverse cardiac events, consisting of all-cause death, any MI, emergent coronary artery bypass grafting, or clinically indicated coronary revascularization, was also assessed (17).

**PERCUTANEOUS INTERVENTION, ANALYSES, AND MONITORING.** The PCI was performed according to standard techniques, current guidelines, and the physician's judgment, as previously described in detail (17). In general, dual antiplatelet therapy was prescribed for 6 to 12 months.

Electrocardiograms were systematically assessed. Laboratory tests included systematic assessment of cardiac markers after the intervention and subsequent serial measurements in case of suspected ischemia. Clinical follow-up was obtained at visits to outpatient clinics or, if not feasible, by telephone follow-up or a medical questionnaire. Study coordination and data management were performed by the clinical research organization Cardio Research Enschede (Enschede, the Netherlands). A formal data safety monitoring committee reviewed the outcome data of the main randomized trial periodically. Data monitoring, processing of clinical outcome data, and independent clinical event adjudication were performed by an independent clinical research organization (Diagram, Zwolle, the Netherlands).

**STATISTICAL ANALYSIS.** For dichotomous and categorical variables, data were reported as frequencies and percentages. Continuous variables were expressed as mean ± SD. The time to primary endpoint and components thereof were assessed according to Kaplan-Meier methods; log-rank testing was applied for between-group comparisons. The Pearson chi-square test or Fisher exact test were used to compare categorical variables, and the Student *t* test to compare continuous variables. We performed Cox proportional hazards regression analyses to investigate the effect of abnormal glucose metabolism on 1-year clinical outcome. The following variables associated with the primary composite endpoint were included in the multivariate models: demographics (sex, age), clinical (hypercholesterolemia, statin use, systolic blood pressure, smoking, body mass index, previous revascularization, previous MI), laboratory (hemoglobin level at admission, renal insufficiency). Using forward stepwise selection, all variables that were significantly different

**FIGURE 1** Prevalence of Disturbed Glucose Metabolism in PCI Patients Without Known Diabetes, and Its Impact on Clinical Outcome




Of the study participants, one-third had an abnormal glucose metabolism, of which 7% had silent diabetes mellitus (DM). At 1-year follow-up, more than one-half of the target vessel failures (TVFs) occurred in patients with abnormal glucose metabolism. Specifically, the 7% silent DM patients accounted for almost a one-quarter of all adverse events. PCI = percutaneous coronary intervention.

remained in the multivariate model, eliminating variables with a nonsignificant association ($p > 0.15$) with the outcome. The final model included age, sex, hypercholesterolemia, previous MI, and previous revascularization. All statistical tests were 2-tailed; p values <0.05 were considered significant. Data analysts remained blinded to the assigned treatment until the evaluation of 1-year follow-up was finished. Statistical analyses were performed with SPSS version 22 (IBM Corporation, Armonk, New York).

## RESULTS

Of the 988 study participants without known diabetes, 330 (33.4%) had an abnormal glucose metabolism based on OGTT or $HbA_{1c}$ with FPG levels, of whom 71 (7.2%) had silent diabetes (Figure 1). Sole use of OGTT data resulted in the detection of silent diabetes in 68 (6.9%) patients and pre-diabetes in 132 (13.4%) patients, whereas 788 (79.8%) patients had normal glucose tolerance. Based on $HbA_{1c}$ and FPG, silent diabetes was present in 33 (3.3%) patients and pre-diabetes in 217 (22.0%) patients, and 738 (74.7%) patients had a normal glucose metabolism.

Baseline characteristics and procedural details of patients with silent diabetes, pre-diabetes, and normal glucose metabolism are presented in Table 2. Patients with abnormal glucose metabolism had a slightly higher body mass index, more often a previous myocardial infarction, and tended to be older than patients with normal glucose metabolism.

At 1-year follow-up, 21 (6.4%) of the 330 patients with abnormal glucose metabolism (based on one or the other diagnostic approach) reached the primary composite endpoint of target vessel failure (vs. 18 [2.7%] in 658 patients with normal glucose metabolism; $p = 0.006$). In other words, more than one-half (54%) of the target vessel failures occurred in the one-third of study participants who had an abnormal glucose metabolism; specifically, silent diabetic patients comprised 7% of the study participants and accounted for 23% of all target vessel failures (Figure 1).

**TABLE 2 Baseline Characteristics**

| | OGTT-Based Metabolic States | | | | $HbA_{1c}$ and FPG Metabolic States | | | |
|---|---|---|---|---|---|---|---|---|
| | Abnormal Glucose Metabolism | | | | Abnormal Glucose Metabolism | | | |
| | Silent DM (n = 68) | Pre-DM (n = 132) | NG (n = 788) | p Value | Silent DM (n = 33) | Pre-DM (n = 217) | NG (n = 738) | p Value |
| Age, yrs | 63.9 ± 9.2 | 62.5 ± 9.8 | 61.3 ± 10.2 | 0.08 | 62.1 ± 8.1 | 63.1 ± 10.3 | 61.2 ± 10.1 | 0.07 |
| Male | 53 (77.9) | 98 (74.2) | 623 (79.1) | 0.46 | 24 (72.7) | 179 (82.5) | 571 (77.4) | 0.20 |
| BMI, kg/m$^2$ | 28.5 ± 4.5 | 28.5 ± 3.8 | 27.0 ± 3.9 | <0.001 | 28.5 ± 4.6 | 28.3 ± 4.1 | 27.0 ± 3.9 | <0.001 |
| Hypertension | 29 (42.6) | 64 (48.5) | 301 (38.2) | 0.07 | 16 (48.5) | 89 (41.0) | 289 (39.2) | 0.52 |
| Systolic blood pressure, mm Hg | 136.2 ± 24.5 | 139.8 ± 24.8 | 133.6 ± 23.8 | 0.02 | 134.3 ± 21.8 | 134.8 ± 24.0 | 134.6 ± 24.2 | 0.99 |
| Hypercholesterolemia | 36 (52.9) | 52 (39.4) | 331 (42.0) | 0.16 | 15 (45.5) | 96 (44.2) | 308 (41.7) | 0.76 |
| Current smoker | 23 (35.4) | 39 (30.5) | 230 (29.7) | 0.63 | 23 (35.4) | 68 (32.4) | 213 (29.3) | 0.57 |
| Family history of coronary artery disease | 31 (49.2) | 70 (54.7) | 398 (52.4) | 0.77 | 17 (56.7) | 109 (52.4) | 373 (52.3) | 0.90 |
| Previous MI | 18 (26.5) | 18 (13.6) | 127 (16.1) | 0.06 | 11 (33.3) | 47 (21.7) | 105 (14.2) | 0.001 |
| Previous PCI | 12 (17.6) | 24 (18.2) | 111 (14.1) | 0.38 | 7 (21.2) | 42 (19.4) | 98 (13.3) | 0.05 |
| Previous CABG | 8 (11.8) | 6 (4.5) | 46 (5.8) | 0.11 | 3 (9.1) | 17 (7.8) | 40 (5.4) | 0.32 |
| Renal insufficiency* | 4 (5.9) | 4 (3.0) | 13 (1.6) | 0.05 | 1 (3.0) | 7 (3.2) | 13 (1.8) | 0.39 |
| Clinical presentation | | | | 0.66 | | | | 0.97 |
| STEMI | 15 (22.1) | 42 (31.8) | 249 (31.6) | | 11 (33.3) | 65 (30.0) | 230 (31.2) | |
| NSTEMI | 12 (17.6) | 28 (21.2) | 147 (18.7) | | 6 (18.2) | 40 (18.4) | 141 (19.1) | |
| Unstable angina | 17 (25.0) | 26 (19.7) | 157 (19.9) | | 8 (24.2) | 42 (19.4) | 150 (20.3) | |
| Stable angina | 24 (35.3) | 36 (27.3) | 235 (29.8) | | 8 (24.2) | 70 (32.3) | 217 (29.4) | |
| Multivessel treatment | 16 (23.5) | 29 (22.0) | 139 (17.6) | 0.23 | 5 (15.2) | 45 (20.7) | 134 (18.2) | 0.60 |
| LAD | 30 (44.1) | 71 (53.8) | 404 (51.3) | 0.26 | 16 (48.5) | 100 (46.1) | 389 (52.7) | 0.22 |
| Total stent length/patient | 51.8 ± 34.2 | 43.8 ± 27.2 | 43.7 ± 30.0 | 0.04 | 48.6 ± 30.0 | 43.9 ± 30.0 | 44.2 ± 30.0 | 0.69 |
| Stents/patient | 2.13 ± 1.23 | 1.94 ± 1.10 | 1.85 ± 1.14 | 0.06 | 2.13 ± 1.23 | 1.94 ± 1.10 | 1.85 ± 1.14 | 0.92 |
| Medication at admission | | | | | | | | |
| Statin | 49 (72.1) | 65 (49.2) | 425 (53.9) | 0.007 | 20 (60.6) | 126 (58.1) | 393 (53.3) | 0.36 |
| β-blocker | 42 (61.8) | 60 (45.5) | 393 (49.9) | 0.09 | 16 (48.5) | 115 (53.0) | 364 (49.3) | 0.63 |
| ACE inhibitor | 21 (30.9) | 24 (18.2) | 178 (22.6) | 0.13 | 9 (27.3) | 56 (25.8) | 158 (21.4) | 0.32 |
| CA-antagonist or ARB | 22 (32.4) | 41 (31.1) | 193 (24.5) | 0.13 | 10 (30.3) | 75 (34.6) | 171 (23.2) | 0.003 |
| Aspirin | 44 (64.7) | 71 (53.8) | 454 (57.6) | 0.33 | 18 (54.5) | 133 (61.3) | 418 (56.6) | 0.45 |
| Oral anticoagulant | 4 (5.9) | 9 (6.8) | 46 (5.8) | 0.91 | 2 (6.1) | 21 (9.7) | 36 (4.9) | 0.03 |
| Medication at discharge | | | | | | | | |
| Statin | 65 (95.6) | 121 (91.7) | 742 (94.2) | 0.45 | 31 (93.9) | 206 (94.9) | 691 (93.6) | 0.78 |
| β-blocker | 59 (86.8) | 115 (87.1) | 659 (83.6) | 0.50 | 28 (84.8) | 187 (86.2) | 618 (83.7) | 0.68 |
| ACE inhibitor | 34 (50.0) | 63 (47.7) | 434 (55.1) | 0.24 | 20 (60.6) | 110 (50.7) | 401 (54.3) | 0.46 |
| CA-antagonist or ARB | 22 (32.4) | 44 (33.3) | 202 (25.6) | 0.11 | 10 (30.3) | 74 (34.1) | 184 (24.9) | 0.03 |
| Antiplatelet therapy | | | | | | | | |
| Aspirin | 68 (100) | 131 (99.2) | 780 (99.0) | 0.69 | 33 (99.1) | 215 (99.1) | 731 (99.1) | 0.85 |
| Clopidogrel | 44 (64.7) | 89 (67.4) | 501 (63.6) | 0.69 | 18 (54.5) | 142 (65.4) | 474 (64.2) | 0.48 |
| Prasugrel or ticagrelor | 24 (35.3) | 41 (31.1) | 287 (36.4) | 0.44 | 15 (45.5) | 75 (34.6) | 262 (35.5) | 0.45 |
| Oral anticoagulant agent | 9 (13.2) | 13 (9.8) | 67 (8.5) | 0.40 | 3 (9.1) | 30 (13.8) | 56 (7.6) | 0.02 |

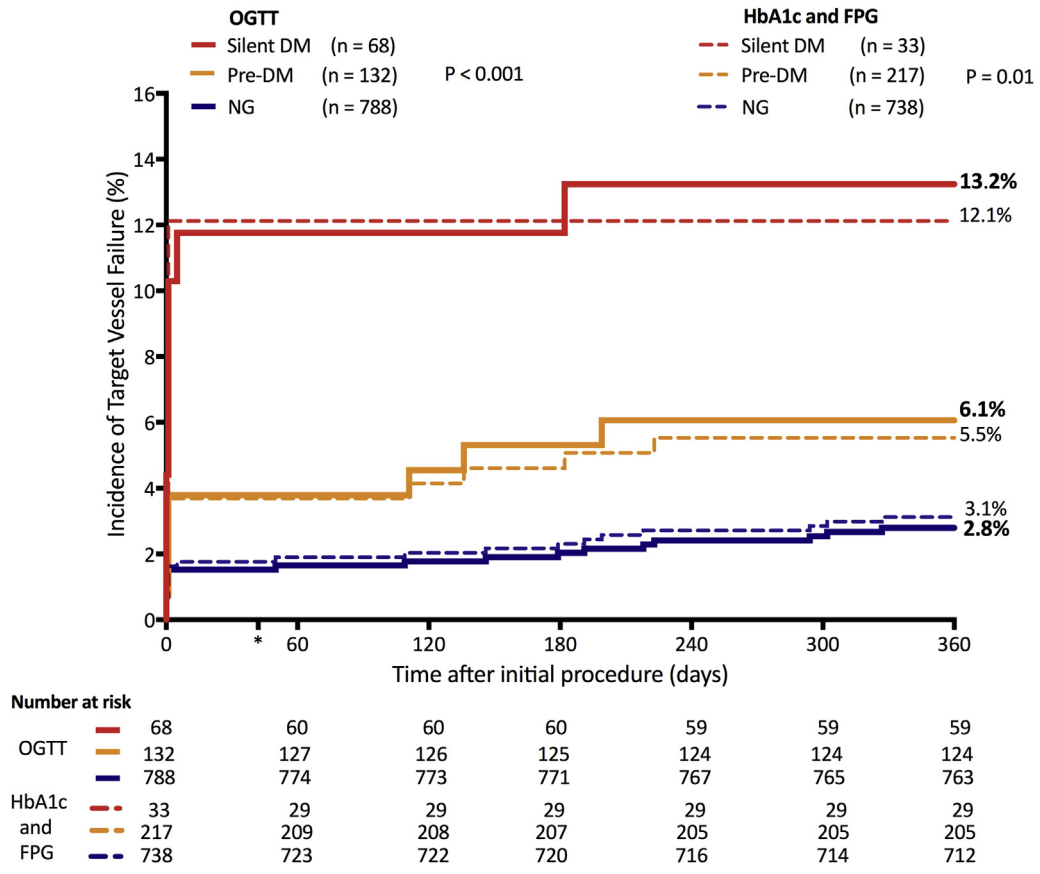
Values are mean ± SD or n (%). *Estimated glomerular filtration rate of <30 ml/min/1.73 m$^2$ of body surface area or the need for dialysis.

ARB = angiotensin receptor blocker; ACE = angiotensin-converting enzyme; BMI = body mass index; CA = calcium antagonist; CABG = coronary artery bypass grafting; DM = diabetes mellitus; LAD = left anterior descending artery; MI = myocardial infarction; NG = normal glucose metabolism; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

The rate of the primary endpoint was significantly higher in patients with silent diabetes as compared with patients with pre-diabetes and normal glucose metabolism, based on OGTT (13.2% vs. 7.6% vs. 4.8%; $p < 0.001$). Primary endpoint rates in metabolic state groups, based on the $HbA_{1c}$ and FPG levels, were similar to rates in OGTT-based analyses (12.1% vs. 5.5% vs. 3.1%; $p = 0.01$); the time-to-event curves are shown in **Figure 2** (landmark analysis in Online Figure 1). Patients with silent diabetes, pre-diabetes, and normal glucose tolerance also differed in several other clinical outcome parameters (**Table 3**).

The incidence of target vessel MI was higher in patients with silent diabetes than in patients with

**FIGURE 2** Kaplan-Meier Curves of Primary Endpoint at 1-Year Follow-Up




Kaplan-Meier curve for the composite endpoint consisting of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization at 1-year follow-up. *Timing of oral glucose tolerance testing (OGTT). DM = diabetes mellitus; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; NG = normal glucose metabolism.

pre-diabetes and normal glucose metabolism (OGTT-based metabolic states: 10.3% vs. 3.8% vs. 1.8%, $p < 0.001$; $HbA_{1c}$ + FPG-based metabolic states: 12.1% vs. 3.7% vs. 1.9%, $p = 0.001$), which was mainly related to MI occurring within 48 h of the PCI procedure ($p < 0.001$). Mortality rates were low for all 3 patient groups (Table 3). The time-to-event curves of target vessel MI and target vessel revascularization at 1-year follow-up are displayed in Figure 3.

Multivariate analyses demonstrated that abnormal glucose metabolism by one or the other diagnostic approach independently predicted adverse event risk (hazard ratio: 2.2; 95% confidence interval: 1.2 to 4.2). Patients with silent diabetes had a 3- to 4-fold higher event risk than did patients with a normal glucose metabolism (Tables 4 and 5).

## DISCUSSION

**MAIN STUDY FINDINGS.** Overall, based on one or the other diagnostic approach, 33% of the 988 study participants without known diabetes had an abnormal glucose metabolism, of whom 7% had silent diabetes. Based on the OGTT findings only, silent diabetes was detected in 7% of the 988 study participants, pre-diabetes in 13%, and normal glucose metabolism in 80%. The corresponding prevalences based on the alternative approach for detecting an abnormal glucose metabolism ($HbA_{1c}$ with FPG levels) were 3%, 22%, and 75%, respectively.

At 1-year follow-up, 6.4% of all patients with abnormal glucose metabolism reached the primary composite endpoint of target vessel failure, whereas this rate was significantly lower (2.7%) in patients

**TABLE 3 Clinical Events at 1-Year Follow-Up (N = 988)**

| | Based on OGTT | | | Log-Rank p Value | | | Based on HbA1c and FPG | | | Log-Rank p Value | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Abnormal Glucose Metabolism | | | | | | Abnormal Glucose Metabolism | | | | | |
| | Silent DM (n = 68) | Pre-DM (n = 132) | NG (n = 788) | Overall | Silent DM vs. NG | Pre-DM vs. NG | Silent DM (n = 33) | Pre-DM (n = 217) | NG (n = 738) | Overall | Silent DM vs. NG | Pre-DM vs. NG |
| TVF (primary endpoint) | 9 (13.2) | 8 (6.1) | 22 (2.8) | <0.001 | <0.001 | 0.05 | 4 (12.1) | 12 (5.5) | 23 (3.1) | 0.01 | 0.005 | 0.09 |
| Death | 1 (1.5) | 0 (0) | 2 (0.3) | 0.17 | 0.10 | 0.56 | 0 (0) | 1 (0.5) | 2 (0.3) | 0.86 | 1.00 | 0.66 |
| Cardiac death | 1 (1.5) | 0 (0) | 0 (0) | 0.001 | 0.001 | – | 0 (0) | 1 (0.5) | 0 (0) | 0.17 | – | 0.07 |
| Any MI | 7 (10.3) | 5 (3.8) | 14 (1.8)* | <0.001 | <0.001 | 0.13 | 4 (12.1) | 8 (3.7) | 14 (1.9)* | 0.001 | <0.001 | 0.12 |
| Periprocedural MI | 7 (10.3) | 5 (3.8) | 12 (1.5) | <0.001 | <0.001 | 0.08 | 4 (12.1) | 8 (3.7) | 12 (1.6) | <0.001 | <0.001 | 0.06 |
| Target vessel MI | 7 (10.3) | 5 (3.8) | 14 (1.8) | <0.001 | <0.001 | 0.13 | 4 (12.1) | 8 (3.7) | 14 (1.9) | 0.001 | <0.001 | 0.12 |
| Q-wave | 0 (0) | 0 (0) | 2 (0.3) | 0.001 | 0.001 | 0.56 | 0 (0) | 0 (0) | 2 (0.3) | 0.71 | 1.00 | 1.00 |
| Non–Q-wave | 7 (10.3) | 5 (3.8) | 12 (1.6) | <0.001 | <0.001 | 0.08 | 4 (12.1) | 8 (3.7) | 12 (1.8) | 0.001 | <0.001 | 0.06 |
| Revascularization, any | 3 (4.4) | 6 (4.5) | 25 (3.2) | 0.65 | 0.57 | 0.42 | 0 (0) | 10 (4.6) | 24 (3.3) | 0.35 | 0.42 | 0.34 |
| Target vessel revascularization | 3 (4.4) | 3 (2.3) | 11 (1.4) | 0.16 | 0.06 | 0.45 | 0 (0) | 5 (2.3) | 12 (1.6) | 0.59 | 0.46 | 0.51 |
| MACE | 9 (13.2) | 7 (5.3) | 22 (2.8) | <0.001 | <0.001 | 0.12 | 4 (12.1) | 12 (5.5) | 22 (3.0) | 0.008 | 0.003 | 0.07 |

Values are n (%). The primary endpoint target vessel failure consists of cardiac death, target vessel myocardial infarction, or target vessel revascularization. Major adverse cardiac events (MACE) consisted of any death, any MI, emergent CABG, or clinically indicated coronary revascularization. *Two patients experienced a myocardial infarction due to a definite stent thrombosis. Of all of the myocardial infarctions, none was fatal.

TVF = target vessel failure; other abbreviations as in Tables 1 and 2.

with normal glucose metabolism. In other words, more than one-half (54%) of the target vessel failures occurred in the one-third of study participants who had an abnormal glucose metabolism; specifically, silent diabetic patients comprised 7% of the study participants and accounted for 23% of all primary endpoints. This was primarily driven by target vessel MI, which mainly occurred within 48 h of the index PCI. Multivariate analyses demonstrated that the presence of silent diabetes, diagnosed by either OGTT or $HbA_{1c}$ with FPG, independently predicted the risk of reaching the primary endpoint.

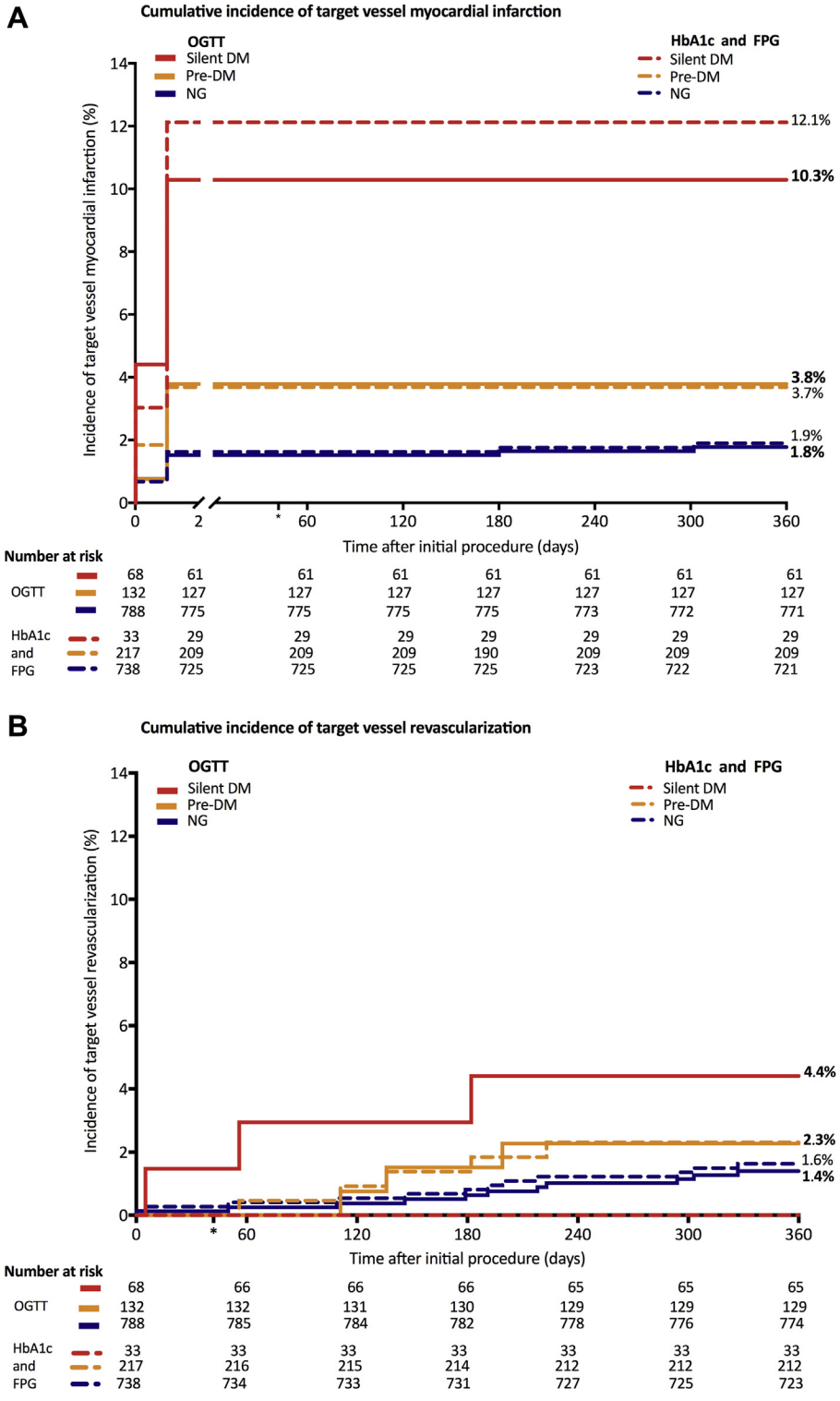
The findings of the prospective BIO-RESORT Silent Diabetes study underline the importance of previously unknown (and untreated) diabetes for clinical outcome after PCI, performed with contemporary DES that recently demonstrated excellent safety and efficacy (17). Significantly, the study was performed in a predominantly white European population in the Netherlands—a country that has a lower prevalence of diabetes than the United States and many other European countries (22), and a health system that is characterized by a fine-meshed net of primary care that offers screening for several common diseases, including diabetes. Therefore, it is fair to assume that the proportion of silent diabetics among PCI patients may be higher than 7%, both in countries with a higher diabetes risk or more difficult access to primary care.

**PREVIOUS STUDIES.** There is a lack of OGTT-based studies investigating the metabolic state and the prevalence of silent diabetes among all-comer patients undergoing PCI. The German Silent Diabetes study, which performed OGTT in a more heterogeneous population of 1,015 "nondiabetic" patients who all underwent coronary angiography but differed significantly regarding the presence and the severity of coronary artery disease, identified silent diabetes in 14% and IGT in 34% of patients (16). Data on 3-year mortality were available in 87.3% of study patients, showing no significant difference in the proportion of silent diabetes at baseline among survivors of 3-year follow-up versus patients who had died (14.1% vs. 19.7%; p = 0.26) (23).

In addition, some previous studies in broad populations of PCI patients used $HbA_{1c}$ instead of OGTT to identify silent diabetics (13,24,25). Of 445 "nondiabetic" patients in the TWENTE trial who had $HbA_{1c}$ measurements, 10% were classified as having silent diabetes and showed a higher risk of periprocedural MI following the implantation of second-generation DES (13). Furthermore, a study from Israel in 760 PCI patients found 29% $HbA_{1c}$-diagnosed silent diabetics; in that study silent diabetes was independently associated with a 1.4-fold increase in the risk of major cerebrovascular and cardiovascular endpoints at 1-year follow-up (24).

Several previous studies focused on specific subsets of PCI patients, such as patients undergoing elective PCI or experiencing non-ST-segment elevation MI or ST-segment elevation MI (25–28). All of these studies used diagnostic approaches other than OGTT to assess the metabolic state. A recent study

**FIGURE 3** Kaplan-Meier Curves at 1-Year Follow-Up




Kaplan-Meier curves for **(A)** target vessel myocardial infarction and **(B)** target vessel revascularization at 1-year follow-up. *Timing of OGTT. Abbreviations as in Figure 2.

**TABLE 4 Clinical Events in Metabolic States Based on OGTT Classifications (N = 988)**

| | OGTT-Based Classification | | | Unadjusted HR (95% CI) | | Adjusted HR* (95% CI) | |
|---|---|---|---|---|---|---|---|
| | Abnormal Glucose Metabolism | | | | | | |
| | Silent DM (n = 69) | Pre-DM (n = 132) | NG (n = 788) | Silent DM vs. NG | Pre-DM vs. NG | Silent DM vs. NG | Pre-DM vs. NG |
| TVF (primary endpoint) | 9 (13.2) | 8 (6.1) | 22 (2.8) | 5.00 (2.30–10.87) | 2.20 (0.98–4.94) | 4.21 (1.93–9.21) | 2.27 (1.00–5.13) |
| Death | 1 (1.5) | 0 (0) | 2 (0.3) | 0.17 (0.02–1.89) | – | – | – |
| Cardiac death | 1 (1.5) | 0 (0) | 0 (0) | – | – | – | – |
| Any MI | 7 (10.3) | 5 (3.8) | 14 (1.8) | 5.95 (2.40–14.74) | 2.14 (0.77–5.93) | 4.79 (1.92–11.96) | 2.14 (0.77–5.97) |
| Periprocedural MI | 7 (10.3) | 5 (3.8) | 12 (1.5) | 6.89 (2.71–17.51) | 2.49 (0.88–7.06) | 5.55 (2.16–14.22) | 2.43 (0.85–6.92) |
| Target vessel MI | 7 (10.3) | 5 (3.8) | 14 (1.8) | 5.95 (2.40–14.74) | 2.14 (0.77–5.93) | 4.79 (1.92–11.96) | 2.14 (0.77–5.97) |
| Revascularization | 3 (4.4) | 6 (4.5) | 25 (3.2) | 1.41 (0.43–4.68) | 1.45 (0.59–3.53) | 1.43 (0.43–4.79) | 1.49 (0.61–3.65) |
| Target vessel revascularization | 3 (4.4) | 3 (2.3) | 11 (1.4) | 3.23 (0.90–11.58) | 1.64 (0.46–5.87) | 2.82 (0.77–10.30) | 1.78 (0.49–6.50) |
| MACE | 9 (13.2) | 7 (5.3) | 22 (2.8) | 5.00 (2.30–10.88) | 1.92 (0.82–4.50) | 4.25 (1.94–9.28) | 1.94 (0.82–4.58) |

Values are n (%) unless otherwise indicated. The primary endpoint (TVF) consists of cardiac death, target vessel MI, or target vessel revascularization. MACE consists of any death, any MI, emergent CABG, or clinically indicated coronary revascularization. *Adjusted by use of multivariate Cox proportional hazards model (including age, sex, hypercholesterolemia, previous MI, and previous revascularization).

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 to 3.

from the United States in patients with ST-segment elevation MI identified silent diabetes in 9.2%; both in-hospital and 3-year mortality of patients with silent diabetes were found to be significantly increased (25). A study in 500 elective PCI patients with $HbA_{1c}$ levels <7.0% showed that an $HbA_{1c}$ between 6% and 7% independently predicted cardiovascular events (26). Another study from the United States identified 14% patients with silent diabetes based on abnormal FPG levels among PCI patients with acute coronary syndromes and showed silent diabetes to independently predict mortality (27). A rate of 18% silent diabetics was reported by another group, showing a significant relation with medium-term follow-up after PCI (28). Nevertheless, most of the aforementioned studies examined patients who were treated with balloon angioplasty or bare-metal stents (26–28)—techniques and devices that have been greatly replaced by PCI with implantation of contemporary DES. More recently, a study in 4,176 Dutch patients with ST-segment elevation MI showed that elevated $HbA_{1c}$ levels were independently associated with mortality, but the prevalence and clinical outcome of patients with silent diabetes were not reported (29).

**IMPLICATIONS.** Our findings suggest that screening for abnormal glucose metabolism may be advisable, as it was associated with an increased adverse event

**TABLE 5 Clinical Events Including HRs in Metabolic States Based on $HbA_{1c}$ and FPG Classifications**

| | $HbA_{1c}$ + FPG-Based Classification | | | Unadjusted HR (95% CI) | | Adjusted HR* (95% CI) | |
|---|---|---|---|---|---|---|---|
| | Abnormal Glucose Metabolism | | | | | | |
| | Silent DM (n = 33) | Pre-DM (n = 217) | NG (n = 738) | Silent DM vs. NG | Pre-DM vs. NG | Silent DM vs. NG | Pre-DM vs. NG |
| TVF (primary endpoint) | 4 (12.1) | 12 (5.5) | 20 (2.7) | 4.09 (1.41–11.83) | 1.80 (0.90–3.61) | 3.31 (1.13–9.70) | 1.65 (0.82–3.33) |
| Death | 0 (0) | 1 (0.5) | 2 (0.3) | – | 1.70 (0.15–18.78) | – | 1.85 (0.17–20.64) |
| Cardiac death | 0 (0) | 1 (0.5) | 0 (0) | – | – | – | – |
| Any MI | 4 (12.1) | 8 (3.7) | 14 (1.9) | 6.55 (2.16–19.91) | 1.96 (0.82–4.67) | 5.38 (1.75–16.62) | 1.83 (0.76–4.40) |
| Periprocedural MI | 4 (12.1) | 8 (3.7) | 12 (1.6) | 7.57 (2.44–23.46) | 2.28 (0.93–5.58) | 6.24 (1.98–19.69) | 2.17 (0.88–5.36) |
| Target vessel MI | 4 (12.1) | 8 (3.7) | 14 (1.9) | 6.55 (2.16–19.91) | 1.96 (0.82–4.67) | 5.38 (1.75–16.62) | 1.83 (0.76–4.40) |
| Revascularization | 0 (0) | 10 (4.6) | 24 (3.3) | – | 1.43 (0.68–2.98) | – | 1.37 (0.65–2.88) |
| Target vessel revascularization | 0 (0) | 5 (2.3) | 12 (1.6) | – | 1.42 (0.50–4.03) | – | 1.24 (0.43–3.54) |
| MACE | 4 (12.1) | 12 (5.5) | 22 (3.0) | 4.27 (1.47–12.39) | 1.88 (0.93–3.80) | 3.50 (1.19–10.30) | 1.75 (0.86–3.56) |

Values are n (%) unless otherwise indicated. The primary endpoint (TVF) consists of cardiac death, target vessel MI, or target vessel revascularization. MACE consists of any death, any MI, emergent CABG, or clinically indicated coronary revascularization. *Adjusted by use of multivariate Cox proportional hazards model (including age, sex, hypercholesterolemia, previous MI, and previous revascularization).

Abbreviations as in Tables 1–4.

risk—in particular of periprocedural MI. The lipid-rich plaque composition and the hypercoagulable state augment the atherothrombotic risk in patients with hyperglycemia and diabetes (7,11), and might have contributed to our findings. Others have also postulated that pre-diabetes poses an increased risk for cardiovascular events, justifying efforts to improve glucose metabolism and delay conversion to diabetes (10,30). Future studies should evaluate approaches aiming at early detection of silent diabetes and pre-diabetes in patients undergoing PCI and ways to reduce their increased adverse event rates. As recently confirmed by the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients) registry the presence of DM is associated with increased thrombotic but not bleeding events, thereby reinforcing the potential need for longer or more potent platelet inhibition in such patients (31). In this context, it will be important to take into account the increased platelet reactivity in diabetics (32) who have shown a reduced sensitivity to antiplatelet drugs (33).

**DIAGNOSTIC TESTS TO DETECT ABNORMAL GLUCOSE METABOLISM.** OGTT is an established approach to assess glucose metabolism and has detected more patients with DM in the general population as well as in patients with coronary disease (14,34). On the other hand, assessment of $HbA_{1c}$ represents a straightforward, robust, and cheap diagnostic test that is more convenient, as it can be done in the nonfasting state, and it showed in previous studies a higher pre-analytical stability and lower measurement variation (13). The fact that $HbA_{1c}$ is not affected by acute, stress-related effects on glucose metabolism makes it more reliable than fasting glucose in the acute setting and particularly valuable to detect abnormal glucose metabolism in patients with acute coronary syndromes (35). Nevertheless, as both diagnostic tests do not necessarily detect the same individuals with abnormal glucose metabolism, they may be complementary rather than competitive. In fact, in an "ideal world" without financial and logistic constraints, it may be of value to assess FPG, 2 h post-load glucose and $HbA_{1c}$ levels in patients who undergo PCI. However, conducting OGTT is much more labor intensive and onerous on patients, and thus more difficult to integrate into routine clinical practice.

Of further note, patients with diabetes and established cardiovascular disease have recently been shown to substantially benefit in terms of reduced cardiovascular mortality (≥20% reductions) from newer diabetes agents, such as empagliflozin and liraglutide, as recently reviewed (36). Thus, detecting silent diabetes may allow more patients to potentially benefit from such therapies sooner. Such testing would also allow better emphasis of and stronger encouragement and support toward positive lifestyle changes to mitigate diabetes development in patients newly identified with pre-diabetes.

**STUDY LIMITATIONS.** Although we almost reached our initial goal of performing OGTT in 1,000 patients, we cannot exclude that somewhat healthier individuals agreed to participate. OGTT was performed 4 to 6 weeks after the index PCI and therefore after the occurrence of any periprocedural events, which excluded patients with PCI-related lethal events. It is unlikely, but cannot be entirely ruled out, that reverse causality might have played a role in the prevalence of silent diabetes in patients who experienced periprocedural events. The timing of OGTT was chosen based on logistic reasons and to avoid any disturbance caused by procedure- and disease-related stress or repair processes after an MI. Data were obtained from patients treated in a single PCI center; however, this high-volume tertiary PCI center was the highest enrolling site in the BIO-RESORT trial, and it exclusively serves an entire region in the east of the Netherlands, which ensured an unselected referral of patients from a large region. All aspects taken together may explain the overall low incidence of clinical events, which is why the results of this study should be considered hypothesis generating only.

## CONCLUSIONS

Abnormal glucose metabolism was detected in 1 of 3 "nondiabetic" PCI patients and was independently associated with a significantly higher event risk. Silent diabetes, either detected by OGTT or $HbA_{1c}$ and FPG, independently predicted worse short-term and 1-year clinical outcomes after treatment with contemporary DES. Future intervention trials should determine whether meaningful benefits accrue from routine glycemia testing in such patients.

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## PERSPECTIVES

**WHAT IS KNOWN?** Diabetic patients have a higher adverse events risk and continue to show a higher mortality despite the development of newer-generation DES. Undetected and thus untreated (silent) diabetes may increase event risks after PCI with contemporary drug-eluting stents.

**WHAT IS NEW?** The BIO-RESORT Silent Diabetes study is the first large-scale study to (also) use OGTT in an all-comer population of "nondiabetic" patients who underwent PCI. The study underlines the importance of silent diabetes and pre-diabetes for post-PCI clinical outcome in all-comers treated with contemporary thin-strut DES. Screening for abnormal glucose metabolism among PCI patients without previously known diabetes is advisable, as it allows identifying subjects at an increased event risk.

**WHAT IS NEXT?** Knowledge about the prevalence of abnormal glucose metabolism among PCI all-comers and the timing of their adverse events is of great importance for developing concepts and future studies aiming at a risk reduction. It may also allow more patients to benefit from newer diabetes therapies with proven benefits in patients with diabetes plus coronary artery disease.

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**KEY WORDS** DES, drug-eluting stent(s), $HbA_{1c}$, impaired glucose tolerance, OGTT, oral glucose tolerance testing, PCI, percutaneous coronary intervention, silent diabetes

**APPENDIX** For a supplemental figure, please see the online version of this paper.