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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;■:■–■) © 2018 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/).

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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

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).

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 Helsinki and was approved by the Medical Ethics

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