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Prediabetes and its Impact on Clinical Outcome After Coronary Intervention in a Broad Patient Population

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ABSTRACT

Aims

It is unclear whether detection of prediabetes(Pre-DM) by routine assessment of glycated haemoglobin A1c(HbA1c) and fasting plasma glucose(FPG) among patients undergoing percutaneous coronary intervention(PCI) with contemporary drug-eluting stents(DES) may help identify subjects with increased event risk. We assessed the relation between glycaemia status and 1-year outcome after PCI.

Methods and results

Glycaemia status was determined in 2,362 non-diabetic BIO-RESORT participants, treated at all four study sites, to identify Pre-DM (HbA1c 42-47mmol/mol; FPG 6.1-6.9mmol/L) and unknown diabetes mellitus(DM) (HbA1c≥48mmol/mol; FPG≥7.0mmol/L). Another 624 patients had medically treated DM. The main composite endpoint consisted of death, myocardial infarction, or revascularisation.

Glycaemic state was known in 2,986 participants: 324(11%) patients had Pre-DM, 793(27%) had DM(known or new), and 1,869(63%) patients had normoglycaemia. Pre-DM and DM patients differed from normoglycemic patients in cardiovascular risk factors. The composite endpoint occurred in 11.1% in Pre-DM, 10.5% in DM, and 5.7% in normoglyacemia($p<0.001$). Pre-DM was associated with a 2-times higher event risk compared to normoglycaemia(adj.HR 2.0, 95%CI:1.4-3.0).

Conclusions

Following PCI with contemporary DES, all-comers with Pre-DM had significantly higher event risks than normoglycemic patients. In non-DM patients requiring PCI, routine assessment of HbA1c and FPG appears to be of value to identify subjects with increased event risk.

Keywords: ***ACS / NSTE-ACS***; ***Stable angina***; Diabetes; Drug-eluting stent; Miscellaneous; Clinical research

Condensed abstract

In all-comer patients who are treated with contemporary drug-eluting stents, prediabetes defined by HbA1c and fasting plasma glucose levels at admission is a strong, independent predictor of increased adverse event risk. Patients with prediabetes had a two-fold higher risk of experiencing the composite endpoint of any death, myocardial infarction or any revascularisation. Routine assessment of HbA1c and FPG at measurement in PCI patients may help identify patients with Pre-DM who are an increased risk of adverse events.

Abbreviations

DES=Drug-eluting stents; DM=Diabetes mellitus; FPG=Fasting plasma glucose; HbA1c=Haemoglobin A1c; IEC=International Expert Committee; MACE=Major adverse cardiac events; NG=Normoglycaemia; NICE=National Institute for Health and Care Excellence; Pre-DM=Pre-diabetes

INTRODUCTION

Before the onset of type 2 diabetes mellitus (DM), some patients can experience for many years an abnormal glucose metabolism which is a risk factor for coronary artery disease.[1,2] A metabolic state with borderline high glucose levels that do not meet the diabetes mellitus (DM) criteria is referred to as prediabetes(Pre-DM), although some prefer the term risk of diabetes.[3] Pre-DM can be detected by measuring glycated haemoglobin A1c(HbA1c), which gives an indication of long-term blood glucose concentration, and fasting plasma glucose (FPG).[4,5] Because HbA1c measurements do not require fasting or a glucose load, and are not affected by acute changes in glucose levels due tot stress or acute illness, they are easy to use in emergency settings and show only limited within-day or day-to-day variation.[4-7]

General population studies have investigated the association between cardiovascular risk and glucose abnormalities to a great extent, showing in subjects without known DM that elevated HbA1c is a risk factor for cardiovascular events.[2,8] In addition, in patients, with or

without known DM, who had an ST-elevation MI, elevated HbA1c levels were associated with increased mortality.[4,9,10] Moreover, DM increases the event risk after coronary stenting.[11-15] Nevertheless, there is a lack of data on the potential relevance of pre-DM for clinical outcome of all-comer patients with proven obstructive coronary disease, who require percutaneous treatment with current drug-eluting stents(DES).

The BIO-RESORT randomised trial recently examined the outcome of all-comer patients, who underwent percutaneous coronary intervention(PCI) with implantation of contemporary DES, showing similar and very low clinical event rates for all stents used.[16] In this pre-specified analysis of the BIO-RESORT trial, we assessed the relation between Pre-DM and 1-year clinical outcome after PCI.

METHODS

Study design and patients

In the investigator-initiated, multicenter, randomised BIO-RESORT trial, all-comer patients were treated with PCI and contemporary biodegradable polymer or durable polymer DES. Both design and primary outcome of BIO-RESORT, which is registered with ClinicalTrials.gov(NCT01674803), has been described previously.[16] All four clinical study sites, located in the Netherlands, were encouraged to determine in non-DM patients HbA1c levels at baseline in order to identify patients with Pre-DM or newly diagnosed DM, if no HbA1c levels were available the fasting plasma glucose levels were used. In addition, the presence of known DM was recorded in the study files. HbA1c was measured using Tina-quant 3rd generation assay on a Cobas 6000 analyser (Roche Diagnostics, Almere, the Netherlands) or Capillarys 2 (Sebia, Lisses, France) calibrated with IFCC standards. The trial complied with the CONSORT 2010 Statement and Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centres. All patients provided written informed consent.

Glycaemic categories

Based on HbA1c and FPG levels measured at the index hospitalisation, and medical history, patients were stratified into three groups. Glycaemic categories were based on the National Institute for Health and Care Excellence(NICE)[17] and International Expert Committee(IEC) 2009 criteria.[18] DM was defined as either known DM for which patients received medical treatment (either insulin or oral antidiabetics) or newly diagnosed DM, defined by an HbA1c ≥48 mmol/mol(≥6.5%), or FPG≥7.0mmol/L. Pre-DM was defined by HbA1c 42–47 mmol/mol (6.0%-6.4%) and FPG 6.1-6.9mmol/L and normoglycaemia by HbA1c levels ≤41 mmol/mol(≤5.9%) or FPG<6.1mmol/L. In addition, we studied glycaemia according to the American Diabetes Association(ADA) recommendations, which advocate for prediabetes an HbA1c≥39mmol/mol(5.7%) but <48 mmol/mol (6.5%), and for new diabetes an HbA1c≥48 mmol/mol (≥6.5%)(consistent with the IEC criteria). Sites were encouraged to assess the levels twice during hospitalization, in case of any discordance between the diagnostic tests, patients were classified into their 'worst' category based on their lab results.

Study endpoints, procedures, and monitoring

Clinical endpoints were pre-specified, using the Academic Research Consortium definitions.[16] Myocardial infarction was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated confirmatory cardiac biomarkers.[19] Revascularisation procedures were considered clinically indicated, if the angiographic percent diameter stenosis of the then treated lesion was ≥50% in the presence of ischemic signs or symptoms, or if the diameter stenosis was ≥70% irrespective of ischemic signs or symptoms.[16,19] The main composite clinical endpoint of the present study comprised (components in hierarchical order): all cause death, myocardial infarction, or revascularisation.[16]

Coronary interventions and concomitant medication did not differ from standard treatment

and were performed according to current medical guidelines.[16] In general, dual anti-platelet therapy was prescribed for 6–12 months. Staged procedures were permitted within 6 weeks and did not count as events. Electrocardiograms were systematically assessed and recommended at routine clinical follow-up. Laboratory tests included systematic assessment of cardiac markers after the intervention and subsequent serial measurements in case of suspected ischemia. Clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone follow-up or a medical questionnaire. There was no routine angiographic follow-up. A formal data safety monitoring committee reviewed the outcome data 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 analyses

Data were reported as frequencies and percentages for dichotomous and categorical variables. Continues variables were expressed as mean±standard deviation(SD). The time to primary endpoint and components thereof was assessed according to Kaplan-Meier methods; the log-rank test was applied for between-group comparisons. Pearson's chi-square test or Fisher's exact test to compare categorical variables were used, and t-test to compare continuous variables.

The relationship between Pre-DM and the composite clinical endpoint of death, myocardial infarction and revascularisation were assessed with cox proportional hazards analyses. A multivariate Cox proportional hazards analysis was used to adjust for potential confounders, accounting for differences in clinical outcome between the groups. Age, gender, body mass index, haemoglobin level at admission, hypertension, positive family history, hypercholesterolemia, smoking, previous MI, previous revascularisation, multivessel disease and clinical syndrome at admission were included in the multivariate analysis. All statistical

tests were two-tailed, P-values<0.05 were considered significant. Statistical analyses were performed with SPSS v.22.

RESULTS

From December 2012 to August 2015, a total of 3,514 participants in the BIO-RESORT trial were treated for obstructive coronary disease with contemporary DES. A total of 624(18%) trial participants had known DM for which they already received medical treatment with insulin or oral antidiabetics at the timing of their PCI. In 2,362 trial participants without known DM, HbA1c levels and FPG were determined at the index procedure: 324(14%) had Pre-DM, 169(7%) had newly diagnosed DM, and 1,869(79%) were normoglycemic.

As a result, glycaemic state was known in 2,986/3,514 (85%) trial participants. They represent the study population of the present analysis, in which Pre-DM was present in 324(11%), DM (known or new) in 793(27%), and normoglycaemia in 1,869(63%) patients. A total of 2,630(99.4%) patients completed 12-month follow-up or had died. Only 2(0.07%) patients were actually lost to follow-up, and 12(0.4%) patients withdrew consent during the trial and were censored (clinical outcome was used until time of withdrawal).

Baseline characteristics of the study population are presented in Table 1. The majority of participants were Caucasian (95%). Patients with Pre-DM and DM were significantly older and had a higher body mass index than normoglycemic patients. Furthermore, they had similar cardiovascular risk profiles with higher rates of hypertension, hypercholesterolemia, and previous myocardial infarction and coronary revascularisation than normoglycemic patients(Table 1). Information on medication prior to hospitalisation and at discharge are provided in *Webappendix T1*.

Clinical outcome data are presented in Table 2. The composite endpoint death, myocardial infarction or revascularisation at 1 year was met by 36(11.1%) pre-DM patients, 83(10.5%)

diabetic patients, and 106(5.7%) normoglycemic patients (p<0.001;Figure 1). The individual components are presented in Figure 2 A, B, and C. Mortality rates were higher in Pre-DM(2.8%) and DM(2.8%) than in normoglycemic patients(1.2%, p=0.006)(Fig.2A). Similar revascularisation rates were found during 1-year follow-up in patients with pre-DM and patients with DM (5.2%, and 5.9%), which were significantly higher than revascularisation rates in normoglycemic patients (3.0%,p<0.001)(Fig.2C).

Multivariate analysis demonstrated that Pre-DM was independently associated with the composite endpoint at 1-year follow-up: Pre-DM patients had a 2-times higher event risk than patients with normoglycaemia (adjusted HR 2.0, 95%CI:1.4-3.0). Adjusted hazard ratios are presented in Table 2 (unadjusted hazard ratios in *Webappendix T2*), there were no significant differences in 1-year event risk between patients with Pre-DM and DM. Revascularisation data on stent level can be found in *Webappendix T3*.

When the ADA definitions were applied, 906(30%) patients were classified as prediabetic with a composite endpoint rate of 8.4% (vs. 5.1% in normoglycemics and 10.6% in diabetics, p<0.001); further details are presented in the *Webappendix T4*.

DISCUSSION

Main findings

In the present prospective study in all-comers, treated with contemporary DES, Pre-DM at baseline was present in 14% of all non-DM patients. Patients with Pre-DM had higher death and revascularisation rates than normoglycemic patients, and the composite clinical endpoint rates were higher in patients with Pre-DM (11.1% versus 5.7%). Multivariate analysis demonstrated a 2-times higher event risk of death, MI and revascularisation in Pre-DM than normoglycaemia.

Patients with Pre-DM and DM showed similar higher risk profiles versus patients with

normoglycaemia, including an older age, higher BMI, and higher rates of hypertension, hypercholesterolemia, prior MI, and prior revascularisation. Most of these variables are components of the metabolic syndrome or linked to insulin resistance, suggesting that individuals with Pre-DM have a 'diabetic phenotype'.[20] Despite the use of contemporary DES, the rates of most clinical endpoints were at least as high in Pre-DM as in DM, which underlines that PCI patients with Pre-DM are prone to experience adverse clinical events. Our data suggest that in non-diabetic all-comer patients scheduled for PCI, routine assessment of HbA1c and FPG may be of great value.

Further studies are needed to corroborate our findings, but the ease of HbA1c and FPG testing, relative cheap cost and the pick-up of somewhere between 11% (using more conservative prediabetes criteria used in Europe) to 30% using the ADA criteria means that many patients at risk of diabetes and a small percentage (4%) with new diabetes are identified with relevant clinical implications for both groups.

Prediabetes and cardiovascular risk

Although oral glucose tolerance testing(OGTT) has been suggested as gold standard in the diagnosis of DM,[21] there has been an increased interest in HbA1c and cardiovascular risk. In 2008 the IEC, appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation, modified previous recommendations and suggested that HbA1c levels would represent a better diagnostic tool for DM than single measures of glucose concentration.[18] The IEC also recommended HbA1c of 6.0-6.4% (42-47mmol/mol) for the identification of an intermediate risk group, i.e. prediabetes, since identification of these individuals provides an opportunity for intervention through lifestyle modification and pharmacological interventions to prevent progression to diabetes.[18] Pragmatic considerations which support the use of HbA1c are that no fasting is required, and that it can be assessed anytime, even shortly after an acute event. This flexibility is different from FPG assessment,

which (ideally) should be performed at least 4 days after an MI to account for the acute phase response.[4-7] As to the comparison of glucose measures for the prediction of *first-onset cardiovascular disease*, results from a meta-analysis of patient-level data from 73 prospective studies suggests that the assessment of HbA1c is equal to or modestly better than the assessment of fasting, random, or post-load plasma glucose.[22]

Several general population studies have been performed to evaluate associations between Pre-DM (according to different definitions) and cardiovascular events, finding an increased risk of composite cardiovascular events, coronary heart disease, stroke, and all cause mortality.[7,8,23]

Previous studies on prediabetes and PCI outcomes

Studies on HbA1c level and clinical outcome after PCI have shown conflicting results. A recent meta-analysis of 20 observational studies involving 22,428 patients, assessed the association between HbA1c level and clinical outcomes in non-diabetic patients with coronary artery disease, showing that elevated HbA1c levels (prediabetes) were associated with long-term mortality.[24] Only 9 of the studies included in this meta-analysis concerned studies in which patients were treated with PCI, of which the majority was treated with bare metal stents or POBA. We will highlight the largest of these studies.

A retrospective, observational study in 4,176 non-diabetic *STEMI patients*, showed that HbA1c levels were independently associated with adverse outcome at 1-year follow-up.[4] In contrast, a Chinese observational registry of STEMI patients with and without DM found that baseline HbA1c levels did not independently predict 30-day clinical outcome (90% had primary PCI with bare metal stents or DES).[25] Nevertheless, follow-up duration of was very short and event rates were low.[25] A single-centre study evaluated the relation between HbA1c and major adverse cardiac events(MACE) in non-diabetic patients, who underwent elective PCI with balloon angioplasty or bare metal stent implantation.[26] The study showed that

abnormal HbA1c was associated with significantly higher risk of MACE and target vessel revascularisation, although it should be noted that event rates were high, which can be explained by the use of bare metal stents. Another recently published retrospective cohort study assessed non-diabetic patients with ischemic heart disease treated with PCI in 2010, with a mean follow-up of 42 months, showing that prediabetes as determined by HbA1c was not associated with long-term adverse cardiovascular outcomes.[27] Again the majority of these patients(>60%) were treated with bare metal stents and groups were relatively small.

A secondary analysis of the EARLY ACS trial showed similar rates of Pre-DM as compared to our trial, in patients who were admitted to the hospital with non-ST-elevated acute coronary syndromes, either treated with PCI or CABG. Their primary outcome was a composite of all-cause death or myocardial infarction at 30-days, showing no significant differences in event rates in prediabetic patients as compared to diabetic patients.[28]

Added value and clinical implications

The previous studies discussed, assessed only specific subsets of PCI patients (i.e. patients with DM, elective patients, or STEMI patients), and generally used techniques or devices that have been greatly replaced (i.e.balloon angioplasty, bare metal stents, or first-generation DES).[4,24-28] Our current study, on the other hand, reports findings of a recent prospective multicentre PCI study in all-comers who were all treated with contemporary newer-generation DES.[16] The findings obtained in patients with Pre-DM, DM, and normoglycaemia, provide present-day evidence of the importance of Pre-DM for the clinical outcome of all-comer patients after PCI with contemporary DES.

Patients with coronary disease share risk factors with the metabolic syndrome and are therefore at an increased risk of developing DM.[5,29] It is important to identify patients with an abnormal glycaemic state as early as possible in order to prevent (or delay) the onset of DM. Routine assessment of glycaemic state in PCI patients may help identify patients with Pre-DM, who are at an increased risk of adverse events. Close follow-up of these patients appears

to be warranted and particular attention should be paid to lifestyle counselling and/or pharmacological therapy to reduce the risk of developing DM, and intensified secondary prevention measure to prevent clinically apparent coronary artery disease (e.g.more aggressive lipid lowering and hypertension treatment). Furthermore, identification of patients with new diabetes can lead them to immediately gain the benefit of newer diabetes therapies that decrease MACE and mortality in patients with diabetes and cardiovascular disease.[30]

Limitations

Glycaemic state was known in 85% of the trial participants, while these proportions are reasonable, data from an even greater share of subjects would have been welcome. OGTT is a well-known method to assess glucose metabolism and has detected more patients with DM in the general population as well as in patients with coronary disease, which is why it ideally would have been assessed also in order to complement the findings of HbA1c and FPG measurements. However, OGTT is more labor intensive and onerous on patients, and thus more difficult to integrate into routine clinical practice. To ensure that results could be generalized as much as possible to common clinical settings, we based the diagnosis of pre-DM, and newly diagnosed DM on HbA1c or FPG values determined at admission. Only in subjects who had a single HbA1c or FPG value determined at the time of discharge, we used that value. For prediabetes there are currently no formal recommendations regarding repeating test for confirmation, however, in the present analysis, in 85% of the patients glycemic testing was performed twice to confirm the diagnosis. Iron deficiency anaemia may increase HbA1c levels; however, Pre-DM is still independently associated with the composite endpoint, despite including haemoglobin levels in the multivariate analysis. Finally, no data were available on the duration of DM before study enrolment or the occurrence of contrast-induced acute kidney injury, which count as predictors of worse prognosis.

CONCLUSIONS

Following PCI with contemporary drug-eluting stents, all-comer patients with Pre-DM had a significantly higher risk of adverse events than normoglycemic patients. In a non-diabetic patient population with obstructive coronary artery disease, routine assessment of HbA1c prior to PCI may be of clinical value.

Impact on daily practice

Routine assessment of HbA1c and fasting plasma glucose in patients requiring PCI with contemporary DES, may help identify a specific subpopulation who are at increased risk of experiencing adverse events. Close follow-up of these patients appears to be warranted and particular attention should be paid to lifestyle counselling and/or pharmacological therapy to reduce the risk of developing DM, and to prevent clinically apparent coronary artery disease.

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Figure Legends

Figure 1. Kaplan-Meier curves of the composite endpoint

Composite clinical endpoint consisting of death, myocardial infarction, or revascularisation at 1-year.

Figure 2. Kaplan-Meier curves of mortality, MI, and revascularisation

A–Event curves for mortality. B–Event curves for myocardial infarction. C–Event curves for revascularisation.

Table 1.Clinical Characteristics

	Study population (n=2,986)			P-values		
	NG	Pre-DM	DM	NG vs. Pre-DM	NG vs. DM	Pre-DM vs. DM
	n=1,869	n=324	n=793			
Age (yrs)	62.9±10.8	65.1±10.8	65.7±10.5	0.001	<0.001	0.40
Men	1393(74.5)	222(68.5)	552(69.6)	0.02	0.009	0.72
BMI (kg/m^2)	26.76±3.8	28.07±4.4	29.11±4.6	<0.001	<0.001	0.001
Hypertension	731(39.1)	160(49.4)	498(62.8)	0.001	<0.001	<0.001
Hypercholesterolemia	668(35.7)	122(37.7)	367(46.3)	0.51	<0.001	0.008
Current smoker	602(33.1)	89(28.4)	190(24.9)	0.11	<0.001	0.23
Family history of CAD	856(47.5)	144(47.2)	318(42.8)	0.93	0.03	0.19
Previous MI	289(15.5)	64(19.8)	184(23.2)	0.05	<0.001	0.21
Previous revascularisation	330(17.7)	83(25.6)	241(30.4)	0.001	<0.001	0.11
Renal insufficiency	32(1.7)	14(4.3)	48(6.1)	0.002	<0.001	0.25
Systolic BP at admission	136±24.5	138±25.9	144±26.2	0.31	<0.001	<0.001
Heart rate (BPM)	68±14.7	70±15.6	74±15.5	0.10	<0.001	<0.001
Hemoglobin at admission(mmol/L)	8.9±0.9	8.7±1.0	8.6±1.0	0.004	<0.001	0.03
LVEF<30%	17(0.9)	7(2.2)	15(2.1)	0.05	0.03	0.77
Clinical syndrome				0.18	<0.001	0.08
STEMI	679(36.3)	99(30.6)	186(23.5)			
NSTEMI	384(20.5)	66(20.4)	187(23.6)			
Unstable Angina	313(16.7)	61(18.8)	146(18.4)			
Stable Angina	493(26.4)	98(30.2)	274(34.6)			
Multivessel treatment	305(16.3)	69(21.3)	145(18.3)	0.03	0.22	0.25
No.of target lesions/pt.	1.29±0.57	1.37±0.65	1.33±0.59	0.02	0.13	0.28
Total stent length/pt.	39.8±27.8	40.9±31.4	39.1±27.2	0.50	0.59	0.35
Number of stents/pt.	1.77±1.07	1.86±1.16	1.78±1.06	0.13	0.81	0.23

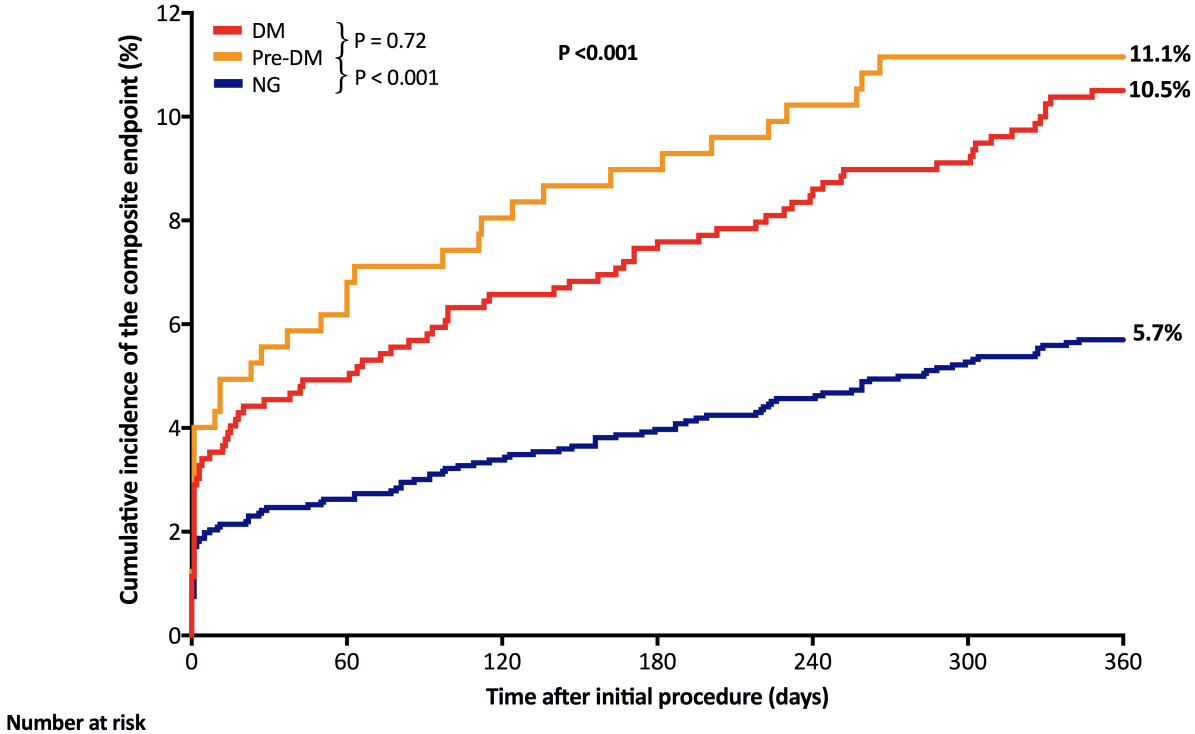
Data are n(%), or mean±SD. BP=blood pressure;BMI=body mass index;CAD=coronary artery disease;DM=Diabetes mellitus; LVEF=Left ventricular ejection fraction;NG=Normoglycaemia;Pre-DM=Prediabetes.

Table 2.Events During 1-Year Follow-up

	Study population (n=2,986)			Log-rank P	Adjusted Hazard ratios* (95%-CI)	
	NG	Pre-DM	DM	Overall	Pre-DM vs. NG	Pre-DM vs. DM
	n=1,869	n=324	n=793			
Death	22(1.2)	9(2.8)	22(2.8)	0.006	2.38 (1.03-5.53)	1.35 (0.56-3.23)
MI	39(2.1)	11(3.4)	26(3.3)	0.12	1.49 (0.74-2.90)	1.19 (0.58-2.48)
Periprocedural MI	32(1.7)	9(2.8)	20(2.5)	0.25	1.39 (0.64-3.00)	1.32 (0.58-3.00)
Any revascularisation†	57(3.0)	17(5.2)	47(5.9)	0.001	1.99 (1.12-3.52)	0.90 (0.50-1.60)
Target vessel revascularisation	28(1.5)	13(4.1)	25(3.2)	0.002	3.11 (1.54-6.27)	1.20 (0.59-2.44)
Target lesion revascularisation	17(0.9)	10(3.2)	15(1.9)	0.003	3.61 (1.57-8.32)	1.87 (0.78-4.45)
Death, MI, or Any revascularisation	106(5.7)	36(11.1)	83(10.5)	<0.001	2.01 (1.35-3.00)	1.20 (0.79-1.82)
Definite stent thrombosis	4(0.2)	1(0.3)	4(0.5)	0.46	1.75 (0.18-17.5)	2.04 (0.18-23.04)

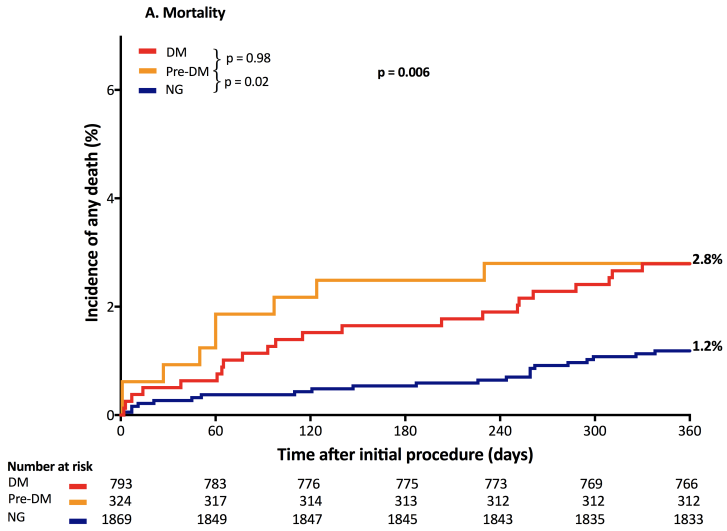
Event rates (n (%)) were calculated by Kaplan-Meier method. †Revascularisations comprised any target-vessel and non-target vessel revascularisation, treated by PCI and/or CABG; all revascularisations were clinically indicated. *Adjusted for age, gender, BMI, hemoglobin level, hypertension, hypercholesterolemia, positive family history, smoking, previous MI, previous revascularization, multivessel disease and clinical syndrome using a Cox proportional hazards model.

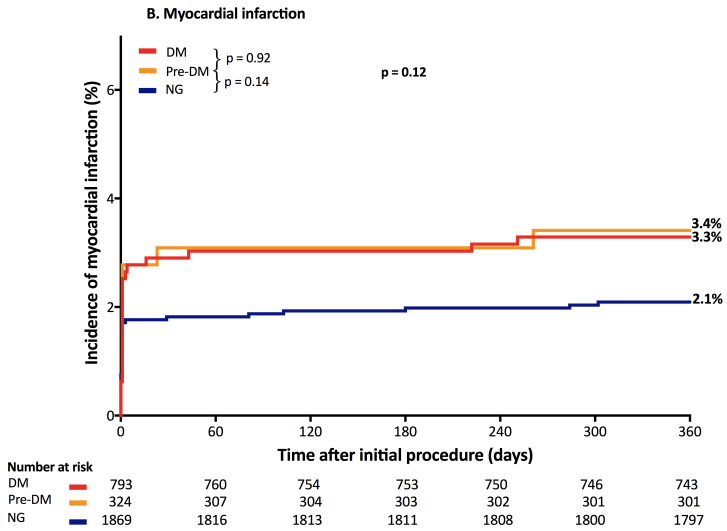
Figure 1. Kaplan-Meier curve of composite endpoint at 1-year follow-up

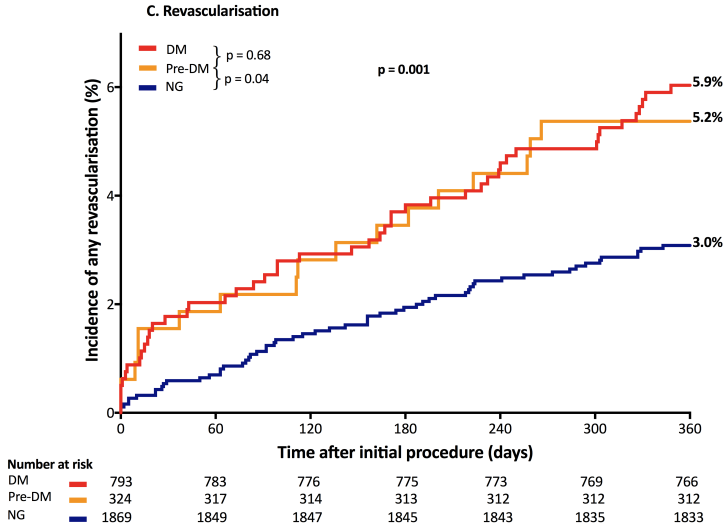


Number at risk

DM	793	750	737	730	722	717	706
Pre-DM	324	302	296	293	289	286	286
NG	1869	1807	1792	1781	1770	1757	1749







SUPPLEMENTAL MATERIAL

Prediabetes and its Impact on Clinical Outcome After Coronary Intervention in a Broad Patient Population

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Webappendix Table 1. Medication at hospitalisation and discharge

	Study population (n=2,986)			P-values			
	NG	Pre-DM	DM	Overall	NG vs. Pre-DM	NG vs. DM	Pre-DM vs. DM
	n=1,869	n=324	n=793				
Medication at hospitalisation							
Aspirin	998 (53.4)	193 (59.6)	527 (66.5)	<0.001	0.04	<0.001	0.03
Oral anticoagulants	173 (9.3)	37 (11.4)	104 (13.1)	0.01	0.22	0.003	0.44
Statin	929 (49.7)	194 (59.9)	568 (71.6)	<0.001	<0.001	<0.001	<0.001
Beta blocker	872 (46.7)	186 (58.1)	500 (63.6)	<0.001	<0.001	<0.001	0.09
Antihypertensive drugs*	751 (40.2)	177 (54.6)	538 (67.8)	<0.001	<0.001	<0.001	<0.001
ACE-inhibitors	382 (20.5)	88 (27.5)	295 (37.5)				
ARB	251 (13.5)	65 (20.3)	197 (25.1)				
Calcium antagonist	288 (15.4)	69 (21.6)	227 (28.9)				
Insulin	-	-	220 (27.7)	-	-	-	-
Oral antidiabetic drugs	-	-	491 (61.9)	-	-	-	-
Medication at discharge							
Aspirin	1835 (98.2)	316 (97.5)	768 (96.8)	0.10	0.43	0.03	0.54
Ticagrelor	869 (46.5)	152 (46.9)	326 (41.1)	0.03	0.89	0.01	0.08
Prasugrel	30 (1.6)	8 (2.5)	17 (2.1)	0.43	0.27	0.34	0.74
Clopidogrel	964 (51.6)	161 (49.7)	443 (55.9)	0.07	0.53	0.04	0.06
Oral anticoagulants	173 (9.3)	37 (11.4)	104 (13.1)	0.01	0.22	0.003	0.44
Statin	1764 (94.4)	307 (94.8)	726 (91.6)	0.02	0.79	0.007	0.07
Beta blocker	1576 (84.4)	283 (87.3)	693 (87.4)	0.08	0.17	0.04	0.98
Antihypertensive drugs	1401 (75.0)	253 (78.1)	653 (82.3)	<0.001	0.23	<0.001	0.10
ACE-inhibitors	1084 (58.0)	188 (58.0)	456 (57.5)				
ARB	210 (14.6)	47 (22.7)	130 (28.3)				
Calcium antagonist	280 (15.0)	67 (20.7)	228 (28.8)				
Insulin	-	-	227 (28.6)	-	-	-	-
Oral antidiabetic drugs	-	-	512 (64.6)	-	-	-	-

*Antihypertensive drugs included ACE-inhibitos, ARB and/or calcium antagonists. ARB=angiotensine receptor blocker.

Webappendix Table 2. Clinical outcome including hazard ratios.

	Study population (n = 2,645)			Unadjusted Hazard Ratios (95% CI)		Log-rank P-values	
	NG	Pre-DM	DM	Pre-DM vs. NG	Pre-DM vs. DM	Pre-DM vs. NG	Pre-DM vs. DM
	n = 1,869	n = 324	n = 793				
Death	22 (1.2)	9 (2.8)	22 (2.8)	2.40 (1.10-5.20)	1.01 (0.47-2.19)	0.02	0.98
MI	39 (2.1)	11 (3.4)	26 (3.3)	1.64 (0.84-3.19)	1.04 (0.51-2.10)	0.14	0.92
Periprocedural MI	32 (1.7)	9 (2.8)	20 (2.5)	1.62 (0.77-3.40)	1.10 (0.50-2.42)	0.19	0.81
Any Revascularization	57 (3.0)	17 (5.2)	47 (5.9)	1.77 (1.03-3.05)	0.89 (0.51-1.55)	0.04	0.68
Target vessel revascularisation	28 (1.5)	13 (4.1)	25 (3.2)	2.76 (1.43-5.34)	1.29 (0.66-2.52)	0.002	0.46
Target lesion revascularisation	17 (0.9)	10 (3.2)	15 (1.9)	3.49 (1.60-7.63)	1.65 (0.74-3.68)	0.001	0.21
Death, MI, or any revascularization	106 (5.7)	36 (11.1)	83 (10.5)	2.02 (1.39-2.95)	1.07 (0.73-1.59)	<0.001	0.72
Definite stent thrombosis	4(0.2)	1(0.3)	4(0.5)	1.46 (0.16-13.06)	0.61 (0.07-5.49)	0.73	0.66

CI=Confidence interval, DM=Diabetes mellitus, MI=Myocardial infarction, NG=normoglycaemia, Pre-DM=Pre-diabetes.

Webappendix Table 3. Revascularisations at 1-year follow-up, data on stent level.

	NG				Pre-DM				DM			
	All	Biodegradable polymer DES	Durable polymer DES	Logrank-p	All	Biodegradable polymer DES	Durable polymer DES	Logrank-p	All	Biodegradable polymer DES	Durable polymer DES	Logrank-p
	n=1,869	n=1,246	n=623		n=324	n=212	n=112		n = 793	n=533	n=260	
Any Revascularization	57 (3.0)	31 (2.5)	26 (4.2)	0.05	17 (5.2)	9 (4.4)	8 (7.3)	0.26	47 (5.9)	30 (5.7)	17 (6.8)	0.59
Target vessel revascularisation	28 (1.5)	14 (1.1)	14 (2.3)	0.06	13 (4.1)	5 (2.4)	8 (7.3)	0.04	25 (3.2)	17 (3.2)	8 (3.2)	0.96
Target lesion revascularisation	17 (0.9)	10 (0.8)	7 (1.1)	0.50	10 (3.2)	3 (1.5)	7 (6.4)	0.02	15 (1.9)	12 (2.3)	3 (1.2)	0.30

DES=drug-eluting stent; DM=diabetes mellitus, NG=normoglycaemia, Pre-DM=Pre-diabetes. Biodegradable polymer DES used were either Orsiro or Synergy, Durable polymer DES was Resolute Integrity.

Table 4. Clinical events by glycemic states based on ADA definitions

	Study population (n=2,986)			Log-rank P-value
	NG	Pre-DM	DM	Overall
	n=1,288	n=906	n=792	
Death	13 (1.0)	18 (2.0)	22 (2.8)	0.01
MI	22(1.7)	28 (3.1)	26 (3.3)	0.04
Any revascularisation†	35 (2.7)	38 (4.3)	48 (6.2)	0.001
Target vessel revascularisation	16 (1.3)	24 (2.7)	26 (3.3)	0.005
Target lesion revascularisation	11 (0.9)	15 (1.7)	16 (2.1)	0.06
Death, MI, or Any revascularisation	65 (5.1)	76 (8.4)	84 (10.6)	<0.001

Event rates, expressed as n (%), were calculated by Kaplan-Meier method. †Revascularizations comprised any target vessel and non-target vessel revascularization, treated by PCI and/or CABG; all revascularisations were clinically indicated. CI=Confidence interval, DM=Diabetes mellitus, MI=Myocardial infarction, NG=normoglycaemia, Pre-DM=Pre-diabetes.
*Hazard ratios adjusted for age, gender, body mass index, hemoglobin level, hypertension, hypercholesterolemia, positive family history, smoking, previous MI, previous revascularization, multivessel disease and clinical syndrome using a Cox proportional hazards model.