Comparison of Frequency of Periprocedural Myocardial Infarction in Patients With and Without Diabetes Mellitus to Those With Previously Unknown but Elevated Glycated Hemoglobin Levels (from the TWENTE Trial)

Kenneth Tandjung, MD[a], K. Gert van Houwelingen, MD[a], Hanneke Jansen, MD, PhD[a,b], Mounir W.Z. Basalus, MD[a], Hanim Sen, MD[a], Marije M. Löwik, PhD[a], Martin G. Stoel, MD[a], J. (Hans) W. Louwerenburg, MD[a], Frits H.A.F. de Man, MD, PhD[a], Gerard C.M. Linssen, MD, PhD[c], Rogier Nijhuis, MD[d], Mark B. Nienhuis, MD, PhD[e], Job van der Palen, PhD[f,g], Ronald P. Stolk, MD, PhD[b], and Clemens von Birgelen, MD, PhD[a,h,*]

In patients without a history of diabetes mellitus, increased levels of glycated hemoglobin (HbA1c) are associated with higher cardiovascular risk. The relation between undetected diabetes and clinical outcome after percutaneous coronary intervention is unknown. To investigate whether these patients may have an increased risk of periprocedural myocardial infarction (PMI), the most frequent adverse event after percutaneous coronary intervention, we assessed patients of the TWENTE trial (a randomized, controlled, second-generation drug-eluting stent trial) in whom HbA1c data were available. Patients were classified as known diabetics or patients without a history of diabetes who were subdivided into undetected diabetics (HbA1c ≥6.5%) and nondiabetics (HbA1c <6.5%). Systematic measurement of cardiac biomarkers and electrocardiographic assessment were performed. One-year clinical outcome was also compared. Of 626 patients, 44 (7%) were undetected diabetics, 181 (29%) were known diabetics, and 401 (64%) were nondiabetics. In undetected diabetics the PMI rate was higher than in nondiabetics (13.6% vs 6.1%, p = 0.01) and known diabetics (13.6% vs 3.7%, p = 0.11). Multivariate analysis adjusting for covariates confirmed a significantly higher PMI risk in undetected diabetics compared to nondiabetics (odds ratio 6.13, 95% confidence interval 2.07 to 18.13, p = 0.001) and known diabetics (odds ratio 3.73, 95% confidence interval 1.17 to 11.89, p = 0.03). After 1 year, target vessel MI rate was significantly higher in undetected diabetics (p = 0.02) than in nondiabetics, which was related mainly to differences in PMI. Target vessel failure was numerically larger in unknown diabetics than in nondiabetics, but this difference did not reach statistical significance (13.6% vs 8.0%, p = 0.25). In conclusion, undetected diabetics were shown to have an increased risk of PMI. **(Am J Cardiol 2012;xx:xxx)**

Periprocedural myocardial infarction (PMI) is the most frequent adverse event after percutaneous coronary interventions (PCI) outside the setting of ST-segment elevation MI. It has previously been shown that PMI is not necessarily a benign event and that patients with PMI may have a worse prognosis.[1,2] Diabetic patients may be particularly prone to PMI because this disease is associated with dyslipidemia, hypercoagulability, increased atheroma burden, vessel wall inflammation, and development of vulnerable plaques.[3–5] In patients with undetected diabetes, metabolic dysregulation and a long-term hyperglycemic state may result in a similar, perhaps even higher, PMI risk. The relation between increased glycated hemoglobin (HbA1c) and the occurrence of PMI has not yet been examined. We hypothesized that undetected diabetes and diabetes mellitus may be related to PMI. In the present study, we therefore assessed this hypothesis in patients of the The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study (TWENTE)—a randomized controlled trial that compared 2 second-generation drug-eluting stents (DESs) in patients

[a]Department of Cardiology, Thoraxcentrum, Twente, and Medisch Spectrum Twente, Enschede, the Netherlands; [b]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [c]Department of Cardiology, Ziekenhuisgroep, Twente, Almelo, the Netherlands; [d]Department of Cardiology, Ziekenhuisgroep, Twente, Hengelo, the Netherlands; [e]Department of Cardiology, Streekziekenhuis Koningin Beatrix, Winterswijk, the Netherlands; [f]Department of Epidemiology, Medisch Spectrum Twente, Enschede, the Netherlands; [g]Department of Research Methodology, Measurement, and Data Analysis and [h]MIRA, Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, the Netherlands. Manuscript received May 14, 2012; revised manuscript received and accepted July 12, 2012.

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*Corresponding author: Tel: 31-53-487-2105; fax: 31-53-487-2107.
E-mail address: c.vonbirgelen@mst.nl (C. von Birgelen).

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Table 1
Baseline characteristics of patients

	Study Population (n = 626)	Undetected DM (n = 44)	No DM (n = 401)	Known DM (n = 181)	p Value	
					Undetected vs No DM	Undetected vs Known DM
Age (years)	64.7 ± 9.9	66.8 ± 9.7	64.1 ± 9.8	65.5 ± 0.3	0.09	0.46
Glycated hemoglobin (%)	6.25 ± 0.94	6.95 ± 0.74	5.77 ± 0.31	7.13 ± 1.15	<0.001	0.32
Men	450 (72%)	32 (73%)	295 (74%)	123 (68%)	0.91	0.54
Body mass index (kg/m^2)	28.0 ± 4.1	27.7 ± 2.8	27.5 ± 3.8	29.2 ± 4.6	0.75	0.10
Insulin treatment	67 (11%)	—	—	67 (37%)		
Insulin treatment and oral glucose-lowering medication	43 (7%)	—	—	43 (24%)		
Chronic renal failure*	24 (4%)	2 (5%)	11 (3%)	11 (6%)	0.50	0.70
Arterial hypertension	382 (61%)	30 (68%)	227 (57%)	125 (69%)	0.28	0.91
Hypercholesterolemia	402/610 (66%)	24/39 (62%)	246/392 (63%)	132/179 (74%)	0.88	0.25
Current smoker	135 (22%)	11 (25%)	90 (22%)	34 (19%)	0.70	0.36
Family history of coronary artery disease	358 (57%)	16 (36%)	235 (59%)	107 (59%)	0.02	0.02
Myocardial infarction (any)	186 (30%)	15 (34%)	118 (29%)	53 (29%)	0.52	0.53
Previous percutaneous coronary intervention	139 (22%)	6 (14%)	84 (21%)	49 (27%)	0.25	0.06
Previous coronary artery bypass grafting	70 (11%)	4 (9%)	43 (11%)	23 (13%)	0.74	0.51
Clinical indication					0.69	0.51
Stable angina pectoris	426 (68%)	30 (68%)	282 (70%)	114 (63%)		
Unstable angina	120 (19%)	10 (23%)	72 (18%)	38 (21%)		
Non–ST-segment elevation myocardial infarction	80 (13%)	4 (9%)	47 (12%)	29 (16%)		
Clinical indication: acute coronary syndrome	200 (32%)	14 (32%)	119 (30%)	67 (37%)	0.77	0.52
Left ventricular ejection fraction <30%†	15/473 (3%)	1/35 (3%)	6/294 (2%)	8/144 (6%)	0.75	0.51

Data are presented as number (percentage) or mean ± SD.
* Chronic renal failure defined by serum creatinine level ≥130 μmol/L.
† Left ventricular ejection fraction assessed with ultrasound, magnetic resonance imaging, or left ventricular angiography.
DM = diabetes mellitus.

with various clinical presentations with the exception of ST-segment elevation MI.[6]

Methods

The present study was performed in a subpopulation of patients enrolled in the TWENTE trial (*http://www.ClinicalTrials.gov*, NCT01066650) in whom HbA1c levels were measured at the time of the index PCI procedure (±1 month). Details of the TWENTE study have previously been described.[6] In brief, TWENTE is an investigator-initiated, patient-blinded, randomized noninferiority study with limited exclusion criteria in a "real-world" patient population treated at the Thoraxcentrum Twente in Enschede, the Netherlands. From June 2008 through August 2010, 1,391 patients with an indication for PCI with DES implantation were randomized for treatment with the second-generation Resolute stent (Medtronic, Inc., Santa Rosa, California) or Xience V stent (Abbott Vascular, Santa Clara, California). There were no angiographic exclusion criteria. The most important exclusion criterion was recent ST-segment elevation MI.[6] The TWENTE trial was approved by the institutional ethics committee, complied with the Declaration of Helsinki, and all patients provided a written informed consent.

All patients were pretreated with acetylsalicylic acid and clopidogrel. At discharge we prescribed the combination of acetylsalicylic acid 100 mg 1 time/day indefinitely and clopidogrel 75 mg 1 time/day for 1 year. Predilation, direct stenting, stent postdilatation, and/or use of glycoprotein IIb/IIIa antagonists were permitted at the operators' discretion.

The study population was grouped into patients with a known history of diabetes mellitus versus patients without a history of diabetes. Patients without a history of diabetes were then subdivided based on a cut-off HbA1c value of 6.5%; patients with an HbA1c level ≥6.5% were classified as undetected diabetics and patients with an HbA1c level <6.5% as nondiabetics.[7] Assessment of HbA1c was performed with a COBAS Integra 800 analysis system (Roche Diagnostics, Basel, Switzerland) at the department of clinical chemistry of our center.

In all patients cardiac biomarkers and electrocardiograms were systematically assessed and analyzed before and after PCI to identify PMI.[8] Cardiac biomarker measurements were scheduled before PCI and 6 to 18 hours after PCI, with subsequent serial measurements for relevant biomarker increases or complaints until peak increase was established. We used the PMI definition of the Academic Research Consortium: creatine kinase (CK) >2 times upper limit of normal with increase of CK-MB and/or troponin. If baseline cardiac biomarkers were above the upper limit of normal or MI was in progress, PMI was established when (1) there was recurrent chest pain or new electrocardiographic changes consistent with MI with an increase of CK >2 times upper limit of

Table 2
Angiographic and procedural characteristics

	Study Population (n = 626)	Undetected DM (n = 44)	No DM (n = 401)	Known DM (n = 181)	p Value	
					Undetected vs No DM	Undetected vs Known DM
Target lesion coronary artery						
Left anterior descending	316 (51%)	16 (36%)	213 (53%)	100 (55%)	0.04	0.16
Left circumflex	216 (35%)	17 (39%)	140 (35%)	59 (33%)	0.62	0.45
Right	222 (36%)	15 (34%)	137 (34%)	70 (39%)	0.99	0.57
Left main	24 (96%)	2 (5%)	13 (3%)	9 (5%)	0.65	0.91
Bypass graft	19 (3%)	1 (2%)	12 (3%)	6 (3%)	0.79	0.72
Multivessel treatment	156 (25%)	6 (14%)	106 (26%)	44 (24%)	0.06	0.13
Total lesions treated per patient					0.13	0.21
1	384 (61%)	29 (66%)	241 (60%)	114 (63%)		
2	172 (28%)	14 (32%)	110 (27%)	48 (27%)		
≥3	70 (11%)	1 (2%)	50 (13%)	19 (11%)		
Number of stents placed	2.08 ± 1.29	1.75 ± 0.99	2.10 ± 1.29	2.11 ± 1.34	0.08	0.10
American College of Cardiology/American Heart Association class B2 or C lesion treated	361 (58%)	19 (43%)	242 (60%)	100 (55%)	0.03	0.15
De novo coronary lesions only*	582 (93%)	42 (96%)	374 (93%)	166 (92%)	0.58	0.40
≥1 chronic total occlusion	57 (9%)	3 (7%)	41 (10%)	13 (7%)	0.47	0.93
≥1 bifurcation	152 (24%)	15 (34%)	92 (23%)	45 (25%)	0.10	0.21
≥1 bifurcation with side branch treatment	96 (15%)	9 (21%)	59 (15%)	28 (16%)	0.32	0.42
≥1 in-stent restenosis	28 (5%)	1 (2%)	17 (4%)	10 (6%)	0.53	0.37
≥1 small vessel (reference vessel diameter <2.75 mm)	419 (67%)	28 (64%)	275 (69%)	116 (64%)	0.50	0.96
≥1 lesion length >27 mm	141 (23%)	5 (11%)	90 (22%)	46 (25%)	0.09	0.05
Preprocedural Thrombolysis In Myocardial Infarction flow (grades 0–1)	43 (7%)	2 (5%)	29 (7%)	12 (7%)	0.51	0.61
Aggressive stent postdilatation of >18 atm	476 (88%)	30 (81%)	300 (88%)	146 (90%)	0.28	0.12
Side branch occlusion	16 (2.6%)	1 (2.3%)	13 (3.2%)	2 (1.1%)	0.73	0.55
Distal embolization	3 (0.5%)	0 (0%)	1 (0.2%)	2 (1.1%)	0.74	0.48

Data are presented as number (percentage) or mean ± SD.
* Including chronic total occlusion but not grafts and in-stent restenosis.
Abbreviation as in Table 1.

normal or (2) if increased CK after the index MI peaked and the CK level returned below the upper limit of normal when there was an increase of CK >2 times upper limit of normal or (3) if increased CK after the index MI peaked and the CK level did not return below the upper limit of normal, an increase in CK ≥50% above the previous level, and >2 times upper limit of normal confirmed by an increase of CK-MB and/or troponin.[8] Clinical end points included target vessel failure within 1 year (composite end point consisting of cardiac death, target-vessel related MI [or not attributable to a nontarget vessel], or clinically driven target vessel revascularization), individual components of target vessel failure, stent thrombosis and a patient-oriented composite end point consisting of all-cause mortality, any MI, and any repeat revascularization. All clinical end points including stent thrombosis were defined according to the Academic Research Consortium.[8,9]

Clinical follow-up data were obtained at visits at outpatient clinics or, if not feasible, by telephone follow-up and/or medical questionnaire. Follow-up data were available in all patients; 2 patients withdrew informed consent before follow-up at 1 year and thus are not included in the follow-up analysis. Processing of clinical data and adjudication of all adverse clinical events were performed by an independent external contract research organization (Cardialysis, Rotterdam, the Netherlands).

All statistical analyses were performed with SPSS 15.0 (SPSS, Inc., Chicago, Illinois).

When comparing undetected diabetics to nondiabetics and undetected diabetics to known diabetics, differences in categorical variables were assessed with chi-square or Fisher's exact tests, as appropriate, whereas continuous variables were assessed with the Wilcoxon rank-sum test or Student's *t* test, as appropriate. Unless otherwise specified, p values and confidence intervals (CIs) were 2-sided and a p value <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to evaluate diabetic status as an independent predictor of PMI in the subpopulation of undetected diabetics and nondiabetics and in the subpopulation of undetected diabetics and known diabetics. All variables were evaluated as possible predictors, and only those with significance at a p value ≤0.15 for PMI were considered candidate variables for multivariate logistic regression analysis and were assessed for their relation with diabetes. If this relation was also present with significance at a p value ≤0.15, they were included in the model. To obtain a parsimonious model, we started with all candidate variables. Subsequently, we eliminated the variables with the highest p value step by step until the estimate for diabetes changed by ≥10% or only significant predictors remained.

Table 3
Medication at discharge

	Study Population (n = 626)	Undetected DM (n = 44)	No DM (n = 401)	Known DM (n = 181)	p Value	
					Undetected vs No DM	Undetected vs Known DM
Antiplatelet therapy						
Acetylsalicylic acid	619 (99%)	44 (100%)	397 (99%)	178 (98%)	0.51	0.39
Clopidogrel	625 (100%)	44 (100%)	400 (100%)	181 (100%)	1.00	1.00
Other medication						
Statin	536 (86%)	35 (80%)	345 (86%)	156 (86%)	0.25	0.27
β Blocker	518 (83%)	34 (77%)	331 (83%)	153 (85%)	0.39	0.25
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker	321 (51%)	27 (61%)	180 (45%)	114 (63%)	0.04	0.84

Data are presented as number (percentage).
Abbreviation as in Table 1.

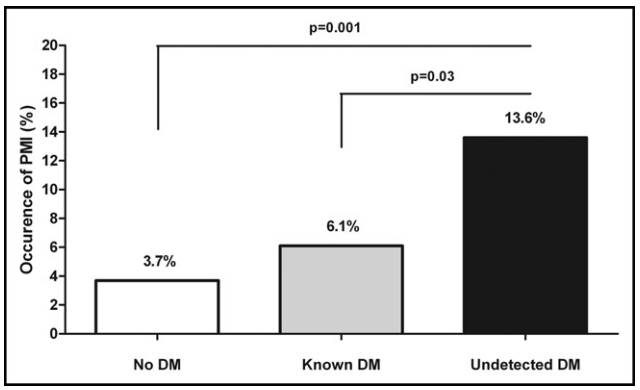

Figure 1. Incidence of periprocedural myocardial infarction (PMI) stratified by diabetic state in patients without a history of diabetes mellitus (DM) and glycated hemoglobin <6.5% (No DM), patients with a history of diabetes mellitus (Known DM), and patients without a history of diabetes mellitus and glycated hemoglobin ≥6.5% (Undetected DM). The p values were calculated with multivariate logistic regression analysis.

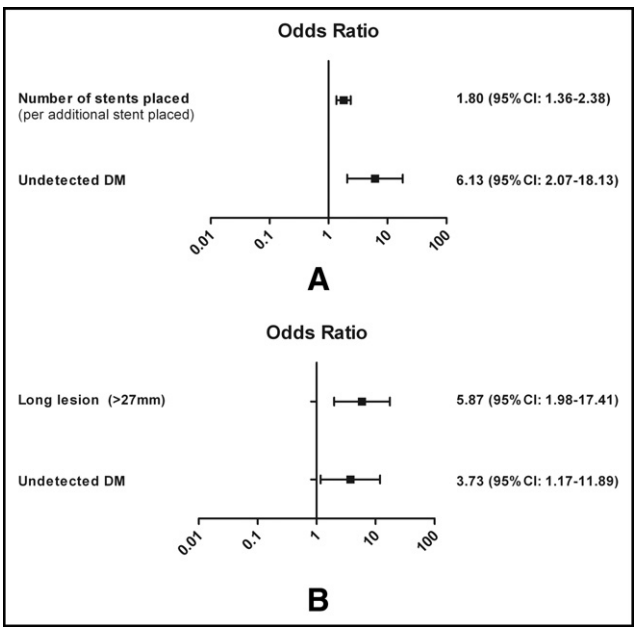

Figure 2. Multivariate adjusted odds ratios for independent predictors of periprocedural myocardial infarction in undetected diabetics and nondiabetics *(A)* and in undetected diabetics and known diabetics *(B)*. Abbreviations as in Figure 1.

Results

Of all patients enrolled in the TWENTE trial, 626 had HbA1c measurements within the predefined time frame and formed the study population of the present analysis. Patients in the study population had more diabetes mellitus (29% vs 16%, p <0.001), chronic renal failure (3.8% vs 1.8%, p = 0.02), hypertension (61% vs 51%, p <0.001), hypercholesterolemia (66% vs 54%, p <0.001), and family history of coronary artery disease (57% vs 50%, p = 0.01) than TWENTE trial patients without HbA1c measurements.

Of the study population 181 (29%) had a history of diabetes mellitus. In addition, 445 patients of the study population (71%) had no history of diabetes mellitus; according to HbA1c levels, 44 patients of the study population were classified as undetected diabetics (7.0%) and 401 as nondiabetic patients (64%).

Baseline characteristics of the study population and subgroups are presented in Table 1. Compared to known diabetic patients and nondiabetic patients, undetected diabetics showed many similarities in baseline characteristics but less often tended to have a family history of coronary artery disease (p = 0.02 for the 2 groups). As may be expected, mean HbA1c levels differed across groups and undetected diabetics had higher HbA1c levels compared to nondiabetic patients (6.95 vs 5.77, p <0.001).

Angiographic and procedural characteristics are presented in Table 2. Undetected diabetics were less frequently treated for left anterior descending coronary artery lesions (36% vs 53%, p = 0.04) and type B2/C lesions (43.2% vs 60.3%, p = 0.03) compared to nondiabetic patients. Diabetic patients were treated more frequently for long lesions (>27 mm) than nondiabetic patients (25% vs 22%, p = 0.05). Side branch occlusion was observed in 2.6% of patients and distal embolization in 0.5%, with no significant difference between groups. Medication at discharge did not differ between groups except for higher rates of angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker prescription in undetected diabetics compared to nondiabetics (p = 0.04; Table 3).

Table 4
Clinical outcome at one year

	Undetected DM (n = 44)	No DM (n = 400)	Known DM (n = 180)	p Value	
				Undetected vs No DM	Undetected vs Known DM
All-cause death	0 (0%)	7 (1.8%)	5 (2.8%)	1.00	0.59
Cardiac death	0 (0%)	5 (1.3%)	4 (2.2%)	1.00	1.00
Target vessel revascularization	1 (2.3%)	13 (3.3%)	10 (5.6%)	1.00	0.70
Target vessel myocardial infarction	6 (13.6%)	16 (4.0%)	14 (7.8%)	0.02	0.24
Periprocedural myocardial infarction	6 (13.6%)	15 (3.8%)	11 (6.1%)	0.01	0.11
Spontaneous myocardial infarction	0 (0%)	1 (0.3%)	3 (1.7%)	1.00	1.00
Target vessel failure	6 (13.6%)	32 (8.0%)	24 (13.3%)	0.25	0.96
Patient-oriented composite end point	6 (13.6%)	42 (10.5%)	31 (17.2%)	0.45	0.57
Target vessel failure without periprocedural myocardial infarction	1 (2.3%)	19 (4.8%)	15 (8.3%)	0.71	0.21
Patient-oriented composite end point without periprocedural myocardial infarction	1 (2.3%)	28 (7.0%)	19 (10.6%)	0.34	0.14
Definite or probable stent thrombosis	0 (0%)	3 (0.8%)	3 (0.8%)	1.00	1.00

Data are presented as number of patients (percentage). Patient-oriented composite end point is a composite consisting of all-cause death, any myocardial infarction, or any revascularization.

Abbreviation as in Table 1.

PMI occurred in 32 patients (5.1%) of the study population. In undetected diabetics, PMI occurred more frequently than in nondiabetic patients (13.6% [6 of 44] vs 3.7% [15 of 401], p = 0.01) and known diabetics (13.6% [6 of 44] vs 6.1% [11 of 181], p = 0.11; Figure 1).

In a model with only nondiabetic patients and undetected diabetics, variables with a univariate association ($p \leq 0.15$) for PMI and diabetic state were multivessel treatment, number of lesions treated, bifurcations, and number of stents placed. Diabetic state and number of stents placed turned out to be independent predictors of PMI in a multivariate model. Using nondiabetic patients as the reference group, the adjusted odds ratio (OR) of PMI was 6.13 in undetected diabetic patients (95% CI 2.07 to 18.13, p = 0.001). In addition, number of stents placed was independently associated with a significantly higher rate of PMI, with an OR of 1.80 (95% CI 1.36 to 2.38, $p < 0.001$) per additional stent placed (Figure 2).

In a separate model with only known diabetics and undetected diabetics, variables with a univariate association ($p \leq 0.15$) for PMI and diabetic state were treatment of ≥1 long lesion (>27 mm) and number of stents placed. Diabetic state and treatment of ≥1 long lesion (>27 mm) were significant independent predictors of PMI. Using known diabetic patients as the reference group, the adjusted OR of PMI was 3.73 in undetected diabetic patients (95% CI 1.17 to 11.89, p = 0.03). In addition, treatment of ≥1 long lesion (>27 mm) was independently associated with a significantly higher rate of PMI (OR 5.87, 95% CI 1.98 to 17.41, p = 0.001; Figure 2).

Clinical follow-up at 1 year is presented in Table 4. Rate of target vessel MI was significantly higher in undetected diabetics (p = 0.02) than in nondiabetic patients caused by increased PMI rates in that group (p = 0.01). In addition, rates of target vessel failure and patient composite end point tended to be lower in nondiabetics compared to undetected diabetics, but this was statistically not significant. When analyzing event rates after discharge from the hospital (thus not including PMI), occurrence of target vessel failure and the patient-oriented composite end point did not differ between groups. Definite or probable stent thrombosis rates were relatively low and similar between groups.

Discussion

The main finding of the present study is that undetected diabetics (i.e., patients without a history of diabetes mellitus but with HbA1c levels ≥6.5%) had a significantly higher risk of PMI compared to nondiabetic patients. Undetected diabetes mellitus was associated with a sixfold increased risk of PMI compared to nondiabetic patients and a risk that was even higher than in known diabetics.

Incidence of PMI, the most common adverse event after stent implantation, ranges from 2% to 20%.[10,11] Various studies have shown that PMI can be associated with an inferior clinical outcome.[1,2,11,12] Risk factors for occurrence of PMI are factors that are associated with an increase of the general atherosclerotic burden such as presence of multivessel disease, lesion eccentricity and calcification, thrombus formation, advanced age, and overt diabetes mellitus.[13,14] Increased risk of adverse events in diabetic patients undergoing PCI persisted after the introduction of DES and was seen in patients treated with first- and second-generation DESs.[14–17]

Studies have shown that even patients without a history of diabetes mellitus but with increased HbA1c levels (i.e., undetected diabetics) have an increased risk of cardiovascular complications,[18,19] but the relation between undetected diabetes mellitus and PMI has yet not been investigated. We hypothesized that patients with undetected (and thus untreated) diabetes mellitus may be prone to PMI because their metabolic dysregulation with its long-term hyperglycemic state leads to dyslipidemia, increased atheroma burden, hypercoagulability, vessel wall inflammation, and vulnerable plaques.[3–5,20]

In the present study, undetected diabetics had a significantly increased risk of PMI compared to nondiabetic patients. PMI may result from macro- or microvascular complications but we did not observe any difference in macrovascular complications such as side branch occlusion or evident distal embolization. This suggests that differences in the incidence of PMI between patient groups may reflect differences in microvascular dysfunction or microvascular obstruction, which may be caused by periprocedural microembolization of atherothrombotic debris as suggested by Böse et al.[21]

A recent study by Timmer et al[19] in nondiabetic patients with ST-segment elevation MI and our present data suggest that a considerable proportion of patients with coronary artery disease are undetected diabetics. As the global disease burden of diabetes mellitus increases,[22] the number of undetected diabetics requiring PCI also is likely to increase. Measurement of HbA1c levels is reproducible and feasible,[7] and it may be a convenient means to assess patients before PCI procedures for risk stratification and potential adjustment of treatment. In the present study, undetected diabetics had a higher PMI risk than known diabetics on antidiabetic medication. Initiation or optimization of pharmacologic treatment for glycemic control before PCI might decrease the hyperglycemia-promoted increase in PMI risk.[4] However, it is still unclear which pharmacologic treatment strategy may be most beneficial in patients without a history of diabetes but with increased HbA1c levels. Initiation of glucose-lowering treatment may be favorable, whereas very intensive glucose regulation could carry an additional risk.[23,24] Other measures to decrease PMI risk may be pretreatment with drugs that have anti-inflammatory and/or antithrombotic properties such as high-dose statins[25] and/or glycoprotein IIb/IIIa antagonists[26,27] or treatment with more aggressive antiplatelet regimens because diabetes is also associated with high platelet reactivity.[28]

Identification of undetected diabetics may also be relevant in the context of clinical studies. Most contemporary randomized DES trials have addressed composite end points, of which PMI is an important component.[6,7,29] It may be prudent to routinely assess the diabetic state before patient enrollment in randomized studies to avoid clustering of these patients in a particular study arm.

The findings of this study should be considered as hypothesis-generating because of the relatively limited number of undetected diabetics. Although we found statistically significant differences in PMI rates, the power of comparison was $<80\%$ (post hoc power analysis revealed that a PMI rate of 15% in the 44 undetected diabetics would have been required to reach 80% power at a significance level of 0.05).

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