Impact of Diabetic Status on Outcomes After Revascularization With Drug-Eluting Stents in Relation to Coronary Artery Disease Complexity

Patient-Level Pooled Analysis of 6081 Patients

Konstantinos C. Koskinas, MD, MSc; George C.M. Siontis, MD; Raffaele Piccolo, MD; Anna Franzone, MD; Alan Haynes, PhD; Julie Rat-Wirtzler, MSc; Sigmund Silber, MD; Patrick W. Serruys, MD; Thomas Pilgrim, MD; Lorenz Räber, MD; Dik Heg, PhD; Peter Jüni, MD; Stephan Windecker, MD

Background—Diabetes mellitus and angiographic coronary artery disease complexity are intertwined and unfavorably affect prognosis after percutaneous coronary interventions, but their relative impact on long-term outcomes after percutaneous coronary intervention with drug-eluting stents remains controversial. This study determined drug-eluting stents outcomes in relation to diabetic status and coronary artery disease complexity as assessed by the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score.

Methods and Results—In a patient-level pooled analysis from 4 all-comers trials, 6081 patients were stratified according to diabetic status and according to the median SYNTAX score ≤11 or >11. The primary end point was major adverse cardiac events, a composite of cardiac death, myocardial infarction, and clinically indicated target lesion revascularization within 2 years. Diabetes mellitus was present in 1310 patients (22%), and new-generation drug-eluting stents were used in 4554 patients (75%). Major adverse cardiac events occurred in 173 diabetics (14.5%) and 436 nondiabetic patients (9.9%; $P<0.001$). In adjusted Cox regression analyses, SYNTAX score and diabetes mellitus were both associated with the primary end point ($P<0.001$ and $P=0.028$, respectively; P for interaction, 0.07). In multivariable analyses, diabetic versus nondiabetic patients had higher risks of major adverse cardiac events (hazard ratio, 1.25; 95% confidence interval, 1.03–1.53; $P=0.026$) and target lesion revascularization (hazard ratio, 1.54; 95% confidence interval, 1.18–2.01; $P=0.002$) but similar risks of cardiac death (hazard ratio, 1.41; 95% confidence interval, 0.96–2.07; $P=0.08$) and myocardial infarction (hazard ratio, 0.89; 95% confidence interval, 0.64–1.22; $P=0.45$), without significant interaction with SYNTAX score ≤11 or >11 for any of the end points.

Conclusions—In this population treated with predominantly new-generation drug-eluting stents, diabetic patients were at increased risk for repeat target-lesion revascularization consistently across the spectrum of disease complexity. The SYNTAX score was an independent predictor of 2-year outcomes but did not modify the respective effect of diabetes mellitus.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00297661, NCT00389220, NCT00617084, and NCT01443104.

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Key Words: coronary artery disease ■ diabetes mellitus ■ drug-eluting stents ■ outcome studies ■ percutaneous coronary intervention

Diabetes mellitus is an established risk factor of atherosclerosis[1] and restenosis after percutaneous coronary interventions (PCI).[2] New-generation drug-eluting stents (DES) provide improved safety and efficacy when compared with balloon angioplasty, bare-metal stents, and early-generation DES,[3] including patients with diabetes mellitus.[4] In addition, advances in medical therapy including high-dose statins seem to mitigate the markedly accelerated progression of native atherosclerosis in diabetic patients.[5] Intriguingly, although diabetes mellitus has historically been considered a powerful

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From the Department of Cardiology, Bern University Hospital, Bern, Switzerland (K.C.K., G.C.M.S., R.P., A.F., T.P., L.R., S.W.); Institute of Social and Preventive Medicine and Clinical Trials Unit (A.H., J.R.-W., D.H., S.W.) and Institute of Primary Health Care (BIHAM) (P.J.), University of Bern, Bern, Switzerland; Department of Cardiology, Heart Center at the Isar, Munich, Germany (S.S.); and International Centre for Circulatory Health, National Heart & Lung Institute, Imperial College London, London, United Kingdom (P.S.).

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Correspondence to Stephan Windecker, MD, Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland. E-mail stephan.windecker@insel.ch

WHAT IS KNOWN

- Patients with diabetes mellitus are prone to develop complex coronary atherosclerotic disease.
- Diabetes mellitus and angiographic coronary artery disease complexity unfavorably affect prognosis after percutaneous coronary interventions, but their inter-relating effect after percutaneous coronary interventions with drug-eluting stents has been controversial.

WHAT THE STUDY ADDS

- In this population undergoing percutaneous coronary interventions with predominantly new-generation drug-eluting stents, the risk of repeat target-lesion revascularization was higher for diabetic versus nondiabetic patients consistently across the spectrum of disease complexity.
- The SYNTAX score emerged as an independent predictor of long-term outcomes but did not modify the respective effect of diabetes mellitus.
- Diabetes mellitus per se, and not higher disease complexity among diabetic patients, is a driver of inferior efficacy and adverse percutaneous coronary interventions outcomes in the era of drug-eluting stents.

predictor of adverse clinical outcomes after PCI, diabetic status did not emerge as a correlate of restenosis[6–8] and was not an independent predictor of mortality in an increasing number of studies in the DES era.[9,10]

The complexity of coronary artery disease (CAD) strongly affects outcomes after PCI. The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score, a comprehensive angiographic scoring system to quantify CAD complexity,[11] can effectively risk-stratify patients undergoing PCI[12,13] and is recommended to guide the choice between revascularization by PCI versus coronary artery bypass grafting (CABG).[14] Although both diabetic status and disease complexity adversely impact prognosis after PCI, their relative contribution to clinical outcomes in the DES era remains controversial. The SYNTAX trial showed a graded risk of repeat revascularization and mortality after PCI in diabetics across higher SYNTAX score values,[15] whereas the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial reported the absence of a prognostic impact of the SYNTAX score in diabetic patients randomized to PCI with early-generation DES.[16] Adding to this conundrum, the SYNTAX score, but not diabetes mellitus, independently predicted the long-term mortality in the SYNTAX trial.[17] Moreover, a pooled analysis of DES trials identified diabetes mellitus as a correlate of repeat revascularization only in the presence of complex lesions, suggesting that DES may mitigate the vasculoproliferative cascade of diabetes mellitus when angiographically simple lesions are treated[18]; however, by focusing only on the focal complexity of treated lesions, that analysis inherently ignored global disease complexity—which is particularly important among diabetics who typically harbor advanced, diffuse disease.

Whether diabetes mellitus remains an independent predictor of adverse outcomes after PCI with DES, ie, outcomes are driven by diabetes mellitus per se or by higher CAD complexity in diabetic patients, is not well established. This study sought to assess the impact of diabetic status on long-term DES outcomes in relation to baseline CAD complexity as assessed by the SYNTAX score. Therefore, we analyzed a large, broadly inclusive population of patients enrolled in 4 all-comers randomized trials and treated with predominantly (75%) new-generation DES.

Methods

Patient Population

Individual patient-level data from 4 randomized clinical studies were pooled: the Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTAX) trial (NCT00297661),[19] the Limus Eluted From a Durable Versus Erodable Stent Coating (LEADERS) trial (NCT00389220),[20] the Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention (RESOLUTE All Comers) trial (NCT00617084),[21] and the Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization (BIOSCIENCE) trial (NCT01443104).[22] All trials had an all-comers design, were conducted between 2004 and 2013 at European institutions with the exclusive use of DES, and had data available on the SYNTAX score.[19–22] Briefly, patients with either stable CAD or acute coronary syndrome were eligible if they had at least 1 lesion with a diameter stenosis ≥50% in a vessel with reference diameter of 2.25 to 4.0 mm (SIRTAX, RESOLUTE All Comers, and BIOSCIENCE trials) or 2.25 to 3.5 mm (LEADERS trial). Inclusion criteria were broad to reflect routine clinical practice. None of the trials imposed restrictions with respect to number of treated lesions, treated vessels, lesion length, or number of stents implanted. In the present analysis, we excluded patients with previous CABG and unavailable SYNTAX scores. All trials were approved by the ethics committees at each study center, and all patients provided written, informed consent.

SYNTAX Score Calculation

Angiographic variables for calculation of the SYNTAX score were prospectively collected by core laboratory analysts in the LEADERS and RESOLUTE trials and retrospectively assessed in the SIRTAX and BIOSCIENCE trials. The SYNTAX score for each patient was calculated by scoring all coronary lesions with diameter stenosis ≥50% in a vessel with reference diameter ≥1.5 mm using the previously described algorithm.[11] All angiograms were scored by 2 experienced interventional cardiologists blinded to patient data; in case of disagreement, the opinion of a third analyst was acquired and the final decision was made by consensus.

Clinical End Points and Definitions

We assessed 2-year clinical outcomes in patients categorized according to diabetic status and SYNTAX score ≤11 or >11, ie, the median value in this cohort. In an exploratory analysis, patients were categorized based on SYNTAX score ≤22 versus >22 using a clinically relevant cutoff introduced in the SYNTAX trial[15] and advocated for decision-making on revascularization by means of PCI or CABG.[14]

The primary end point was major adverse cardiac events (MACE), a composite of cardiac death, nonfatal myocardial infarction (MI), and clinically indicated target lesion revascularization (TLR). The principal efficacy end point was clinically indicated TLR, defined as any repeat percutaneous or surgical intervention caused by a stenosis

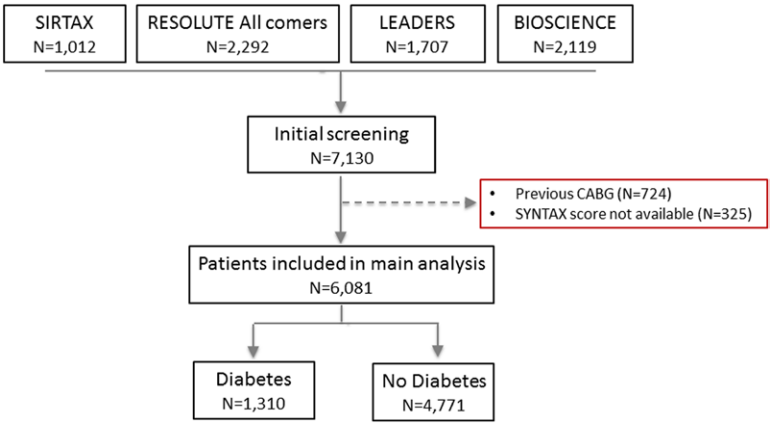

Figure 1. Overview of the study scheme. BIOSCIENCE indicates Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization; LEADERS, Limus Eluted From a Durable Versus Erodable Stent Coating; RESOLUTE, Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; SIRTAX, Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Revascularization; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

within the stent or within the 5-mm borders proximal or distal to the stent. Secondary end points included individual components of the composite end point and target-vessel revascularization (TVR), defined as any revascularization within the major coronary vessel proximal or distal to a target lesion including side branches and the target lesion itself. Cardiac death was defined as any death caused by an immediate cardiac cause, procedure-related mortality, and death of unknown cause. The definition of MI across trials is presented in Table I in the Data Supplement. Stent thrombosis was adjudicated based on Academic Research Consortium criteria.[23] End point definitions were comparable across the trials, and pooled meta-analyses of these trials have been previously published.[24] A blinded clinical events committee independently adjudicated all adverse events for each trial.

Statistical Analyses

Continuous variables are presented as mean±SD or median with interquartile range and were compared using independent samples Student *t* test. Categorical variables are expressed as counts and percentages and were compared using χ^2 or Fisher exact tests as appropriate. Baseline lesion variables were analyzed using General or Generalized Linear-Mixed models, accounting for lesions nested within patients. Clinical outcomes within 2 years were expressed as counts with incidence rates computed according to Kaplan–Meier method. Cox regression analysis was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). Adjusted HR were derived from multiple imputation estimated Cox regressions (20 data sets created using chained equations and estimates combined using Rubin rule), adjusting for baseline variables associated with the primary composite end point (age, sex, body mass index, hypercholesterolemia, renal failure defined as glomerular filtration rate <60 mL/min, history of MI, left ventricular ejection fraction, and clinical indication for index PCI, ie, stable CAD versus STEMI or non–ST-elevation acute coronary syndrome). Multiple-chained equations were used[25] to impute missing values (Table II in the Data Supplement), using all the information of the baseline variables and the primary end point (predictive mean matching with the nearest 5 neighboring continuous variables, logistic regression for binary variables, and ordinal regression for clinical indication). In addition to SYNTAX score categories based on the median value, SYNTAX score was analyzed as a continuous variable to explore the effects of increasing SYNTAX score values on the primary end point. The effect of ln-transformed SYNTAX score was modeled using adjusted Cox's regressions, and an interaction test between diabetic status and SYNTAX score was applied. Analyses were performed with STATA version 14 (Stata Corp, College Station, TX). Differences were considered statistically significant at the 0.05 level.

Results

The present analysis included 6081 patients: 1310 diabetics (22%) and 4771 patients (78%) without medically treated diabetes mellitus (Figure 1). The majority of patients (4554; 75%) received new-generation DES. Median SYNTAX score was 11 (interquartile range, 7–18) and the mean was 13.1±8.7 (Figure 2). Follow-up was available in 5912 patients (97%) at 2 years.

Baseline Characteristics

Baseline characteristics are summarized in Table 1 and Table III in the Data Supplement. Patients with diabetes mellitus were older and more commonly women, had a more advanced cardiovascular risk factor profile, and presented more frequently with stable CAD than nondiabetic patients. Table 2 summarizes angiographic and procedural characteristics. Diabetic patients had higher SYNTAX scores (13.9±8.8 versus 12.9±8.7; $P<0.001$), more frequently underwent multivessel

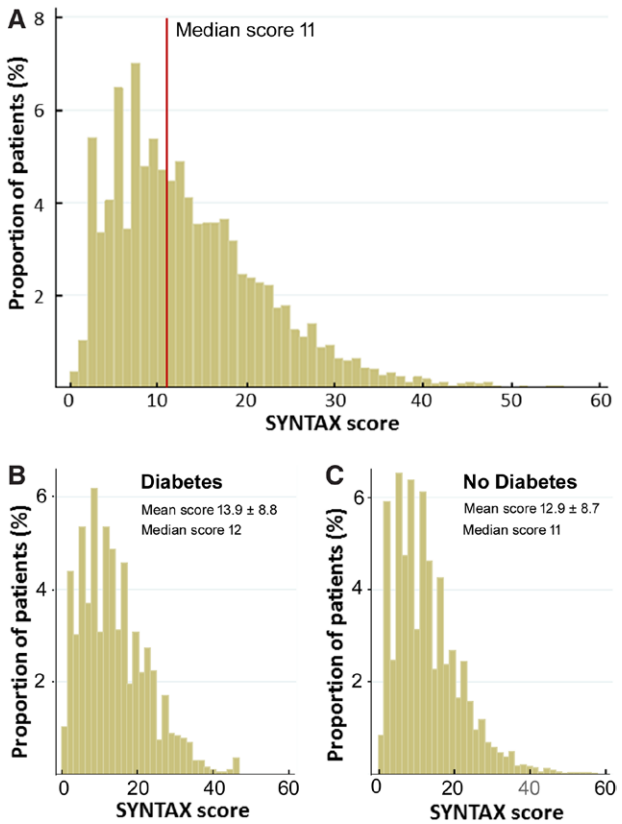

Figure 2. Distribution of the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) scores in the entire population (**A**), in patients with diabetes mellitus (**B**), or without diabetes mellitus (**C**).

Table 1. Baseline Characteristics of Patients With or Without Diabetes Mellitus

Variable	Diabetes Mellitus (n=1310)	No Diabetes Mellitus (n=4771)	*P* Value
Age, y	66.3±10.1	63.5±11.4	<0.001
Female sex, n (%)	372 (28)	1,125 (24)	<0.001
Body mass index, kg/m^2	29.4±4.9	27.1±4.1	<0.001
Insulin-requiring diabetes mellitus, n (%)	431 (33)	…	…
Hypertension, n (%)	1104 (84)	3054 (64)	<0.001
Hypercholesterolemia, n (%)	943 (72)	2906 (61)	<0.001
Renal failure, n (%)	277 (23)	520 (12)	<0.001
GFR, mL/min	81.5±28.5	86.3±28.3	<0.001
Current smoking, n (%)	266 (20)	1,563 (33)	<0.001
Family history of CAD, n (%)	369 (30)	1,584 (35)	0.001
Previous MI, n (%)	359 (28)	1,116 (24)	0.002
Previous PCI, n (%)	458 (35)	1,226 (26)	<0.001
LVEF (%)	55.4±12.5	56.4±11.5	0.02
Clinical presentation, n (%)	n=1235	n=4609	<0.001
Stable CAD	609 (49)	1791 (39)	<0.001
Unstable angina/NSTEMI	454 (37)	1752 (38)	0.43
STEMI	172 (14)	1066 (23)	<0.001
SYNTAX score			
Mean	13.9±8.8	12.9±8.7	<0.001
Median	12	11	<0.001

CAD indicates coronary artery disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

treatment (25% versus 22%; *P*=0.03), but had similar numbers of lesions treated per patient and similar numbers of stents implanted per lesion as did nondiabetic patients.

Clinical Outcomes in Relation to Diabetic Status

At 1 year, diabetic compared with nondiabetic patients had higher unadjusted, but similar adjusted risks of MACE (HR, 1.15; 95% CI, 0.93–1.42; *P*=0.20), TLR (HR, 1.36; 95% CI, 1.00–1.84; *P*=0.051), cardiac death (HR, 1.29; 95% CI, 0.81–2.05; *P*=0.28), and MI (HR, 0.89; 95% CI, 0.64–1.23; *P*=0.47; Figure I in the Data Supplement).

Clinical outcomes within 2 years are shown in Figure 3. In crude analyses, diabetic patients had higher rates of the primary end point (14.5% versus 9.9%), TLR (8.6% versus 5.1%), TVR (9.8% versus 6.5%), cardiac death (4.4% versus 2.2%; *P*<0.001 for all), but not of MI (4.7% versus 4.6%; *P*=0.84). After multivariable adjustment, differences remained significant for MACE (HR, 1.25; 95% CI, 1.03–1.53; *P*=0.026), TLR (HR 1.54, 95% CI 1.18–2.01; *P*=0.002), and TVR (HR, 1.38; 95% CI, 1.08–1.76; *P*=0.011), whereas there was no difference for cardiac death (HR, 1.41; 95% CI, 0.96–2.07; *P*=0.08) and MI (HR, 0.89; 95% CI, 0.64–1.22; *P*=0.45). The risk of definite stent thrombosis did not differ significantly in diabetic versus nondiabetic patients (HR, 1.65; 95% CI, 0.93–2.93; *P*=0.09). A sensitivity analysis in patients treated with new-generation DES (n=4554) showed higher adjusted risk of TLR (HR, 1.63; 95% CI, 1.16–2.27; *P*=0.005) and TVR (HR, 1.41; 95% CI, 1.04–1.92; *P*=0.026), but not of MACE (HR, 1.19; 95% CI, 0.95–1.49; *P*=0.13) in diabetic versus nondiabetic patients (Figure II in the Data Supplement).

Two-Year Clinical Outcomes in Relation to Diabetic Status and SYNTAX Score

The rate of MACE was higher in diabetic versus nondiabetic patients with SYNTAX score ≤11 (11.8% versus 7.2%; *P*<0.001) and >11 (16.7% versus 12.7%; *P*<0.001). In multivariable analyses, there was no formal interaction (P_{int}=0.58) for MACE between diabetic and nondiabetic patients in relation to SYNTAX score ≤11 (HR, 1.46; 95% CI, 1.06–2.03; *P*=0.022) and >11 (HR, 1.10; 95% CI, 0.85–1.41; *P*=0.48). Similarly, there was no interaction of the SYNTAX score with diabetic status on TLR (P_{int}=0.12), TVR (P_{int}=0.38), cardiac death (P_{int}=0.12), MI (P_{int}=0.10), and definite stent thrombosis (P_{int}=0.50; Figure 3). Kaplan–Meier curves for MACE and TLR in relation to diabetic status and SYNTAX score ≤11 versus >11 are shown in Figure 4.

Consistently, an exploratory analysis using SYNTAX score >22 (n=864; 14% of patients) versus ≤22 showed no interaction between the SYNTAX score category and diabetic status on MACE (P_{int}=0.10), TLR (P_{int}=0.43), TVR (P_{int}=0.73), cardiac death (P_{int}=0.99), and MI (P_{int}=0.10; Figure III in the Data Supplement).

Analyses of MACE and TLR in relation to SYNTAX score as a continuous variable are shown in Figure 5. In Cox regression analyses, the HRs of MACE and TLR were associated with the SYNTAX score (*P*<0.001 for both end points)

Table 2. Angiographic and Procedural Characteristics

Variable	Diabetes Mellitus (n=1310)	No Diabetes Mellitus (n=4771)	*P* Value
No. of treated lesions per patient*	1.50±0.72	1.45±0.73	0.22
Multivessel treatment per patient, n (%)	321 (25)	1032 (22)	0.03
No. of lesions	1965	6930	
Target-vessel location per lesion, n (%)			0.17
Left main artery	20 (1)	67 (1.0)	0.79
Left anterior descending artery	811 (41)	3049 (44)	0.03
Left circumflex artery	464 (24)	1587 (23)	0.50
Right coronary artery	668 (34)	2225 (32)	0.12
De novo lesion, n (%)	1810 (93)	6540 (95)	0.001
Occlusion, n (%)	158 (8)	630 (9)	0.16
No. of stents per lesion	1.30±0.65	1.29±0.64	0.87
Total stent length per lesion, mm	24.55±15.65	24.22±14.90	0.40
Mean stent diameter per lesion, mm	2.96±0.47	2.98±0.46	0.04

P values comparing diabetes mellitus vs no diabetes mare derived from *Poisson regression; otherwise *P* values from mixed models for the per-lesion analyses, accounting for lesions nested within patients.

	Diabetes (%) N = 1,310	No diabetes (%) N = 4,771	Crude Analysis HR (95%CI)	p-value	p-value interaction	Adjusted Analysis HR (95%CI)	p-value	p-value interaction
Primary endpoint					0.260			0.58
Overall	173 (14.5)	436 (9.9)	1.46 (1.23-1.75)	< 0.001		1.25 (1.03-1.53)	0.026	
Syntax score ≤11	61 (11.8)	159 (7.2)	1.63 (1.21-2.19)	0.001		1.46 (1.06-2.03)	0.022	
Syntax score >11	112 (16.7)	277 (12.7)	1.31 (1.05-1.63)	0.015		1.10 (0.85-1.41)	0.479	
Cardiac death					0.560			0.125
Overall	52 (4.4)	94 (2.2)	2.03 (1.45-2.85)	< 0.001		1.41 (0.96-2.07)	0.079	
Syntax score ≤11	13 (2.5)	33 (1.5)	1.65 (0.87-3.14)	0.124		1.43 (0.70-2.93)	0.323	
Syntax score >11	39 (5.9)	61 (2.9)	2.08 (1.39-3.10)	< 0.001		1.34 (0.85-2.13)	0.210	
Any MI					0.366			0.102
Overall	59 (4.7)	209 (4.6)	1.03 (0.77-1.38)	0.837		0.89 (0.64-1.22)	0.455	
Syntax score ≤11	22 (4.0)	77 (3.4)	1.19 (0.74-1.92)	0.464		1.18 (0.71-1.96)	0.518	
Syntax score >11	37 (5.3)	132 (5.9)	0.90 (0.63-1.30)	0.588		0.71 (0.47-1.07)	0.102	
Cardiac death or MI					0.952			0.783
Overall	103 (8.4)	282 (6.3)	1.34 (1.07-1.67)	0.012		1.06 (0.82-1.37)	0.644	
Syntax score ≤11	32 (6.0)	103 (4.6)	1.30 (0.87-1.93)	0.194		1.24 (0.80-1.91)	0.330	
Syntax score >11	71 (10.5)	179 (8.2)	1.28 (0.97-1.68)	0.079		0.93 (0.68-1.28)	0.651	
Clinically-indicated TLR					0.245			0.12
Overall	98 (8.6)	220 (5.1)	1.65 (1.30-2.10)	< 0.001		1.54 (1.18-2.01)	0.002	
Syntax score ≤11	37 (7.5)	81 (3.7)	1.94 (1.31-2.86)	< 0.001		1.60 (1.04-2.46)	0.033	
Syntax score >11	61 (9.6)	139 (6.5)	1.44 (1.07-1.95)	0.017		1.47 (1.05-2.08)	0.027	
Clinically-indicated TVR					0.116			0.38
Overall	112 (9.8)	279 (6.5)	1.49 (1.20-1.86)	< 0.001		1.38 (1.08-1.76)	0.011	
Syntax score ≤11	43 (8.7)	100 (4.6)	1.83 (1.28-2.61)	< 0.001		1.52 (1.02-2.27)	0.039	
Syntax score >11	69 (10.7)	179 (8.4)	1.27 (0.96-1.67)	0.096		1.27 (0.93-1.74)	0.138	
Definite stent thrombosis					0.421			0.502
Overall	21 (1.8)	53 (1.2)	1.45 (0.88-2.41)	0.147		1.65 (0.93-2.93)	0.088	
Syntax score ≤11	8 (1.6)	18 (0.8)	1.86 (0.81-4.28)	0.143		2.00 (0.81-4.96)	0.134	
Syntax score >11	13 (1.9)	35 (1.6)	1.21 (0.64-2.28)	0.563		1.44 (0.69-3.03)	0.335	
Definite or probable stent thrombosis					0.276			0.603
Overall	35 (2.9)	98 (2.1)	1.31 (0.89-1.92)	0.174		1.18 (0.76-1.84)	0.460	
Syntax score ≤11	13 (2.6)	32 (1.4)	1.70 (0.89-3.23)	0.108		1.77 (0.88-3.57)	0.107	
Syntax score >11	22 (3.1)	66 (3.0)	1.08 (0.67-1.75)	0.751		0.90 (0.51-1.59)	0.713	

Figure 3. Two-year outcomes in relation to diabetic status and Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score ≤11 vs >11. Hazard ratios (HRs) with respective 95% confidence intervals (CIs) and *P* values are derived from Cox regressions. Adjusted HRs (95% CI) and *P* values are based on multiple imputation estimated Cox regressions, adjusting for baseline variables associated with the primary outcome (age, sex, body mass index, hypercholesterolemia, renal failure, history of myocardial infarction [MI], left ventricular ejection fraction, and clinical indication for percutaneous coronary interventions). TLR indicates target lesion revascularization; and TVR, target-vessel revascularization.

and with diabetes mellitus (*P*=0.028 and *P*=0.04, respectively) without significant interaction (*P*int=0.07 and 0.17, respectively). Similar results were derived in an ancillary analysis imputing SYNTAX scores in patients who were excluded from the main analyses because of missing SYNTAX scores (Table IV in the Data Supplement).

Multivessel treatment at index procedure was an independent predictor of 2-year MACE (*P*=0.008); this association was not significant when the SYNTAX score was entered into the multivariable model (*P*=0.15).

Discussion

This study explored the inter-relating effects of diabetes mellitus and angiographic CAD complexity on long-term PCI outcomes in a sizable, broadly inclusive population of patients treated with predominantly new-generation DES. We found unfavorable efficacy outcomes for diabetic versus nondiabetic patients as reflected by 25% higher adjusted risk of the device-oriented primary end point and 54% higher risk of TLR; diabetic status, however, was not associated with higher cardiac mortality or MI risk in multivariable analyses. Notably, differences in outcomes between diabetic and nondiabetic patients persisted across the spectrum of disease complexity. Although the SYNTAX score was an independent predictor of clinical outcomes, it did not modify the respective effect of diabetes mellitus throughout 2 years of follow-up. Together these findings indicate that diabetes mellitus per se, and not higher disease complexity among diabetic patients, is a driver of inferior efficacy and adverse PCI outcomes in the era of DES.

Impact of Diabetes Mellitus on PCI Outcomes

The role of diabetes mellitus in the pathobiology of native atherosclerosis and in-stent restenosis is well characterized.[26] Studies with balloon angioplasty, bare-metal stents, and early-generation DES consistently identified diabetes mellitus as a risk factor of mortality and repeat revascularization.[1,2,27] Nonetheless, growing evidence has somewhat challenged that notion by demonstrating no excess of angiographic and clinical restenosis in diabetics versus nondiabetic patients treated with DES[6–8] and by identifying diabetes mellitus as a univariate, but not as a multivariate predictor of mortality after PCI.[9,10,17] In the present analysis, diabetes mellitus emerged as an independent predictor of long-term MACE, a difference driven by higher rates of TLR. Although new-generation DES have shown superior efficacy and safety than earlier devices within diabetic populations,[4] in this study, repeat target-lesion revascularizations remained more frequent in diabetic patients, including a sensitivity analysis focusing on new-generation DES. The nondiffering risk of MACE in relation to diabetic status in that sensitivity analysis is a notable hypothesis-generating finding that requires definitive evaluation in prospective trials using contemporary, new-generation DES. Our finding that event rates were numerically higher in diabetic patients at 1 year (Figure I in the Data Supplement)

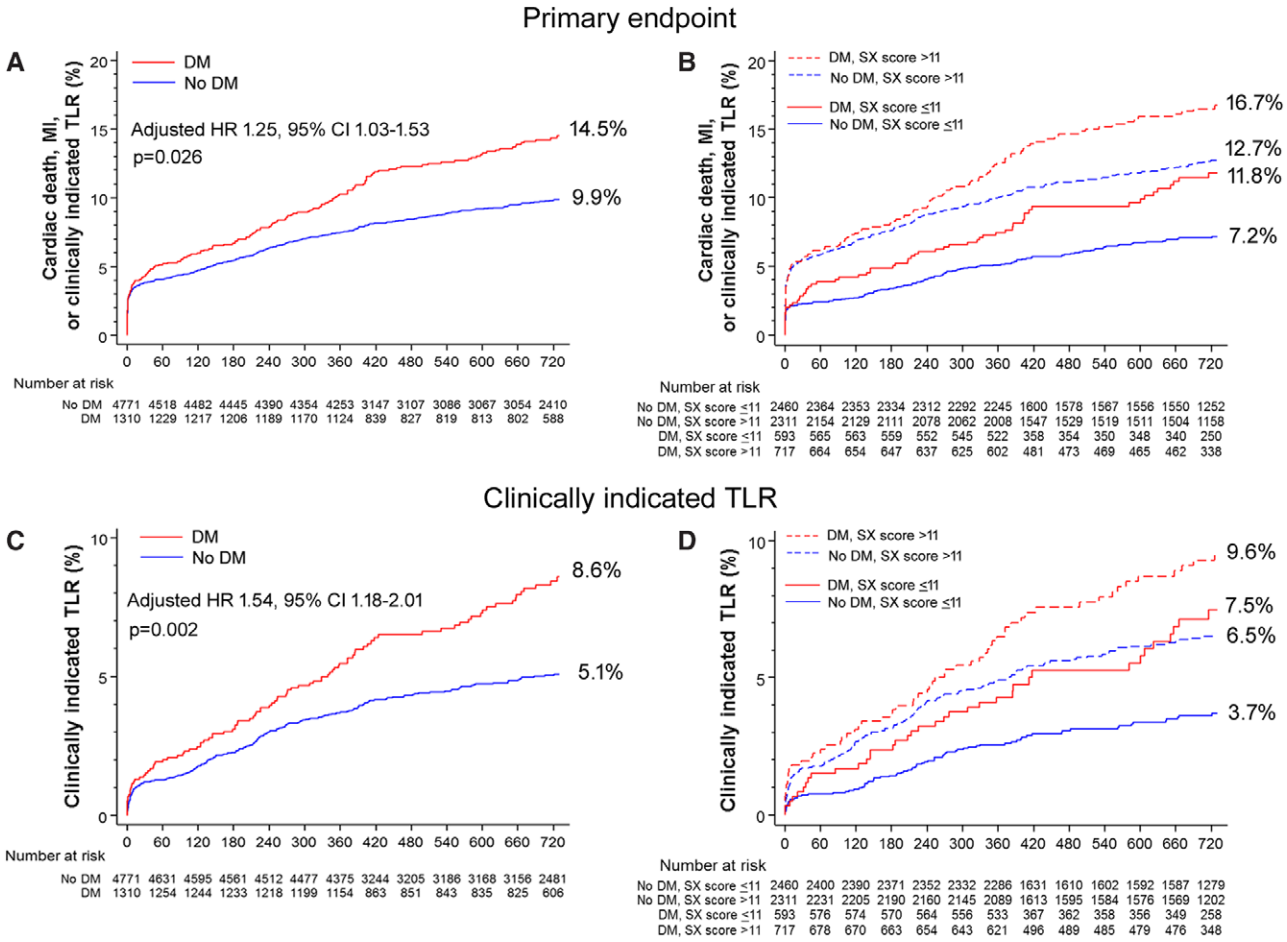

Figure 4. Kaplan–Meier cumulative event curves for the composite end point of cardiac death, myocardial infarction (MI), or clinically indicated target lesion revascularisation (TLR; **A** and **B**) and for the principle efficacy end point, clinically indicated TLR (**C** and **D**) in patients stratified according to diabetic status (**A** and **C**) and further according to Synergy Between PCI With Taxus and Cardiac Surgery (SX) score ≤11 vs >11 (**B** and **D**). CI indicates confidence interval; DM, diabetes mellitus; and HR, hazard ratio.

but only accrued to reach statistical significance within 2 years reflects the cumulative pathobiological sequelae of diabetes mellitus on the coronary vasculature and highlights the caveat of assessing short-term PCI outcomes in diabetic patients.

We found that diabetes mellitus was associated with cardiac death and MI in univariable, but not in multivariable analyses. Although DES did not mitigate the prorestenotic impact of diabetes mellitus in this analysis, cardiac mortality and MI (which are frequently triggered from nontarget lesions that are not treated during the index procedure[28]) were comparable between diabetic and nondiabetic patients. The fact that the individual components of MACE were secondary end points, however, requires consideration. Although in the absence of serial angiographic assessment, this study cannot address progression of native atherosclerotic disease, these findings likely reflect the effectiveness of secondary prevention measures in improving clinical outcomes and attenuating the accelerated progression of coronary atherosclerosis[5] among diabetic patients treated with evidence-based adjunctive medical therapies.

Combined Impact of Diabetes Mellitus and Disease Complexity on 2-Year Clinical Outcomes

Previous analyses of the combined effect of diabetes mellitus and anatomic CAD complexity on PCI outcomes have led to contradictory results. The FREEDOM trial found no significant prognostic impact of the SYNTAX score on outcomes after PCI or CABG in diabetic patients[16] although the SYNTAX score only became operational during that trial.[29] In contrast, in the SYNTAX trial, adverse events increased incrementally across higher SYNTAX score tertiles, driven largely by more frequent revascularization[15]; diabetes mellitus was not an independent predictor of long-term mortality and was therefore not included among the clinical variables of the SYNTAX score II.[17] The present analysis sought to address the relative contribution of diabetes mellitus and CAD complexity to PCI outcomes in a cohort with overall less complex disease, yet with a greater number of patients with intermediate/high (>22) SYNTAX scores (n=864) than the respective PCI subgroups of the SYNTAX and FREEDOM trials. Although SYNTAX score emerged as an independent predictor of MACE and TLR in the present analysis, event rates were consistently higher in diabetic versus nondiabetic patients across the spectrum of CAD complexity. Our finding of similar risks of MACE and TLR between diabetic patients with SYNTAX score ≤11 and nondiabetic counterparts with SYNTAX scores >11 (Figure 4B and 4D) signifies that long-term PCI outcomes are driven by diabetic status per se and not necessarily by the higher disease complexity among diabetic

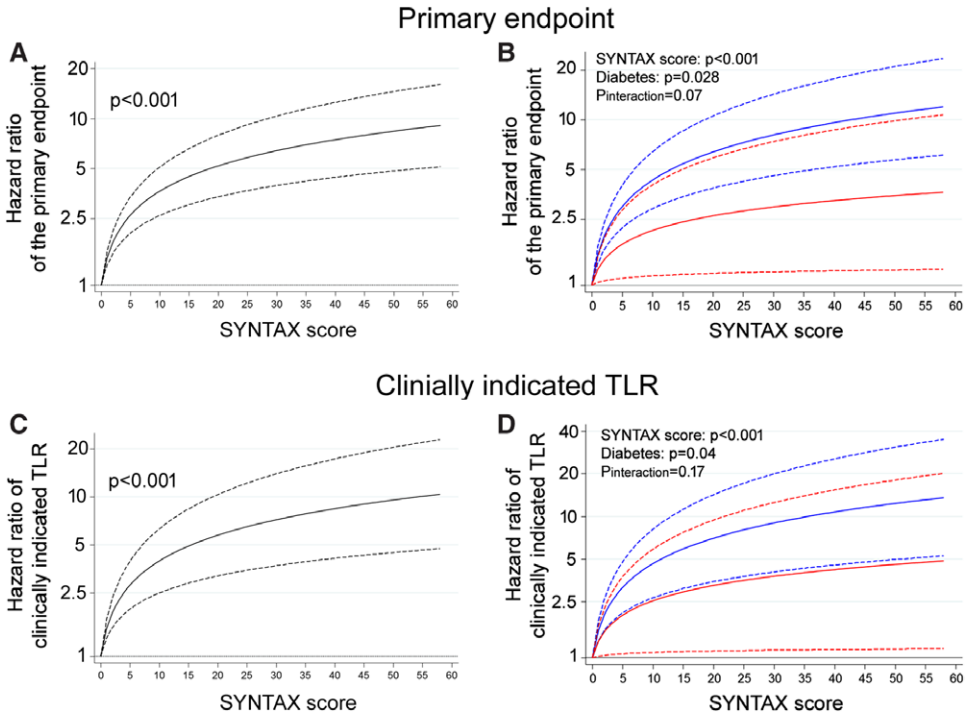

Figure 5. Effects of ln-transformed Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score on the primary composite end point (**A** and **B**) and on clinically indicated target lesion revascularization (TLR; **C** and **D**). Average-adjusted effect of SYNTAX score (**A** and **C**), and stratified by the presence of diabetes mellitus (red lines) or the absence of diabetes (blue lines; **B** and **D**) with *P* values derived from full model. Curves (solid lines) are presented with respective 95% confidence intervals (dashed lines). Patients with SYNTAX score 0 are considered to represent the reference (horizontal line set at hazard ratio=1).

patients. Thus, diabetes mellitus remains a major determinant of restenosis in the era of new-generation DES, even in patients with noncomplex anatomies. These observations support the importance of preventing long-term PCI complications (eg, be means of meticulous attention to the acute PCI result and evidence-based adjunctive medical treatment) particularly in diabetic patients, irrespective of their angiographic extent of disease.

The ability to risk-stratify patients who undergo myocardial revascularization has broad implications for the selection of the preferred treatment strategy (CABG versus PCI).[14] In current European guidelines,[14] PCI is an acceptable alternative to CABG in the setting of SYNTAX scores 23 to 32 in nondiabetic patients but is not advocated in diabetics with SYNTAX scores ≥23 on the basis of the SYNTAX diabetic substudy[30] and a meta-analysis of the SYNTAX and FREEDOM trials.[31] As both trials[15,16] used early-generation DES, one may speculate that newer-generation DES might bridge the existing gap between CABG and PCI with bare-metal stents or earlier DES.[32] In this study—even though there was formally no significant interaction for the primary end point in our exploratory analysis using the 22 score cutoff—point estimates indicate higher MACE and TLR rates in diabetic versus nondiabetic patients with SYNTAX scores ≤22, but not in those with scores >22. In the absence of a CABG group, this analysis cannot address the relative value of each revascularization mode in relation to SYNTAX scores and diabetic status. Randomized trials using exclusively new-generation DES (Evaluation of XIENCE PRIME Everolimus Eluting Stent System [EECSS] or XIENCE V EECSS or XIENCE Xpedition EECSS or XIENCE PRO EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL] trial [NCT01205776]; A Comparison of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention and Coronary Artery Bypass Graft Surgery in Patients With Multivessel Coronary Artery Disease [FAME-3] trial [NCT02100722]) are expected to determine whether PCI outcomes using novel devices remain inferior in diabetic patients with intermediate/high SYNTAX scores, and to define optimal prognostic cutoffs and revascularization strategies in diabetic and nondiabetic patients.

Kedhi et al[18] previously showed that TLR and TVR within one year following PCI with DES were more frequent in diabetic versus nondiabetic patients only in the presence of American College of Cardiology/American Heart Association complex target lesions, without differences when simple lesions were treated. Although the concept that DES may offset the prorestenotic impact of diabetes mellitus for local lesion recurrence in the setting of noncomplex lesion is pathobiologically plausible, that analysis did not account for disease complexity beyond the treated lesion—which is particularly important in diabetic patients who typically harbor diffuse disease. The present study provides complementary insights by assessing global CAD complexity, using an established angiographic tool for this purpose.

This study advances our understanding of the combined impact of diabetes mellitus and CAD complexity on PCI outcomes in several ways. First, in contrast to previous investigations focusing on patients with 3-vessel CAD and left main disease,[15,16] the present analysis provides a more

representative view of routine clinical practice by including patients across a wide range of CAD complexity from single, simple lesions to advanced multivessel disease. Thereby, this study identifies diabetics—even with angiographically less complex disease—as higher-risk patients for long-term PCI complications. Second, unlike previous evidence focusing on early-generation DES,[15,16] the use in this analysis of predominantly new-generation DES—which provide improved safety and efficacy when compared with early-generation DES[3,4]—adds new insights that require further investigation in prospective studies using exclusively new-generation DES. Third, our analysis of the SYNTAX score as a continuous variable averts the possibly confounding effect of categorization and extends the established ability of higher SYNTAX tertiles to risk-stratify patients undergoing PCI.[11–13]

Limitations

The trials included in this post hoc analysis were not designed to evaluate outcomes in relation to diabetic status and CAD complexity; still, this is one of the largest cohorts with available SYNTAX scores to date, and it is strengthened by the broadly inclusive, all-comers design to reflect real-world practice. As in any nonrandomized comparison of treatment strategies, baseline differences were substantial; although multivariable adjustments were performed for prognostically significant variables, a possible effect of unmeasured confounders cannot be excluded. Patients with SYNTAX score >22 were under-represented in this cohort; the respective stratified analysis is, therefore, presented as a hypothesis-generating finding that requires cautious interpretation. It is unclear whether these results apply for longer follow-up durations, considering that adverse outcomes in diabetics tend to aggregate over time. Our analyses may be prone to inflated type I error because of multiple testing. The end point of any revascularization during follow-up was not available in this pooled analysis. The definition of MI was not identical but was similar across the trials; these differences are not likely to have biased our findings, as indicated also by comparable MI rates across trials (Table V in the Data Supplement).

Conclusions

In this sizable all-comers population treated with predominantly new-generation DES, diabetic patients were at high risk for MACE and repeat target-lesion revascularization but not for cardiac death or MI, consistently across the spectrum of disease complexity. The SYNTAX score was an independent predictor of clinical outcomes but did not modify the respective effect of diabetes mellitus within 2 years of follow-up.

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Disclosures

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References

1. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287:2570–2581.
2. Van Belle E, Périé M, Braune D, Chmaït A, Meurice T, Abolmaali K, McFadden EP, Bauters C, Lablanche JM, Bertrand ME. Effects of coronary stenting on vessel patency and long-term clinical outcome after percutaneous coronary revascularization in diabetic patients. *J Am Coll Cardiol*. 2002;40:410–417.
3. Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, Di Nisio M, Silletta MG, Maione A, Alfonso F, Clemmensen PM, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head S, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter D, Schauerte P, Sousa Uva M, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Kolh P, Jüni P. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ*. 2014;348:g3859.
4. Bangalore S, Kumar S, Fusaro M, Amoroso N, Kirtane AJ, Byrne RA, Williams DO, Slater J, Cutlip DE, Feit F. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ*. 2012;345:e5170.
5. Stegman B, Puri R, Cho L, Shao M, Ballantyne CM, Barter PJ, Chapman MJ, Erbel R, Libby P, Raichlen JS, Uno K, Kataoka Y, Nissen SE, Nicholls SJ. High-intensity statin therapy alters the natural history of diabetic coronary atherosclerosis: insights from SATURN. *Diabetes Care*. 2014;37:3114–3120. doi: 10.2337/dc14-1121.
6. Billinger M, Räber L, Hitz S, Stefanini GG, Pilgrim T, Stettler C, Zanchin T, Pulver C, Pfäffli N, Eberli F, Meier B, Kalesan B, Jüni P, Windecker S. Long-term clinical and angiographic outcomes of diabetic patients after revascularization with early generation drug-eluting stents. *Am Heart J*. 2012;163:876–886.e2. doi: 10.1016/j.ahj.2012.02.014.
7. Iijima R, Ndrepepa G, Mehilli J, Markwardt C, Bruskina O, Pache J, Ibrahim M, Schömig A, Kastrati A. Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. *Am Heart J*. 2007;154:688–693. doi: 10.1016/j.ahj.2007.06.005.
8. Mahmud E, Ormiston JA, Turco MA, Popma JJ, Weissman NJ, O'Shaughnessy CD, Mann T, Hall JJ, McGarry TF, Cannon LA, Webster MW, Mandinov L, Baim DS. TAXUS Liberté attenuates the risk of restenosis in patients with medically treated diabetes mellitus: results from the TAXUS ATLAS program. *JACC Cardiovasc Interv*. 2009;2:240–252. doi: 10.1016/j.jcin.2008.12.009.
9. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Ståhle E. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J*. 2012;33:3105–3113. doi: 10.1093/eurheartj/ehs367.
10. Farooq V, Vergouwe Y, Räber L, Vranckx P, Garcia-Garcia H, Diletti R, Kappetein AP, Morel MA, de Vries T, Swart M, Valgimigli M, Dawkins KD, Windecker S, Steyerberg EW, Serruys PW. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score. *Eur Heart J*. 2012;33:3098–3104. doi: 10.1093/eurheartj/ehs295.
11. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219–227.
12. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol*. 2010;56:272–277. doi: 10.1016/j.jacc.2010.03.044.
13. Kim YH, Park DW, Kim WJ, Lee JY, Yun SC, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes

after unprotected left main coronary revascularization. *JACC Cardiovasc Interv*. 2010;3:612–623. doi: 10.1016/j.jcin.2010.04.004.
14. Windecker S, Kolh P, Alfonso F, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2014;35:2541–2619.
15. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972. doi: 10.1056/NEJMoa0804626.
16. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S III, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375–2384. doi: 10.1056/NEJMoa1211585.
17. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639–650. doi: 10.1016/S0140-6736(13)60108-7.
18. Kedhi E, Généreux P, Palmerini T, McAndrew TC, Parise H, Mehran R, Dangas GD, Stone GW. Impact of coronary lesion complexity on drug-eluting stent outcomes in patients with and without diabetes mellitus: analysis from 18 pooled randomized trials. *J Am Coll Cardiol*. 2014;63:2111–2118. doi: 10.1016/j.jacc.2014.01.064.
19. Windecker S, Remondino A, Eberli FR, Jüni P, Räber L, Wenaweser P, Togni M, Billinger M, Tüller D, Seiler C, Roffi M, Corti R, Sütsch G, Maier W, Lüscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med*. 2005;353:653–662. doi: 10.1056/NEJMoa051175.
20. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372:1163–1173. doi: 10.1016/S0140-6736(08)61244-1.
21. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med*. 2010;363:136–146. doi: 10.1056/NEJMoa1004130.
22. Pilgrim T, Heg D, Roffi M, Tüller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Jüni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. *Lancet*. 2014;384:2111–2122. doi: 10.1016/S0140-6736(14)61038-2.
23. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.685313.
24. Stefanini GG, Kalesan B, Pilgrim T, Räber L, Onuma Y, Silber S, Serruys PW, Meier B, Jüni P, Windecker S. Impact of sex on clinical and angiographic outcomes among patients undergoing revascularization with drug-eluting stents. *JACC Cardiovasc Interv*. 2012;5:301–310. doi: 10.1016/j.jcin.2011.11.011.
25. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. 1999;18:681–694.
26. Bittl JA. Percutaneous coronary interventions in the diabetic patient: where do we stand? *Circ Cardiovasc Interv*. 2015;8:e001944. doi: 10.1161/CIRCINTERVENTIONS.114.001944.
27. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med*. 1996;335:217–225.
28. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235. doi: 10.1056/NEJMoa1002358.
29. Serruys PW, Farooq V. Revascularization strategies in patients with diabetes. *N Engl J Med*. 2013;368:1454–1455. doi: 10.1056/NEJMc1301244#SA4.
30. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ; SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg*. 2013;43:1006–1013. doi: 10.1093/ejcts/ezt017.
31. Hakeem A, Garg N, Bhatti S, Rajpurohit N, Ahmed Z, Uretsky BF. Effectiveness of percutaneous coronary intervention with drug-eluting stents compared with bypass surgery in diabetics with multivessel coronary disease: comprehensive systematic review and meta-analysis of randomized clinical data. *J Am Heart Assoc*. 2013;2:e000354. doi: 10.1161/JAHA.113.000354.
32. Bangalore S, Toklu B, Feit F. Outcomes with coronary artery bypass graft surgery versus percutaneous coronary intervention for patients with diabetes mellitus: can newer generation drug-eluting stents bridge the gap? *Circ Cardiovasc Interv*. 2014;7:518–525. doi: 10.1161/CIRCINTERVENTIONS.114.001346.

Impact of Diabetic Status on Outcomes After Revascularization With Drug-Eluting Stents in Relation to Coronary Artery Disease Complexity: Patient-Level Pooled Analysis of 6081 Patients

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A Patient-Level Pooled Analysis of 6,081 Patients

Konstantinos C Koskinas, MD; George CM Siontis, MD; Raffaele Piccolo, MD;
Anna Franzone, MD; Alan Haynes, PhD; Julie Rat-Wirtzler, MSc; Sigmund Silber, MD;
Patrick Serruys, MD; Thomas Pilgrim, MD; Lorenz Räber, MD;
Dik Heg, PhD; Peter Jüni, MD; Stephan Windecker, MD

Supplemental Material

Supplemental Table 1. Definitions or myocardial infarction in the 4 pooled trials.

Trial	Definition of myocardial infarction
SIRTAX	• Presence of new Q waves in at least two contiguous ECG leads and elevated CK-MB levels. • In the absence of pathologic Q waves: increase of CK levels >2x ULN with elevated levels of CK-MB or troponin I.
LEADERS	• Electrocardiographic criteria of the Minnesota code manual, or CK levels >2x ULN, with elevated levels of CK-MB or troponin I or T.
RESOLUTE All-Comers	• Definition of Q-wave MI in the absence of cardiac enzyme data: history of chest pain or other acute symptoms consistent with myocardial ischemia together with new pathological Q waves in two or more contiguous ECG leads. • Definition of Q-wave MI in the presence of elevated cardiac enzymes: new pathological Q waves in two or more contiguous ECG leads. • MI defined according to an "extended" historical protocol definition.[1]
BIOSCIENCE	• Typical rise and fall of CK-MB fraction or troponin in the presence of at least one of several conditions: ischaemic symptoms, new pathological Q waves, ischaemic electrocardiographic changes, or pathological evidence of acute myocardial infarction.[2]

Electrocardiographic criteria of the Minnesota code manual applied in all trials.[3]

1. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention*. 2010;5:871-874.
2. Thygesen K, Alpert JS, Jaffe AS, and the Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007;116: 263-2653.
3. Prineas R, Crow R, Blackburn H. The Minnesota code manual of electrocardiographic findings. Littleton, MA: John Wright-PSG, 1982.

Supplemental Table 2. Baseline characteristics with missing information.

Variable	Number of patients with missing data
Age	n = 0
Gender	n = 0
Body mass index	n = 34
Diabetes	n = 0
Arterial hypertension	n = 2
Hypercholesterolemia	n = 1
Renal failure (eGFR<60 ml/min)	n = 405
Current smoking	n = 39
Family history of CAD	n = 318
Previous MI	n = 38
Previous PCI	n = 0
Left ventricular ejection fraction	n = 1595
Clinical presentation	n = 237
SYNTAX score	n = 0

CAD indicates coronary artery disease; eGFR, estimated glomerular filtrat6in rate; MI, myocardial infarction; and PCI, percutaneous coronary intervention. Diabetes and SYNTAX score were non-missing variables by definition.

Supplemental Table 3. Baseline characteristics in patients stratified according to diabetic status and SYNTAX score ≤11 or >11.

	Syntax score ≤11			Syntax score >11			P value for interaction
	Diabetes (n=593)	**No diabetes** (n=2,460)	**p-value**	**Diabetes** (n=717)	**No diabetes** (n=2,311)	**p-value**	
Age	65.1 ± 9.8	62.6 ± 11.4	<0.001	67.4 ± 10.3	64.4 ± 11.3	<0.001	0.44
Female gender, n (%)	168 (28.3)	612 (24.9%)	0.09	204 (28.5)	513 (22.2)	0.001	0.27
Body mass index (kg/m^2)	29.5 ± 4.9	27.2 ± 4.1	<0.001	29.4 ± 4.9	27.0 ± 4.0	<0.001	0.80
Insulin-requiring diabetes, n (%)	172 (29.0)	0 (0.0)	<0.001	259 (36.1)	0 (0.0)	<0.001	
Arterial hypertension, n (%)	510 (86.1)	1,580 (64.2)	<0.001	594 (82.8)	1,474 (63.8)	<0.001	0.16
Hypercholesterolemia, n (%)	421 (71.0)	1,534 (62.4)	<0.001	522 (72.8)	1,372 (59.4)	<0.001	0.11
Renal failure, n (%)	110 (19.7)	237 (10.4)	<0.001	167 (25.0)	283 (13.1)	<0.001	0.80
GFR (ml/min)	83.6 ± 28.9	87.2 ± 31.2	0.013	79.7 ± 28.0	85.2 ± 24.7	<0.001	0.29
Current smoking, n (%)	131 (22.1)	828 (33.9)	<0.001	135 (18.8)	735 (32.1)	<0.001	0.43
Family history of CAD, n (%)	175 (31.0)	821 (34.9)	0.08	194 (29.1)	763 (35.0)	0.005	0.49
Previous MI, n (%)	137 (23.2)	566 (23.1)	0.96	222 (31.4)	550 (24.0)	<0.001	0.01
Previous PCI, n (%)	207 (34.9)	649 (26.4)	<0.001	251 (35.0)	577 (25.0)	<0.001	0.56
LVEF (%)	57.6 ± 11.9	58.0 ± 10.7	0.59	53.5 ± 12.6	54.6 ± 12.2	0.07	0.33
Clinical presentation, n (%)	564	n = 2,379	<0.001	n = 671	n = 2,230	<0.001	< 0.001
Stable CAD	321 (56.9)	989 (41.6)	<0.001	288 (42.9)	802 (36.0)	0.001	
Unstable angina/NSTEMI	190 (33.7)	930 (39.1)	0.018	264 (39.3)	822 (36.9)	0.25	
STEMI	53 (9.4)	460 (19.3)	<0.001	119 (17.7)	606 (27.2)	<0.001	
SYNTAX Score	6.4 ± 2.9	6.4 ± 2.9	0.97	20.1 ± 7.1	19.9 ± 7.2	0.40	

CAD indicates coronary artery disease; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; and PCI: percutaneous coronary intervention.

Supplemental Table 4. Ancillary analysis: adjusted assessment of the primary endpoint, MACE, and the principle efficacy endpoint, clinically-indicated TLR at 2 years, including multiple imputation for the SYNTAX score.

	Adjusted Analysis		
	HR (95%CI)	**p-value**	**p-value interaction**
Primary endpoint (MACE)			
Diabetes	1.30 (1.08-1.57)	0.006	
Model with diabetes and SYNTAX score			0.08
Diabetes	1.26 (1.04-1.53)	0.016	
SYNTAX score	1.03 (1.02-1.04)	<0.001	
Clinically-indicated TLR			
Diabetes	1.59 (1.24-2.06)	<0.001	
Model with diabetes and SYNTAX score			0.24
Diabetes	1.55 (1.20-2.01)	0.001	
SYNTAX score	1.03 (1.02-1.04)	<0.001	

Adjusted Hazard Ratios HR (95% CI) and p-values are from multiple imputation estimated Cox Regressions (20 data-sets using Rubin's rule to combine estimates), adjusting for baseline variables associated with the primary outcome.

SYNTAX score was imputed in n = 322 patients. Total number of patients n=6,403; diabetic patients, n=1,398; non-diabetic patients, n=5,005.

MACE indicates major adverse cardiac events; and TLR, target lesion revascularization.

Supplemental Table 5. Event rates for the composite primary endpoint, MACE, and its components within two years of follow-up in the four pooled trials: SIRTAX, LEADERS, RESOLUTE All-comers, and BIOSCIENCE. Adjusted p-values are derived from multiple imputation estimated Cox Regressions.

	SIRTAX n= 858	**LEADERS** n=1,352	**RESOLUTE** n=2,026	**BIOSCIENCE** n=1,845	**p-value**	**Adjusted p-value**
Primary endpoint (MACE), n (%)	112 (13.1)	159 (11.8)	210 (10.5)	128 (11.7)	0.009	0.002
Cardiac death, n (%)	20 (2.3)	50 (3.7)	41 (2.1)	35 (2.6)	0.03	0.044
MI, n (%)	34 (4.0)	73 (5.4)	97 (4.8)	64 (5.6)	0.17	0.19
Clinically indicated TLR, n (%)	86 (10.2)	82 (6.2)	97 (4.9)	53 (6.9)	<0.001	<0.001

MACE indicates major adverse cardiac events; MI, myocardial infarction; and TLR, target lesion revascularization.

Supplemental Figure Legends

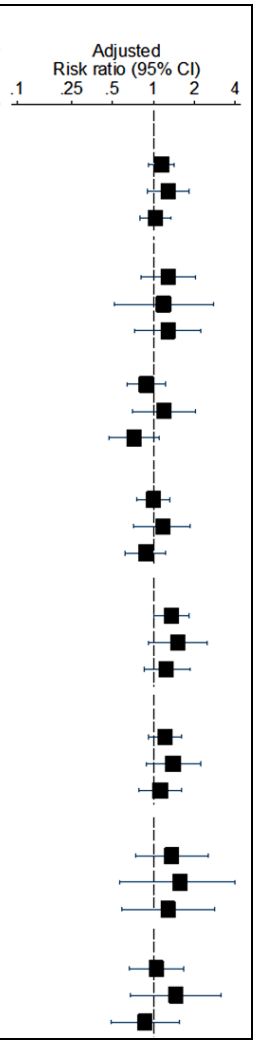
Supplemental Figure 1. One-year outcomes in relation to diabetic status and SYNTAX score ≤11 vs. >11. Hazard ratios (HR) with respective 95% confidence intervals (CI) and p-values are derived from Cox regressions. Adjusted HR (95% CI) and p-values are from Multiple Imputation estimated Cox Regressions (20 data-sets using Rubin's rule to combine estimates), adjusting for baseline variables associated with the primary outcome: age, gender, body mass index, hypercholesterolemia, renal failure, history of MI, LVEF, and clinical indication for PCI.

Supplemental Figure 2. Two-year outcomes in relation to diabetic status and SYNTAX score ≤11 vs. >11 in a sensitivity analysis of patients treated with new-generation DES (n=4,554). Hazard ratios (HR) with respective 95% confidence intervals (CI) and p-values are derived from Cox regressions. Adjusted HR (95% CI) and p-values are from Multiple Imputation estimated Cox Regressions (20 data-sets using Rubin's rule to combine estimates), adjusting for baseline variables associated with the primary outcome.

Supplemental Figure 3. Exploratory analysis: two-year outcomes in relation to diabetic status and SYNTAX score ≤22 vs. >22. Hazard Ratios (HR) with respective 95% confidence intervals (CI) and p-values are from Cox Regressions. Adjusted HR (95% CI) and p-values are from Multiple Imputation estimated Cox Regressions (20 data-sets using Rubin's rule to combine estimates), adjusting for baseline variables associated with the primary outcome.

Supplemental Figure 1.

	Diabetes (%) N = 1310	No diabetes (%) N = 4771	Crude Analysis HR (95%CI)	Crude Analysis p-value	Crude Analysis p-value interaction	Adjusted Analysis HR (95%CI)	Adjusted Analysis p-value	Adjusted Analysis p-value interaction
Primary endpoint					0.699			0.313
Overall	144 (11.1)	384 (8.1)	1.38 (1.14-1.67)	0.001		1.15 (0.93-1.42)	0.202	
Syntax score ≤11	48 (8.1)	143 (5.9)	1.40 (1.01-1.94)	0.043		1.28 (0.90-1.82)	0.163	
Syntax score >11	96 (13.5)	241 (10.5)	1.29 (1.02-1.64)	0.033		1.04 (0.80-1.36)	0.779	
Cardiac death					0.577			0.687
Overall	36 (2.8)	65 (1.4)	2.03 (1.35-3.05)	0.001		1.29 (0.81-2.05)	0.282	
Syntax score ≤11	9 (1.5)	23 (1.0)	1.62 (0.75-3.50)	0.219		1.19 (0.52-2.75)	0.684	
Syntax score >11	27 (3.8)	42 (1.8)	2.10 (1.29-3.40)	0.003		1.28 (0.73-2.25)	0.390	
Any MI					0.432			0.179
Overall	54 (4.2)	188 (4.0)	1.05 (0.77-1.42)	0.765		0.89 (0.64-1.23)	0.471	
Syntax score ≤11	19 (3.2)	66 (2.7)	1.19 (0.72-1.99)	0.496		1.20 (0.70-2.05)	0.516	
Syntax score >11	35 (5.0)	122 (5.3)	0.93 (0.64-1.35)	0.686		0.72 (0.47-1.10)	0.125	
Cardiac death or MI					0.955			0.481
Overall	84 (6.5)	238 (5.0)	1.29 (1.00-1.65)	0.046		1.00 (0.76-1.32)	0.993	
Syntax score ≤11	25 (4.2)	83 (3.4)	1.25 (0.80-1.95)	0.330		1.17 (0.72-1.88)	0.531	
Syntax score >11	59 (8.3)	155 (6.7)	1.23 (0.91-1.66)	0.177		0.88 (0.62-1.24)	0.453	
Clinically-indicated TLR					0.418			0.303
Overall	70 (5.5)	174 (3.7)	1.49 (1.13-1.96)	0.005		1.36 (1.00-1.84)	0.051	
Syntax score ≤11	25 (4.3)	62 (2.6)	1.68 (1.06-2.67)	0.029		1.52 (0.93-2.50)	0.096	
Syntax score >11	45 (6.5)	112 (4.9)	1.32 (0.93-1.87)	0.114		1.25 (0.85-1.85)	0.262	
Clinically-indicated TVR					0.437			0.272
Overall	81 (6.3)	219 (4.7)	1.37 (1.06-1.76)	0.016		1.22 (0.92-1.62)	0.164	
Syntax score ≤11	28 (4.8)	77 (3.2)	1.52 (0.98-2.34)	0.059		1.39 (0.88-2.21)	0.158	
Syntax score >11	53 (7.6)	142 (6.3)	1.23 (0.89-1.68)	0.204		1.12 (0.78-1.60)	0.545	
Definite stent thrombosis					0.719			0.664
Overall	18 (1.4)	47 (1.0)	1.40 (0.81-2.41)	0.225		1.37 (0.74-2.55)	0.314	
Syntax score ≤11	6 (1.0)	16 (0.7)	1.55 (0.61-3.97)	0.357		1.57 (0.57-4.29)	0.380	
Syntax score >11	12 (1.7)	31 (1.4)	1.26 (0.65-2.45)	0.502		1.28 (0.59-2.80)	0.530	
Definite or probable stent thrombosis					0.581			0.331
Overall	31 (2.4)	90 (1.9)	1.26 (0.84-1.89)	0.271		1.05 (0.66-1.67)	0.826	
Syntax score ≤11	10 (1.7)	29 (1.2)	1.43 (0.70-2.93)	0.331		1.46 (0.68-3.13)	0.333	
Syntax score >11	21 (3.0)	61 (2.7)	1.12 (0.68-1.83)	0.664		0.87 (0.49-1.55)	0.638	



Supplemental Figure 2.

	Diabetes (%)	No Diabetes (%)	Crude analysis			Adjusted analysis			Adjusted HR (95% CI)
	N = 1012	N = 3542	HR (95% CI)	P-value	P-value Interaction	HR (95% CI)	P-value	P-value Interaction	.1 .25 .5 1 2 4
Primary endpoint					0.061			0.713	
Overall	136 (15.4)	325 (10.3)	1.47 (1.20-1.79)	<0.001		1.19 (0.95-1.49)	0.133		
Syntax score ≤11	54 (15.0)	123 (8.0)	1.83 (1.33-2.52)	<0.001		1.50 (1.05-2.14)	0.025		
Syntax score >11	82 (15.9)	202 (12.7)	1.23 (0.95-1.59)	0.112		0.99 (0.73-1.32)	0.926		
Cardiac death					0.930			0.577	
Overall	31 (3.5)	65 (2.2)	1.66 (1.08-2.55)	0.020		1.18 (0.73-1.91)	0.502		
Syntax score ≤11	10 (2.5)	26 (1.7)	1.57 (0.76-3.25)	0.227		1.24 (0.54-2.84)	0.615		
Syntax score >11	21 (4.2)	39 (2.6)	1.64 (0.96-2.78)	0.069		1.15 (0.63-2.10)	0.649		
Any MI					0.168			0.064	
Overall	46 (4.8)	153 (4.6)	1.05 (0.75-1.46)	0.775		0.87 (0.60-1.25)	0.454		
Syntax score ≤11	18 (4.6)	53 (3.3)	1.38 (0.81-2.36)	0.235		1.35 (0.76-2.39)	0.310		
Syntax score >11	28 (5.1)	100 (5.9)	0.86 (0.56-1.30)	0.466		0.64 (0.40-1.03)	0.065		
Cardiac death or MI					0.354			0.23	
Overall	71 (7.6)	204 (6.3)	1.21 (0.93-1.59)	0.161		0.96 (0.70-1.30)	0.768		
Syntax score ≤11	25 (6.5)	73 (4.6)	1.40 (0.89-2.20)	0.150		1.26 (0.76-2.07)	0.370		
Syntax score >11	46 (8.6)	131 (8.0)	1.07 (0.76-1.49)	0.700		0.78 (0.53-1.15)	0.209		
Clinically-indicated TLR					0.037			0.511	
Overall	66 (7.9)	123 (4.1)	1.90 (1.41-2.56)	<0.001		1.63 (1.16-2.27)	0.005		
Syntax score ≤11	29 (8.3)	44 (3.0)	2.76 (1.73-4.41)	<0.001		2.03 (1.21-3.41)	0.007		
Syntax score >11	37 (7.6)	79 (5.1)	1.44 (0.97-2.12)	0.069		1.37 (0.88-2.14)	0.165		
Clinically-indicated TVR					0.025			0.857	
Overall	76 (9.0)	163 (5.4)	1.65 (1.26-2.16)	<0.001		1.41 (1.04-1.92)	0.026		
Syntax score ≤11	33 (9.5)	58 (4.0)	2.38 (1.56-3.66)	<0.001		1.80 (1.12-2.88)	0.015		
Syntax score >11	43 (8.8)	105 (6.9)	1.26 (0.88-1.79)	0.209		1.18 (0.79-1.77)	0.417		
Definite stent thrombosis					0.214			0.942	
Overall	13 (1.4)	23 (0.7)	1.98 (1.00-3.91)	0.049		1.94 (0.90-4.19)	0.091		
Syntax score ≤11	7 (1.8)	9 (0.5)	3.16 (1.18-8.49)	0.022		3.17 (1.11-9.05)	0.031		
Syntax score >11	6 (1.1)	14 (0.8)	1.32 (0.51-3.44)	0.566		1.18 (0.36-3.86)	0.783		
Definite or probable stent thrombosis					0.051			0.143	
Overall	24 (2.5)	65 (1.9)	1.29 (0.81-2.06)	0.282		1.06 (0.63-1.80)	0.816		
Syntax score ≤11	12 (3.1)	22 (1.3)	2.22 (1.10-4.48)	0.027		2.22 (1.04-4.73)	0.038		
Syntax score >11	12 (2.1)	43 (2.5)	0.86 (0.45-1.63)	0.642		0.58 (0.27-1.24)	0.157		

Supplemental Figure 3.

	Diabetes (%)	No diabetes (%)	Crude Analysis			Adjusted Analysis			Adjusted HR (95% CI)
	N = 1310	N = 4771	HR (95%CI)	p-value	p-value interaction	HR (95%CI)	p-value	p-value interaction	.1 .25 .5 1 2 4
Primary endpoint					0.098			0.103	
Overall	173 (14.5)	436 (9.9)	1.46 (1.23-1.75)	< 0.001		1.25 (1.03-1.53)	0.026		
Syntax score ≤22	134 (13.6)	333 (8.8)	1.55 (1.27-1.90)	< 0.001		1.36 (1.09-1.70)	0.008		
Syntax score >22	39 (18.8)	103 (16.9)	1.09 (0.75-1.57)	0.661		0.89 (0.58-1.37)	0.595		
Cardiac death					0.870			0.989	
Overall	52 (4.4)	94 (2.2)	2.03 (1.45-2.85)	< 0.001		1.41 (0.96-2.07)	0.079		
Syntax score ≤22	36 (3.7)	69 (1.9)	2.00 (1.34-2.99)	< 0.001		1.50 (0.95-2.38)	0.081		
Syntax score >22	16 (7.8)	25 (4.3)	1.87 (1.00-3.51)	0.050		1.02 (0.49-2.11)	0.965		
Any MI					0.178			0.104	
Overall	59 (4.7)	209 (4.6)	1.03 (0.77-1.38)	0.837		0.89 (0.64-1.22)	0.455		
Syntax score ≤22	47 (4.5)	159 (4.1)	1.13 (0.81-1.56)	0.474		1.00 (0.70-1.43)	0.990		
Syntax score >22	12 (5.6)	50 (7.9)	0.69 (0.37-1.30)	0.251		0.56 (0.27-1.16)	0.117		
Cardiac death or MI					0.267			0.222	
Overall	103 (8.4)	282 (6.3)	1.34 (1.07-1.67)	0.012		1.06 (0.82-1.37)	0.644		
Syntax score ≤22	78 (7.7)	213 (5.6)	1.40 (1.08-1.81)	0.011		1.17 (0.88-1.57)	0.287		
Syntax score >22	25 (11.9)	69 (11.1)	1.04 (0.66-1.64)	0.877		0.72 (0.42-1.23)	0.223		
Clinically-indicated TLR					0.442			0.434	
Overall	98 (8.6)	220 (5.1)	1.65 (1.30-2.10)	< 0.001		1.54 (1.18-2.01)	0.002		
Syntax score ≤22	76 (8.1)	172 (4.6)	1.71 (1.30-2.24)	< 0.001		1.56 (1.16-2.11)	0.004		
Syntax score >22	22 (11.1)	48 (8.1)	1.36 (0.82-2.25)	0.235		1.45 (0.80-2.64)	0.219		
Clinically-indicated TVR					0.637			0.726	
Overall	112 (9.8)	279 (6.5)	1.49 (1.20-1.86)	< 0.001		1.38 (1.08-1.76)	0.011		
Syntax score ≤22	84 (8.9)	216 (5.8)	1.50 (1.17-1.93)	0.002		1.35 (1.02-1.79)	0.037		
Syntax score >22	28 (13.9)	63 (10.6)	1.32 (0.85-2.06)	0.218		1.46 (0.87-2.45)	0.154		
Definite stent thrombosis					0.404			0.446	
Overall	21 (1.8)	53 (1.2)	1.45 (0.88-2.41)	0.147		1.65 (0.93-2.93)	0.088		
Syntax score ≤22	16 (1.7)	38 (1.0)	1.61 (0.90-2.89)	0.110		1.86 (0.96-3.60)	0.064		
Syntax score >22	5 (2.3)	15 (2.4)	0.97 (0.35-2.68)	0.961		1.12 (0.33-3.78)	0.854		
Definite / probable stent thrombosis					0.123			0.092	
Overall	35 (2.9)	98 (2.1)	1.31 (0.89-1.92)	0.174		1.18 (0.76-1.84)	0.460		
Syntax score ≤22	28 (2.8)	70 (1.8)	1.53 (0.98-2.36)	0.059		1.47 (0.89-2.41)	0.131		
Syntax score >22	7 (3.2)	28 (4.4)	0.73 (0.32-1.66)	0.450		0.55 (0.20-1.54)	0.257		