Original Investigation

Percutaneous Coronary Intervention in Patients With Insulin-Treated and Non–Insulin-Treated Diabetes Mellitus
Secondary Analysis of the TUXEDO Trial

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IMPORTANCE Prior studies have shown that patients with insulin-treated diabetes mellitus (ITDM) have a higher risk of cardiovascular events. However, this finding is controversial, as other studies have shown that the increased risk of cardiovascular events disappears after risk adjustment. In addition, the choice of a drug-eluting stent (limus- vs taxol-eluting) in ITDM is controversial, with studies showing worse outcomes with an everolimus-eluting stent compared with a paclitaxel-eluting stent.

OBJECTIVES To assess the outcomes of patients with ITDM vs non-ITDM who underwent percutaneous coronary intervention and to assess the efficacy and safety of an everolimus-eluting stent vs a paclitaxel-eluting stent based on insulin use status.

DESIGN, SETTING, AND PARTICIPANTS A prespecified analysis was conducted of the Taxus Element vs Xience Prime in a Diabetic Population (TUXEDO) clinical trial, which enrolled 1830 patients with ITDM and non-ITDM from June 23, 2011, to March 12, 2014. Patients were randomized 1:1 to receive either a paclitaxel-eluting stent or an everolimus-eluting stent.

MAIN OUTCOMES AND MEASURES The primary end point was target vessel failure, defined as the composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target vessel revascularization at 1 year after the intervention.

RESULTS Among the 1830 patients (1377 male) in the TUXEDO trial, 747 patients (40.8%) were receiving insulin (ITDM group). Compared with the 1083 patients with non-ITDM, those with ITDM had a significant increase in target vessel failure (42 [5.6%] vs 36 [3.3%]; $P = .02$), death or myocardial infarction (43 [5.8%] vs 35 [3.2%]; $P = .009$), death (26 [3.5%] vs 18 [1.7%]; $P = .01$), and subacute stent thrombosis (8 [1.1%] vs 3 [0.3%]; $P = .03$). However, in a propensity score–adjusted analysis to account for baseline differences between the 2 groups, the differences in outcomes were no longer significant. In patients with ITDM, everolimus-eluting stents reduced the rate of target vessel failure (13 of 382 [3.4%] vs 29 of 365 [7.9%]; $P = .007$), major adverse cardiac events (15 of 382 [3.9%] vs 30 of 365 [8.2%]; $P = .01$), myocardial infarction (5 of 382 [1.3%] vs 16 of 365 [4.4%]; $P = .01$), stent thrombosis (2 of 382 [0.5%] vs 11 of 365 [3.0%]; $P = .009$), target lesion revascularization (4 of 382 [1.0%] vs 19 of 365 [5.2%]; $P = .001$), and target vessel revascularization (4 of 382 [1.0%] vs 19 of 365 [5.2%]; $P = .001$) when compared with paclitaxel-eluting stents. The results largely trended in the same direction in patients with non-ITDM ($P > .05$ for the interaction).

CONCLUSIONS AND RELEVANCE Patients with ITDM had a significant increase in the risk of cardiovascular events in unadjusted models that was largely attenuated after propensity score adjustment. Everolimus-eluting stents reduced the rate of cardiovascular events, including stent thrombosis, when compared with paclitaxel-eluting stents in patients with ITDM.

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Patients with diabetes mellitus (DM) often have rapidly progressive, extensive coronary artery disease leading to long and diffuse lesions in small-caliber coronary arteries, which renders revascularization challenging.[1] As such, when compared with patients without DM, patients with DM have had worse outcomes following percutaneous coronary intervention (PCI) in the balloon angioplasty era, bare-metal stent (BMS) era, and even in the drug-eluting stent era, with higher rates of in-stent restenosis, stent thrombosis, death, and myocardial infarction (MI).[1-4] Among patients with DM undergoing revascularization, those treated with insulin have been shown to have worse outcomes compared with those not treated with insulin.[5-8] However, this finding is controversial, as other studies have shown that the increased possibility of adverse cardiovascular outcomes in patients with insulin-treated DM (ITDM) disappears after risk adjustment.[9]

Moreover, the choice of a stent in patients with ITDM is controversial. In an analysis from the National Heart, Lung, and Blood Institute Dynamic Registry, when compared with BMSs, drug-eluting stents reduced death or MI in patients with non-insulin-treated diabetes mellitus (non-ITDM) but not in patients with ITDM.[10] The controversy has persisted in the era of second-generation drug-eluting stents. In a combined analysis from the SPIRIT II (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System), SPIRIT III, SPIRIT IV, and COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTÉ stent in all-comers) trials, everolimus-eluting stents reduced the rate of ischemia-driven target lesion revascularization when compared with paclitaxel-eluting stents in patients with non-ITDM (31 of 878 [3.5]% vs 29 of 497 [5.8]%; $P = .04$).[11] However, in patients with ITDM, there was a trend toward worse outcomes with everolimus-eluting stents (31 of 310 [10.0%] vs 10 of 184 [5.4%]; $P = .08$), with a significant test for interaction ($P = .01$). The authors concluded that "further studies are required to determine the optimal stent choice for patients with ITDM."[11(p899)]

In the Taxus Element vs Xience Prime in a Diabetic Population (TUXEDO) trial, an investigator-initiated, multicenter, randomized clinical trial of 1830 patients with DM and coronary artery disease undergoing PCI, paclitaxel-eluting stents were not shown to be noninferior to everolimus-eluting stents, and they resulted in higher rates of target vessel failure, MI, stent thrombosis, and target vessel revascularization at 1 year.[12] Our objectives with this prespecified analysis from the TUXEDO trial were to assess the outcomes of patients with ITDM vs non-ITDM who underwent PCI and to assess the efficacy and safety of everolimus-eluting stents vs paclitaxel-eluting stents based on insulin use status.

Key Points

Question What are the outcomes and what is the stent of choice for patients with insulin-treated diabetes mellitus (ITDM) vs those with non-ITDM?

Findings Among 1830 patients in the Taxus Element vs Xience Prime in a Diabetic Population clinical trial, patients with ITDM had a significant increase in cardiovascular events vs patients with non-ITDM that were attenuated in the propensity score–adjusted analysis. Moreover, everolimus-eluting stents reduced the rate of target vessel failure compared with paclitaxel-eluting stents (13 of 382 patients [3.4%] vs 29 of 365 [7.9%]) and other outcomes, including stent thrombosis, in patients with ITDM.

Meaning Patients with ITDM had similar outcomes when compared with those with non-ITDM after risk adjustment, and use of everolimus-eluting stents was superior to paclitaxel-eluting stents in such patients.

Methods

Study Population

In this prespecified analysis from the TUXEDO trial conducted from June 23, 2011, to March 12, 2014, patients were randomized 1:1 to receive either a paclitaxel-eluting stent or an everolimus-eluting stent. The main results have been previously published.[12] For this analysis, patients were divided into 2 groups based on insulin use status: ITDM or non-ITDM. Institutional review boards at each participating center[12] approved the study, and written informed consent was obtained from all patients.

Study Procedures and Follow-up

Percutaneous coronary intervention was performed using standard technique. Prior to the index procedure, all patients received oral aspirin, 350 mg, and a loading dose of clopidogrel, 600 mg; prasugrel, 60 mg; or ticagrelor, 180 mg. Dual antiplatelet therapy of aspirin, 75 to 150 mg daily, and clopidogrel, at least 75 mg daily; prasugrel, 10 mg daily; or ticagrelor, 90 mg twice daily, was prescribed for at least 12 months after stent implantation. Patients were followed up at 30 days, 180 days, and 1 year after the index procedure.

Study End Points

The primary end point for this study was target vessel failure at 1 year (the primary end point of the TUXEDO trial), which was defined as the composite of cardiac death, target vessel MI, or ischemia-driven target vessel revascularization. The major secondary end points were major adverse cardiac event (MACE; a composite of cardiac death, MI, or ischemia-driven target lesion revascularization), composite of death or MI, and composite of cardiac death or MI. Other outcomes evaluated were individual components of the primary and secondary end points (all-cause death, cardiac death, MI, ischemia-driven target lesion revascularization, and target vessel revascularization) and stent thrombosis as defined by the Academic Research Consortium.[12] The members of the clinical event adjudication committee adjudicated all outcomes and were masked to the randomized stent group.[12]

Statistical Analysis

Patient groups (ITDM vs non-ITDM) were compared using χ^2 tests or Fisher exact tests for categorical variables and t tests for continuous variables. The risk of primary, secondary, and other outcomes were compared between the ITDM and non-ITDM groups. Regression adjustment to a propensity score was

Table 1. Baseline Characteristics

Characteristic	ITDM (n = 747)	Non-ITDM (n = 1083)	*P* Value[a]
Age, mean (SD), y	58.52 (8.63)	58.27 (9.52)	.56
BMI, mean (SD)	26.13 (4.18)	25.61 (4.10)	.008
Male sex, No. (%)	530 (71.0)	847 (78.2)	<.001
Hypertension, No. (%)	490 (65.6)	727 (67.1)	.49
Hypercholesterolemia, No. (%)	569 (76.2)	843 (77.8)	.40
Current smoker, No. (%)	92 (12.3)	181 (16.7)	.01
Diabetes duration, mean (SD), y	8.09 (7.51)	5.29 (6.19)	<.001
Hemoglobin A_{1c}, mean (SD), %	8.87 (1.84)	7.89 (1.57)	<.001
Previous myocardial infarction, No. (%)	277 (37.1)	465 (42.9)	.01
Unstable angina, No. (%)	466 (62.4)	609 (56.2)	.009
Previous percutaneous coronary intervention, No. (%)	82 (11.0)	63 (5.8)	<.001
Previous coronary artery bypass graft surgery, No. (%)	16 (2.1)	16 (1.5)	.29
Left ventricular ejection fraction, mean (SD), %	53.47 (11.50)	55.65 (12.36)	<.001
Left ventricular ejection fraction <40%, No. (%)	84 (11.2)	83 (7.7)	.009
eGFR, No. (%)			
≤60 mL/min/1.73 m^2	164 (22.0)	183 (16.9)	.007
>60 mL/min/1.73 m^2	580 (77.6)	894 (82.5)	.007
Clinical presentation at admission, No. (%)			
Acute coronary syndrome	397 (53.1)	577 (53.3)	.96
Chronic stable angina	207 (27.7)	314 (29.0)	.55
Post ST-elevation myocardial infarction	70 (9.4)	142 (13.1)	.01
Asymptomatic	73 (9.8)	50 (4.6)	<.001
Target lesions treated, No. (%)			
1	534 (71.5)	810 (74.8)	.12
2	178 (23.8)	213 (19.7)	.03
3	29 (3.9)	37 (3.4)	.60
Target lesions per patient, mean (SD)	1.32 (0.54)	1.27 (0.52)	.06
Device success, No. (%)			
PES	361 (48.3)	535 (49.4)	.65
EES	380 (50.9)	524 (48.4)	.30
Procedure success, No. (%)			
PES	359 (48.1)	533 (49.2)	.63
EES	378 (50.6)	522 (48.2)	.31
Target lesions, No.	977	1347	NA
Coronary artery, No. of lesions (%)			
Left anterior descending	444 (45.4)	659 (48.9)	.10
Left circumflex	262 (26.8)	311 (23.1)	.04
Right	270 (27.6)	377 (28.0)	.85
Reference vessel diameter, mean (SD), mm	2.85 (0.35)	2.91 (0.37)	<.001
Diameter stenosis, mean (SD), mm	87.36 (8.34)	87.44 (8.65)	.84
Lesion length, mean (SD), mm	19.74 (7.68)	20.40 (7.63)	.04

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EES, everolimus-eluting stent; eGFR, estimated glomerular filtration rate; ITDM, insulin-treated diabetes mellitus; NA, not applicable; Non-ITDM, non–insulin-treated diabetes mellitus; PES, paclitaxel-eluting stent.

[a] *P* values were calculated by using χ^2 and Fisher exact tests for categorical data and by using *t* tests for continuous data.

used to adjust for baseline differences between the ITDM and non-ITDM groups. The propensity score is a conditional probability of having a particular exposure (ITDM vs non-ITDM) given a set of measured covariates at baseline[13,14] and was estimated using a nonparsimonious multivariable logistic regression model[15] using ITDM as the dependent variable and the baseline characteristics (including stent type but not other angiographic variables) outlined in **Table 1** as covariates. A logistic regression model was then constructed using the primary and secondary outcomes as the dependent variable, and the effect of ITDM on these outcomes was evaluated after adjusting to the propensity score in the model.

Further analysis was performed to compare primary, secondary, and other outcomes for paclitaxel-eluting stents vs everolimus-eluting stents in the ITDM cohort. The consistency of treatment effect for paclitaxel-eluting stents vs everolimus-eluting stents for the ITDM vs non-ITDM cohorts were compared using a test for interaction from a logistic regression model. Kaplan-Meier survival estimate curves for time-to-event variables were obtained for each group. All

Table 2. Clinical Outcomes

Outcome	No. (%) ITDM (n = 747)	Non-ITDM (n = 1083)	*P* Value	Propensity Score, Adjusted Hazard Ratio (95% CI)	*P* Value
Target vessel failure	42 (5.6)	36 (3.3)	.02	1.31 (0.78-2.20)	.31
Major adverse cardiac events	45 (6.0)	40 (3.7)	.02	1.28 (0.78-2.12)	.32
Death or myocardial infarction	43 (5.8)	35 (3.2)	.009	1.17 (0.69-2.00)	.55
Cardiac death or myocardial infarction	35 (4.7)	31 (2.9)	.04	1.19 (0.68-2.09)	.54
Cardiac death or target vessel myocardial infarction	31 (4.1)	27 (2.5)	.05	1.19 (0.65-2.16)	.57
Death					
All	26 (3.5)	18 (1.7)	.01	1.09 (0.52-2.29)	.82
Cardiac	18 (2.4)	14 (1.3)	.07	1.10 (0.48-2.55)	.82
Noncardiac	8 (1.1)	4 (0.4)	.07	1.05 (0.21-5.31)	.96
Myocardial infarction					
All	21 (2.8)	19 (1.8)	.13	1.24 (0.60-2.56)	.55
Target vessel related	17 (2.3)	14 (1.3)	.11	1.36 (0.60-3.08)	.46
Non-target vessel related	5 (0.7)	6 (0.6)	.75	0.74 (0.19-2.84)	.66
Q-wave	7 (0.9)	2 (0.2)	.04	3.45 (0.60-19.83)	.16
Non-Q-wave	15 (2.0)	17 (1.6)	.48	1.01 (0.45-2.23)	.99
Stent thrombosis[a]					
All	13 (1.7)	10 (0.9)	.12	1.57 (0.58-4.22)	.37
Definite	9 (1.2)	8 (0.7)	.31	1.04 (0.33-3.26)	.95
Probable	4 (0.5)	2 (0.2)	.23	5.86 (0.59-58.45)	.13
Thrombosis					
Acute	0 (0.0)	1 (0.1)	>.99	-	>.99
Subacute	8 (1.1)	3 (0.3)	.03	3.11 (0.73-13.20)	.12
Late	5 (0.7)	6 (0.6)	.75	0.85 (0.19-3.83)	.83
Target lesion revascularization	23 (3.1)	19 (1.8)	.06	1.43 (0.71-2.88)	.32
Target vessel revascularization	23 (3.1)	19 (1.8)	.06	1.43 (0.71-2.88)	.32

Abbreviations: ITDM, insulin-treated diabetes mellitus; Non-ITDM, non–insulin-treated diabetes mellitus.

[a] Defined according to the Academic Research Consortium.

statistical analyses were performed with SAS, version 9.3 (SAS Institute Inc). $P < .05$ (2-sided) was considered statistically significant. Because of the descriptive nature of our analyses, no correction for multiple testing was made.

Results

Baseline Characteristics

Among the 1830 patients in the TUXEDO trial, 747 (40.8%) were receiving insulin and 1083 (59.2%) were not receiving insulin. Baseline characteristics of the 2 groups are outlined in Table 1. Patients with ITDM were more likely to be women, had a higher body mass index (calculated as weight in kilograms divided by height in meters squared), had a longer duration of DM, had a higher hemoglobin A_{1c}, were more likely to have undergone prior PCI, were more likely to have chronic kidney disease (estimated glomerular filtration rate, ≤60 mL/min/1.73 m^2), and were more likely to be asymptomatic but were less likely to have experienced prior MI, less likely to currently smoke, and had lower left ventricular ejection fraction when compared with patients with non-ITDM (Table 1).

Clinical Outcomes: ITDM vs non-ITDM

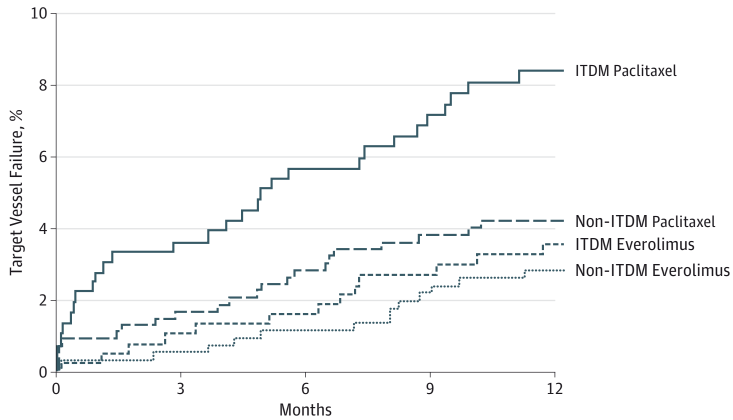
Compared with patients with non-ITDM, patients with ITDM had significantly higher rates of target vessel failure (42 [5.6%] vs 36 [3.3%]; *P* = .02), MACE (45 [6.0%] vs 40 [3.7%]; *P* = .02), death or MI (43 [5.8%] vs 35 [3.2%]; *P* = .009), and cardiac death or MI (35 [4.7%] vs 31 [2.9%]; *P* = .04) (**Table 2**). In addition, patients with ITDM had higher rates of death (26 [3.5%] vs 18 [1.7%]; *P* = .01), Q-wave MI (7 [0.9%] vs 2 [0.2%]; *P* = .04), and subacute stent thrombosis (8 [1.1%] vs 3 [0.3%]; *P* = .03), as well as higher numbers of cardiac death, target lesion revascularization, and target vessel revascularization, although they were not significant (Table 2). The rate of target vessel failure was higher in those with a hemoglobin A_{1c} of 7% or more vs those with a hemoglobin A_{1c} of less than 7% for patients with both ITDM (5.7% vs 4.8%) and non-ITDM (3.2% vs 2.9%).

In the regression adjustment to a propensity score model after accounting for baseline variables, the above higher cardiovascular risks with ITDM were no longer statistically significant (Table 2).

Paclitaxel-Eluting Stents vs Everolimus-Eluting Stents

In patients with ITDM, everolimus-eluting stents reduced the rate of target vessel failure (13 of 382 [3.4%] vs 29 of 365 [7.9%]; *P* = .007) (**Figure 1**), MACE (15 of 382 [3.9%] vs 30 of 365 [8.2%]; *P* = .01), MI (5 of 382 [1.3%] vs 16 of 365 [4.4%]; *P* = .01), any stent thrombosis (2 of 382 [0.5%] vs 11 of 365 [3.0%]; *P* = .009), definite stent thrombosis (1 of 382 [0.3%] vs 8 of 365 [2.2%]), target lesion revascularization (4 of 382 [1.0%] vs 19 of 365 [5.2%]; *P* = .001), and target vessel revascularization (4 of 382

Figure 1. Cumulative Incidence of Target Vessel Failure Based on Insulin Use Status and Stent Type



No. at risk	0	3	6	9	12
ITDM Paclitaxel	365	331	321	310	286
Non-ITDM Paclitaxel	549	510	497	479	427
ITDM Everolimus	382	363	358	348	311
Non-ITDM Everolimus	534	493	487	472	425

Survival plot of target vessel failure in patients with insulin-treated diabetes mellitus (ITDM) and non–insulin-treated diabetes mellitus (non-ITDM) who received everolimus-eluting stents and paclitaxel-eluting stents.

[1.0%] vs 19 of 365 [5.2%]; $P = .001$) compared with paclitaxel-eluting stents (**Figure 2**). In patients with non-ITDM, everolimus-eluting stents reduced the rate of target vessel–related MI compared with paclitaxel-eluting stents (3 of 534 [0.6%] vs 11 of 549 [2.0%]) (Figure 2) and trended in the same direction as that of the ITDM cohort for other outcomes ($P > .05$ for interaction). However, the absolute risk reduction for target vessel failure with everolimus-eluting stents was greater in those with ITDM compared with patients with non-ITDM (4.5% vs 1.4%) (Figure 2).

Discussion

In patients with DM enrolled in the TUXEDO trial, those with ITDM had significantly worse outcomes when compared with patients with non-ITDM, including increases in target vessel failure, MACE, death or MI, cardiac death or MI, all-cause death, Q-wave MI, and subacute stent thrombosis. After adjustment using propensity scores, the higher risk of cardiovascular events in patients with ITDM was no longer statistically significant. Compared with paclitaxel-eluting stents, everolimus-eluting stents reduced the rates of target vessel failure, MACE, MI, any stent thrombosis, definite stent thrombosis, target lesion revascularization, and target vessel revascularization in patients with ITDM. The absolute risk reduction of everolimus-eluting stents vs paclitaxel-eluting stents was greater for patients with ITDM when compared with those with non-ITDM.

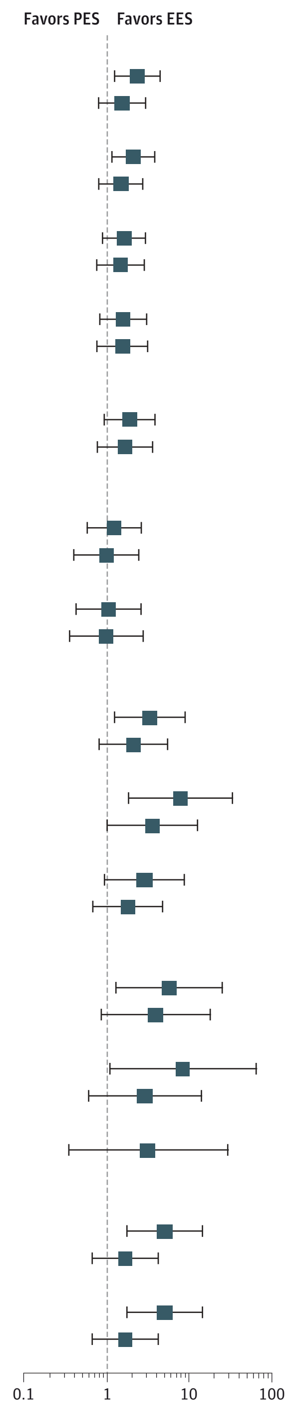
ITDM vs Non-ITDM

Among patients with DM, approximately 1 in 4 patients in the United States are treated with insulin.[16] Insulin-treated DM represents a higher-risk group of patients with a more prolonged duration of DM that is difficult to control and who has a higher hemoglobin A_{1c}. Insulin-treated DM is also associated with insulin resistance and associated risk factors, such as hypertension and dyslipidemia. Other studies have shown an association between required dose of exogenous insulin and coronary heart disease, implicating the "hyperinsulinemia-hypertriglyceridemia syndrome" as a powerful cardiovascular risk factor in patients with type 2 DM.[17] Consequently, serum levels of insulin, proinsulin, and insulin antibodies have been shown to be related to the risk of coronary heart disease in patients with type 2 DM.[18] These studies suggest that insulin may be pro-inflammatory, promote pro-inflammatory macrophage response, and accelerate atherogenesis.[19] Other mechanisms of the direct effect of insulin include increased thrombogenesis[20] and impaired fibrinolysis.[21] Thus, the increased risk of cardiovascular events in patients with ITDM has been attributed to difficult-to-control DM with a greater prevalence of concomitant cardiovascular risk factors as well as a direct atherogenic and thrombogenic effect of insulin.

However, the contribution of comorbidities vs a direct atherogenic and thrombogenic effect of insulin in patients with ITDM is controversial. In an analysis of the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial, patients with ITDM had significant increases in cardiovascular events compared with those with non-ITDM, and the risk for the primary outcome persisted even after controlling for baseline risk factors, suggesting perhaps an independent deleterious effect of insulin.[7] Other studies have shown that the increased possibility of adverse cardiovascular events in patients with ITDM disappears after risk adjustment, suggesting perhaps that other concomitant risk factors are likely contributory to the increased risk.[9] In our study, patients with ITDM had increased risks of cardiovascular events, which were attenuated in a propensity score–adjusted model that accounted for baseline risk factors, implying that the increased possibility of adverse cardiovascular events in patients with ITDM could be accounted for by difference in comorbidities, DM duration, and DM control.

Figure 2. Outcomes for the Insulin-Treated Diabetes Mellitus (ITDM) and Non–Insulin-Treated Diabetes Mellitus (non-ITDM) Cohorts

	PES (N=914)	EES (N=916)	Relative Risk (95% CI)	*P* Value for Interaction
Target vessel failure				
ITDM	29/365 (7.9)	13/382 (3.4)	2.33 (1.23-4.42)	.35
Non-ITDM	22/549 (4.0)	14/534 (2.6)	1.53 (0.79-2.96)	
Major adverse cardiac events				
ITDM	30/365 (8.2)	15/382 (3.9)	2.09 (1.15-3.83)	.40
Non-ITDM	24/549 (4.4)	16/534 (3.0)	1.46 (0.78-2.72)	
Death or myocardial infarction				
ITDM	26/365 (7.1)	17/382 (4.5)	1.60 (0.88-2.90)	.82
Non-ITDM	21/549 (3.8)	14/534 (2.6)	1.46 (0.75-2.84)	
Cardiac death or myocardial infarction				
ITDM	21/365 (5.8)	14/382 (3.7)	1.57 (0.81-3.04)	.96
Non-ITDM	19/549 (3.5)	12/534 (2.2)	1.54 (0.76-3.14)	
Cardiac death or target vessel myocardial infarction				
ITDM	20/365 (5.5)	11/382 (2.9)	1.90 (0.92-3.92)	.78
Non-ITDM	17/549 (3.1)	10/534 (1.9)	1.65 (0.76-3.58)	
Death				
All				
ITDM	14/365 (3.8)	12/382 (3.1)	1.22 (0.57-2.60)	.71
Non-ITDM	9/549 (1.6)	9/534 (1.7)	0.97 (0.39-2.43)	
Cardiac death				
ITDM	9/365 (2.5)	9/382 (2.4)	1.05 (0.42-2.61)	.92
Non-ITDM	7/549 (1.3)	7/534 (1.3)	0.97 (0.34-2.75)	
Myocardial infarction				
All				
ITDM	16/365 (4.4)	5/382 (1.3)	3.35 (1.24-9.05)	.50
Non-ITDM	13/549 (2.4)	6/534 (1.1)	2.11 (0.81-5.50)	
Target vessel related				
ITDM	15/365 (4.1)	2/382 (0.5)	7.85 (1.81-34.08)	.42
Non-ITDM	11/549 (2.0)	3/534 (0.6)	3.57 (1.00-12.71)	
Non-Q-Wave				
ITDM	11/365 (3.0)	4/382 (1.0)	2.88 (0.92-8.96)	.53
Non-ITDM	11/549 (2.0)	6/534 (1.1)	1.78 (0.66-4.79)	
Stent thrombosis (ARC definition)				
All				
ITDM	11/365 (3.0)	2/382 (0.5)	5.76 (1.28-25.79)	.71
Non-ITDM	8/549 (1.5)	2/534 (0.4)	3.89 (0.83-18.24)	
Definite				
ITDM	8/365 (2.2)	1/382 (0.3)	8.37 (1.05-66.61)	.43
Non-ITDM	6/549 (1.1)	2/534 (0.4)	2.92 (0.59-14.39)	
Probable				
ITDM	3/365 (0.8)	1/382 (0.3)	3.14 (0.33-30.05)	.97
Non-ITDM	2/549 (0.4)	0/534 (0.0)		
Target lesion revascularization				
ITDM	19/365 (5.2)	4/382 (1.0)	4.97 (1.71-14.47)	.12
Non-ITDM	12/549 (2.2)	7/534 (1.3)	1.67 (0.66-4.20)	
Target vessel revascularization				
ITDM	19/365 (5.2)	4/382 (1.0)	4.97 (1.71-14.47)	.12
Non-ITDM	12/549 (2.2)	7/534 (1.3)	1.67 (0.66-4.20)	



Outcomes with everolimus-eluting stents (EES) and paclitaxel-eluting stents (PES) in patients with ITDM and non-ITDM. ARC indicates Academic Research Consortium.

Choice of Drug-Eluting Stent in Patients With ITDM

The choice of a drug-eluting stent (limus- vs taxol-eluting) in patients with ITDM is controversial even in the era of second-generation drug-eluting stents. In an analysis from the SPIRIT and COMPARE trials, everolimus-eluting stents were associated with worse outcomes compared with paclitaxel-eluting stents in patients with ITDM.[11] In the only well-powered, head-to-head randomized trial of everolimus-eluting vs paclitaxel-eluting stents in patients with DM—the TUXEDO trial—clear superiority of everolimus-eluting stents for reducing the risk of cardiovascular events, including stent thrombosis, was demonstrated vs paclitaxel-eluting stents.[12] Our study extends this observation to patients with ITDM in that everolimus-eluting stents reduced the risk of cardiovascular events, including stent thrombosis, vs paclitaxel-eluting stents. The test for interaction was not significant, suggesting that the benefits of everolimus-eluting stents vs paclitaxel-eluting stents are seen in patients with both ITDM and non-ITDM. With 747 patients with ITDM, our sample size is 1.5 times larger than the sample size of patients with ITDM (494) in the combined analysis from the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE trials[11] and therefore offers important insights into the treatment of patients with ITDM.

This study has some limitations. Although this study is a prespecified subgroup analysis from the TUXEDO trial, the trial was not designed nor powered to evaluate outcome differences in the ITDM or non-ITDM subgroups. The multivariable model does not account for unmeasured confounders (such as patient frailty). The decision as to whether to treat a patient with insulin was left to the treating physicians. For most end points in the non-ITDM cohort, the difference between everolimus-eluting stents and paclitaxel-eluting stents was not statistically significant. This finding likely occurred because of lower event rates in the non-ITDM cohort and, hence, this subgroup is likely underpowered. Moreover, results of the test for interaction (stent type × insulin use status) were not statistically significant, suggesting similar effects of everolimus-eluting stents in both the ITDM and non-ITDM cohorts.

Conclusions

In patients with DM enrolled in the TUXEDO trial, those with ITDM had significantly worse outcomes compared with patients with non-ITDM in the unadjusted analysis. However, this finding was largely attenuated in the propensity score–adjusted analysis, implying that the increased possibility of adverse cardiovascular events in patients with ITDM is accounted for by the differences in baseline risk factors, DM duration, and DM control. Everolimus-eluting stents reduced the rate of cardiovascular events, including stent thrombosis, when compared with paclitaxel-eluting stents in patients with ITDM.

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