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Paclitaxel-Eluting Coronary Stents in Patients With Diabetes Mellitus

Pooled Analysis From 5 Randomized Trials

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Objectives We sought to examine the safety and efficacy of paclitaxel-eluting stents (PES) in patients with diabetes mellitus (DM).

Background Compared with patients without DM, patients with DM undergoing percutaneous coronary intervention are at increased risk for mortality and restenosis. The safety of drug-eluting stents in diabetic patients has recently been called into question by a published meta-analysis of randomized trials.

Methods Patient-level data were pooled from 5 prospective, double-blind, randomized trials of PES versus bare-metal stents (BMS) (n = 3,513). Safety and efficacy outcomes through 4 years of follow-up were assessed among the 827 randomized patients (23.6%) with DM.

Results Patients treated with PES and BMS has similar baseline characteristics among both the diabetic and nondiabetic cohorts within these trials. At 4-year follow-up, there were no significant differences between PES and BMS among diabetic patients in the rates of death (8.4% vs. 10.3%, respectively, p = 0.61), myocardial infarction (6.9% vs. 8.9%, p = 0.17), or stent thrombosis (1.4% vs. 1.2%, p = 0.92). Treatment of diabetic patients with PES compared with treatment with BMS was associated with a significant and durable reduction in target lesion revascularization over the 4-year follow-up period (12.4% vs. 24.7%, p < 0.0001). The relative safety and efficacy of PES compared with the relative safety and efficacy of BMS in diabetic patients extended to both those requiring and not requiring insulin.

Conclusions In these 5 randomized trials in which patients with single, primarily noncomplex lesions were enrolled, treatment with PES compared with treatment with BMS was safe and effective, resulting in markedly lower rates of target lesion revascularization at 4 years, with similar rates of death, myocardial infarction, and stent thrombosis. (J Am Coll Cardiol 2008;51:708–15) © 2008 by the American College of Cardiology Foundation

After stent implantation, patients with diabetes mellitus (DM) are more likely to develop restenosis and require repeat revascularization procedures compared with those without DM (1), and are also at greater risk for stent thrombosis (2), myocardial infarction (MI), and death (1,3). Although drug-eluting stents (DES) reduce angiographic and clinical restenosis compared with bare-metal stents (BMS) (4,5), late stent thrombosis has been reported to occur more frequently after DES implantation, while overall rates of death and MI are similar between DES and BMS (6–9). Whether DES are similarly safe and effective in the higher risk cohort of diabetic patients remains controversial. In particular, a recent meta-analysis of double-blind, randomized trial data reported greater long-term mortality in patients with DM treated with sirolimus-eluting stents (SES) compared with those treated with BMS, an effect

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that was absent in patients without DM (7). A similar analysis with polymer-based paclitaxel-eluting stents (PES) has not been undertaken.

Therefore, we sought to determine the long-term outcomes of patients with and without DM from the 5 major double-blind, prospective randomized trials of PES versus BMS.

Methods

Study description. The databases from the prospective, multicenter, double-blind, placebo-controlled randomized TAXUS-I (10), -II (11), -IV (5), -V (12), and -VI (13) trials of PES versus BMS were pooled for a patient-level meta-analysis. These studies were chosen as they comprise the only double-blind randomized trials of PES versus BMS, and were utilized for regulatory approval in the U.S. and European Union. The primary study comparison for this analysis was between the randomized treatment arms (PES vs. BMS) among both diabetic and nondiabetic patients. Further analyses of PES versus BMS were conducted in the 827 diabetic patients in these studies to assess for differences among the subgroups of patients with insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM).

In each trial, patients with a single de-novo lesion in a native coronary artery were prospectively assigned in equal proportions to stent implantation with either a PES or an otherwise equivalent BMS (both Boston Scientific, Natick, Massachusetts), although the entry criteria, device specifications, and geography of study location varied somewhat among the trials, as outlined in Table 1. Each trial is still blinded with follow-up planned to 5 years, with neither the patients, investigators, nor study personnel knowing which stent individual subjects received. Overall, 72.1% of patients in the study population underwent protocol-mandated angiographic follow-up (70.1% for patients with DM and 72.5% for patients without DM).

End points and definitions. Target lesion revascularization (TLR) and target vessel revascularization (TVR) were examined as clinical measures of stent efficacy. The following end points were examined to assess stent safety: stent thrombosis (as prospectively defined in the study protocols), MI (all, Q-wave, and non–Q-wave), death (all cause, cardiac, and noncardiac), composite death or MI, composite death or Q-wave MI, and composite cardiac death or MI. Stent thrombosis data adjudicated by the Academic Research Consortium (ARC) definitions (14) were also available in trials testing the slow-release version of the PES (TAXUS-I, TAXUS-II SR [Slow Release], TAXUS-IV, and TAXUS-V). Data from the original databases as prospectively defined and adjudicated by the clinical events committees for each individual study were used in the present analysis (5,10–13).

Statistical analysis. Categorical variables were compared by chi-square or Fisher exact test. Continuous variables are described as mean ± standard deviation and were compared by unpaired *t* tests. At the time of this report, data were available for TAXUS-I to 5 years, for TAXUS-II and -IV to 4 years, for TAXUS-VI to 3 years, and for TAXUS-V to 2 years. Time-to-event data are reported and displayed as Kaplan-Meier estimates for the primary analyses, with comparisons between groups by the log-rank test (or exact log-rank test whenever there were <5 observations for any end point). Hazard ratios (HRs) derived from univariate Cox models for the comparisons between PES and BMS are also displayed. Analyses were truncated at 4 years of follow-up due to the small number of patients with available data thereafter. All analyses are by intention-to-treat, with all patients randomized to each stent included. Tests for heterogeneity of treatment effect across these studies demonstrated no significant heterogeneity with regards to the end points of death, MI, stent thrombosis, TLR, or TVR. Additionally, first-order tests of interaction terms for primary end points were conducted according to diabetic status (vs. nondiabetic status) as well as according to insulin-requirement. An alpha of <0.05 was used for statistical significance. All analyses were performed by an academic statistician at the Cardiovascular Research Foundation (M.F.) without sponsor involvement.

Abbreviations And Acronyms

- **ARC** = Academic Research Consortium
- **BMS** = bare-metal stent(s)
- **CI** = confidence interval
- **DES** = drug-eluting stent(s)
- **DM** = diabetes mellitus
- **HR** = hazard ratio
- **IDDM** = insulin-dependent diabetes mellitus
- **MI** = myocardial infarction
- **NIDDM** = noninsulin-dependent diabetes mellitus
- **PES** = paclitaxel-eluting stent(s)
- **RVD** = reference vessel diameter
- **SES** = sirolimus-eluting stent(s)
- **TLR** = target lesion revascularization
- **TVR** = target vessel revascularization

Table 1 Characteristics of Included Trials

	Number Randomized	Geography	Stent Platform	Drug Release Kinetics	Percentage of Patients With Diabetes	Reference Vessel Diameter (mm)	Lesion Length (mm)
TAXUS-I	61	Germany	NIRx	Slow	11 (18.1%)	3.0 to 3.5	≤12
TAXUS-II	536	Global	NIRx	Slow and moderate	58 (10.8%)	3.0 to 3.5	≤12
TAXUS-IV	1,314	U.S.	Express	Slow	318 (24.2%)*	2.5 to 3.75	10 to 28
TAXUS-V	1,156	U.S.	Express2	Slow	356 (30.8%)*	2.25 to 4.0	10 to 46
TAXUS-VI	446	Europe	Express	Moderate	89 (20.0%)	2.5 to 3.75	18 to 40

*Randomization to paclitaxel-eluting stent versus bare-metal stent was stratified by presence of diabetes at baseline.

Results

Baseline and angiographic characteristics. The baseline demographic and procedural characteristics of the randomized PES- and BMS-treated groups were well matched in patients both with and without DM (Table 2), except for a slightly higher prevalence of hyperlipidemia among diabetic patients randomized to PES. Baseline angiographic characteristics including reference vessel diameter (RVD) and lesion length were also similar among patients treated with PES and BMS (Table 2).

Compared with patients without DM, patients with DM were older, more likely to be women, and more frequently had concomitant cardiovascular risk factors such as hypertension and hyperlipidemia. Patients with DM also had smaller treated vessels (mean RVD 2.64 vs. 2.77 mm, $p < 0.001$) and longer treated lesions (15.9 vs. 14.8 mm, $p = 0.002$), with a greater number of stents used (1.25 vs. 1.18, $p = 0.001$) and longer overall stent length (25.6 vs. 23.9 mm, $p = 0.002$) compared with nondiabetic patients.

Efficacy end points. At 4 years in the entire study population, patients with DM compared with those without DM had higher rates of TLR (18.6% vs. 14.1%, $p = 0.005$) and TVR (27.3% vs. 19.2%, $p < 0.001$). As seen in Table 3 and Figures 1 and 2, the use of PES compared with BMS resulted in marked reductions in ischemic TLR both in patients with DM (HR 0.42 [95% confidence interval (CI) 0.30 to 0.60]) and without DM (HR 0.47 [95% CI 0.38 to 0.59]). The use of PES also reduced ischemic TVR independent of diabetic status (HR 0.67 [95% CI 0.50 to 0.89] in patients with DM and 0.61 [95% CI 0.51 to 0.73] in patients without DM). The magnitude of the reductions in TLR and TVR was similar among patients with and without DM (all p for interaction = NS). In patients both with and without DM, the difference in clinical restenosis rates in the 2 randomized study arms peaked by 1 year and then remained stable through 4 years (Fig. 1).

Safety end points. At 4 years in the entire study population, patients with DM compared with those without DM had a higher rate of death (9.4% vs. 5.5%, $p < 0.001$) and a trend toward a slightly higher rate of MI (7.9% vs. 6.3%, $p = 0.13$), but similar rates of stent thrombosis (1.3% vs. 1.0%, $p = 0.63$). The rates of protocol-defined stent thrombosis between PES and BMS were not significantly different at 4 years both in patients with DM (1.4% [4 events] vs. 1.2% [5 events], $p = 0.92$) and in patients without DM (1.3% [16 events] vs. 0.8% [9 events], $p = 0.16$) (Table 4). Among patients treated in the trials of the slow-release formulation of the PES compared with those treated with BMS, there were no significant differences in rates of overall ARC thrombosis or definite/probable thrombosis in either diabetic patients or nondiabetic patients (Table 4). There were no significant differences in the 4-year rates of all-cause mortality between PES and BMS in patients with DM (8.4% vs. 10.3%, respectively, $p = 0.61$) or in patients without DM (5.4% vs. 5.5%, $p = 0.92$); cardiac and noncardiac mortality rates were also similar. The 4-year rates of MI in patients treated with PES and BMS were comparable in diabetic patients (6.9% vs. 8.9%, $p = 0.17$) and nondiabetic patients (7.1% vs. 5.6%, $p = 0.17$), without differences in rates of Q-wave or non–Q-wave MI. The rates of composite end points (death or MI, cardiac death or MI, and all-cause death or Q-wave MI) were also similar in PES-treated and BMS-treated patients with and without DM. The

Table 2 Baseline Demographic and Angiographic Characteristics

	No DM		DM	
	PES (n = 1,347)	BMS (n = 1,339)	PES (n = 408)	BMS (n = 419)
Median follow-up, days (interquartile range)	1,401 (1,079, 1,449)	1,407 (1,080, 1,452)	1,102 (867.5, 1,439)	1,109 (968, 1,442)
Age (yrs)	62.18 ± 11.00	61.95 ± 10.63	63.15 ± 10.29	62.80 ± 10.32
Women	24.4% (328/1,347)	25.7% (344/1,339)	38.2% (156/408)	32.5% (136/419)
Insulin-dependent diabetes	—	—	31.1% (127/408)	32.9% (138/419)
Current smoker	25.3% (338/1,337)	24.4% (325/1,333)	18.5% (75/405)	18.3% (76/416)
Hypertension	65.9% (887/1,347)	63.1% (842/1,335)	80.9% (330/408)	83.3% (349/419)
Hyperlipidemia	68.3% (915/1,339)	70.8% (943/1,332)	77.8% (315/405)	70.2% (294/419)
Target coronary artery				
Left anterior descending	41.9% (562/1,340)	42.0% (561/1,335)	42.3% (171/404)	40.5% (169/417)
Left circumflex	24.2% (324/1,340)	22.8% (305/1,335)	29.7% (120/404)	27.3% (114/417)
Right	33.4% (447/1,340)	34.5% (460/1,335)	28.0% (113/404)	31.7% (132/417)
Pre-reference vessel diameter	2.77 ± 0.49 (1,333)	2.77 ± 0.51 (1,325)	2.64 ± 0.55 (406)	2.64 ± 0.50 (417)
Pre-lesion length	14.78 ± 7.62 (1,332)	14.90 ± 7.98 (1,330)	16.13 ± 8.60 (403)	15.57 ± 7.91 (416)
Pre-minimal luminal diameter	0.91 ± 0.34 (1,334)	0.92 ± 0.37 (1,331)	0.88 ± 0.38 (404)	0.89 ± 0.35 (417)
Pre-diameter stenosis (%)	67.0 ± 10.7 (1,334)	66.8 ± 11.6 (1,331)	66.9 ± 11.7 (404)	66.5 ± 11.2 (417)
Number stents implanted	1.19 ± 0.46 (1,339)	1.17 ± 0.44 (1,333)	1.26 ± 0.54 (407)	1.23 ± 0.50 (419)
Total stent length	23.9 ± 10.8 (1,331)	23.8 ± 11.0 (1,320)	26.0 ± 12.3 (404)	25.2 ± 11.7 (413)

Unless otherwise indicated, numbers in parentheses indicate the number of patients. All p = NS between paclitaxel-eluting stents (PES) and bare-metal stents (BMS) except for p = 0.01 for comparison of hyperlipidemia between PES and BMS in diabetic patients.
DM = diabetes mellitus.

Table 3 4-Year Efficacy Outcomes

	No DM				DM			
Efficacy End Points	**PES**	**BMS**	**HR (95% CI)**	**p Value**	**PES**	**BMS**	**HR (95% CI)**	**p Value**
TLR	9.5% (122)	18.6% (241)	0.47 (0.38–0.59)	<0.0001	12.4% (44)	24.7% (97)	0.42 (0.30–0.60)	<0.0001
PTCA	8.5% (108)	16.2% (212)	0.48 (0.38–0.61)	<0.0001	11.9% (42)	19.5% (78)	0.52 (0.35–0.75)	0.0004
CABG	1.1% (14)	3.1% (39)	0.35 (0.19–0.65)	0.0005	0.5% (2)	6.3% (22)	0.09 (0.02–0.39)	<0.0001
TVR	15.3% (191)	23.1% (294)	0.61 (0.51–0.73)	<0.0001	24.4% (81)	30.2% (115)	0.67 (0.50–0.89)	0.005
PTCA	13.3% (165)	20.2% (259)	0.60 (0.49–0.73)	<0.0001	18.7% (66)	23.7% (92)	0.70 (0.51–0.96)	0.025
CABG	2.2% (28)	4.3% (52)	0.53 (0.34–0.84)	0.006	6.5% (17)	8.8% (29)	0.59 (0.33–1.08)	0.083

Values are displayed as Kaplan-Meier estimate rates (number of events).

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; PTCA = percutaneous transluminal coronary angioplasty; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 2.

effects of PES versus BMS upon the occurrence of any of the individual safety end points were additionally similar when stratified by diabetic status (all p for interaction = NS).

Outcomes in IDDM versus NIDDM. Patients with IDDM compared with those with NIDDM were more often women (40.4% vs. 32.9%, p = 0.042); the baseline demographic and procedural characteristics were otherwise comparable between the 2 groups. In addition, the pre-procedural RVD, lesion length, total stent length, and number of stents implanted were similar among patients with IDDM and NIDDM (data not shown).

The magnitude of reduction in ischemic TLR was similar among patients with IDDM and NIDDM (Table 5) (p for interaction = 0.93). Despite a significant reduction in TLR with PES compared with that in BMS in patients with IDDM (12.5% vs. 22.9%, p = 0.009), the 4-year rates of TVR were similar (26.4% vs. 27.0%, p = 0.66). Ischemic TVR was reduced in patients with NIDDM assigned to PES (23.8% vs. 31.7%, p =

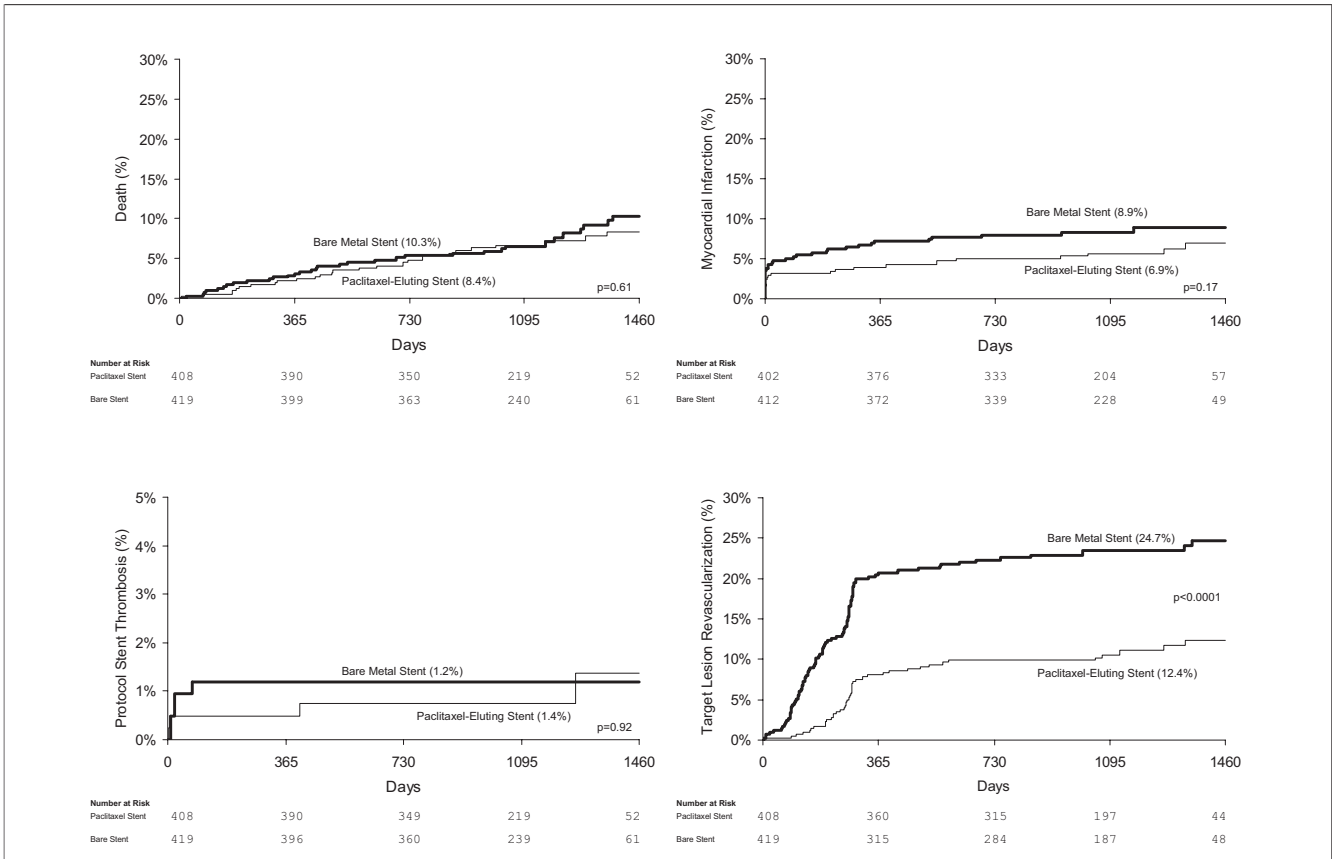

Figure 1 Diabetes

Kaplan-Meier estimates representing the 4-year cumulative rates of death **(top left)**, myocardial infarction **(top right)**, protocol-defined stent thrombosis **(bottom left)**, and target lesion revascularization **(bottom right)** for the pooled randomized trials of paclitaxel-eluting stents versus bare-metal stents in patients with diabetes mellitus. The number of patients at risk for each year is provided, equal to the number of patients with follow-up at each time period less those with earlier events.

JACC Vol. 51, No. 7, 2008
February 19, 2008:708–15

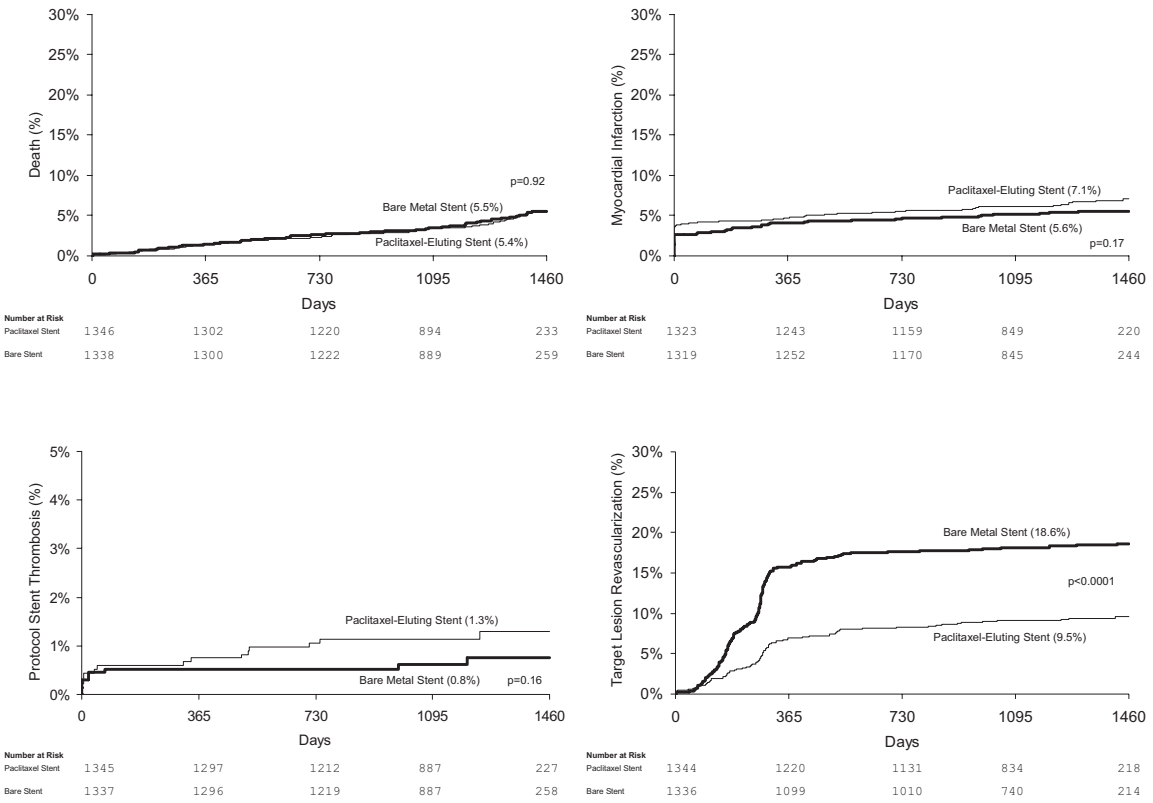

Figure 2 **No Diabetes**

Kaplan-Meier estimates representing the 4-year cumulative rates of death **(top left)**, myocardial infarction **(top right)**, protocol-defined stent thrombosis **(bottom left)**, and target lesion revascularization **(bottom right)** for the pooled randomized trials of paclitaxel-eluting stents versus bare-metal stents in patients without diabetes mellitus. The number of patients at risk for each year is provided, equal to the number of patients with follow-up at each time period less those with earlier events.

0.002). Nonetheless, there was no significant interaction between IDDM and NIDDM as regards the treatment effect of PES in reducing TVR (p for interaction = 0.16).

Rates of stent thrombosis, all-cause mortality, cardiac death, and noncardiac death were similar among patients treated with PES versus BMS irrespective of IDDM or

Table 4 **4-Year Safety Outcomes**

	No DM				DM			
Safety End Points	**PES**	**BMS**	**HR (95% CI)**	**p Value**	**PES**	**BMS**	**HR (95% CI)**	**p Value**
Death	5.4% (58)	5.5% (59)	0.98 (0.68–1.41)	0.92	8.4% (28)	10.3% (33)	0.88 (0.53–1.45)	0.61
Cardiac death	1.9% (21)	2.7% (28)	0.75 (0.43–1.32)	0.31	4.0% (15)	3.7% (14)	1.10 (0.53–2.28)	0.80
Noncardiac death	3.6% (37)	2.9% (31)	1.19 (0.74–1.92)	0.47	4.5% (13)	6.8% (19)	0.71 (0.35–1.44)	0.34
MI	7.1% (87)	5.6% (70)	1.24 (0.91–1.70)	0.17	6.9% (24)	8.9% (35)	0.70 (0.41–1.17)	0.17
Q-wave	1.6% (20)	1.0% (11)	1.82 (0.87–3.79)	0.11	0.5% (2)	1.5% (6)	0.34 (0.07–1.70)	0.26
Non–Q-wave	5.7% (69)	4.7% (61)	1.13 (0.80–1.59)	0.49	6.4% (22)	7.3% (29)	0.77 (0.45–1.35)	0.36
Stent thrombosis								
Per protocol*	1.3% (16)	0.8% (9)	1.77 (0.78–4.01)	0.16	1.4% (4)	1.2% (5)	0.83 (0.22–3.09)	0.92
ARC (all)†	3.6% (33)	4.0% (33)	1.00 (0.62–1.62)	1.00	4.8% (15)	3.1% (11)	1.38 (0.63–3.00)	0.42
ARC (definite/probable)†	2.1% (20)	1.6% (15)	1.33 (0.68–2.60)	0.40	2.2% (6)	1.4% (5)	1.22 (0.37–4.01)	0.74
Death or MI	11.9% (139)	10.5% (123)	1.13 (0.89–1.44)	0.31	14.1% (48)	16.2% (60)	0.81 (0.56–1.19)	0.28
Cardiac death or MI	8.6% (104)	7.8% (93)	1.12 (0.85–1.48)	0.43	9.8% (35)	10.7% (43)	0.83 (0.53–1.29)	0.40
Death or Q-wave MI	6.8% (75)	6.3% (68)	1.11 (0.80–1.54)	0.55	8.8% (30)	11.8% (39)	0.79 (0.49–1.27)	0.33

Values are displayed as Kaplan-Meier estimate rates (number of events). *Per-protocol definitions of stent thrombosis do not count thrombosis events occurring after an intervening target lesion revascularization; †these data were available only from patients in the trials testing the slow-release version of the PES.

ARC = Academic Research Consortium definitions; MI = myocardial infarction; other abbreviations as in Tables 2 and 3.

Table 5 Efficacy and Safety Outcomes Among Diabetic Patients According to Insulin-Dependent Status

	NIDDM				IDDM			
	PES	BMS	HR (95% CI)	p Value	PES	BMS	HR (95% CI)	p Value
Efficacy end points								
TLR	12.2% (31)	25.5% (67)	0.42 (0.27–0.64)	<0.0001	12.5% (13)	22.9% (30)	0.43 (0.22–0.82)	0.009
PTCA	11.8% (30)	18.7% (50)	0.56 (0.36–0.89)	0.012	11.8% (12)	21.2% (28)	0.43 (0.22–0.84)	0.011
CABG	0.4% (1)	8.5% (20)	0.05 (0.01–0.37)	<0.0001	0.8% (1)	1.7% (2)	0.54 (0.05–5.95)	0.61
TVR	23.8% (51)	31.7% (80)	0.58 (0.41–0.83)	0.002	26.4% (30)	27.0% (35)	0.90 (0.55–1.46)	0.66
PTCA	18.1% (44)	22.8% (59)	0.71 (0.48–1.04)	0.079	19.9% (22)	25.3% (33)	0.69 (0.40–1.18)	0.17
CABG	6.6% (9)	10.5% (24)	0.37 (0.17–0.80)	0.008	6.8% (8)	5.2% (5)	1.74 (0.57–5.33)	0.32
Safety end points								
Death	6.3% (15)	8.0% (18)	0.84 (0.43–1.68)	0.623	12.7% (13)	15.0% (15)	0.93 (0.44–1.95)	0.85
Cardiac death	3.1% (8)	2.2% (6)	1.33 (0.46–3.84)	0.59	6.0% (7)	7.0% (8)	0.95 (0.34–2.62)	0.92
Noncardiac death	3.3% (7)	6.0% (12)	0.60 (0.23–1.51)	0.27	7.1% (6)	8.6% (7)	0.91 (0.30–2.70)	0.86
MI	6.9% (17)	8.0% (22)	0.76 (0.41–1.44)	0.40	7.0% (7)	10.8% (13)	0.58 (0.23–1.45)	0.23
Q-wave	0.4% (1)	2.3% (6)	0.17 (0.02–1.38)	0.10	0.8% (1)	0.0% (0)	N/A	0.96
Non–Q-wave	6.5% (16)	5.7% (16)	1.00 (0.50–1.99)	0.99	6.2% (6)	10.8% (13)	0.49 (0.19–1.29)	0.14
Stent thrombosis (per protocol)	0.7% (2)	1.4% (4)	0.50 (0.09–2.74)	0.60	2.7% (2)	0.7% (1)	2.13 (0.19–23.53)	0.71
Death or MI	11.9% (29)	14.7% (38)	0.75 (0.46–1.22)	0.25	18.6% (19)	19.2% (22)	0.92 (0.50–1.70)	0.79
Cardiac death or MI	8.7% (22)	9.8% (27)	0.80 (0.46–1.41)	0.44	12.0% (13)	12.8% (16)	0.87 (0.42–1.82)	0.72
Death or Q-wave MI	6.6% (16)	10.3% (24)	0.66 (0.35–1.25)	0.20	13.5% (14)	15.0% (15)	1.01 (0.49–2.09)	0.99

Values are displayed as Kaplan-Meier estimate rates (number of events).

IDDM = insulin-dependent diabetes mellitus; MI = myocardial infarction; NIDDM = noninsulin-dependent diabetes mellitus; other abbreviations as in Tables 2 and 3.

NIDDM status. There was a trend toward a lower incidence of Q-wave MI among PES-treated patients with NIDDM compared with that seen in patients with IDDM (0.4% vs. 2.3%, p = 0.10), although Q-wave MI occurred relatively infrequently in this group of patients (7 total events). There were no differences in the 4-year composite rates of death or MI, death or Q-wave MI, or cardiac death or MI between PES and BMS in patients with IDDM or in patients with NIDDM (Table 5).

Discussion

The principal findings from this patient-level pooled meta-analysis of patients with single, de-novo coronary lesions enrolled in the 5 prospective double-blind, randomized trials of PES versus BMS through 4-year follow-up are: 1) treatment with PES rather than BMS resulted in marked reductions in ischemic TLR in both patients with and without DM; 2) the rates of stent thrombosis, MI, and death were comparable with PES and BMS throughout the follow-up period in both patients with and without DM; and 3) the relative safety and efficacy profile of PES compared with those seen with BMS in patients with DM extended to both those requiring and not requiring insulin.

Efficacy of PES in diabetic patients. As expected, patients enrolled in the TAXUS trials in whom DM was present had higher rates of revascularization at 4 years than those seen in patients without DM. The present analysis also demonstrates a marked reduction in ischemic TLR and TVR with PES compared with that seen with BMS at 4 years in both diabetic and nondiabetic patients. These results are consistent with the primary mechanism of PES in reducing neointimal hyperplasia after stent implantation. While the maximal difference between PES and BMS in TLR occurred by 1 year (and in absolute terms may have been somewhat exaggerated due to the performance of angiographic follow-up in a subset of patients in these studies) (15), there was no late catch-up observed even among the cohort with DM. However, consistent with prior studies demonstrating that progression of disease remote from the target lesion is the cause of the majority of subsequent revascularizations in patients with DM (1), the difference in TVR rates between PES and BMS narrowed somewhat between 3 and 4 years in the diabetic cohort (although remaining significantly different). This finding was especially evident in patients with insulin-requiring DM, in whom there was no difference in TVR at 4 years between PES and BMS, despite a marked reduction in TLR with PES. This may have resulted from more rapid progression of native atherosclerosis in insulin-requiring compared with noninsulin-requiring diabetic patients.

The early impact of PES in reducing restenosis compared with BMS is consistent with prior studies with follow-up to 1 year (16,17). The persistent benefit of PES in our study beyond this period, however, contrasts with the findings recently reported from the observational T-SEARCH (Taxus-Stent Evaluated At Rotterdam Cardiology Hospital) registry, in which the benefit of PES compared with that of BMS was attenuated over 2-year follow-up in propensity-adjusted analyses (18). As a "real-world registry," T-SEARCH enrolled more complex patients than those in the trials included in the present meta-analysis. Though the present study results, comprised of patient-level data from monitored randomized trials, may be considered more

robust, further study is required to determine the long-term benefits of PES in higher-risk patients.

The long-term durable benefit of PES in terms of enhancing freedom from repeat revascularization in patients with and without DM is similar to that reported in a recent meta-analysis from the 4 principal randomized trials of SES versus BMS (7). Randomized and registry studies examining the relative efficacy of PES and SES in patients with DM have reported conflicting results (16,18–26). Thus, an adequately powered randomized trial is required to appropriately address this issue.

Safety of PES in diabetic patients. In the present study, the 4-year mortality rates were approximately doubled in patients with versus without DM. As such, antirestenosis therapies for patients with DM are required that ideally would reduce mortality, or at least not negatively impair survival while enhancing freedom from revascularization. In this regard it is noteworthy that at 4 years the rates of mortality in diabetic patients treated with PES were numerically but not significantly lower than those seen in patients treated with BMS, with similar rates of stent thrombosis observed with both stents. The relative safety profile of PES in this regard was comparable in diabetic patients requiring and not requiring insulin. While these data should be regarded cautiously given limited power to detect differences in low-frequency safety events, this is the largest comparison to date of PES versus BMS in DM patients using randomized clinical trial data. These findings, thus, can provide early reassurance that PES is not associated with significant safety concerns in diabetic patients.

The present data contrast with the recently reported pooled patient-level analysis of diabetic patients enrolled in the 4 major prospective, double-blind randomized trials of the polymer-based SES versus BMS (7). In the study by Spaulding et al. (7) of 428 diabetic patients from the RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization), SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions), C-SIRIUS (Canadian Sirolimus-Eluting Stent in Coronary Lesions), and E-SIRIUS (European and Latin American Sirolimus-Eluting Stent in Coronary Lesions) trials, treatment with SES rather than BMS was associated with greater mortality during the 4-year follow-up period (12.2% vs. 4.4%, $p = 0.004$), with a small excess of very late stent thrombosis seen among this cohort of patients (11 vs. 3 events). The finding of higher mortality among SES-treated patients in this analysis may have been due to better-than-expected survival among the diabetic patients treated with BMS in these 4 trials and/or spurious results due to the modest-sized diabetic cohort ($n = 428$) in this series. Nonetheless, with data from 827 randomized patients with DM to examine in the present patient-level pooled meta-analysis of the TAXUS trials, it is reassuring that the 4-year mortality rate was numerically lower in patients with diabetes treated with PES compared that seen in patients treated with BMS (8.4% vs. 10.3%), with similar numbers of patients experiencing stent thrombosis (4 vs. 5, respectively).

Study strengths and limitations. The relatively infrequent occurrence of death, MI, and stent thrombosis as well as the limited number of diabetic patients studied in these trials (even when pooled) are insufficient to produce tight CIs around these low event rates, and, thus, this analysis should be viewed as hypothesis-generating. However, the upper bound of the CI for the hazard of PES compared with BMS as regards 4-year death or MI was 1.19, and, as such, it is unlikely that a major safety issue exists. Additionally, the present analysis applies only to the types of patients, lesions, and stent platforms studied within these 5 randomized trials (i.e., single discrete de-novo native coronary arterial lesions in relatively stable ischemic syndromes). The rates of both efficacy and safety end points may vary in a more unselected patient population in which stents are implanted in more complex and higher-risk situations, such as in true bifurcation lesions, multivessel disease, and acute MI. This analysis additionally incorporated trials of both the commercial slow rate-release formulation of PES as well as the noncommercialized moderate rate-release formulation that releases more paclitaxel. However, no major clinical differences have been described between these 2 versions in comparative studies (11).

Finally, the control arm in these trials was BMS rather than coronary artery bypass graft surgery or medical therapy, and, as such, the performance of PES compared with the performance of these 2 therapeutic alternatives in diabetic patients is unknown. Given the similar infarct-free survival rates between PES and BMS in the present study, it is unlikely that PES would be shown to reduce death or MI compared with optimal medical therapy in diabetic patients with stable angina (27). However, freedom from angina, medication use, and rehospitalization for unplanned revascularization would also be expected to be significantly greater with PES than as recently described for BMS compared with more conservative medical treatment (27). Ongoing large-scale randomized trials are also underway to determine the relative safety and efficacy of DES compared with that of bypass graft surgery in patients with diabetes and multivessel disease.

Conclusions

The present study demonstrates that with follow-up to 4 years, treatment of single de-novo native coronary artery lesions with PES rather than BMS results in sustained efficacy in reducing clinical restenosis among diabetic patients, with no apparent safety concerns evident. The emphasis for future trials should thus shift to investigating through appropriately powered randomized trials whether there are true differences between different DES in patients with (and without) diabetes, establishing the safety and efficacy of DES in more complex lesions than those studied in the randomized trials to date, and studying the relative

risks and benefits of DES compared with those of the alternatives of medical therapy and bypass graft surgery in simple and complex patients with and without DM.

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