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CME

Diabetic and Nondiabetic Patients With Left Main and/or 3-Vessel Coronary Artery Disease

Comparison of Outcomes With Cardiac Surgery and Paclitaxel-Eluting Stents

Adrian P. Banning, MD,* Stephen Westaby, MS, PHD,* Marie-Claude Morice, MD,† A. Pieter Kappetein, MD, PHD,‡ Friedrich W. Mohr, MD,§ Sergio Berti, MD,‖ Mattia Glauber, MD,‖ Mirle A. Kellett, MD,¶ Robert S. Kramer, MD,¶ Katrin Leadley, MD,# Keith D. Dawkins, MD,# Patrick W. Serruys, MD, PHD‡

Oxford, United Kingdom; Massy, France; Rotterdam, the Netherlands, Leipzig, Germany; Massa, Italy, Portland, Maine; and Natick, Massachusetts

Objectives This study was designed to compare contemporary surgical revascularization (coronary artery bypass graft surgery [CABG]) versus TAXUS Express (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stents (PES) in diabetic and nondiabetic patients with left main and/or 3-vessel disease.

Background Although the prevalence of diabetes mellitus is increasing, the optimal coronary revascularization strategy in diabetic patients with complex multivessel disease remains controversial.

Methods The SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) study randomly assigned 1,800 patients (452 with medically treated diabetes) to receive PES or CABG.

Results The overall 1-year major adverse cardiac and cerebrovascular event rate was higher among diabetic patients treated with PES compared with CABG, but the revascularization method did not impact the death/stroke/myocardial infarction rate for nondiabetic patients (6.8% CABG vs. 6.8% PES, $p = 0.97$) or for diabetic patients (10.3% CABG vs. 10.1% PES, $p = 0.96$). The presence of diabetes was associated with significantly increased mortality after either revascularization treatment. The incidence of stroke was higher among nondiabetic patients after CABG (2.2% vs. PES 0.5%, $p = 0.006$). Compared with CABG, mortality was higher after PES use for diabetic patients with highly complex lesions (4.1% vs. 13.5%, $p = 0.04$). Revascularization with PES resulted in higher repeat revascularization for nondiabetic patients (5.7% vs. 11.1%, $p < 0.001$) and diabetic patients (6.4% vs. 20.3%, $p < 0.001$).

Conclusions Subgroup analyses suggest that the 1-year major adverse cardiac and cerebrovascular event rate is higher among diabetic patients with left main and/or 3-vessel disease treated with PES compared with CABG, driven by an increase in repeat revascularization. However, the composite safety end point (death/stroke/myocardial infarction) is comparable between the 2 treatment options for diabetic and nondiabetic patients. Although further study is needed, these exploratory results may extend the evidence for PES use in selected patients with less complex left main and/or 3-vessel lesions. (SYNergy Between PCI With TAXus and Cardiac Surgery [SYNTAX]; NCT00114972) (J Am Coll Cardiol 2010;55:1067–75) © 2010 by the American College of Cardiology Foundation

Diabetes mellitus is a common life-threatening illness of increasing prevalence. More than 171 million (2.8%) people are currently diagnosed worldwide, with a projected increase to 366 million (4.4%) by 2030 (1). Diabetes increases the risk of developing cardiovascular disease (2), and is a consistent predictor of mortality, myocardial infarction (MI), and restenosis after balloon angioplasty (3) and bare-metal stenting (4). Although drug-eluting stents (DES) reduce restenosis in

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From the *John Radcliffe Hospital, Oxford, United Kingdom; †Institut Hospitalier Jacques Cartier, Massy, France; ‡Thorax Center, Erasmus University Medical Center, Rotterdam, the Netherlands; §Herzzentrum Universität Leipzig, Leipzig, Germany; ‖Institute of Clinical Physiology, CNR Massa, Massa, Italy; ¶Maine Medical Center, Portland, Maine; and the #Boston Scientific Corporation, Natick, Massachusetts. This study was funded by Boston Scientific Corporation, Natick, Massachusetts. Drs. Banning, Kellett, and Kramer have received research grant support from and Drs. Leadley and Dawkins have stock options/equity interest and are salary/full-time employees of Boston Scientific. Dr. Banning is partially funded by the NIHR Biomedical Research Centre in Oxford, United Kingdom.

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery

CVA = cerebrovascular accident

DES = drug-eluting stent(s)

MACCE = major adverse cardiac and cerebrovascular event

MI = myocardial infarction

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

TIA = transient ischemic attack

comparison with bare-metal stents in diabetic patients (5), DES studies have consistently shown higher repeat revascularization rates after percutaneous coronary intervention (PCI) compared with surgical revascularization (6–11). However, most prior studies comparing DES with surgery in diabetic patients have studied a limited range of lesion complexity, were not randomized, and typically did not distinguish between DES types (i.e., sirolimus versus paclitaxel).

In randomized controlled trials of patients with less complex 1- and 2-vessel disease, 4-year repeat revascularization rates in patients treated with paclitaxel-eluting stents (PES) were similar for diabetic and nondiabetic patients (12). The SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) study is the first to compare coronary artery bypass graft surgery (CABG) and the TAXUS Express PES (Boston Scientific, Natick, Massachusetts) in nondiabetic and diabetic patients with complex left main and/or 3-vessel disease.

Methods

Study design and device description. The SYNTAX trial is a prospective, 85-center clinical trial (13,14). Patients with de novo left main and/or 3-vessel disease were randomly allocated 1:1 to either the TAXUS Express PES or CABG, with a priori stratification based on the presence or absence of medically treated diabetes and left main disease. Exploratory subgroup analysis of patients with medically treated diabetes was prespecified per study protocol; no formal statistical hypotheses were defined a priori to test for superiority or noninferiority between CABG and PES in diabetic patients.

The institutional review board at each participating center approved the protocol, and all patients provided written consent. The protocol and consent forms were consistent with the International Conference on Harmonisation Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki, and all local regulations, as appropriate. The study is registered on the National Institutes of Health website as identifier NCT00114972.

Definitions. For the primary analysis, medically treated diabetes was defined as treatment with oral hypoglycemic agents or insulin at the time of enrollment in accordance with prior studies (12,15–17). Further analyses of all patients with diabetes (included those treated by diet alone) and with fasting plasma glucose ≥126 mg/dl (7.0 mmol/l) were also conducted. Major adverse cardiac and cerebrovascular events (MACCE) included a composite of all-cause death, cerebrovascular accident (CVA), MI, or repeat revascularization (any subsequent PCI or CABG procedure in any coronary vessel) (14).

Statistical methods. Analysis of the intent-to-treat sample was conducted using SAS system software, version 8.0 or higher (SAS Institute, Cary, North Carolina). Data are summarized using descriptive statistics, presented as proportions (%, count/sample size) or mean ± SD. Continuous variables were compared with the use of the Student *t* test; differences in discrete variables were assessed by means of the chi-square test or Fisher exact test, as appropriate. The p values for interaction between diabetic status and treatment were generated by logistic regression. Binary 12-month MACCE rates were reported by SYNTAX score tercile for coronary anatomic complexity (low ≥22, intermediate 23 to 32, and high ≥33) (18). Logistic regression was used to determine predictors of composite death/CVA/MI and repeat revascularization in diabetic and nondiabetic patients (see Online Supplement).

Results

Patients included in the analysis. Of the 1,800 patients with left main (isolated or in addition to 1-, 2-, or 3-vessel disease) or isolated 3-vessel disease randomly allocated into SYNTAX, 452 (221 CABG, 231 PES) had medically treated diabetes. An additional 59 patients with diabetes treated by diet alone were included in the nondiabetic group (n = 1,348). Among patients with medically treated diabetes, 182 (40.3%) were treated with insulin, and 270 (59.7%) were treated with oral hypoglycemic agents only. Type 2 diabetes accounted for 94% of patients with medically treated diabetes. One-year MACCE was evaluated in 849 (94.6%) CABG patients (645 nondiabetic and 204 with medically treated diabetes) and 891 (98.7%) PES patients (664 nondiabetic and 227 with medically-treated diabetes). While pre-specified, these subgroup analyses are intended to be observational and hypothesis generating, as the primary end point was not met.

Patient demographic, lesion, and procedural characteristics. Patient baseline and lesion characteristics were relatively well matched in the SYNTAX randomized cohort (14) and between patients with medically treated diabetes and patients treated with either CABG and PES, with the exception of increased incidence of high triglycerides (≥150 mg/dl) in CABG compared with PES (47.1% vs. 37.0%, p = 0.04) and increased incidence of elevated blood pressure ≥130/85 mm Hg in PES (65.2% vs. 74.5%, p = 0.03). In nondiabetic patients, there were no significant differences in baseline patient or lesion characteristics, with the exception of a higher incidence of smoking (70.5% vs. 60.7%, p < 0.001), triglycerides ≥150 mg/dl (36.0% vs. 30.6%, p = 0.046), and high-density lipoprotein <40 mg/dl male or <50 mg/dl female (48.6% vs. 42.3%, p = 0.03) in CABG patients compared with PES patients.

Overall, compared with nondiabetic patients, diabetic patients had increased incidence of comorbid risk factors and increased lesion complexity (Table 1).

Table 1 Baseline Patient Demographics and Lesion Characteristics

	Nondiabetic (n = 1,348)	Diabetic (n = 452)	p Value
Age, yrs	65.0 ± 9.9 (1,348)	65.4 ± 9.2 (452)	0.41
Male	79.9 (1,077/1,348)	71.0 (321/452)	<0.001
Comorbid risk factors			
Body mass index (kg/m^2)	27.5 ± 4.4 (1,347)	29.5 ± 5.2 (452)	<0.001
Metabolic syndrome*	37.4 (398/1,064)	69.9 (258/369)	<0.001
Increased waist circumference	42.0 (502/1,194)	60.6 (238/393)	<0.001
Triglycerides ≥150 mg/dl†	33.3 (409/1,230)	41.7 (170/408)	0.002
Low high-density lipoprotein†	45.4 (544/1,199)	61.2 (238/389)	<0.001
Blood pressure ≥130/85 mm Hg	65.3 (880/1,348)	69.9 (316/452)	0.07
Fasting glucose ≥110 mg/dl	27.8 (260/934)	82.2 (286/348)	<0.001
HbA1c ≥7.0%†	2.6 (31/1,179)	56.9 (215/378)	<0.001
Hyperlipidemia	76.7 (1,029/1,341)	81.5 (362/444)	0.03
Cardiac history			
Current smoker	21.7 (292/1,343)	15.8 (71/450)	0.006
Prior MI	33.2 (442/1,333)	32.0 (143/447)	0.65
Congestive heart failure	3.7 (50/1,334)	7.4 (33/444)	0.001
Chronic obstructive pulmonary disease	8.1 (109/1,348)	10.0 (45/452)	0.22
Carotid artery disease	7.3 (99/1,348)	10.8 (49/452)	0.02
Prior CVA	3.8 (51/1,341)	6.0 (27/448)	0.046
Prior TIA	4.3 (58/1,341)	5.8 (26/448)	0.20
Peripheral vascular disease	8.2 (111/1,348)	14.6 (66/452)	<0.001
Creatinine >200 μmol/l	1.0 (13/1,348)	2.9 (13/452)	0.003
Unstable angina	28.0 (378/1,348)	29.6 (134/452)	0.51
Left ventricular ejection fraction <30%‡	1.6 (21/1,348)	2.9 (13/452)	0.07
Lesion complexity			
Diffuse disease or small vessels†	10.2 (136/1,338)	13.4 (60/449)	0.06
Average implanted stent diameter (PES only), mm	3.5 ± 0.5	3.4 ± 0.5	<0.001
Total stent length (PES only), mm	85.3 ± 47.5	88.6 ± 49.0	0.37
EuroSCORE (26)	3.7 ± 2.6 (1,348)	4.0 ± 2.7 (452)	0.03
Parsonnet score (27)	7.5 ± 6.8 (1,348)	11.3 ± 6.4 (452)	<0.001
SYNTAX score† (18)	28.6 ± 11.5 (1,340)	29.0 ± 11.2 (449)	0.52
Number of lesions†	4.3 ± 1.8 (1,340)	4.6 ± 1.8 (449)	0.003
Left main, any†	35.9 (480/1,338)	29.0 (130/449)	0.007
Left main only	3.9 (52/1,338)	2.2 (10/449)	0.10
Left main + 1 vessel	5.6 (75/1,338)	4.0 (18/449)	0.19
Left main + 2 vessels	12.0 (160/1,338)	11.1 (50/449)	0.64
Left main + 3 vessels	14.4 (193/1,338)	11.6 (52/449)	0.13
3-vessel disease only†	64.1 (858/1,338)	71.0 (319/449)	0.007

Values are shown as mean ± SD (N) or % (n/N) *Metabolic syndrome defined as at least 3 of the following: 1) waist circumference >40 inches male or >35 inches female; 2) triglycerides ≥150 mg/dl; 3) high-density lipoprotein <40 mg/dl in males or <50 mg/dl females; 4) blood pressure ≥130/≥85 mm Hg; and 5) fasting glucose ≥110 mg/dl (28). †Core laboratory reported. ‡Or indicated by clinical site as "poor" if exact value not available.

CVA = cerebrovascular accident; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HbA1c = hemoglobin A1c; MI = myocardial infarction; PES = paclitaxel-eluting stent(s); TIA = transient ischemic attack.

Average procedure time was 3.5 ± 1.2 h and 1.7 ± 0.9 h in the CABG and PES groups, respectively ($p < 0.001$), in patients with diabetes, and 3.4 ± 1.1 h and 1.7 ± 0.9 h, respectively, in patients without diabetes ($p < 0.001$).

The rate of complete revascularization in the PES group was lower among diabetic (49.1%) compared with nondiabetic patients (59.3%, $p = 0.007$) whereas among CABG-treated patients, complete revascularization was comparable for diabetic (60.7%) and nondiabetic (64.0%) patients ($p = 0.39$).

Medication use. For patients treated with PES, glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, or tirofiban) were used in 34.3% (79 of 230) and 35.4% (236 of 666) of diabetic and nondiabetic patients, respectively. Statin use at baseline was balanced between CABG and PES patients in both diabetic patients (71.5% vs. 71.0%, $p = 0.91$) and nondiabetic patients (76.6% vs. 75.3%, $p = 0.57$). However, at discharge, statin use was significantly lower in the CABG group for both diabetic patients (73.8% vs. 83.0%, $p = 0.02$) and nondiabetic patients (74.7% vs. 88.0%, $p < 0.001$). Thienopyridine antiplatelet use at 1-year post-procedure was 19.0% and 71.8% in diabetic patients and 13.8% and 70.8% in nondiabetic patients, the CABG and PES groups, respectively. Other post-procedure

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cardiac-related medical therapy use in the SYNTAX study has been reported elsewhere (14).

1-year clinical results in nondiabetic and diabetic patients. One-year outcomes comparing CABG versus PES treatment in diabetic and nondiabetic patients and binary regression interaction effects at 1 year between diabetic status and treatment arm are shown in Table 2. In diabetic patients, the 1-year composite MACCE rate was significantly higher after PES treatment compared with CABG treatment. In nondiabetic patients, MACCE was slightly higher in the PES group compared with the CABG group, but the difference was not statistically significant. The number needed to treat by CABG to avoid 1 MACCE event is 9 for diabetic patients and 31 for nondiabetic patients.

There were no statistically significant differences between the CABG and PES groups in the composite safety end point of death/CVA/MI, or in symptomatic graft occlusion or stent thrombosis for either diabetic or nondiabetic patients. The treatment by diabetes status interaction p value for death/CVA/MI was 0.98. Mortality was significantly higher among diabetic versus nondiabetic patients after both PES ($p < 0.001$) and CABG ($p = 0.01$) treatments, with no significant interaction between treatment arm and diabetes status. In nondiabetic patients, the CVA rate was higher after CABG compared with PES treatment; this effect did not reach statistical significance in diabetic patients, possibly because of the small sample size in that group.

Repeat revascularization (PCI or CABG in any vessel) was significantly higher in the PES group compared with the CABG group in both diabetic and nondiabetic patients, driving the statistically significant increase in composite MACCE in PES-treated diabetic patients. The majority of repeat revascularizations in PES-treated patients was by PCI. Similar results were seen in an overall diabetic cohort that included diet-treated patients and when diabetes was defined as fasting plasma glucose ≥126 mg/dl (data not shown).

Repeat revascularization was significantly higher in diabetic versus nondiabetic patients after PES treatment ($p < 0.001$) but not CABG treatment ($p = 0.74$). Medically treated diabetes was a significant independent predictor of repeat revascularization in the PES arm (odds ratio: 2.93, 95% confidence interval: 1.69 to 5.08, $p < 0.001$), but not in the CABG arm (Online Supplement A). The interaction p value for the effect of diabetes status by treatment arm on repeat revascularization was 0.13. For patients with medically treated diabetes, PES treatment was a significant predictor of repeat revascularization but not death/CVA/MI (Online Supplement A).

Degree of pre-procedure glycemic control was not a significant predictor of 1-year outcomes for diabetic patients, and differences between the CABG and PES arms were similar regardless of whether patients had good or poor glycemic control (Online Supplement B).

Insulin- versus noninsulin-requiring diabetic patients. Diabetic patients treated with insulin (n = 182) had a greater incidence of several comorbid risk factors compared

Table 2 1-Year Clinical Outcomes in Patients With and Without Medically Treated Diabetes

	No Diabetes (n = 1,348)*				Medically Treated Diabetes (n = 452)				
	CABG (n = 676)	PES (n = 672)	Relative Risk [95% CI]	p Value	CABG (n = 221)	PES (n = 231)	Relative Risk [95% CI]	p Value	Interaction p Value†
Composite MACCE	11.8 (76/645)	15.1 (100/664)	1.28 (0.97–1.69)	0.08	14.2 (29/204)	26.0 (59/227)	1.83 (1.22–2.73)	0.003	0.12
Safety outcomes									
Death/CVA/MI (composite)	6.8 (44/645)	6.8 (45/664)	0.99 (0.67–1.48)	0.97	10.3 (21/204)	10.1 (23/227)	0.98 (0.56–1.72)	0.96	0.98
Death	2.6 (17/645)	3.0 (20/664)	1.14 (0.60–2.16)	0.68	6.4 (13/204)	8.4 (19/227)	1.31 (0.67–2.59)	0.43	0.75
Cardiac death	1.6 (10/645)	2.6 (17/664)	1.65 (0.76–3.58)	0.20	3.9 (8/204)	7.0 (16/227)	1.80 (0.79–4.11)	0.16	0.86
CVA	2.2 (14/645)	0.5 (3/664)	0.21 (0.06–0.72)	0.006	2.5 (5/204)	0.9 (2/227)	0.36 (0.07–1.83)	0.26	0.60
MI	2.9 (19/645)	4.8 (32/664)	1.64 (0.94–2.86)	0.08	4.4 (9/204)	4.8 (11/227)	1.10 (0.46–2.60)	0.83	0.45
Graft occlusion/stent thrombosis‡	3.8 (23/601)	3.4 (22/639)	0.90 (0.51–1.60)	0.72	2.2 (4/186)	2.9 (6/209)	1.33 (0.38–4.66)	0.76	0.57
Acute (≤1 day)	0.5 (3/664)	0.3 (2/666)	0.66 (0.11–3.96)	0.69	0.0 (0/206)	0.0 (0/230)	—	—	
Subacute (2–30 days)	0.5 (3/662)	2.1 (14/665)	4.65 (1.34–16.09)	0.008	0.0 (0/206)	1.8 (4/228)	—	0.13	
Late (31–365 days)	2.6 (17/653)	1.1 (7/654)	0.41 (0.17–0.98)	0.04	2.0 (4/201)	0.9 (2/220)	0.46 (0.08–2.47)	0.43	
Efficacy outcomes									
Repeat revascularization§	5.7 (37/645)	11.1 (74/664)	1.94 (1.33–2.84)	<0.001	6.4 (13/204)	20.3 (46/227)	3.18 (1.77–5.71)	<0.001	0.13
PCI	4.8 (31/645)	9.6 (64/664)	2.01 (1.32–3.04)	<0.001	4.4 (9/204)	16.7 (38/227)	3.79 (1.88–7.65)	<0.001	
CABG	1.1 (7/645)	2.4 (16/664)	2.22 (0.92–5.36)	0.07	2.0 (4/204)	4.0 (9/227)	2.02 (0.63–6.47)	0.22	

Values are shown as % (n/N). The p values for diabetic versus nondiabetic comparison, coronary artery bypass graft surgery (CABG) and paclitaxel-eluting stent (PES), respectively: major adverse cardiac and cerebrovascular events (MACCE): 0.36 CABG, <0.001 PES; death/cerebrovascular accident (CVA)/myocardial infarction (MI): 0.10, 0.10; death: 0.01, <0.001; cardiac death 0.05, 0.002; MI 0.31, 0.99; graft occlusion/stent thrombosis 0.27, 0.69; repeat revascularization 0.74, <0.001. *Includes patients with diagnosed diabetes treated by diet only and nondiabetic patients. †Binary regression interaction term for diabetes status by treatment arm. ‡Symptomatic. §Any vessel.
CI = confidence interval; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

with diabetic patients treated only with oral hypoglycemic agents (n = 270), including increased baseline rates of prior MI (39.7% vs. 26.9%, p = 0.005), peripheral vascular disease (20.3% vs. 10.7%, p = 0.005), and hemoglobin A1c ≥7.0% (77.1% vs. 43.1%, p < 0.001). However, other baseline characteristics examined were relatively well matched between insulin-treated and noninsulin-treated diabetic patients.

There were no significant differences in death, MI, or CVA between the PES and CABG groups in either the oral hypoglycemic-treated or insulin-treated diabetic patients (Table 3); however, the insulin status by treatment group interaction term for composite death/CVA/MI was 0.06, with higher rates in the CABG arm for diabetic patients taking oral medications, and higher rates in the PES arm for insulin-treated patients. The mortality rate for PES-treated insulin-requiring diabetic patients (12.5%) was nonsignificantly higher than for CABG-treated insulin-requiring diabetic patients (5.7%, p = 0.12) and PES-treated diabetic patients receiving oral medications (5.8%, p = 0.07). In the CABG arm, mortality rates were comparable between diabetic patients taking oral medications and patients taking insulin (p = 0.75) (rates listed in Table 3).

As was seen in the overall diabetic cohort, repeat revascularization rates were higher in the PES arm versus the CABG arm in both the oral hypoglycemic-treated and the insulin-treated diabetic patients. However, within each treatment arm, repeat revascularization rates were comparable regardless of whether insulin was required (PES: 20.5% insulin vs. 20.1% oral hypoglycemic agents, p = 0.95; CABG: 9.2% insulin vs. 4.3% oral hypoglycemic agents, p = 0.15).

Effect of lesion complexity on outcomes in patients with diabetes. The SYNTAX score (18) grades the angiographic lesion complexity of coronary disease to provide an evidence-based tool for selecting the optimal revascularization strategy (CABG or PCI).

There were no significant differences in composite safety (death/CVA/MI) between the PES and CABG groups in any SYNTAX score tercile in either diabetic (Fig. 1) or nondiabetic (Fig. 2) patients. Patients with higher SYNTAX scores had increased repeat revascularization after PES treatment compared with CABG, driving increased MACCE, particularly for diabetic patients. However, for patients in the lowest SYNTAX score tercile, MACCE was not significantly different between treatments arms, with comparable repeat revascularization between the CABG and PES groups in nondiabetic patients. For PES-treated patients, mortality rates increased with increasing SYNTAX scores such that in patients with the highest lesion complexity (SYNTAX scores ≥33) mortality was significantly increased compared with CABG for both diabetic and nondiabetic patients. The mortality interaction term for treatment group by SYNTAX score tercile is p = 0.15 for patients with diabetes and p = 0.05 for patients without diabetes.

Table 3 1-Year Clinical Outcomes in Diabetic Patients Treated With Oral Hypoglycemic Agents or Insulin

	Oral Hypoglycemic Agents (n = 270)				Insulin (n = 182)				
	CABG (n = 128)	PES (n = 142)	Relative Risk [95% CI]	p Value	CABG (n = 93)	PES (n = 89)	Relative Risk [95% CI]	p Value	Interaction p Value*
Composite MACCE	14.5 (17/117)	23.7 (33/139)	1.63 (0.96–2.78)	0.06	13.8 (12/87)	29.5 (26/88)	2.14 (1.16–3.97)	0.01	0.48
Safety outcomes									
Death/CVA/MI (composite)	12.0 (14/117)	7.2 (10/139)	0.60 (0.28–1.30)	0.19	8.0 (7/87)	14.8 (13/88)	1.84 (0.77–4.38)	0.16	0.06
Death	6.8 (8/117)	5.8 (8/139)	0.84 (0.33–2.17)	0.72	5.7 (5/87)	12.5 (11/88)	2.18 (0.79–6.00)	0.12	0.18
Cardiac death	4.3 (5/117)	5.0 (7/139)	1.18 (0.38–3.62)	0.77	3.4 (3/87)	10.2 (9/88)	2.97 (0.83–10.59)	0.08	0.28
CVA	4.3 (5/117)	0.7 (1/139)	0.17 (0.02–1.42)	0.10	0.0 (0/87)	1.1 (1/88)	—	>0.99	0.97
MI	4.3 (5/117)	5.0 (7/139)	1.18 (0.38–3.62)	0.77	4.6 (4/87)	4.5 (4/88)	0.99 (0.26–3.83)	>0.99	0.84
Graft occlusion/stent thrombosis†	2.9 (3/104)	1.5 (2/130)	0.53 (0.09–3.13)	0.66	1.2 (1/82)	5.1 (4/79)	4.15 (0.47–36.34)	0.20	0.15
Acute (≤1 day)	0.0 (0/118)	0.0 (0/141)	0.0 (NA)	—	0.0 (0/88)	0.0 (0/89)	—	—	
Subacute (2–30 days)	0.0 (0/118)	0.0 (0/140)	0.0 (NA)	—	0.0 (0/88)	4.5 (4/88)	—	0.12	
Late (31–365 days)	2.6 (3/114)	1.5 (2/137)	0.55 (0.09–3.26)	0.66	1.1 (1/87)	0.0 (0/83)	0.0 (NA)	>0.99	
Efficacy outcomes									
Repeat revascularization‡	4.3 (5/117)	20.1 (28/139)	4.71 (1.88–11.82)	<0.001	9.2 (8/87)	20.5 (18/88)	2.22 (1.02–4.84)	0.04	0.24
PCI	3.4 (4/117)	17.3 (24/139)	5.05 (1.80–14.14)	<0.001	5.7 (5/87)	15.9 (14/88)	2.77 (1.04–7.35)	0.03	
CABG	0.9 (1/117)	2.9 (4/139)	3.37 (0.38–29.71)	0.38	3.4 (3/87)	5.7 (5/88)	1.65 (0.41–6.68)	0.72	

Values are shown as % (n/N). *Binary regression interaction term for insulin status by treatment arm. †Symptomatic. ‡Any vessel.
NA = not available; other abbreviations as in Tables 1 and 2.

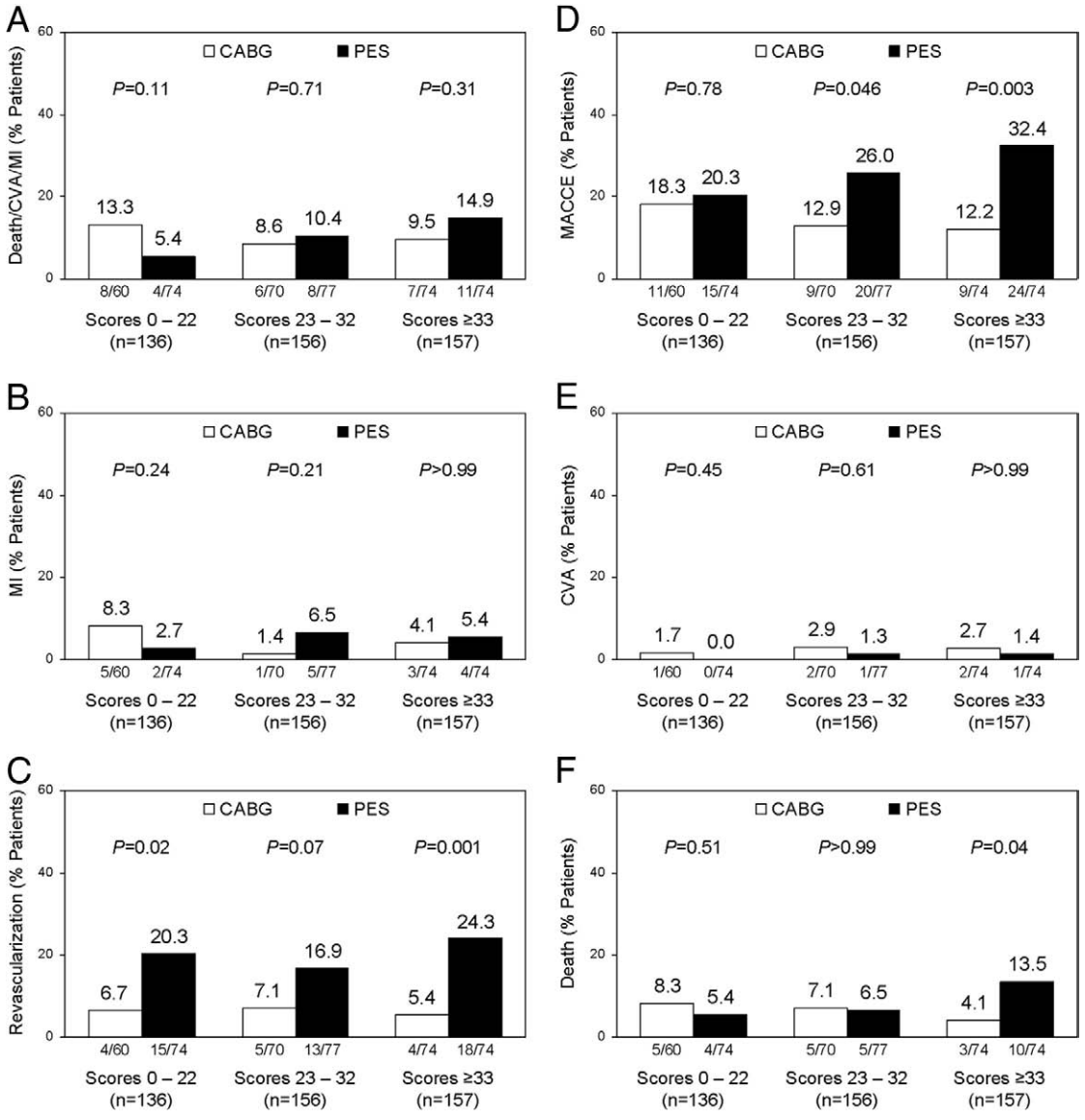

Figure 1 **Diabetic Patient Outcomes According to SYNTAX Score Tercile**

One-year rates of **(A)** composite death/cerebrovascular accident (CVA)/myocardial infarction (MI), **(B)** MI, **(C)** revascularization, **(D)** major adverse cardiac and cerebrovascular events (MACCE), **(E)** CVA, and **(F)** all-cause death in diabetic patients treated with coronary artery bypass graft surgery (CABG) or TAXUS paclitaxel-eluting stents (PES). Rates are separated by the SYNTAX study scores indicating low (0 to 22), medium (23 to 32), and high (≥33) anatomic lesion complexity.

Discussion

The patients enrolled in the SYNTAX trial, which included only patients with left main and/or 3-vessel disease, are the most complex ever studied in a coronary artery revascularization trial. Among patients with medically treated diabetes in the SYNTAX trial, 71.0% were treated for 3-vessel disease and 29.0% for left main disease; furthermore, 78.5% of patients with left main disease had concurrent 2- or 3-vessel disease. Thus, it is important to interpret the results of this study in the context of the high-risk conditions included. Furthermore, as the primary end point of the overall SYNTAX study was not met (14), these observational subgroup results are to be considered hypothetical and hypotheses generating only, and should not necessarily dictate any change in current practice patterns.

At 1 year, the key findings of this observational pre-defined subgroup analysis are as follows. 1) In patients with left main and/or 3-vessel disease, MACCE rates were significantly higher in the PES arm compared with the CABG arm in diabetic patients, and directionally higher (but nonsignificant) in nondiabetic patients. Although there was no statistically powered pre-specified primary end point of this subgroup analysis, this result suggests that MACCE after PES treatment might be inferior to CABG treatment

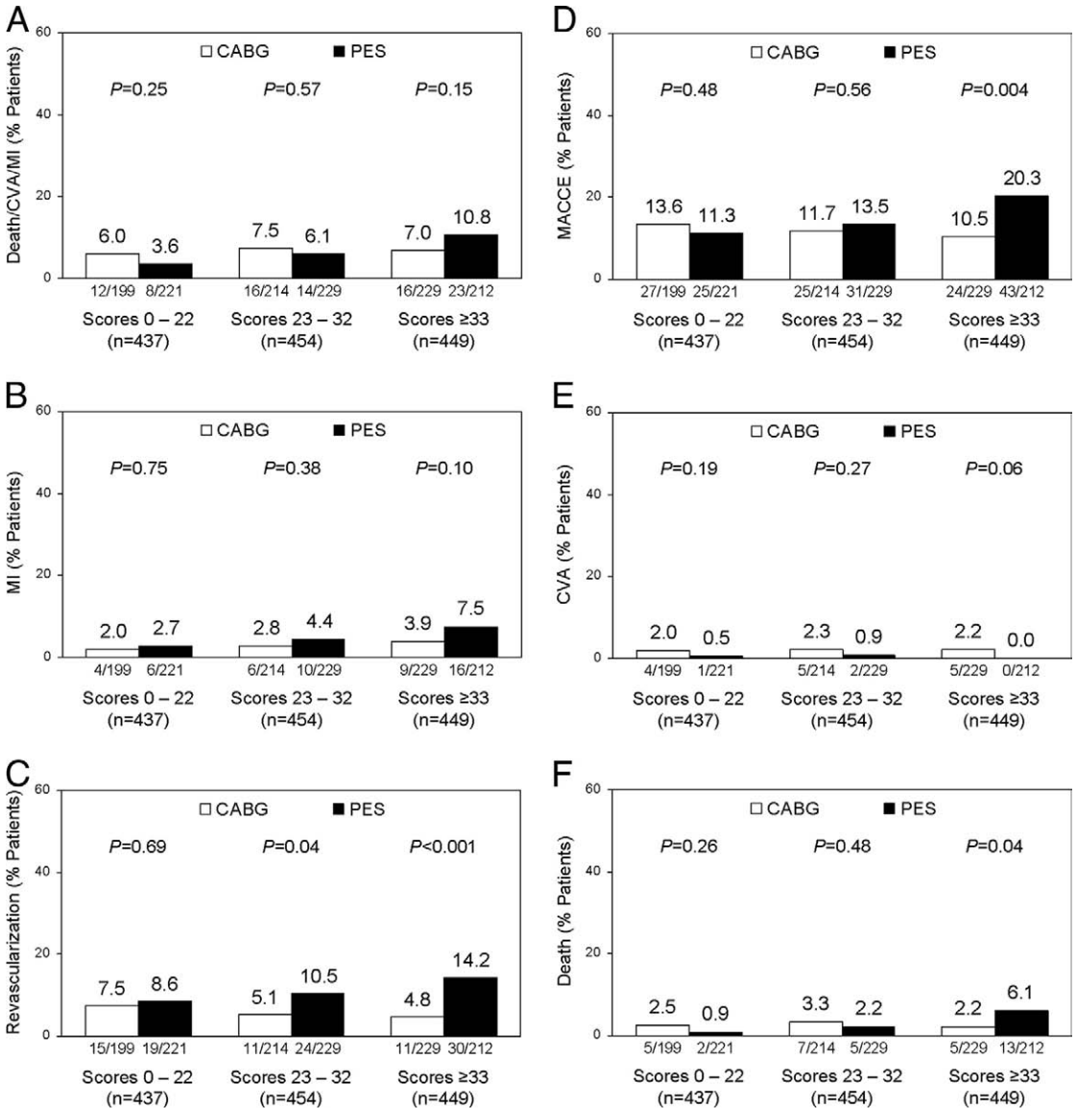

Figure 2 **Nondiabetic Patient Outcomes According to SYNTAX Score Tercile**

See the legend to Figure 1 for further descriptive details and abbreviations.

for diabetic patients with left main and/or 3-vessel disease. 2) There were no significant differences in composite death/CVA/MI or in the individual components of death or MI between the CABG and PES groups regardless of diabetic status or lesion complexity. Compared with nondiabetic patients, patients with diabetes had increased mortality in both the CABG and PES groups. 3) In both diabetic and nondiabetic patients with the greatest anatomical complexity (SYNTAX scores ≥33), mortality was significantly increased with PES treatment compared with CABG. 4) Repeat revascularization was higher with PES compared with CABG in both diabetic and nondiabetic patients. 5) Patients with diabetes had significantly increased repeat revascularization rates compared with nondiabetic patients when treated with PES, but not when treated with CABG. 6) Repeat revascularization rates after PES treatment (and hence the relative difference between the PES and CABG groups) tended to increase with increasing lesion complexity (i.e., higher SYNTAX score), particularly in patients with diabetes; in nondiabetic patients with low lesion complexity, repeat revascularization rates were similar between treatment arms. These analyses were consistent with an analysis of all patients diagnosed with diabetes at enrollment (including those not receiving medical treatment; data not shown).

This analysis confirms prior studies of diabetic patients with less complex multivessel disease that show no difference in

mortality between CABG and DES patients overall (6–10,19); however, diabetic compared with nondiabetic patients had increased mortality after either PES or CABG, demonstrating that neither treatment option can eliminate the increased mortality risk conferred by diabetes (2). The mortality rate in PES-treated diabetic patients requiring insulin was 12.5%, compared with 5.7% in CABG-treated patients taking insulin and 5.8% in PES-treated diabetic patients taking oral medications, although this difference did not reach statistical significance. While the sample sizes in these groups are too small to allow firm conclusions and there was no significant interaction effect for mortality between diabetes status and treatment arm, this finding may warrant further study. This effect was also seen in a study comparing diabetic versus nondiabetic patients treated with DES for unprotected left main disease (20). In addition, in patients with highly complex left main and/or 3-vessel lesions (SYNTAX scores $\geq$33), mortality was increased in the PES group compared with the CABG group, with a significant SYNTAX score by treatment arm interaction term in nondiabetic patients and an interaction p value of 0.15 in diabetic patients. This finding is not unexpected, given that lesion complexity does not impact technical success with CABG as it does with PCI, and that PCI does not prevent ischemia due to disease progression outside the stented segment.

Published studies have demonstrated higher DES repeat revascularization rates compared with CABG (6–11), an effect that was replicated in the SYNTAX study. The relative risk of repeat revascularization of PES over CABG was 3.18 (95% confidence interval: 1.77 to 5.71) in diabetic patients compared with 1.94 (95% confidence interval: 1.33 to 2.84) in nondiabetic patients. While the interaction term for diabetes status by treatment arm for revascularization was $p = 0.13$, p values >0.10 may not necessarily rule out the possibility of a meaningful interaction, due at least in part to the low power of the test (21).

Prior studies of PES usage in randomized trials suggest that in patients with mainly 1- and 2-vessel disease, angiographic restenosis and target lesion revascularization rates are comparable in diabetic and nondiabetic patients after PES implantation (12,15,16,22). In contrast, the SYNTAX study results demonstrate that in diabetic patients with highly complex 3-vessel and/or left main disease (a population not previously studied in DES randomized trials), revascularization is higher in diabetic than in nondiabetic patients treated with PES. It is important to note that by definition, repeat revascularization in the SYNTAX study included revascularization in any vessel, not just a single target vessel or lesion revascularization as in prior studies. In this regard, it is likely that aggressive progression of diffuse disease in patients with diabetes will impact the PES cohort more noticeably than the CABG group, in which grafts placed distally minimize the impact of progressive disease in the entire upstream proximal vessel.

Results similar to those of the SYNTAX study were seen in the CARDia (Coronary Artery Revascularization in Diabetes) and ARTS II (Arterial Revascularization Therapies Study–Part II) studies comparing sirolimus-eluting stents to CABG in diabetic patients with multivessel disease (8,23). In the CARDia study (23), 1-year death/CVA/MI in DES-treated diabetic patients (11.6%) was comparable to that in CABG-treated diabetic patients (12.4%), whereas revascularization was significantly higher in the DES arm compared with CABG. In comparison to the present results, it is also important to note that the primary end point of the CARDia study (death/CVA/MI) did not include revascularization, which was included in the SYNTAX study primary MACCE end point.

This study also demonstrated that diabetic patients with more complex coronary disease, as reflected by higher SYNTAX scores, tended to have increased repeat revascularization rates when treated with PES, driving differences in total MACCE. Again, this is likely due to accelerated disease progression in diabetic patients, which would influence repeat revascularization rates in the PES arm but not in the CABG arm. Nondiabetic patients with the lowest angiographic complexity had similar repeat revascularization rates in both treatment arms. Thus, accelerated atheroma, the active inflammatory process, and increased lesion complexity may all underlie the observed differences between the CABG and PES groups in diabetic patients.

Study limitations. There are several important limitations to consider when interpreting the results of this study. First, follow-up at 1 year may not yet reflect the true long-term differences between CABG and PES treatments of diabetic patients based on the previously reported BARI (Bypass Angioplasty Revascularization Investigation) study (24) that demonstrated reduced long-term mortality in CABG compared with balloon angioplasty; the SYNTAX study follow-up to 5 years is ongoing. Second, although prespecified, these subgroup analyses are intended to be observational and hypothesis generating because of the small samples sizes and event numbers in the subgroups analyzed. Third, fasting glucose and hemoglobin A1c levels were available at baseline only; glycemic control information and subsequent diagnoses of diabetes during the course of follow-up are unknown. Fourth, although the patients included in the BARI-2D study (25) are not comparable to patients enrolled in the SYNTAX study (BARI-2D enrollment was limited primarily to stable angina with only 21% multivessel disease, and only 35% DES use in the PCI arm), the SYNTAX study did not include an optimal medical therapy arm with which to compare to such analyses (although medical therapy alone would not be appropriate for the advanced multivessel atherosclerotic disease in most of the SYNTAX trial patients). Finally, because the SYNTAX study enrolled only patients with left main and/or 3-vessel disease, diabetic patients in this study may not be typical of all diabetic patients undergoing coronary revascularization procedures. In addition, the low percentage of patients with diffuse disease and small vessel lesions in the diabetes cohort may indicate that this sample is not representative of a typical population of patients with diabetes. Other study limitations not specific to the diabetes subanalysis have been reported previously (14).

Conclusions

These 1-year SYNTAX results suggest that in patients with left main and/or 3-vessel disease, MACCE is increased for PES-treated diabetic patients compared with CABG-treated patients, driven by an increase in repeat revascularization. Composite safety and mortality end points are comparable between the CABG and PES arms. Although further study is needed, these exploratory results may extend the evidence base for DES use (particularly PES) in selected diabetic and nondiabetic patients with left main and/or 3-vessel disease.

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Reprint requests and correspondence: Dr. Adrian Banning, Room 2557, Cardiology Department, Level 2, John Radcliffe Hospital, Headley Way, Headington, Oxford 0X3 9DU, United Kingdom. E-mail: adrian.banning@orh.nhs.uk.

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Key Words: drug-eluting stent ■ coronary artery bypass grafting ■ diabetes ■ paclitaxel ■ multivessel.

APPENDIX

For supplementary information and tables, please see the online version of this article.