Outcomes of Patients Treated with the Everolimus- versus the Paclitaxel-Eluting Stents in a Consecutive Cohort of Patients at a Tertiary Medical Center

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Abstract

In this study, we compare the outcomes of the paclitaxel-eluting stent (PES) versus the everolimus-eluting stent (EES) treated patients at a tertiary medical center and up to 2 years follow-up. Unselected consecutive patients were retrospectively recruited following stenting with PES (159 patients) or EES (189 patients). The primary endpoint of the study was target lesion failure (TLF), defined as the combined endpoint of cardiac death, nonfatal myocardial infarction (MI), or target lesion revascularization (TLR). Secondary endpoints included target vessel revascularization (TVR), TLR, target vessel failure (TVF), acute stent thrombosis (ST), total death, cardiac death, and nonfatal MI. Patients treated with the PES stent had less congestive heart failure and restenotic lesions, but a higher prevalence of longer lesions, nonleft main bifurcations, required more stents per patient (4.3 ± 2.8 vs. 2.9 ± 2.1). TLF occurred in 32.3% PES versus 21.5% EES ($p = 0.027$). The secondary unadjusted endpoints for PES versus EES, respectively, were TVF 38.6 versus 30.7% ($p = 0.140$), TVR 35.7 versus 26.5% ($p = 0.079$), definite and probable ST 1.2 versus 0.0%, nonfatal MI 4.5 versus 4.2%, and mortality 9.6 versus 4.0%. Logistic regression analysis showed that the numbers of stents per patient ($p = 0.001$), age ($p = 0.01$), and renal failure ($p = 0.045$) were independent predictors of TLF. Using univariate analysis, EES had lower TLF than PES in a cohort of unselected patients undergoing percutaneous coronary intervention at 2 years follow-up. Multivariate analysis showed that the numbers of stents per patient, age, and renal failure, but not stent type, were predictors of TLF.

Keywords

- coronary stent
- drug-eluting stent
- paclitaxel
- everolimus
- outcome
- target lesion revascularization
- stent thrombosis

The paclitaxel-eluting stent (PES) Taxus Liberte (Boston Scientific, Natick, MA) and the everolimus-eluting stent (EES) Xience (or Promus) (Abbott Laboratories, Abbott Park, IL) are second generation drug-eluting stents (DES) that outperformed bare metal stents in reducing restenosis and target lesion revascularization (TLR).^{1–4}

Randomized trials have shown that EES is superior to PES stents in reducing the composite endpoint of target

lesion failure (TLF), stent thrombosis (ST), myocardial infarction (MI), and TLR.^{5–7} The diabetic subgroup, however, failed to show an advantage of EES over PES.^{5,8} Furthermore, in real life registries where patient selection was left to the interventionalist rather than limited by a set of inclusion and exclusion criteria of a randomized trial, EES was safe and effective but did not show an advantage over PES.^{9,10}

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Table 1 Demographics and clinical variables

	n ^a	Paclitaxel	n ^a	Everolimus	p value
Age (years)	158	67.2 ± 12.2	188	65.6 ± 11.4	0.213
Body mass index	159	30.6 ± 6.9	186	30.9 ± 6.6	0.701
Male (%)	96/159	60.4	125/189	66.7	0.314
New York Heart Class (%)	158		188		NA
No symptoms/Class I	145	91.8	157	83.5	
Class II	7	4.4	26	13.8	
Class III	4	2.5	3	1.6	
Class IV	2	1.3	2	1.1	
New York Heart Class (symptomatic patients)	16/158	10.1	52/188	27.7	0.001
Prior percutaneous coronary intervention (%)	103/159	64.8	141/188	75.0	0.045
Prior coronary artery bypass surgery (%)	32/159	20.1	46/189	24.3	0.369
Previous myocardial infarction (%)	53/159	33.3	73/189	38.6	0.316
Family history of premature CAD (%)	65/157	41.4	75/185	40.5	0.912
Renal failure (%)	19/159	11.9	8/185	4.3	0.014
Peripheral vascular disease (%)	25/159	15.7	21/189	11.1	0.266
History of hypertension (%)	133/159	83.6	152/189	80.4	0.486
Cerebrovascular disease (%)	4/158	2.5	9/189	4.8	0.396
Hyperlipidemia (%)	144/159	90.6	160/189	84.7	0.108
History of smoking (current and ex-smoker) (%)	99/159	62.3	120/188	63.8	0.823
Diabetes mellitus (%)	60/159	37.7	69/188	36.7	0.911

Abbreviations: CAD, coronary artery disease; NA, nonapplicable.

^aDenominator reflects number of patients with data available.

Long-term randomized studies also indicated that event-free survival continues to diverge beyond the first 3 years in favor of EES with consistent improvement in its long-term safety and efficacy.¹¹ Registry data, on the other hand, is mostly limited to 1 year follow-up.^{9,10}

In this single center study, we compare Taxus Liberté PES to Xience (Promus) EES for late outcome at 2 years in an unselected consecutive group of patients at a single tertiary medical center.

Methods

Unselected consecutive patients were retrospectively recruited from a single center following stenting with PES or EES. Both de novo and restenotic lesions were included. Exclusion criteria included patients with bypass graft stenting or who received mixed stents. There were no prespecified institutional criteria to the choice of the DES which was left to individual operator. The first 100 consecutive patients in each cohort underwent syntax scoring by an independent investigator blinded to patients' outcomes trained in syntax scoring using the online tutorial on the SYNTAX score Web site (www.syntaxscore.com) and performing an additional 50 cases under close supervision by an experienced cardiologist.

► **Tables 1 and 2** show the demographics, procedural, and clinical variables collected by reviewing medical records.

Angiographic variables are shown in ► **Table 3** and were obtained by an independent blinded review of the angiograms to patients' clinical variables and outcomes. Ejection fraction (EF) was obtained from left ventriculography during the index angiographic procedure.

Follow-up was at 2 years from the index procedure using medical records, phone calls, or both. Patients were initially mailed a brief letter describing the protocol, followed by a phone call to obtain verbal consent to be part of the study (using an institutional review board [IRB]-approved standardized script). All events reported by patients were verified by cross reference to medical records. Patients who expired had their death certificate retrieved when possible to evaluate the cause of their death.

The primary outcome of the study was TLF, defined as cardiac death, nonfatal MI related to target vessel, and TLR. Secondary outcomes included target vessel revascularization (TVR), target vessel failure (TVF) (defined as cardiac death, nonfatal MI, and TVR), acute ST as defined by the Academic Research Consortium,¹² nonfatal MI, and cardiac death.

Statistical Analysis

Descriptive analysis was performed on all variables. *t* testing was used for continuous variables and chi-square testing for dichotomous variables. Univariate analysis compared the demographic, clinical, angiographic, and outcome variables

Table 2 Indications for angiography and coronary artery distribution

	Paclitaxel	Everolimus	<i>p</i> value
Number of patients treated (<i>n</i>)	159	189	
Number of vessels treated (<i>n</i>) ^a	322	304	
Number of segments treated (<i>n</i>) ^b	602	476	
Indications for angiography (%)			1.000 ^c
Unstable angina/NSTEMI	46.1	49.5	
STEMI	4.5	2.4	
Abnormal perfusion test with symptoms	12.9	15.4	
Abnormal perfusion test with no symptoms	6.2	6.3	
Cardiomyopathy/congestive heart failure	1.1	0.5	
Staged intervention	24.7	24.0	
Arrhythmias	1.7	0.5	
Recent decrease in ejection fraction	0.6	1	
Progressive dyspnea	2.2	0	
Syncope	0	0.5	
Distribution of coronary artery disease (per number of vessels) (%)			0.574
RCA	30.1	21.1	
LM	6.6	9.9	
LAD	33.9	35.9	
RI	2.3	4.6	
LCX	27.1	28.6	

Abbreviations: LAD, left anterior descending artery; LCX, left circumflex; LM, left main; NSTEMI, non-ST elevation myocardial infarction; RCA, right coronary artery; RI, ramus intermedius; STEMI, ST elevation myocardial infarction.

^aThe following were considered vessels per patient and counted when treated: LAD, LCX, RI, RCA, and LM.

^bThe following segments were considered per vessel and counted when treated: LAD—proximal, mid, distal, diagonal 1 and 2; LCX—proximal, distal, obtuse marginal 1 and 2, posterolateral branch 1 and 2; RCA—proximal, mid, distal, acute marginal, posterior descending artery, posterolateral 1 and 2; disease in LM and RI was considered as one segment per vessel.

^cAcute coronary syndrome (unstable angina, NSTEMI, STEMI) versus all others.

between the two groups. Survival analysis (Kaplan–Meier) was performed for TLF over the 2 years follow-up. Logistic regression analysis with backward elimination was performed modeling for age, gender, diabetes, New York Heart Class, prior percutaneous coronary intervention (PCI), renal insufficiency, percent of patients with nonleft main (LM) bifurcating disease, ostial lesions or restenotic lesions, length of disease treated per patient, number of stents use per patient, and stent type. SPSS (IBM, NY) software was used to conduct the analysis.

Results

A total of 182 PES and 207 EES unselected patients were initially screened to be recruited to the study. Patients were excluded if they refused verbal consent required by the IRB (*n* = 17 PES; *n* = 10 EES) or lost to follow-up (*n* = 5 PES; *n* = 8 EES). A total of 159 PES patients (322 vessels, 602 segments) and 189 EES patients (304 vessels, 476 segments) were included in the final analysis.

Descriptive analysis on all patients is shown in ►Table 1. There was a high incidence of patients who had prior PCI and

prior bypass surgery in both cohorts. Approximately two-thirds of patients were current or prior smokers and 37% were diabetics.

The indication of the procedure was similar in both groups with about half the patients treated for an acute coronary syndrome. The distribution of disease was also similar between both cohorts with 7 to 10% of patients had their LM treated (►Table 2).

Angiographic and procedural variables are shown in ►Table 3. Longer disease was treated in the PES group leading to more stents placed per patient compared with the EES cohort (4.3 vs. 2.9, *p* = 0.001). On the contrary, more patients had restenotic lesions in the EES versus PES cohort (42.9 vs. 18.9%, *p* = 0.001). The SYNTAX scores of the first 100 consecutive patients, which reflect angiographic complexity, were statistically similar between PES and EES (20.3 ± 13.9 vs. 20.4 ± 13.8, *p* = 0.97). EF was also similar in both groups.

At 2 years, follow-up was completed for 82.3% of all patients enrolled (Promus 92.9% and Taxus 71.5%). The primary unadjusted outcome of TLF occurred in 32.3% PES versus 21.5% EES (*p* = 0.027) (►Fig. 1, ►Table 4). The secondary unadjusted endpoints for PES versus EES, respectively,

Table 3 Angiographic and procedural variables

	Paclitaxel	Everolimus	p value
Per patient analysis	n = 159	n = 188	
Ejection fraction (%), mean $\pm$ SD	49.0 $\pm$ 14.7 (n = 101)	51.5 $\pm$ 14.3 (n = 152)	0.142
Stents use per patient (n), mean $\pm$ SD	4.3 $\pm$ 2.8	2.9 $\pm$ 2.1	0.001
Length of disease treated per patient (mm), mean $\pm$ SD	85.2 $\pm$ 56.4	52.2 $\pm$ 43	0.001
Patients treated with restenotic lesions (%)	18.9	42.9	0.001
Percentage of patients with non-LM bifurcating disease (%)	64.8	50.5	0.009
SYNTAX (first 100 consecutive patient in each group), mean $\pm$ SD	20.3 $\pm$ 13.9	20.4 $\pm$ 13.8	0.967
Per vessel analysis	n = 322	n = 304	
Stents used per vessel (n), mean $\pm$ SD	2.2 $\pm$ 1.4	1.8 $\pm$ 1.2	0.001
Length of disease treated per vessel (mm), mean $\pm$ SD	42.5 $\pm$ 33.8	32.4 $\pm$ 26.4	0.001
Per segment analysis	n = 602	n = 476	
Prelesion severity (%), mean $\pm$ SD	84.0 $\pm$ 12.2	84.5 $\pm$ 11.9	0.467
Postlesion severity (%)	0.0	0.0	1
Diameter (mm), mean $\pm$ SD	3.0 $\pm$ 0.6	3 $\pm$ 0.5	0.635
Stents used per segment (n), mean $\pm$ SD	1.2 $\pm$ 0.4	1.2 $\pm$ 0.4	0.550
Length of disease treated per segment (mm), mean $\pm$ SD	22.8 $\pm$ 13.5	20.7 $\pm$ 12.6	0.008
Segments treated with restenotic lesions (%)	9.3	34.1	0.001
Ostial segments treated (%)	5.3	8.2	0.063

Abbreviation: LM, left main.

were TVF 38.6 versus 30.7% ($p = 0.140$), TVR 35.7 versus 26.5% ($p = 0.079$), definite and probable ST 1.2 versus 0.0%, nonfatal MI 4.5 versus 4.2%, and mortality 9.6 versus 4.0%. To account for differences between the two cohorts, multivariate analysis was performed using logistic regression with backward elimination. This showed that the numbers of stents per patient ($p = 0.001$), age ($p = 0.01$), and renal failure

($p = 0.045$) were independent predictors of TLF. Stent type was not predictive of TLF.

Clinical History of Patients with Definite or Probable Acute Stent Thrombosis

There were two patients who had definite or probable ST in the PES cohort. The first patient was a 60-year-old man with a history of prior PCI and bypass surgery, hypertension, hyperlipidemia, current smoker, and diabetic. His index procedure was for an acute coronary syndrome involving the left circumflex artery with a 100% occlusion of a restenotic lesion. ST occurred 36 days postindex procedure. He was on clopidogrel and aspirin. His lesion was retreated successfully. The second patient was an 80-year-old woman with a history of prior PCI, hypertension, hyperlipidemia, and diabetes mellitus. She had an EF of 20%. Her index procedure was for an acute coronary syndrome involving a de novo LAD lesion. She had sudden cardiac death at day 28 after her procedure. She was on clopidogrel and aspirin.

Discussion

In this study, the primary unadjusted outcome of TLF occurred in 21.5% of EES versus 32.3% of PES ($p = 0.027$). Although this higher rate of TLF could be explained by the longer lesions treated and higher prevalence of non-LM bifurcation lesions in the PES group, the EES group also had a higher rate of restenotic lesions, a predictor of restenosis. Multivariate analysis does not show superior results of EES

Fig. 1 Kaplan-Meier curve showing unadjusted TLF survival for the paclitaxel-eluting stent (interrupted line) versus the everolimus stent (full line). TLF, target lesion failure.

Table 4 Outcome of patients censored at 2 years follow-up (nonpropensity-matched analysis)

	Paclitaxel	Everolimus	p value
TLR per segment (%)	17.7	9.5	0.001
TLR per vessel (%)	22.5	12.6	0.001
TLR per patient (%)	29.6	17.2	0.007
TVR per segment (%)	15.5	11.9	0.104
TVR per vessel (%)	28.2	18.3	0.004
TVR per patient (%)	35.7	26.5	0.079
Target lesion failure (%)	32.3	21.5	0.027
TLR	29.1	17.2	
Cardiac death	1.9	3.7	
Nonfatal MI	4.5	4.3	
Target vessel failure (%)	38.6	30.7	0.140
Stent thrombosis (%)			NA
Definite or probable	1.2	0.0	
Possible	2.6	1.1	
Percent of patients on clopidogrel on follow-up (%)	89.5	80	0.024
Percent of patients on aspirin on follow-up (%)	94.8	97.7	0.118
Death classification on follow-up (%)			
No	90.4	96.0	NA
Noncardiac	3.8	2.0	
Unknown	0.0	0.7	
Cardiac sudden death probable	2.0	0.6	
Cardiac nonstent thrombosis	3.8	0.7	
Acute NSTEMI, nonfatal (%)	3.2	1.6	0.476
Acute STEMI, nonfatal (%)	1.3	2.6	0.462

Abbreviations: MI, myocardial infarction; NA, nonapplicable; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

over PES at 2 years follow-up. This finding is in contrast with data from prospective randomized trials. In the SPIRIT III trial and at 2 years follow-up, patients treated with EES compared with PES had a significant 32% reduction in TVF (10.7 vs. 15.4%; $p = 0.04$) and a 45% reduction in major adverse cardiac events (cardiac death, MI, or TLR; 7.3 vs. 12.8%; $p = 0.004$).¹³ This benefit continued at 3 years.¹¹ In SPIRIT IV,⁵ TLF was also reduced with EES compared with PES (4.2 vs. 6.8%; $p = 0.001$), a consistent finding in all subgroups except the diabetics (6.4 vs. 6.9%; $p = 0.80$). Furthermore, in COMPARE,⁶ the primary composite endpoint of all-cause mortality, MI, and TVR at 1 year occurred in 6% in EES versus 9% in PES ($p = 0.02$). Finally, a meta-analysis of randomized trials between EES versus PES⁷ also showed that EES had less MI, ST, and TVR than PES.

Our findings, however, are consistent with published real-world registries.^{9,10} When broader lesion categories are included, the difference between the two stents at 1 year follow-up becomes less apparent. In the REWARDS TLX multicenter registry,⁹ the primary composite endpoint of all-cause death, Q-wave MI, TVR, and ST at 1 year was similar between EES and PES (7.8 vs. 10.8%; $p = 0.082$) with an

overall trend toward more ST in the PES group (0.3 vs. 1.2%; $p = 0.107$). In the Washington Hospital Center experience of 6,615 patients treated with PES, EES, and sirolimus-eluting stents,¹⁰ multivariate analysis showed so significant difference between EES versus PES in the rate of death and TVR. Definite ST was slightly higher with PES (0.0 vs. 0.7%; $p = 0.09$). Similarly, in our study, multivariate analysis showed stent type is not a predictor of TLF at 2 years. This finding could be attributed to the high prevalence of diabetics (37–38%) in the two cohorts that may have reduced the advantage of EES over PES.^{5,8} Also, our study may have not been powered to detect statistical differences between PES versus EES at 2 years. Notably, TLF was higher in our study than reported for both PES and EES. This could be explained by the higher complexity of disease such as a high prevalence of diabetics, LM, long lesions, restenotic lesions, and bifurcations. Also, ST appears to be higher with PES than EES (1.3 vs. 0%) consistent with both randomized trials and registry data.

Limitations of the Study

The study is limited by its retrospective nature and inherently selection bias. Also, the relatively small number of patients

yielded significant baseline differences between the two groups. Although multivariate analysis was performed to model for independent predictors of TLF and adjust for differences between the EES versus PES cohorts, this cannot completely mitigate potential influence of these variables on the final outcome. In univariate analysis, EES outperformed PES which could not be seen in the multivariate model, a potentially false-negative finding given the small number of patients and baseline differences. Also, syntax scoring was limited to the first consecutive 100 patients in each cohort. However, the strikingly similar results between the two cohorts likely predict no difference in syntax scoring for the entire cohort. Furthermore, the follow-up of patients in the study was limited to 2 years, a relatively short period of time as differences between the two stents may not become statistically apparent until later follow-up. Finally, higher rates of TLR and TLF were seen compared with published data. This may be explained by a complex patient population with a large number of restenotic lesions, longer lesions, and high prevalence of LM and bifurcating disease.

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