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Efficacy and Safety of a Double-Coated Paclitaxel-Eluting Coronary Stent: The EUCATAX Trial

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Objectives: The aim of this study was the comparison of a new double-coated paclitaxel-eluting coronary stent with bare-metal stent (BMS) in patients undergoing percutaneous coronary intervention. Background: Stent coating with biodegradable polymers as a platform for elution of drugs has the potential for complete elution of drugs and for decreasing the risk of late complications. Methods: Multicenter randomized trial comparing a paclitaxel-eluting stent (PES) coated with a biodegradable polymer and glycocalyx with the equivalent BMS. We randomly assigned 422 patients with *de novo* coronary lesions to PES (211 patients) or to BMS (211 patients). Primary end point was target vessel failure (TVF) defined as cardiac death, myocardial infarction, and target vessel revascularization. Clinical secondary end points were target vessel revascularization, target lesion revascularization, stent thrombosis (ST), and major adverse cardiovascular events (MACE). Angiographic secondary end points were late loss and binary restenosis. Results: At 1 year of follow-up, TVF rate was 9.5% in the PES group and 17.1% in the BMS group ($P = 0.02$), and MACE rate was 10% in PES and 19% in BMS arm ($P = 0.009$). All other secondary end points were reached but ST. ST rate was low and similar in both study arms. Conclusions: The study shows that patients treated with PES with dual coating technology had significantly lower incidence of TVF and MACE than those treated with BMS design; however, longer follow-up should be necessary to assess true advantages of this technology compared with the previous one.

Key words: percutaneous coronary intervention (PCI); restenosis (RSTN); acute coronary syndrome (ACS); drug delivery (DDEL); quantitative coronary angiography (QCA)

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INTRODUCTION

Biodegradable polymers, compared with durable polymers, as a platform for elution of drugs in coronary stent technology have the advantages of a complete elution of drugs and less inflammatory response, with the potential for decreasing the risk of late complications such as stent strut uncovering, malapposition, endothelial dysfunction, and thrombosis [1–6].

The purpose of this randomized study was to compare the efficacy and safety of a new paclitaxel-eluting stent (PES) coated with a biodegradable polymer and glycocalyx with an equivalent bare-metal stent (BMS). First in man observational study with this technology has been previously conducted [7].

METHODS

Study Design

Multicenter, unblended, and randomized study. The study includes (1) seven sites, (2) an independent committee for the adjudication of clinical events whose members were blinded to patient's assigned treatment, (3) an angiographic core laboratory, and (4) a safety and ethics independent committee. The Cardiovascular Research Center, a nonprofit organization, was in charge of the trial management, the accuracy of the data analyses, and the completeness of the material reported.

The protocol of this study was approved by the Ethics Committee of the participating centers of the study and by the Argentina National Regulatory Agency for Drug, Food, and Medical Technology. The study was conducted according to the principles of the Declaration of Helsinki, and all the patients signed a written informed consent to be included in this trial. The trial was registered as Clinical Trials list (NCT00825279).

Patients

All patients with a *de novo* stenosis (≥70% stenosis on visual assessment) in a major coronary artery, suitable for stent deployment and clinical indication to revascularization, were eligible for the study. Exclusion criteria were age <18 years, acute myocardial infarction (MI) in the preceding 72 hr, venous graft as the target vessel, anticipated noncompliance to dual antiplatelet treatment, previous percutaneous coronary intervention (PCI) with drug-eluting stents (DES), in-stent restenosis, severe left ventricular dysfunction (left ventricular ejection fraction <30%), severe comorbidities with decreased life expectancy, and participation in another study.

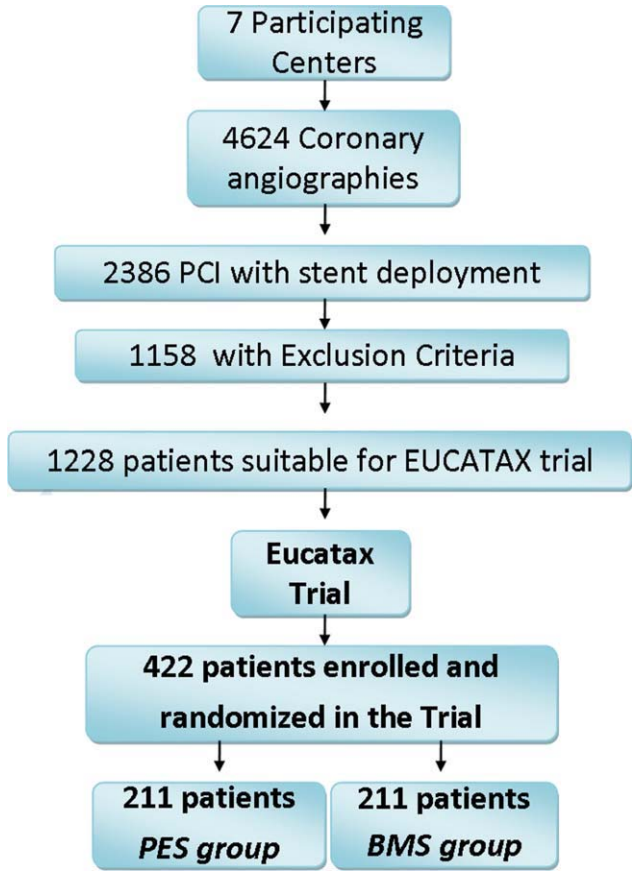

Fig. 1. Patient population in the EUCATAX trial. PES, paclitaxel-eluting stent; BMS, bare-metal stent.

Randomization and Treatment

All eligible patients were randomized to PES with biodegradable polymer or BMS. The randomization process in each center was performed in a blind manner from the coordinating center, with the use of an internet system containing a block randomization sequence for each participating center.

Stent Design

The PES stent is a stainless steel open cell (strut thickness 85 μm) modular design with three connecting fins per modulo. A double coating including a bioadsorbable polymer as the platform for paclitaxel elution and glycocalyx to increase hemocompatibility [7–9] was used. Glycocalyx layer is a symmetric coating using a Camouflage nanotechnology [8], whereas the bioadsorbable polymer is poly(D,L-lactide-*co*-glycolide), is an asymmetric coating, coating thickness 2.5 μm for luminal side and 5 μm in the abluminal side. Paclitaxel is loaded, in relation to stent length, at a concentration of 11–43 μg.

Camouflage nanocoating [8,9] was coated with hemoparin, which is a polymer-analogously modified heparin that no longer possesses an active anticoagulation effect because of the removal of the sulfate groups. This eliminates the strongly negative charge of heparin molecule, and its passive nature is reflected in the lack of plasma protein binding of the substance [8]. Hemoparin is permanently bound to the stent surface by multiple covalent binding. It is a polysaccharide present in every human cell. A systemic effect of hemoparin can be excluded because of the low total mass of the coating in the range of 10–12 picomoles. Usefulness of this passive coating was suggested in preclinical [8,9] and observational studies [10,11]. Over this hemoparin coat, the bioabsorbable polyester polymer served as the carrier of the paclitaxel. Poly-(D,L-lactide-*co*-glycolide) has been well known to be a biocompatible, nontoxic, biodegradable polymer and is in use in the form of a wide variety of products. The monomers, L-lactate, D-lactate, and glycolate, produced by biodegradation of the material, are also nontoxic.

Because these substances are also produced by the cells themselves, they are integrated as intrinsic intermediates of cellular metabolism and undergo rapid degradation. The end products of degradation have been shown to be carbon dioxide and water [7].

A controlled release of the immunosuppressive agent was achieved with the complete degradation of the polymer, where the paclitaxel was loaded, between 6 and 8 weeks after stent implantation. Stent diameters and length available for the study were 2.5–4.0 mm and 13–33 mm, respectively. The PES stent and the equivalent BMS were provided by Eucatech AG (Reinhelfeden, Germany).

PCI was performed using standard techniques. All patients received 325 mg/day of aspirin indefinitely and clopidogrel as a loading dose of 300 mg in the day of the procedure and 75 mg/day thereafter for 3 months in BMS arm for 6 months in PES. Statins were given to all patients indefinitely.

The follow-up included patient interviews at 1, 3, 6, and 12 months and twice a year beyond that. Nine-month coronary angiography was scheduled in a predefined subgroup of 150 patients during initial randomization process. Unscheduled angiography in this subgroup of patients was allowed according to clinical indication, and anticipated angiography findings were considered for the angiographic analysis.

End Points

The primary end point of the study is target vessel failure (TVF) defined as cardiac death, or MI or clinically driven target vessel revascularization (TVR). Secondary end points are (1) major adverse cardiovascular events (MACE) defined as death from any cause, MI, stroke, and clinically driven TVR; (2) clinically driven TVR; (3) clinically driven target lesion revascularization (TLR); (4) stent thrombosis (ST); (5) late lumen loss; and (6) binary restenosis. Clinically driven TVR and TLR were defined as repeat PCI because of the presence of recurrent symptoms, or positive ischemic stress tests with significant stenosis of the target lesion, or $\geq$70% target lesion stenosis in asymptomatic patients scheduled for follow-up angiography.

The diagnosis of acute MI was based on typical chest pain combined with either new pathological Q waves or an increase in creatine kinase to more than three times the upper limit of normal, with a concomitant increase in the myocardial band isoenzyme. ST was classified according to the Academic Research Consortium and previous own definitions [12,13]. All end points were analyzed by intention to treat principle.

TABLE I. Baseline Demographic, Clinical, and Angiographic Characteristics

Patient characteristics	PES ($n = 211$)	BMS ($n = 211$)	P value
Age, years	63.8 ± 10.2	64.7 ± 12.2	0.50
Male, *n* (%)	176 (83.4)	167 (79.1)	0.26
Hypertension, *n* (%)	135 (64.0)	140 (66.4)	0.60
Hypercholesterolemia, *n* (%)	120 (56.9)	108 (51.2)	0.24
Chronic renal failure, *n* (%)	11 (5.2)	8 (3.8)	0.48
Current smokers, *n* (%)	45 (21.3)	50 (23.7)	0.56
Diabetes mellitus, *n* (%)	49 (23.2)	34 (16.1)	0.07
Family history of CAD, *n* (%)	16 (7.6)	13 (6.2)	0.56
Peripheral vascular disease, *n* (%)	14 (6.6)	17 (8.1)	0.57
Previous stroke, *n* (%)	7 (3.3)	11 (5.2)	0.33
Previous STEMI, *n* (%)	43 (20.4)	36 (17.1)	0.38
Previous revascularization, *n* (%)	75 (35.5)	51 (24.2)	0.11
Multiple vessel disease, *n* (%)	116 (55.0)	127 (60.2)	0.27
Clinical presentation			
Unstable angina (BC), *n* (%)	126 (59.7)	141 (66.8)	0.13
Treated vessels			
RCA, *n* (%)	43 (17.6)	59 (25.1)	0.11
LAD, *n* (%)	153 (62.8)	114 (48.5)	0.08
LCX, *n* (%)	45 (18.5)	56 (23.8)	0.23
Left Main, *n* (%)	3 (1.2)	6 (2.5)	0.30
No. vessels	244	235	0.83
No. lesions	277	262	0.71
Plaque type B2/C, %	50.2	56.9	0.46
No. implanted stents per patient	1.36 ± 0.55	1.29 ± 0.54	0.21
Small vessels (RVD <2.75 mm), %	60.3	46.4	0.22

CAD, coronary artery disease; STEMI, ST elevation myocardial infarction; BS, Braunwald classification of unstable angina; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; RVD, reference vessel diameter.

TABLE II. Cumulative Clinical Results at 12 Months of Follow-up in the Paclitaxel-Eluting Stent (PES) and Bare Metal Stent (BMS) Groups

	PES ($n = 211$)	BMS ($n = 211$)	P value
In-hospital results, *n* (%)			
Overall death	0 (0.0)	3 (1.4)	0.24
Acute myocardial infarction	1 (0.5)	2 (0.9)	1.00
Stroke	0 (0.0)	0 (0.0)	1.00
TVR	1 (0.4)	3 (1.3)	0.58
TLR	1 (0.4)	2 (0.8)	0.96
TVF	1 (0.5)	4 (1.9)	0.37
MACE	1 (0.5)	5 (2.4)	0.21
Out of hospital results, *n* (%)			
Overall death	5 (2.4)	5 (2.4)	1.00
Acute myocardial infarction	5 (2.4)	3 (1.4)	0.72
Stroke	0 (0.0)	1 (0.5)	1.00
TVR	19 (7.8)	32 (13.7)	0.03
TLR	16 (5.8)	31 (11.8)	0.01
TVF	19 (9.0)	33 (15.6)	0.03
MACE	19 (9.0)	35 (16.6)	0.02
Cumulative results, *n* (%)			
Overall death	5 (2.4)	8 (3.8)	0.39
Cardiac death	4 (1.9)	4 (1.9)	1.00
Acute myocardial infarction	6 (2.8)	5 (2.4)	1.00
ST elevation MI	5 (2.4)	4 (1.9)	1.00
Non-ST elevation MI	1 (0.5)	1 (0.5)	1.00
Stroke	0 (0.0)	1 (0.5)	1.00
TVR	20/244 (8.2)	35/235 (15.0)	0.02
TLR	17/277 (6.1)	33/262 (12.6)	0.01
TVF	20 (9.5)	36 (17.1)	0.02
MACE	21 (10.0)	40 (19.0)	0.009
Stent thrombosis, ARC definition,[a] *n* (%)			
Overall stent thrombosis	3 (1.4)	4 (1.9)	0.99
Definitive	3 (1.4)	1 (0.5)	0.37
Probable	0 (0.0)	3 (1.4)	0.33
Possible	0 (0.0)	0 (0.0)	1.00
Acute (<30 days)	1 (0.5)	2 (0.9)	0.99
Late (30–365 days)	2 (0.9)	2 (0.9)	0.99

[a]Definition of the Academic Research Consortium (Ref. 12).MI, myocardial infarction; MACE, major adverse cardiovascular events; TVR, target vessel revascularization; TLR, target lesion revascularization; TVF, target vessel failure.

Angiographic Data

Coronary angiograms obtained at baseline, after completion of the stent procedure, and at 9-month follow-up were digitally recorded and analyzed by a central core laboratory whose operator was blinded to treatment assignment. The analysis was performed using an automated edge-detection software (CMS; Medis Medical Imaging Systems, Leiden, The Netherlands). The analysis segment comprises the stent segment and the 5 mm adjacent to the proximal and distal stent edges. The same orthogonal views (an average of two) were selected for angiograms performed before and immediately after the stenting procedure, and at follow-up.

Each angiography sequence was preceded by an intracoronary injection of nitroglycerin. Acute gain was defined as the difference between minimal luminal diameter (MLD) before and at the end of PCI and stent deployment. Late lumen loss was calculated as the difference in MLD immediately after the procedure and at 9-month follow-up. Net gain was the difference between MLD at follow-up and before the interventional procedure [14].

Statistical Analysis

The sample size of the study was determined using a test for trend analysis based on an estimation of the incidence of the primary end point of TVF and MACE at 9 months of follow-up among patients treated with DES and BMS in previous concluded randomized studies. We assumed a 22% incidence of TVF and MACE at 9 months in BMS arm [15] and a $\geq$50% reduction in TVF and MACE with DES therapy [2,15–17]. Using a two-sided test for differences in independent binomial proportions with an alpha level of 0.05, 210 patients for each arm were needed for a statistical power of 80%.

Continuous variables were expressed as mean $\pm$ standard deviation, and categorical variables as percentages. Continuous variables were compared using analysis of variance with Bonferroni correction. Categorical variables were compared using χ^2 analysis or Fisher's exact test. Freedom from survival end points at follow-up were assessed using Kaplan–Meier curves and compared by log-rank test. Logistic regression and Cox regression analyses were performed to determine the independent predictors of clinical outcome. Variables entered in the univariable analysis were age, male gender, hypertension, dyslipidemia, chronic renal failure, cardiac heart failure, body mass index, current smoker, diabetes mellitus, family history of coronary artery disease, peripheral vascular disease, previous stroke, previous MI, previous revascularization procedure, unstable angina, multivessel disease, left main disease, numbers of vessel and lesion treated, number of stents deployed, and randomization group. A P value of <0.05 was considered statistically significant. All analyses were performed using the SPSS v14.0 package (SPSS, Chicago, IL).

RESULTS

Between August 2007 and August 2009, 4,624 patients were screened. Of these, 1,228 patients met the study inclusion criteria. Eight-hundred and six patients refused to participate in the study, whereas 422 patients could be randomized (9.1%); 211 patients

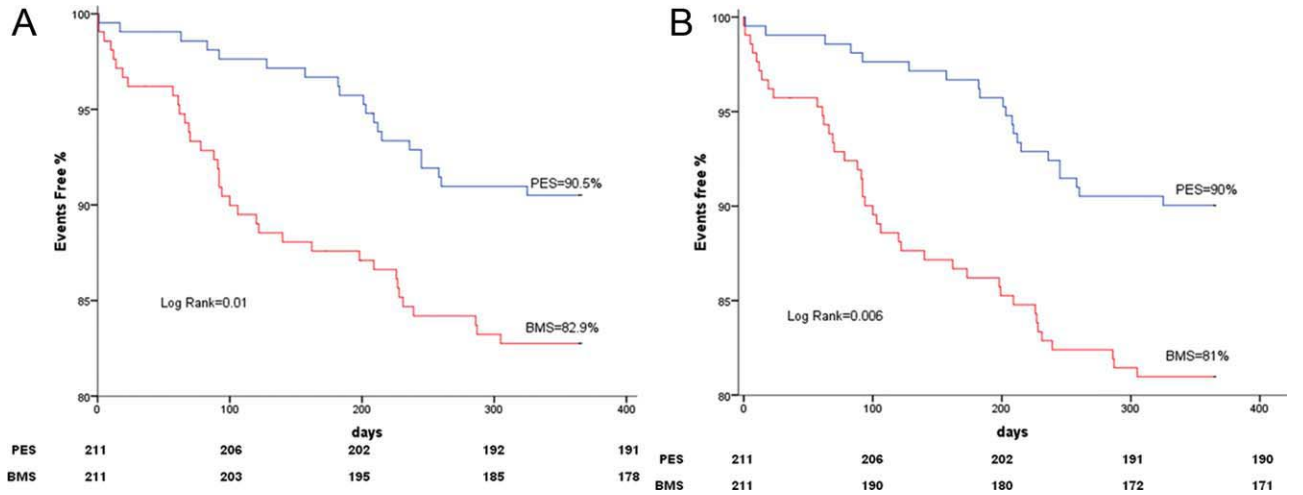

Fig. 2. Freedom from target vessel failure (A) and major adverse cardiovascular events (B) in paclitaxel-eluted (PES) and bare-metal stent (BMS) groups.

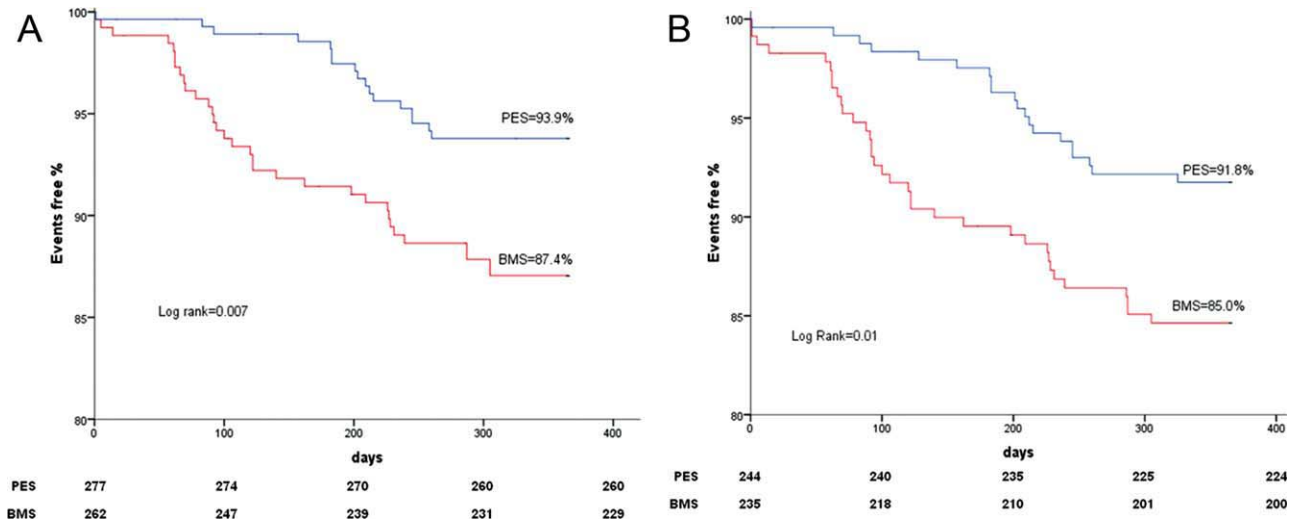

Fig. 3. Freedom from target lesion revascularization (A) and target vessel revascularization (B) in paclitaxel-eluted (PES) and bare-metal stent (BMS) groups.

were included in the PES arm and 211 in the BMS arm (Fig. 1). Baseline clinical, angiographic, and procedural characteristics of the study population are summarized in Table I. No significant differences in baseline characteristics between both groups were seen.

One-Year Clinical Outcome

Table II summarizes 12-months clinical outcomes. Clinical follow-up rate was 100%. TVF rate was 9.5% in PES and 17.1% BMS arm, $P = 0.02$. MACE rate was 10% in the PES arm and 19% in the BMS arm ($P = 0.009$). There were no differences between arms in mortality, cardiac mortality, MI, and stroke, and difference in TVF and MACE rates were driven by difference in TLR and TVR rate; TLR was 6.1% in PES and 12.6% in BMS arm, $P = 0.01$ (Table II). There were no differences between arms in ST rates (1.4% in PES and 1.9% in BMS arms, $P = 0.99$). At 9 months, where sample size was estimated for, differences in MACE rate (7.1% in PES and 17.1% in BMS arm, $P = 0.012$) allowed to reach the power of the study.

Figure 2 shows the survival curves of freedom from TVF (2A) and MACE (2B), and Fig. 3 shows survival curves of freedom from TLR (3A) and TVR (3B). At 12 months of follow-up, freedom from TVF was 90.5% in PES arm and 82.9% in BMS arm ($P = 0.01$). Freedom from TLR and TVR were also significant in favor of the PES design; freedom from TLR was 93.9% in PES and 87.4% in BMS arm, $P = 0.007$

(Fig. 3). After multivariable analysis, the independent predictors of TVF were BMS treatment assignment (odds ratio, 1.975; 95% confidence interval, 1.163–3.356; $P = 0.012$) and current smokers (odds ratio, 2.277; 95% confidence interval, 1.034–5.014; $P = 0.027$); identical independent predictors were identified into presence of MACE (Table III).

Angiographic Follow-up

Baseline and follow-up angiographic findings are shown in Table IV. MLD, acute gain, lesion length, and stent length were similar in both groups, whereas the reference vessel diameter was lower in the PES group.

Follow-up angiography was performed in all 150 patients scheduled for. In-segment late luminal loss was 0.50 mm in the PES group and 0.91 mm in the BMS group ($P = 0.001$). The binary restenosis ($\geq$50% stenosis) rate was 13.2% (13 of 98 lesions) in PES arm and 34% (30 of 88 lesions) in BMS arm ($P < 0.001$).

TABLE III. Cox Regression Analysis: Multivariate Predictors of Target Vessel Failure (Cardiac Death, MI, and TVR) and the Composite of Death, MI, Stroke, and TVR (MACE)

			95% CI	
Variable	Significance	Odds ratio	Lower	Upper
A: Target vessel failure				
Group (BMS)	0.012	1.975	1.163	3.356
Smoker	0.027	2.277	1.034	5.014
B: MACE				
Group (BMS)	0.004	2.105	1.260	3.515
Smoker	0.044	2.143	1.021	4.496

MI, myocardial infarction; TVR, target vessel revascularization.

DISCUSSION

This prospective, randomized multicenter and controlled clinical trial demonstrates that patients treated with the PES with biodegradable polymer and glycocalyx coating exhibit a significant improvement in clinical outcome compared with those treated with BMS. Furthermore, the population included in this study represents a relatively high-risk "real-world population" as reflected by the presence of diabetes in 23.5% of the patients, a RVD size <2.75 mm in 60%, multivessel disease, including left main stenosis, in 60%, and an acute coronary syndrome in 60%. Many of these lesions met the off-label indication for DES, which has been associated with poor outcome [18–20].

The particular dual-coated design of the PES used in our study could be associated with safety outcome; a BMS coated with a layer that mimics endothelium glycocalyx remains in place after the polymer, and the immunosuppressive drugs are completely vanished. This particular coating was established in preclinical studies [8,9] as a promoter of stent re-endothelization. Moreover, the safety profile of this design was clinically confirmed by observational clinical studies in a high-risk patient population for acute thrombotic complications, such as those with ST elevation MI or patients required to discontinue clopidogrel therapy soon after stent deployment [10,11].

Recent data from other DES designs with biodegradable polymer showed similar safety and efficacy results from the ones that we are presenting here. One-year clinical outcome from the LEADERS trial [1] in a similar patient cohort reported an incidence of clinically indicated TLR and TVR of 6.5% and 7.8%, respectively, which are comparable with the 6.1% and 8.2%

TABLE IV. Quantitative Coronary Analysis (QCA) for Both Groups

	PES ($n = 169$ lesions)	BMS ($n = 153$ lesions)	P value
A: Baseline QCA analysis			
Reference diameter (mm)	2.75 ± 0.5	2.85 ± 0.5	0.086
Minimal luminal diameter (mm)	0.86 ± 0.4	0.85 ± 0.5	0.78
Lesion length (mm)	16.2 ± 6.1	15.6 ± 6.3	0.41
Stent length (mm)	21.7 ± 5.6	20.0 ± 4.8	0.16
Stent size (mm)	2.96 ± 0.4	2.93 ± 0.5	0.78
B. Immediately after PCI QCA analysis			
Reference diameter (mm)	2.91 ± 0.44	2.96 ± 0.43	0.34
Minimal luminal diameter (mm)	2.68 ± 0.42	2.72 ± 0.43	0.40
C: Follow-up QCA analysis	PES ($n = 98$ lesions)	BMS ($n = 88$ lesions)	
Reference diameter (mm)	2.75 ± 0.48	2.75 ± 0.36	0.99
Minimal luminal diameter (mm)	2.16 ± 0.51	1.81 ± 0.75	0.007
Stenosis diameter (%)	27.4 ± 29.8	39.6 ± 23.9	0.005
Acute gain	1.82 ± 0.47	1.87 ± 0.62	0.45
Net gain	1.3 ± 0.49	0.93 ± 0.63	0.002
Late loss (in-stent)	0.52 ± 0.59	0.94 ± 0.70	0.002
Late loss (in-segment)	0.50 ± 0.56	0.91 ± 0.69	0.001
Angiographic restenosis	13.2% (13/98)	34% (30/88)	0.001

reported in our study. In addition, all definitions of ST are similar in both studies. Although the late loss of the DES arm reported by us was higher, this angiographic finding difference is in agreement with those reported by other randomized comparisons between limus- and paclitaxel-eluting stent trials [21,22].

Study Limitations

We recognize certain limitations in our study. First, the study was not blinded, and this introduces a potential for bias; however, all adverse clinical events, including angiographic data, were blindly adjudicated by the clinical event and angiographic core laboratory committee. Second, the study does not compare this novel technology with other DES designs, although our clinical results are similar to previous randomized trials. In agreement, results from other DES trials with durable polymers in a comparable patient cohort [18,23] reported similar amount of late loss and angiographic restenosis [18] but greater incidence of TVF and MACE [18,23] than that reported by us. Third, although both groups had a nonsignificant baseline differences, patients located in the PES arm had, in general, greater incidence of comorbidities associated with poor outcome after PCI, as higher incidence of diabetics, previous revascularization, small reference vessel size, and LAD stenosis.

Finally, the amount of angiographic luminal diameter loss was greater than expected for a new DES design; therefore, we cannot discard some degree of inflammation during the process of polymer degradation in a number of patients.

CONCLUSIONS AND CLINICAL IMPLICATIONS

In summary, this study demonstrates that PES with biodegradable polymer and glycocalyx coating compared with BMS is associated with a significant reduction in TVF and MACE without any increase in death, MI, or ST at 1 year of follow-up. However, taking into account that the amount of angiographic late loss of this stent design was higher than that we would expect, the safety and efficacy advantages of this new DES technology cannot be presently determined, and longer follow-up assessment should be necessary to assess its true benefits in comparison with old stent designs.

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APPENDIX

The following are the participants of the EUCATAX study:

Steering and Executive Committee: Alfredo E. Rodriguez, MD, PhD, Principal Investigator (Argentina); Igor F. Palacios, MD, (USA); David Antoniucci, MD (Italy); and Michael Giesse, PhD (Germany).

Safety and Ethics Committee: Jorge Tronge, MD, President (Buenos Aires, Argentina); Arnoldo Dubin, MD, PhD (Buenos Aires, Argentina); Cristina Sivori, PhD (Buenos Aires, Argentina); and Alejandro Crespo, PhD (Houston, Texas).

Clinical Events Committee: Pablo Boskis, MD, FACC, and Omar Santaera, MD (Buenos Aires, Argentina, on behalf of the Argentina Society for Cardiovascular Interventions); Miguel Russo-Felssen, MD; and Valeria Curotto, MD.

Coordinating Center: Centro de Estudios en Cardiologia Intervencionista (CECI); Alfredo M. Rodriguez-Granillo, BS.

Statistics: Gaston A. Rodriguez-Granillo, MD, PhD.

Angiographic and Intravascular Ultrasound Core Laboratory: Gaston Rodriguez-Granillo, MD, PhD; Claudio Llaurado, PhD; and Alejandro Incarbone, PhD.

Participating Hospitals and Clinical Investigators—Otamendi Hospital (Buenos Aires): Alfredo E. Rodriguez, MD, PhD, Juan Mieres, MD, Gustavo Risau, MD, and Bibiana Rubilar, MD; Sanatorio Las Lomas (San Isidro-Buenos Aires): Juan Mieres, MD, and Gilberto Perez, MD; Clinica Medica Adrogue (Adrogue-Buenos Aires): Carlos Fernandez-Pereira, MD, Carlos Mauvecin, MD, and Gustavo Allende, MD; Sanatorio Belgrano (Mar del Plata-Buenos Aires): Alejandro Delacasa, MD; Sanatorio El Salvador (Cordoba): Cesar F. Vigo, MD, and Mario Fernandez, MD; Clinica del Sol (Buenos Aires): Victor Bernardi, MD, and Maximo Rodriguez-Alemparte, MD; and Sanatorio Guemes (Buenos Aires): Marcelo Bettinotti, MD, and Alejandro Goldsmit, MD.

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