Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 63, No. 14, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.12.006

A Randomized Comparison of Drug-Eluting Balloon Versus Everolimus-Eluting Stent in Patients With Bare-Metal Stent–In-Stent Restenosis

The RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs. Everolimus-eluting Stent)

Fernando Alfonso, MD,*† Maria Jose Pérez-Vizcayno, MD,† Alberto Cárdenas, MD,† Bruno García del Blanco, MD,‡ Bernhard Seidelberger, MD,* Andrés Iñiguez, MD,§ Manuel Gómez-Recio, MD,‖ Mónica Masotti, MD,¶ M. Teresa Velázquez, MD,# Juan Sanchís, MD,** Arturo García-Touchard, MD,†† Javier Zueco, MD,‡‡ Armando Bethencourt, MD,§§ Rafael Melgares, MD,‖‖ Angel Cequier, MD,¶¶ Antonio Dominguez, MD,## Vicente Mainar, MD,*** José R. López-Mínguez, MD,††† José Moreu, MD,‡‡‡ Vicens Martí, MD,§§§ Raúl Moreno, MD,‖‖‖ Pilar Jiménez-Quevedo, MD,† Nieves Gonzalo, MD,† Cristina Fernández, MD,† Carlos Macaya, MD,† for the RIBS V Study Investigators, under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology

Madrid, Barcelona, Vigo, Almería, Valencia, Santander, Palma de Mallorca, Granada, Málaga, Alicante, Badajoz, and Toledo, Spain

Objectives This study sought to compare the efficacy of drug-eluting balloons (DEB) with that of everolimus-eluting stents (EES) in patients with bare-metal stents (BMS) in-stent restenosis (ISR).

Background Treatment of patients with ISR remains a challenge.

Methods This was a prospective, multicenter, randomized trial comparing DEB with EES in patients with bare-metal stents (BMS) in-stent restenosis (ISR). The primary endpoint was the minimal lumen diameter at 9 months' follow-up.

Results A total of 189 patients with BMS-ISR from 25 Spanish sites were included (95 were allocated to DEB and 94 to EES). Procedural success was achieved in all patients. At late angiography (median 249 days; 92% of eligible patients), patients in the EES arm had a significantly larger minimal lumen diameter (2.36 ± 0.6 mm vs. 2.01 ± 0.6 mm, $p < 0.001$; absolute mean difference: 0.35 mm; 95% confidence interval [CI]: 0.16 to 0.53) and a lower percent of diameter stenosis (13 ± 17% vs. 25 ± 20%, $p < 0.001$). However, late loss (0.04 ± 0.5 mm vs. 0.14 ± 0.5 mm, $p = 0.14$) and binary restenosis rate (4.7% vs. 9.5%, $p = 0.22$) were very low and similar in both groups. Clinical follow-up (median 365 days) was obtained in all (100%) patients. Occurrences of the combined clinical outcome measure (cardiac death, myocardial infarction, and target vessel revascularization; 6% vs. 8%; hazard ratio [HR]: 0.76; 95% CI: 0.26 to 2.18, $p = 0.6$) and the need for target vessel revascularization (2% vs. 6%; HR: 0.32: 95% CI: 0.07 to 1.59, $p = 0.17$) were similar in the 2 groups.

Conclusions In patients with BMS-ISR, both DEB and EES provided excellent clinical results with a very low rate of clinical and angiographic recurrences. However, compared with DEB, EES provide superior late angiographic findings. (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs. Everolimus-eluting Stent [RIBS V]; NCT01239953) (J Am Coll Cardiol 2014;63:1378–86) © 2014 by the American College of Cardiology Foundation

From the *Hospital Universitario de La Princesa, Madrid, Spain; †Hospital Universitario Clínico San Carlos, Madrid, Spain; ‡Hospital Universitario Vall d'Hebron, Barcelona, Spain; §Complejo Hospitalario Universitario de Vigo, Pontevedra, Spain; ‖Hospital Universitario de Torrecárdenas, Almería, Spain; ¶Hospital Universitario Clinic de Barcelona, Barcelona, Spain; #Hospital Universitario 12 de Octubre, Madrid, Spain; **Hospital Universitario Clínico de Valencia, Valencia, Spain; ††Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; ‡‡Hospital Universitario Marqués de Valdecilla, Santander, Spain; §§Hospital Universitario Son Espases, Palma de Mallorca, Spain; ‖‖Hospital Universitario Virgen de las Nieves, Granada, Spain; ¶¶Hospital Universitario de Bellvitge, Barcelona, Spain; ##Hospital Universitario Virgen de la Victoria, Málaga, Spain; ***Hospital Universitario de Alicante, Alicante, Spain; †††Hospital Universitario Infanta Cristina Badajoz, Badajoz,

Bare-metal stents (BMS) are still widely used in coronary interventions, although they may be associated with the appearance of in-stent restenosis (ISR) (1). Currently, treatment of ISR remains a challenge (2–10). Many coronary interventions have been advocated in this setting, but data from randomized clinical trials suggest that drug-eluting stents (DES) provide superior long-term clinical and angiographic results (2–10). More recently, drug-eluting balloons (DEB) have also proven to be highly effective for ISR (11–16). In patients with BMS-ISR or DES-ISR, DEB have proven to be superior to conventional balloon angioplasty and comparable to first-generation DES (11–16).

New-generation DES appear to be not only more effective but also safer than first-generation DES (17–19). In particular, everolimus-eluting stents (EES) have demonstrated excellent long-term clinical and angiographic results (17–19). Notably, the clinical value of second-generation DES has also been demonstrated in subsets of complex lesions, including patients presenting with ISR (8). However, the relative efficacy of second-generation DES compared with that of DEB in patients with ISR remains unknown.

In this randomized clinical trial, we sought to compare the results of DEB with those of EES in patients presenting with BMS-ISR.

Methods

Patient selection and study design. The RIBS V (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs. Everolimus-eluting Stent) study was designed as a multicenter, prospective, open-label, active treatment-controlled, randomized clinical trial to compare the results of DEB with those of EES in patients with BMS-ISR (ID: NCT01239953; for a list of participating physicians and institutions, please see the Online Appendix). Briefly, patients with BMS-ISR (>50% diameter stenosis on visual assessment) presenting with angina or objective evidence of ischemia were eligible (2,4). Patients with BMS-ISR in small vessels (≤2.0 mm in diameter) or very diffuse lesions (>30 mm in length) were excluded (2,4). In addition, patients with very early (<1 month) ISR and those presenting with an acute myocardial infarction or with images of intracoronary thrombi also were excluded. Patients with edge-ISR were eligible only when the stent border was clearly affected. In those cases, the use of intracoronary imaging techniques was recommended to confirm the involvement of the stent edge. Patients with contraindications to aspirin or clopidogrel therapy, severe renal or hepatic failure, severe peripheral vascular disease, life expectancy of <1 year, or any major concomitant systemic disease potentially interfering with clinical or angiographic follow-up were not included.

The primary endpoint was the in-segment minimal lumen diameter at 9 months' follow-up as measured by quantitative coronary angiography.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DEB = drug-eluting balloon(s)
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
ISR = in-stent restenosis

Twenty-five university hospitals from Spain participated in this trial (see the Online Appendix). Telephone randomization (1:1 to DEB or EES) was performed at the coordinating center, using a computer-generated sequence (2,4). Patients were stratified according to ISR length and location (edge vs. intra-stent) based on visual assessment. Data collection, management, and analysis were performed at the coordinating center (Clínico San Carlos University Hospital, Madrid). The study was an investigator-driven initiative and was conducted under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology. Unrestricted research grants were obtained from both B. Braun Surgical and Abbott Vascular. Patients and investigators were not masked to treatment allocation, but clinical events and angiographic findings were assessed by blinded individuals to prevent ascertainment bias. The study was performed according to the provisions of the Declaration of Helsinki, and the study protocol was approved by the Institutional Ethics Committees of all participating centers. Written informed consent was obtained from all patients.

Interventions. Patients were pre-treated with aspirin and clopidogrel. A loading dose of clopidogrel (300 to 600 mg) was administered before the intervention to clopidogrel-naïve patients. Full anticoagulation was obtained during the procedure with unfractionated heparin (initial bolus of 100 mg/kg, with additional boluses as required to achieve an activated clotting time >250 s). Lesions were pre-dilated with relatively short balloons to avoid damaging adjacent coronary segments. Care was also taken to prevent balloon slippage and watermelon seeding phenomena. Special attention was given to correct underlying underexpanded stents. In this situation, the use of noncompliant balloons at very high pressures was recommended (4). After adequate lesion pre-dilation, patients received the allocated treatment. DEB (SeQuent Please, B.Braun Surgical, Melsungen, Germany) were selected with a balloon-to-artery ratio of 1.1:1 and inflated at nominal pressures (12 to 14 atm) for 60 s. In this arm, cross-over to bailout stenting was allowed only for dilation failure (>50% residual stenosis) or major dissections. Alternatively, EES (Xience Prime, Abbott Vascular, Abbott Park, Illinois) were implanted using a final balloon-to-artery ratio of 1.1:1 and relatively high pressure (>14 bar). After EES implantation, post-dilation with noncompliant balloons was allowed at the operator's

Spain; ‡‡‡Hospital Universitario Virgen de la Salud Toledo, Toledo, Spain; §§§Hospital Universitario Sant Pau, Barcelona, Spain; and the ‖‖‖Hospital Universitario La Paz, Madrid, Spain. This study was supported by unrestricted research grants from B. Braun Surgical and Abbott Vascular. Dr. Gonzalo has received speaker honoraria from St. Jude Medical and Terumo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 18, 2013; revised manuscript received November 12, 2013, accepted December 3, 2013.

discretion. The use of intracoronary imaging techniques to assess stent expansion and optimize procedural final results was suggested in the protocol, but the selection of these techniques and the final optimization strategies were left to the discretion of the local investigators.

Serum creatine kinase (with MB determinations when abnormal) and troponin levels and 12-lead electrocardiograms were serially obtained for 24 h (4). Clopidogrel (75 mg/day) was recommended for 1 year after EES implantation and for 3 months after DEB therapy. All patients were treated with aspirin indefinitely.

Protocol, definitions, and follow-up. Patients were followed at 6 to 9 months and at 1 year. Angiographic follow-up was scheduled at 6 to 9 months, but it was performed earlier if clinically indicated. Case report forms were completed at each site by local investigators and submitted to the coordinating center. Data were monitored and reviewed for completeness and consistency. When required, specific queries were sent back from the coordinating center to the sites. All data were prospectively entered into a dedicated, relational database designed specifically for the RIBS studies (2,4). Clinical events (death, myocardial infarction, and target vessel revascularization) were adjudicated by an independent Clinical Events Committee that was unaware of the therapeutic strategy, after the review of all corresponding source documents. All deaths were considered cardiac related unless a clear noncardiac cause could be established. The diagnosis of myocardial infarction required 2 of the following: 1) prolonged (>30 min) chest pain; 2) a rise in creatine kinase levels more than twice the local upper normal value (with abnormal MB fraction); and 3) development of persistent ischemic electrocardiographic changes (with or without new pathological Q waves) (2,4). The protocol indicated that during follow-up, all repeated interventions were required to be clinically justified. All angiograms of patients with target vessel revascularization were reviewed to identify target lesion revascularization. The Academic Research Consortium definition was used to assess the presence of stent thrombosis (20).

Angiographic analysis. All coronary angiograms were analyzed at the angiographic core laboratory by trained personnel blinded to treatment allocation by using standard methodology (2,4). The Mehran (21) and American College of Cardiology/American Heart Association (22) classifications were used to assess lesion shape. An automatic edge-detection system (CASS II System, Pie Medical, Maastricht, the Netherlands) was used for offline quantitative measurements. Carefully selected orthogonal, angiographic views (without vessel foreshortening or side-branch overlap) were obtained after nitroglycerin administration. Matched projections were repeated after intervention and at follow-up. In-lesion and in-segment (the treated segment plus 5 mm proximal/distal margins) analyses were performed. Reference vessel diameter, minimal lumen diameter, percent of diameter stenosis, late loss, loss index, and binary restenosis rate (>50% diameter stenosis) were determined.

Statistical analysis. Categorical data are presented as percentages and were compared using the chi-square test or Fisher exact test. Continuous data are presented as mean ± SD or medians (interquartile range) after data distribution (Kolmogorov-Smirnov test) was analyzed. The Student *t* test or Mann-Whitney *U* test was used for the comparison of continuous variables. Main effects estimates are presented as absolute differences and 95% confidence intervals (CIs) after assessment of variance homogeneity. Kaplan-Meier curves were constructed to estimate event-free survival rates. Hazard ratios and corresponding 95% CIs were assessed using Cox models and were compared using the Wald test. Sample size calculations required several assumptions based on previous data, although results of EES in this setting were unavailable at the time of study design. Based on the RIBS I and II trials (2,4), a minimal lumen diameter of 2.6 mm was anticipated immediately after stent implantation. Assuming a late loss of 0.3 mm (2), a minimal lumen diameter at follow-up of 2.3 ± 0.7 mm was expected. On the same basis, a minimal lumen diameter of 2.2 mm was anticipated after DEB treatment (2,4). Assuming a late loss of 0.2 mm (12), a minimal lumen diameter at follow-up of 2.0 ± 0.7 mm was calculated. Accordingly, 172 patients (86 patients per arm) were required to detect the superiority of EES compared with DEB (power of 80%; alpha error of 5%). A total of 190 patients were eventually estimated, to be able to accommodate a dropout rate of ~10% in the late angiographic study. Analyses were performed according to the intention to treat principle unless otherwise specified. SPSS version 15.00 statistical software was used. A p value <0.05 was considered statistically significant.

Results

From January 2010 to January 2012, 189 patients with BMS-ISR were enrolled in the study (95 allocated to DEB and 94 to EES) (Fig. 1). Baseline clinical characteristics were well matched in the 2 groups, except for a higher frequency of elderly patients and a lower rate of smokers in the DEB arm (Table 1). Baseline angiographic findings were similar in both groups, although lesions in the EES arm tended to be more severe (Table 1). Procedural success was obtained in all patients, although 8 patients (8%) in the DEB arm eventually required stent implantation (DES in 7 patients) as a result or suboptimal results or significant coronary dissections. All patients in the EES arm successfully received the allocated stent.

On quantitative coronary angiography, acute angiographic results were better in the EES arm. Patients treated with EES obtained a larger minimal lumen diameter (2.38 ± 0.5 mm vs. 2.16 ± 0.5 mm, respectively), a lower residual stenosis (11 ± 11% vs. 19 ± 11%, respectively), and a larger acute gain (1.45 ± 0.5 vs. 1.14 ± 0.6, respectively; all

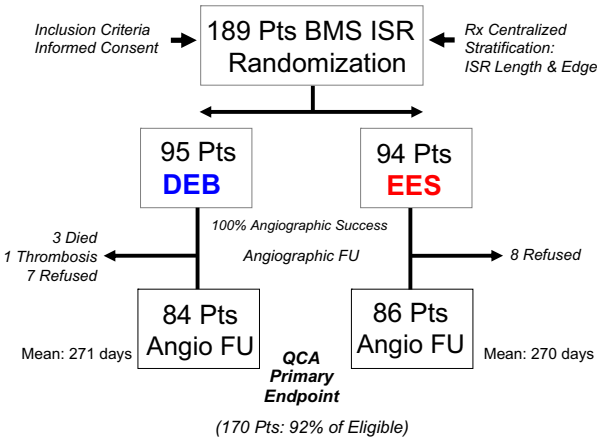

Figure 1 Study Flow Chart Detailing Patients Randomized and Patients With Late Angiography

BMS = bare-metal stent(s); DEB = drug-eluting balloon(s); EES = everolimus-eluting stent(s); FU = follow-up; ISR = in-stent restenosis; Pts = patients; QCA = quantitative coronary angiography; Rx = prescription.

Table 1 Baseline Clinical, Angiographic, and Procedural Characteristics

	DEB (n = 95)	EES (n = 94)	p Value
Age, yrs	67 ± 11	64 ± 12	0.04
Female	13 (14)	12 (13)	0.85
Risk factors			
Diabetes mellitus	30 (32)	19 (20)	0.08
Hyperlipidemia	69 (73)	62 (66)	0.32
Hypertension	68 (72)	68 (72)	0.91
Ever smoked	56 (59)	70 (75)	0.02
Clinical features			0.74
Unstable angina	38 (40)	42 (45)	
Stable angina	43 (45)	41 (44)	
Silent ischemia	14 (15)	11 (12)	
Previous myocardial infarction	57 (60)	56 (60)	0.95
Previous bypass surgery	4 (4)	7 (7)	0.34
>1 intervention on target lesion	6 (6)	2 (2)	0.28
Time to restenosis, days (range)	390 (142–2,815)	350 (151–2,679)	0.78
Ejection fraction, %	58 ± 13	59 ± 12	0.71
Target arteries			0.72
Left anterior descending	35 (37)	37 (39)	
Left circumflex	21 (22)	22 (23)	
Right coronary	37 (39)	32 (34)	
Saphenous vein graft	2 (2)	3 (3)	
Procedural characteristics			
Length of the previous stent, mm	19 ± 6	18 ± 6	0.51
Length of current EES/DEB, mm	20 ± 7	23 ± 9	0.01
Maximal pressure, atm	18 ± 4	19 ± 3	0.08
IVUS or OCT	22 (23)	31 (33)	0.14
Balloon-to-artery ratio	1.25 ± 0.2	1.23 ± 0.2	0.52
Cross-over	8 (8)	0 (0)	0.007
Angiographic successes	95 (100)	94 (100)	1.00

Values are mean ± SD or n (%) unless otherwise specified.
DEB = drug-eluting balloon(s); EES = everolimus-eluting stent(s); IVUS = intravascular ultrasound; OCT = optical coherence tomography.

$p < 0.01$) (Table 2). Late angiographic studies (median 249 days) were obtained in 170 patients (92% of those eligible [excluding 3 patients who died and 1 who experienced stent thrombosis before late angiography]). At late follow-up, minimal lumen diameter in the in-segment analysis (the primary study endpoint) was larger (2.36 ± 0.6 mm vs. 2.01 ± 0.6 mm, respectively, $p < 0.001$; absolute mean difference: 0.35 mm, 95% CI: 0.16 to 0.53), and the percent diameter stenosis was lower (13 ± 17% vs. 25 ± 20%, respectively, $p < 0.001$) in the EES arm than in the DEB arm. Differences in minimal lumen diameter in favor of EES persisted (absolute mean difference: 0.29 mm, 95% CI: 0.18 to 0.55, $p < 0.001$), despite adjustment for imbalances in baseline characteristics (including age, diabetes, smoking, and percent of stenosis diameter). In addition, the net lumen gain (1.41 ± 0.6 mm vs. 0.99 ± 0.6 mm, respectively, $p < 0.001$) was also larger in the EES arm (Table 2). However, the angiographic late loss (mean 0.14 ± 0.5 mm [DEB] vs. 0.04 ± 0.5 mm [EES]; median 0.07 mm [−0.16 to 0.33 mm] vs. 0.001 mm [−0.21 to 0.19 mm], $p = 0.14$) and the binary restenosis rate (8 [9.5%] vs. 4 [4.7%], respectively, $p = 0.22$) were similar in both groups (Table 2). Overall, angiographic results of the in-lesion analysis were largely similar to those found in the in-segment analysis (Table 2). Results were also similar in the per-protocol analysis. Cumulative frequency distribution curves of minimal lumen diameter and percent diameter stenosis at different time intervals are shown in Figures 2 and 3. Notably, the results of the primary endpoint were consistent across 10 pre-specified patient and lesion subsets after formal interaction testing (Fig. 4).

Table 3 summarizes all major adverse clinical events during hospitalization, at 9 months, and at 1 year. During hospital stay, 4 patients (all in the EES arm) experienced a periprocedural myocardial infarction (3 as the result of a side-branch loss), but no patient died or required repeated coronary interventions at the target vessel (Table 3). By late follow-up, 4 patients died (all in the DEB group), 1 from cardiac cause and 3 from noncardiac causes. The rates of myocardial infarction were similar in both groups. Only 1 patient in the DEB arm experienced definitive stent thrombosis (due to clopidogrel discontinuation), which presented as a myocardial infarction requiring urgent revascularization. No cases of probable stent thrombosis were found. The rates of target vessel revascularization were low and similar in both groups, although a trend was found in favor of the EES arm on target lesion revascularization. The occurrence of major adverse events and the rate of major cardiac adverse events were similar in both groups (Table 3). Estimates of event-free survival are presented in Figure 5.

Table 2 Angiography Results

	DEB	EES	p Value
Qualitative features	(n = 95)	(n = 94)	
Mehran class I, II, III–IV	38 (40), 45 (47), 12 (13)	34 (36), 42 (45), 18 (19)	0.54
B2-C lesion	48 (51)	51 (54)	0.61
Edge ISR	6 (6)	7 (7)	0.76
Quantitative findings before the procedure	(n = 95)	(n = 94)	
Reference vessel diameter, mm	2.64 ± 0.6	2.64 ± 0.6	0.96
Minimal lumen diameter, mm	1.02 ± 0.4	0.93 ± 0.4	0.12
Stenosis, % of lumen diameter	61 ± 14	65 ± 13	0.05
Lesion length, mm	13.7 ± 7	13.8 ± 6	0.96
Diffuse lesions >10 mm	58 (62)	66 (71)	0.18
Quantitative findings after the procedure, in segment	(n = 95)	(n = 94)	
Reference vessel diameter, mm	2.69 ± 0.6	2.68 ± 0.5	0.94
Minimal lumen diameter, mm	2.16 ± 0.5	2.38 ± 0.5	0.001
Stenosis, % of lumen diameter	19 ± 11	11 ± 11	<0.001
Acute gain, mm	1.14 ± 0.6	1.45 ± 0.5	<0.001
Quantitative findings after the procedure, in lesion	(n = 95)	(n = 94)	
Reference vessel diameter, mm	2.69 ± 0.6	2.76 ± 0.5	0.39
Minimal lumen diameter, mm	2.20 ± 0.5	2.50 ± 0.4	<0.001
Stenosis, % of lumen diameter	18 ± 11	9 ± 13	<0.001
Acute gain, mm	1.17 ± 0.6	1.57 ± 0.5	<0.001
Quantitative findings at follow-up, in segment	(n = 84)	(n = 86)	
Reference vessel diameter, mm	2.70 ± 0.5	2.73 ± 0.5	0.60
Minimal lumen diameter, mm	2.01 ± 0.6	2.36 ± 0.6	<0.001
Stenosis, % of lumen diameter	25 ± 20	13 ± 17	<0.001
Binary restenosis	8 (9.5)	4 (4.7)	0.22
Mean/median late loss mm	0.14 ± 0.5/0.07 (−0.16 to 0.33)	0.04 ± 0.5/0.001 (−0.21 to 0.19)	0.14
Mean/median loss index	0.06 ± 0.6/0.07 (−0.14 to 0.33)	0.002 ± 0.4/0.001 (−0.15 to 0.14)	0.13
Net gain, mm	0.99 ± 0.6	1.41 ± 0.6	<0.001
Quantitative findings at follow-up, in lesion	(n = 84)	(n = 86)	
Reference vessel diameter, mm	2.70 ± 0.5	2.81 ± 0.5	0.18
Minimal lumen diameter, mm	2.03 ± 0.6	2.44 ± 0.6	<0.001
Stenosis, % of lumen diameter	24 ± 20	13 ± 15	<0.001
Binary restenosis	8 (9.5)	4 (4.7)	0.22

Values are n (%) or mean ± SD unless otherwise specified.
DEB = drug-eluting balloon(s); EES = everolimus-eluting stent(s); ISR = in-stent restenosis.

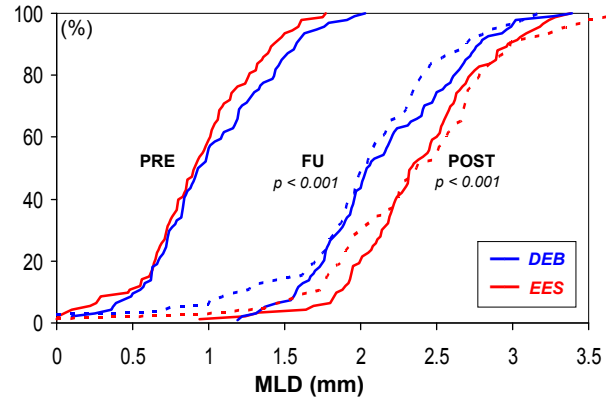

Figure 2 Cumulative Frequency Distribution Curves of Minimal Lumen Diameters

Minimal lumen diameters (MLDs) are shown before the procedure (PRE), after the intervention (POST), and at late follow-up (FU) **(dashed lines)**.

Discussion

This randomized clinical trial supports the value of DEB and EES in patients with BMS-ISR. Both therapeutic strategies were associated with excellent 1-year clinical outcomes. In particular, the appearance of clinical restenosis and the need for target vessel revascularization were very low and similar in the 2 groups. Furthermore, late angiographic findings were also excellent in the 2 arms, with single digit figures of binary angiographic restenosis and a very low angiographic late loss. However, late angiographic results were superior in the EES arm. Indeed, minimal lumen diameter (the primary endpoint of the study), the percent of diameter stenosis, and the net angiographic gain were significantly better in the EES arm. The consistency of these findings was supported by the uniform effect found across all pre-specified patient and lesion subsets.

The larger acute gain obtained after EES appears to explain the better late angiographic results achieved in this arm as late loss was very low and similar in both groups.

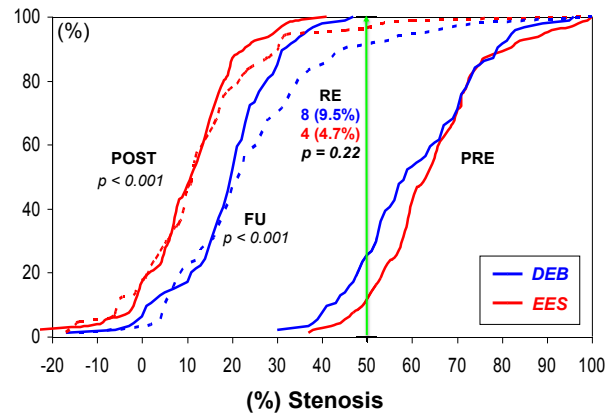

Figure 3 **Cumulative Frequency Distribution Curves of Diameter Stenosis**

Cumulative frequency distribution curves of the percentages of diameter stenosis before the procedure (PRE), after the intervention (POST), and at late follow-up (FU) **(dashed lines)** are shown. The intersection of the **green line** (50%) with the distribution curves at FU **(dashed lines)** determined the binary restenosis (RE) rates in both arms.

However, the superior late angiographic findings seen in the EES arm did not translate into improved long-term clinical outcomes compared with the DEB arm. This may be explained by the excellent late angiographic results also seen in the DEB arm. Patients treated with DEB obtained a lower acute gain but benefited from a uniquely small angiographic late loss during follow-up. Indeed only 9.5% of these patients developed angiographic restenosis, and only 6% required repeat revascularization at 1-year follow-up. These findings demonstrate that, from a clinical standpoint, both strategies are highly effective in this scenario.

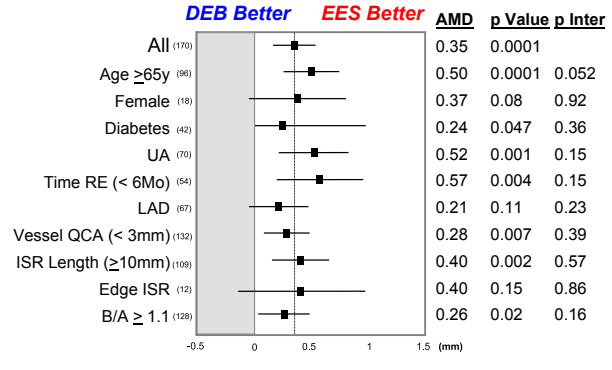

Figure 4 **Analysis of Absolute Difference of Minimal Lumen Diameter at Follow-Up in the 10 Pre-Specified Variables**

All interaction tests were negative (p Inter). AMD = absolute mean difference, mm; B/A = balloon/artery ratio; LAD = left anterior descending coronary artery; MLD = minimal lumen diameter; Mo = month; UA = unstable angina; other abbreviations as in Figure 1.

Our study was unable to find differences in the composite clinical outcome measure and was largely underpowered to detect differences in individual events, including repeat revascularization. Nevertheless, we cannot exclude the fact that the superior angiographic findings obtained with EES might eventually translate into a clear net clinical benefit. Classical studies of first-generation DES suggest that below a given late loss (<0.5 mm), this angiographic parameter is no longer predictive of the clinical need for target lesion revascularization during follow-up (23). It was suggested that these relatively large residual lumens were able to provide enough "room" to prevent any clinical consequences (23). However, subsequent larger studies and meta-analysis have demonstrated that even minor differences in late angiographic findings eventually translated into different clinical outcomes, driven mainly by repeated revascularization rates (24). In this regard, the trends toward a lower rate of target vessel and target lesion revascularization in the EES arm are of interest. Therefore, further studies, including larger series of patients or extended follow-up periods (powered to detect differences in individual clinical endpoints), are needed to examine this intriguing possibility.

Previous studies. A classical study (11) demonstrated that in patients with BMS-ISR, DEB were superior to balloon angioplasty alone. In that small but pivotal study, patients were randomly allocated to receive DEB (n = 26) or balloon angioplasty (n = 26). Late angiographic results were superior in the DEB arm (minimal lumen diameter: 2.22 ± 0.57 mm; late loss: 0.03 ± 0.48 mm), with no episodes of repeat revascularization at 1 year. Subsequently, another randomized trial compared DEB (n = 66) with paclitaxel-eluting DES (n = 65) in patients with BMS-ISR (12). At follow-up, DEB were able to reduce the late loss but provided a minimal lumen diameter (0.17 ± 0.42 mm and 2.03 ± 0.56 mm, respectively) similar to that of paclitaxel-eluting DES.

The value of DEB in patients with DES-ISR has also been established (13–16). A small single-center randomized study demonstrated that in patients with limus-DES-ISR, DEB were superior to balloon angioplasty (13). Subsequently, a multicenter randomized trial (14) confirmed the superiority of DEB compared with balloon angioplasty in patients with DES-ISR. The ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 3) multicenter randomized trial (15) investigated the efficacy of DEB, paclitaxel-eluting DES, and balloon angioplasty in patients with limus-eluting DES-ISR. A late loss of 0.37 mm was found in the DEB arm. The study demonstrated noninferiority of DEB compared with paclitaxel-eluting DES but also the superiority of these 2 strategies compared with balloon angioplasty (15). Finally, a recent randomized study suggested that DEB are more effective in patients with BMS-ISR than in those with DES-ISR (16). This would explain the larger late loss seen after DEB for DES-ISR in all previous studies (11–16).

Table 3 Major Adverse Clinical Events

	DEB (n = 95)	EES (n = 94)	p Value	RR/HR (95% CI)
Hospital events				RR (95% CI)
Death	0 (0)	0 (0)	1.00	—
Cardiac death	0 (0)	0 (0)	1.00	—
Myocardial infarction	0 (0)	4 (4)	0.06	—
Target lesion revascularization	0 (0)	0 (0)	1.00	—
Target vessel revascularization	0 (0)	0 (0)	1.00	
Coronary angioplasty	0 (0)	0 (0)	1.00	—
Coronary surgery	0 (0)	0 (0)	1.00	—
Composite MACE	0 (0)	4 (4)	0.06	—
Events at 9 months				HR (95% CI)
Death	3 (3)	0 (0)	0.38	—
Cardiac death	0 (0)	0 (0)	1.00	—
Myocardial infarction	2 (2)	4 (4)	0.41	2.06 (0.38–11.2)
Target lesion revascularization	4 (4)	0 (0)	0.31	—
Target vessel revascularization	4 (4)	1 (1)	0.21	0.25 (0.03–2.20)
Coronary angioplasty	4 (4)	1 (1)	0.21	0.25 (0.03–2.20)
Coronary surgery	0 (0)	0 (0)	1.00	—
Composite MACE	5 (5)	5 (5)	0.97	1.02 (0.30–3.53)
Events at 1 yr				
Death	4 (4)	0 (0)	0.31	—
Cardiac death	1 (1)	0 (0)	0.61	—
Myocardial infarction	3 (3)	4 (4)	0.68	1.37 (0.31–6.11)
Target lesion revascularization	6 (6)	1 (1)	0.09	0.16 (0.02–1.32)
Target vessel revascularization	6 (6)	2 (2)	0.17	0.32 (0.07–1.59)
Coronary angioplasty	6 (6)	2 (2)	0.17	0.32 (0.07–1.59)
Coronary surgery	0 (0)	0 (0)	1.00	—
Composite MAE	11 (12)	6 (6)	0.24	0.55 (0.20–1.49)
Composite MACE	8 (8)	6 (6)	0.60	0.76 (0.26–2.18)

Values are n (%) unless otherwise specified. Patients with more than 1 event were counted only once for the composite clinical endpoint, although each event was listed separately in the corresponding category. p values were obtained from Cox analysis.

CI = confidence interval; FU = follow-up; HR = hazard ratio (events at follow-up); MACE = major adverse cardiac events (cardiac death, myocardial infarction, target vessel revascularization); MAE = major adverse events (death, myocardial infarction, target vessel revascularization); RR = risk ratio (hospital events); other abbreviations as in Tables 1 and 2.

Together, the data from the available randomized clinical trials strongly suggest that DEB are superior to conventional balloon angioplasty and similar to first-generation DES in patients with BMS- or DES-ISR (11–16). Interestingly, in all of these studies, only a specific DEB, using iopromide as a hydrophilic spacer, was used (11–16). Likewise, only paclitaxel-eluting DES were used in the comparator arm (12,15). However, until now, whether new-generation DES are superior to DEB in patients with ISR remained unknown. Accordingly, the purpose of the current study was to compare DEB with a second-generation EES for the indication of BMS-ISR.

New insights on the treatment of in-stent restenosis. The use of second-generation DES in this setting appears particularly attractive (17–19). Many previous randomized studies and meta-analyses suggested that in "de novo" lesions, EES are not only more effective but also safer than first-generation DES (17–19). However, data supporting the value of the new DES in patients with ISR are scarce. In a previous prospective multicenter registry (8), we found that in patients presenting with DES-ISR, second-generation DES were more effective than first-generation DES. The use of EES in patients with ISR is highly appealing to ensure optimal acute results and subsequently benefit from their powerful antirestenosis properties (17–19). In this scenario, DEB are also very effective and therefore provide an attractive comparator (11–16). The present study represents the first controlled clinical trial comparing DEB versus EES in patients with BMS-ISR. Both strategies were associated with excellent and similar late clinical outcomes. However, our study demonstrated that EES are able to provide superior late angiographic findings. EES maximize acute lumen gain and minimize late loss, therefore providing uniquely favorable late angiographic results.

From a methodological perspective, some issues deserve further consideration. The classical endpoint of angiographic late loss is not appropriate for comparisons of strategies that provide different acute gains (i.e., balloons and stents), as the acute gain directly influences the late angiographic loss and clinical restenosis is best reflected by a variable that reflects both acute diameter increase and late injury response (2,4). The loss index provides some mechanistic insights as it takes into account the acute gain. However, we selected the minimal lumen diameter at follow-up as the primary endpoint for the efficacy analysis. This is a more clinical-oriented endpoint that in our study was closely related to

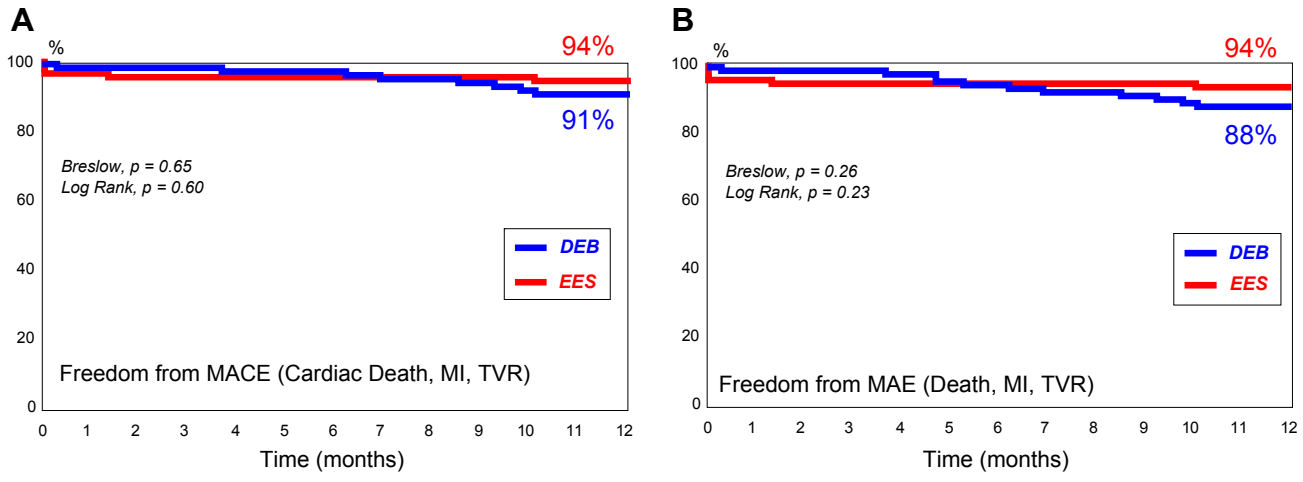

Figure 5 Kaplan-Meier Estimates of the Event-Free Survival

(A) Estimates are shown for freedom from major adverse cardiac events (MACE) (e.g., cardiac death, myocardial infarction [MI] and target vessel revascularization [TVR]). **(B)** Estimates are shown for freedom from major adverse events (MAE) (death, MI, TVR). DEB = drug-eluting balloon(s); EES = everolimus-eluting stent(s).

results of percentage of diameter stenosis at late follow-up. On the other hand, geographic miss may represent a problem with both DES and DEB (2,4,11,12). However, we did not observe significant edge-effects (similar results in the in-lesion and -segment analyses), probably due to our careful protocol aimed at preventing this phenomenon. Finally, our study was unable to find differences in the combined clinical endpoint, and it was largely underpowered to compare individual endpoints. However, some clinical signals merit further discussion. All 4 deaths occurred in the DEB arm, but 3 of them were noncardiac related. Likewise, the 4 procedure-related myocardial infarctions were seen in the EES arm, and 3 of them were related to a side-branch loss on angiography. Whether repeat stent implantation has a higher risk for this complication compared with DEB warrants additional studies, although this phenomenon was not detected in previous studies of repeat stenting (2,4). Finally, although the rates of target lesion revascularization were similar in both groups, there was a trend toward a lower rate of target lesion revascularization after EES. This signal is consistent with the differences in the late angiographic findings, but, considering the low number of events and the similar rates of angiographic restenosis, this should be interpreted with great caution and would require confirmation by additional studies.

An important finding of the current study was the excellent late angiographic results seen after DEB, in keeping with previous DEB studies in this setting (11–16). Indeed, the late loss after DEB (only 0.14 mm) was drastically reduced compared with the late loss found in the RIBS I (0.73 mm) (2) and II (0.69 mm) (4) studies that used conventional balloon angioplasty in patients with BMS-ISR. Therefore, for the first time (10), we have in our armamentarium 2 simple yet highly effective therapeutic modalities to offer to patients presenting with BMS-ISR. EES provide better late angiographic results but pay the price of a new metal layer (25). Alternatively, DEB obviate the need for an additional metal layer but result in inferior late angiographic findings compared with EES. We were unable to identify clinical or angiographic features that could be used to favor 1 of these therapies over the other in selected patients. However, it is clear that the better angiographic results provided by DES are particularly attractive in patients with ISR. Alternatively, in a real-world clinical setting, one may speculate that DEB may be preferred over EES in patients who already have multiple metal layers at the lesion site, in those with ISR encompassing large side branches, and in those who are at higher risk for bleeding complications from a prolonged dual antiplatelet regimen. Further studies will be required to identify patients more likely to benefit from each intervention.

Study limitations. First, studies with protocol-mandated late angiographic assessment may overestimate the rate of repeat revascularization. However, our study emphasized the need for a clinical indication before proceeding with any reintervention, and actually, repeat revascularization rates were very low. Second, our trial was not powered to detect differences in individual clinical endpoints (including revascularization) between the 2 groups. Larger studies with longer follow-up will be required to further establish the late clinical and angiographic outcomes with these therapeutic strategies. Third, although the value of intracoronary imaging (intravascular ultrasound or optical coherence tomography) has been suggested for use in patients with ISR, these tools were not systematically used in the present study. It remains possible, however, that aggressive procedural optimization

under intracoronary imaging may have improved the acute results of these interventions, particularly in the DEB arm. Fourth, we used only a particular DEB-releasing paclitaxel from an iopromide excipient. Accordingly, our findings might not be generalizable to other DEB as they may have variable efficacy. Finally, we did not include patients with DES-ISR. Previous studies have suggested that treatment of those patients is particularly challenging (16). Moreover, the results of second-generation DES in those patients remain to be determined. The currently ongoing RIBS IV trial (DEB vs. EES in patients with DES-ISR) will determine the relative efficacy of these therapeutic strategies in patients with DES-ISR.

Conclusions

This randomized clinical trial suggests that in patients with BMS-ISR, both DEB and EES provide excellent clinical results with a very low rate of clinical and angiographic recurrences. However, compared with DEB, EES provide superior late angiographic findings.

Reprint requests and correspondence: Dr. Fernando Alfonso, Departamento de Cardiología, Hospital Universitario de La Princesa, IIS-IP, Universidad Autónoma de Madrid, c/Diego de León 62. Madrid 28006, Madrid, Spain. E-mail: falf@hotmail.com.

REFERENCES

1. Díaz JF, de La Torre JM, Sabaté M, Goicolea J. Spanish Cardiac Catheterization and Coronary Intervention Registry. 21st official report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2011). Rev Esp Cardiol (Engl Ed) 2012;65:1106–16.
2. Alfonso F, Zueco J, Cequier A, et al. A randomized comparison of repeat stenting with balloon angioplasty in patients with restenosis after coronary stenting. J Am Coll Cardiol 2003;42:796–805.
3. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165–71.
4. Alfonso F, Pérez-Vizcayno MJ, Hernandez R, et al. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. J Am Coll Cardiol 2006;47:2152–60.
5. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. J Am Coll Cardiol 2010;55:2710–6.
6. Stone GW, Ellis SG, O'Shaughnessy CD, et al., TAXUS V ISR Investigators. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. JAMA 2006;295:1253–63.
7. Dibra A, Kastrati A, Alfonso F, Seyfarth M, Pérez-Vizcayno MJ, Mehilli J, Schömig A. Effectiveness of drug-eluting stents in patients with bare-metal in-stent restenosis: meta-analysis of randomized trials. J Am Coll Cardiol 2007;49:616–23.
8. Alfonso F, Pérez-Vizcayno MJ, Dutary J, et al. Implantation of a drug-eluting stent with a different drug (switch strategy) in patients with drug-eluting stent restenosis. Results from a prospective multicenter study (RIBS III [Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent]). J Am Coll Cardiol Intv 2012;5:728–37.
9. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol 2010;56:1897–907.
10. Alfonso F. Treatment of drug-eluting stent restenosis the new pilgrimage: quo vadis? J Am Coll Cardiol 2010;55:2717–20.
11. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med 2006;355:2113–24.
12. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation 2009;119:2986–94.
13. Habara S, Mitsudo K, Kadota K, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. J Am Coll Cardiol Intv 2011;4:149–54.
14. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol 2012;59:1377–82.
15. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet 2013;381:461–7.
16. Habara S, Iwabuchi M, Inoue N, et al. A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. Am Heart J 2013;166:527–33.
17. Alfonso F, Fernandez C. Second-generation drug-eluting stents. Moving the field forward. J Am Coll Cardiol 2011;58:26–9.
18. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393–402.
19. Bangalore S, Kumar S, Fusaro M, et al. Short and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873–91.
20. Cutlip DE, Windecker S, Mehran R, et al. Clinical end-points in coronary stent trials. A case for standardized definitions. Circulation 2007;115:2344–51.
21. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis. Classification and implications for long-term outcome. Circulation 1999;100:1872–8.
22. Alfonso F, Cequier A, Angel J, et al. Value of the American College of Cardiology/American Heart Association angiographic classification of coronary lesion morphology in patients with in-stent restenosis. Am Heart J 2006;151:681.e1–9.
23. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.
24. Schömig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1373–80.
25. Alfonso F, García J, Pérez-Vizcayno MJ, et al. New stent implantation for recurrences after stenting for in-stent restenosis: implications of a third metal layer in human coronary arteries. J Am Coll Cardiol 2009;54:1036–8.

Key Words: device thrombosis ■ drug-eluting balloon ■ everolimus-eluting stent ■ in-stent restenosis.

APPENDIX

For a list of participating physicians and institutions, please see the online version of this article.