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# Long-Term Results of Everolimus-Eluting Stents Versus Drug-Eluting Balloons in Patients With Bare-Metal In-Stent Restenosis

## 3-Year Follow-Up of the RIBS V Clinical Trial

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## ABSTRACT

**OBJECTIVES** The aim of this study was to compare the long-term efficacy of everolimus-eluting stents (EES) and drug-eluting balloons (DEB) in patients with bare-metal stent in-stent restenosis (ISR).

**BACKGROUND** The relative long-term clinical efficacy of current therapeutic modalities in patients with ISR remains unknown.

**METHODS** The 3-year clinical follow-up (pre-specified endpoint) of patients included in the RIBS V (Restenosis Intra-Stent of Bare-Metal Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent Implantation) randomized clinical trial was analyzed. All patients were followed yearly using a pre-defined structured questionnaire.

**RESULTS** A total of 189 patients with bare-metal stent ISR were allocated to either EES (n = 94) or DEB (n = 95). Clinical follow-up at 1, 2, and 3 years was obtained in all patients (100%). Compared with patients treated with DEB, those treated with EES obtained better angiographic results, including larger minimal luminal diameter at follow-up (primary study endpoint; 2.36 ± 0.6 mm vs. 2.01 ± 0.6 mm; $p < 0.001$). At 3 years, the rates of cardiac death (2% vs. 1%), myocardial infarction (4% vs. 5%) and target vessel revascularization (9% vs. 5%) were similar in the DEB and EES arms. Importantly, however, at 3 years, the rate of target lesion revascularization was significantly lower in the EES arm (2% vs. 8%; $p = 0.04$; hazard ratio: 0.23; 95% confidence interval: 0.06 to 0.93). The need for "late" (>1 year) target vessel (3 [3.2%] vs. 3 [3.2%]; $p = 0.95$) and target lesion (1 [1%] vs. 2 [2.1%]; $p = 0.54$) revascularization was low and similar in the 2 arms. Rates of definite or probable stent thrombosis (1% vs. 0%) were also similar in the 2 arms.

**CONCLUSIONS** The 3-year clinical follow-up of the RIBS V clinical trial confirms the sustained safety and efficacy of EES and DEB in patients treated for bare-metal stent ISR. In this setting, EES reduce the need for target lesion revascularization at very long-term follow-up. (RIBS V [Restenosis Intra-Stent of Bare Metal Stents: Paclitaxel-Eluting Balloon vs Everolimus-Eluting Stent] [RIBS V]; NCT01239953) (J Am Coll Cardiol Intv 2016;9:1246–55)


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Implantation of bare-metal stents (BMS) or drug-eluting stents (DES) represents the default strategy during coronary interventions (1,2). DES drastically inhibit neointimal proliferation, reducing restenosis risk and the need for reintervention, and currently are used in most patients undergoing coronary revascularization. However, BMS are still widely used, especially in patients with perceived high risk for bleeding and in those considered unable to maintain prolonged dual-antiplatelet therapy (1,2). In-stent restenosis (ISR) is frequently encountered in clinical practice after BMS implantation because of the increased neointimal proliferation elicited by these devices. In addition, DES may also develop ISR, especially when used in untoward clinical and anatomic settings (3,4). Accordingly, treatment of patients with ISR remains a significant clinical burden (3,4).

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The therapy of choice for patients presenting with ISR remains unsettled (3,4). Several clinical trials have demonstrated that DES represent an effective strategy for patients with either BMS ISR or DES ISR (5–9). Likewise, many randomized studies have demonstrated that drug-eluting balloons (DEB) are also highly effective in patients with BMS ISR or DES ISR (10–16). Notably, recent clinical practice guidelines suggest that these 2 therapeutic strategies (DES and DEB) currently represent the best available interventions (both with level of recommendation IA) for patients with ISR (17). In these patients, DEB are superior to classical therapeutic modalities and at least equivalent to first-generation DES (10–16). However, there is very little evidence on the relative efficacy of DEB versus "new-generation" DES in patients with ISR. This is of relevance, as new-generation DES have been demonstrated to be not only more effective but also safer than first-generation DES in different scenarios (18,19). The RIBS V (Restenosis Intra-Stent of Bare-Metal Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent) randomized clinical trial demonstrated that in patients with BMS ISR, the use of everolimus-eluting stents (EES) provided superior late angiographic results compared with DEB (20). However, the 1-year clinical outcomes were favorable and comparable in both arms (20). Alternatively, in patients with DES ISR, the RIBS IV randomized clinical trial recently demonstrated that EES provide not only significantly better long-term angiographic results but also improved 1-year clinical outcomes, driven mainly by a reduced need for repeat revascularization (21).

The long-term outcomes (>1 year) of second-generation DES in patients with ISR remain unknown. This is of importance because late recurrences may occur in these patients. In this pre-specified analysis of the RIBS V randomized clinical trial, we sought to assess the long-term (3-year follow-up) relative clinical efficacy and safety of EES versus DEB in patients with BMS ISR.

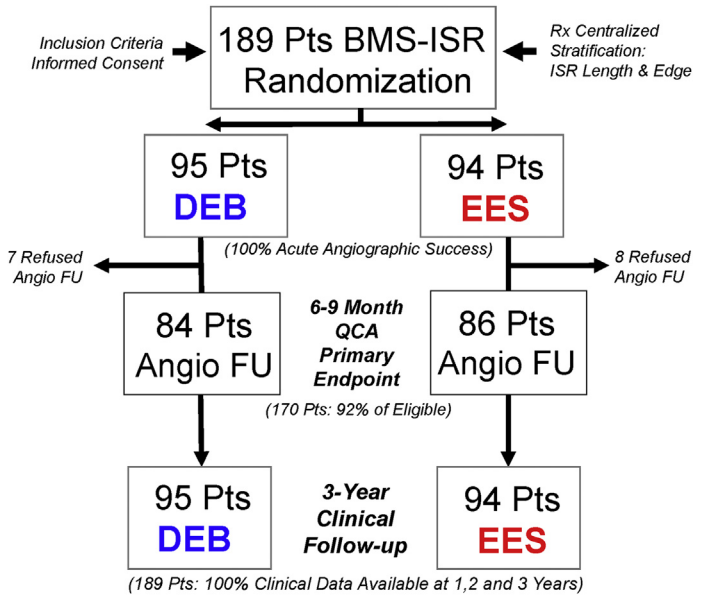
**ABBREVIATIONS AND ACRONYMS**

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

## METHODS

The RIBS-V study was a prospective, multicenter, controlled, open-label, randomized clinical trial that compared the results of DEB with those of EES in patients with BMS ISR (20) (Online Appendix). From January 2010 to January 2012, 189 patients with BMS ISR were randomly allocated to DEB (n = 95) or EES (n = 94) (20) (**Figure 1**). Inclusion and exclusion criteria have been previously described (20) and were largely similar to those used in previous RIBS trials (5,7,9). Patients with significant ISR (defined as >50% diameter stenosis on visual assessment) with angina or objective demonstration of ischemia (abnormal results on noninvasive tests or invasive fractional flow reserve <0.80) were eligible. Any type of BMS developing ISR was eligible. Patients with ISR in small vessels (≤2.0 mm in diameter), long lesions (>30 mm in length), or total occlusions (Thrombolysis In Myocardial Infarction flow grade 0) were not included (5,7,9,20). Likewise, patients with very early ISR (<1 month after initial stent implantation), those presenting clinically with acute myocardial infarction, and those showing large angiographic thrombi, within the stent or at its edges, were excluded. Nevertheless, patients with multiple interventions for ISR at the same site (including those undergoing restenting) could be included. Similarly, patients with edge ISR were eligible if the stent edge was clearly involved (if required, intracoronary imaging was recommended to identify edge involvement). Patients with allergies or contraindications to aspirin or clopidogrel were excluded. Patients with severe systemic diseases (hepatic and renal), those with life expectancy <1 year, and those with presumed difficulties complying with the scheduled late angiographic follow-up were not included. Written informed consent was obtained in all patients. Randomization was performed by directly calling to the coordinating center, where a computer-generated code was used. Randomization (1:1) was stratified according to ISR angiographic characteristics, determined by visual analysis at the sites

**FIGURE 1 Flow Diagram Illustrating Patients Allocated to Each Therapeutic Strategy, Those With 6- to 9-Month Angiographic Assessment, and Those With Final Clinical Evaluation (100%)**




Angio = angiographic; 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.

(length [≤ or >10 mm] and edge ISR [yes or no] [20,21]).

Data monitoring was organized by the coordinating center (Hospital Universitario Clínico San Carlos, Madrid, Spain) (20). The study was an investigator-driven initiative developed under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology. Unrestricted research grants from B. Braun Surgical and Abbott Vascular supported the study. Fundación Interhospitalaria de Investigación Cardiovascular was the research promoter. The study protocol was approved by the institutional ethics committees of the participating centers. The primary endpoint of RIBS V was the comparison of the in-segment minimal luminal diameter at late angiographic follow-up in the 2 arms (20).

**INTERVENTIONS.** Interventions were performed from the radial or femoral route as per local practice. All patients were pretreated with aspirin and clopidogrel. Unfractionated heparin (initial intravenous bolus 70 IU/kg) was used during the procedure (with additional intravenous boluses as required for prolonged procedures), targeting an activated clotting time >250 s. The importance of preforming adequate lesion pre-dilation using high-pressure dilations but, at the same time, trying to avoid any damage to the adjacent coronary segments was emphasized in the protocol. Importantly, extreme care was taken to tackle underexpanded stents using noncompliant balloons at very high pressures (20). Once adequate lesion pre-dilation was ensured, patients underwent the allocated intervention. The allocated intervention (DEB or EES) was targeted to cover the entire pre-treated segment to avoid "geographic miss" phenomena. Patients allocated to DEB (SeQuent Please, B. Braun Surgical, Melsungen, Germany) were dilated using a 1.1:1 balloon-to-artery ratio at nominal pressures (12 to 14 atm) for 60 s. When required because of ischemia or hemodynamic compromise, 2 sequential 30-s dilations, with the balloon located at the same site, were allowed. Crossover to bailout stenting was discouraged but was permitted in cases with dilation failure (>50% residual stenosis on visual estimation) or major (type C or worse) dissections. Patients allocated to EES (Xience Prime; Abbott Vascular, Abbott Park, Illinois) were treated selecting a 1.1:1 balloon-to-artery ratio and high (>14 bar) pressures. In this arm, pre-dilation was also required, and final post-dilation with noncompliant balloons was recommended, although left to the operator's discretion. Guidance by intracoronary imaging (optical coherence tomography or intravascular ultrasound) was suggested, but the use of intracoronary imaging was also left to the operator's criteria (20).

Serial (every 8 h) assessments of cardiac biomarkers and 12-lead electrocardiograms were systematically obtained. All patients were to take aspirin indefinitely and clopidogrel for 1 year after EES implantation and for 3 months after DEB implantation.

**FOLLOW-UP.** Late angiographic follow-up was scheduled at 6 to 9 months, but earlier evaluations were advised in patients with recurrent symptoms. Clinical follow-up was obtained at 6 to 9 months and subsequently at 1, 2, and 3 years. The assessment of clinical results at 3-year follow-up was a pre-defined clinical outcome measure. Source documents were obtained in all patients experiencing adverse events. Adverse clinical events were centrally adjudicated by an independent clinical events committee whose members were blinded to the assigned therapy. This committee carefully reviewed the anonymized source documents. All deaths were considered cardiac deaths unless noncardiac causes could be convincingly demonstrated. The diagnosis of myocardial infarction has remained unchanged in all

the RIBS trials (5,7,9,20,21) and included at least 2 of the following: 1) prolonged (>30 min) chest pain, 2) a rise in creatine-kinase level more than twice the local upper normal value (with abnormal MB fraction), and 3) the development of new and persisting ischemic electrocardiographic changes (with or without the appearance of new pathological Q waves). The protocol emphasized that all repeated interventions had to be clinically justified, and reasons for reintervention had to be declared in the case report forms. Angiograms of all patients requiring target vessel revascularization were carefully reviewed at the core laboratory to precisely identify the exact site of the reintervention. In all these cases, the corresponding images were subsequently forwarded to the clinical events committee to differentiate target lesion from target vessel revascularization. Stent thrombosis was analyzed and defined using the Academic Research Consortium criteria (22).

**ANGIOGRAPHIC ANALYSIS.** Coronary angiograms were analyzed in a central core laboratory by trained personnel blinded to the therapeutic strategy using a standard methodology (5,7,9,20,21). Lesion characteristics were assessed after the administration of intracoronary nitroglycerin using the Mehran (23) and the American College of Cardiology and American Heart Association (24) angiographic classifications. Three orthogonal angiographic views were selected to display the target segment, avoiding vessel foreshortening and side-branch overlap. These views were repeated immediately after intervention and at late angiographic follow-up. An automatic edge-detection quantitative angiographic system (CAAS II System, Pie Medical, Maastricht, the Netherlands) was used for analysis (20,21). Analyses included both the in-lesion and the in-segment (lesion + treated segment +5-mm margins on both sides) measurements.

**STATISTICAL ANALYSES.** Categorical variables are presented as percentages and were compared using the chi-square test or Fisher exact test according to the number of expected values. For continuous variables, data distribution normality was evaluated using the Kolmogorov-Smirnov test. Continuous data are presented as mean ± SD or as median (interquartile range) and were compared using the Student *t* test or the Mann-Whitney *U* test, as required. Kaplan-Meier curves were constructed to estimate the cumulative incidence of events at 1, 2, and 3 years and were compared using the log-rank and Breslow exact tests. Effect estimates (and 95% confidence intervals) for main outcome measures were calculated and are presented as risk ratios or hazard ratios determined using Cox proportional hazards models and compared using the Wald test. Interactions between treatment effects and 10 prespecified subset variables used as covariates were also analyzed using Cox proportional hazards models (5,7,9,20,21). The proportional hazards assumption was fulfilled in all cases. Analyses were performed using the intention-to-treat principle unless specified otherwise. SPSS version 15.00 (SPSS, Chicago, Illinois) was used. All p values are 2 sided, and a p value $<0.05$ was considered to indicate statistical significance.

## RESULTS

The 2 arms were well matched regarding baseline patient and lesion characteristics, although patients in the DEB arm were older and less frequently smokers (**Table 1**). Procedural characteristics were also similar, although higher dilation pressures tended to be used in the EES arm. Angiographic success was obtained in all patients. The main angiographic results are summarized in **Table 2**. Before the intervention, angiographic characteristics were comparable in the 2 groups, although lesions tended to be more severe in the EES group. However, after intervention, the EES group obtained a significantly larger acute luminal gain and final minimal luminal diameter and had lower residual stenosis. Late angiographic findings, including the study primary endpoint (in-segment minimal luminal diameter at follow-up) were also superior in the EES arm (**Table 2**) (20).

Clinical follow-up at 1, 2, and 3 years was obtained in all patients (100%), allowing a complete ascertainment of the main combined clinical endpoint (**Figure 1**). All major adverse clinical events are summarized in **Table 3**. Cardiac mortality was similar in both groups, although total mortality was numerically higher (difference not significant) in the DEB group. The main clinical outcome measure (a composite of cardiac death, myocardial infarction, and target vessel revascularization) was similar in the 2 arms (**Table 3**, **Figures 2A and 2B**). However, at 3-year follow-up, there was a numerically lower rate of the combined clinical endpoint of all-cause death, myocardial infarction, and target lesion revascularization in the EES arm, but the difference was not statistically significant (**Figure 2C**). The number of adverse events after the first year was small and similar in both groups (**Table 3**). In particular, the

**TABLE 1 Baseline 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/silent ischemia | 57 (60) | 52 (55) | |
| >1 intervention on target lesion | 6 (6) | 2 (2) | 0.28 |
| Time to restenosis (day) | 390 (142–2,815) | 350 (151–2,679) | 0.78 |
| Ejection fraction (%) | 58 ± 13 | 59 ± 12 | 0.71 |
| Target artery | | | 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 | | | |
| Maximal pressure (atm) | 18 ± 4 | 19 ± 3 | 0.08 |
| Balloon-to-artery ratio | 1.25 ± 0.2 | 1.23 ± 0.2 | 0.52 |
| Crossover | 8 (8) | 0 (0) | 0.007 |
| Angiographic success | 95 (100) | 94 (100) | 1 |

Values are mean ± SD, n (%), or median (interquartile range).
DEB = drug-eluting balloon(s); EES = everolimus-eluting stent(s).

**TABLE 2 Angiographic Results at 6- to 9-Month Follow-Up**

| | 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 |
| Type B2 or C lesion | 48 (51) | 51 (54) | 0.61 |
| Quantitative findings | | | |
| Before the procedure | (n = 95) | (n = 94) | |
| Reference vessel diameter (mm) | 2.64 ± 0.6 | 2.64 ± 0.6 | 0.96 |
| Minimal luminal diameter (mm) | 1.02 ± 0.4 | 0.93 ± 0.4 | 0.12 |
| Stenosis (% of luminal diameter) | 61 ± 14 | 65 ± 13 | 0.05 |
| Lesion length (mm) | 13.7 ± 7 | 13.8 ± 6 | 0.96 |
| After the procedure (in segment) | (n = 95) | (n = 94) | |
| Reference vessel diameter (mm) | 2.69 ± 0.6 | 2.68 ± 0.5 | 0.94 |
| Minimal luminal diameter (mm) | 2.16 ± 0.5 | 2.38 ± 0.5 | 0.001 |
| Stenosis (% of luminal diameter) | 19 ± 11 | 11 ± 11 | <0.001 |
| At follow-up (in segment) | (n = 84) | (n = 86) | |
| Reference vessel diameter (mm) | 2.70 ± 0.5 | 2.73 ± 0.5 | 0.60 |
| Minimal luminal diameter (mm) | 2.01 ± 0.6 | 2.36 ± 0.6 | <0.001 |
| Stenosis (% of luminal diameter) | 25 ± 20 | 13 ± 17 | <0.001 |
| Restenosis | 8 (9.5) | 4 (4.7) | 0.22 |
| 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 |

Values are n (%), mean ± SD, or mean ± SD/median (interquartile range).
IQR = interquartile range; other abbreviations as in Table 1.

rates of "late" target vessel revascularization (3 [3.2%] vs. 3 [3.2%]; p = 0.95) and of "late" target lesion revascularization (1 [1%] vs. 2 [2.1%]; p = 0.54) were comparable in both arms. The rate of target vessel revascularization was also numerically lower in the EES group (Figure 3A). Notably, at 3-year follow-up, a statistically significant reduction in the rate of target lesion revascularization was found in the EES arm (2% vs. 8%; p = 0.04; hazard ratio: 0.23; 95% confidence interval: 0.06 to 0.93) (Table 3, Figure 3B). Results of the main combined clinical outcome measure and of target vessel and target lesion revascularization were consistent across prespecified subgroups, without any significant interaction detected after formal testing. Finally, results were consistent in the "as-treated analysis," with a significant reduction in the need for target lesion revascularization in favor of EES arm (Online Appendix, Online Figure 4).

At 3 years, most patients (90% in the DEB group vs. 89% in the EES group, p = NS) were on aspirin, and a small number of patients were on dual-antiplatelet therapy (19% in the DEB group and 27% in the EES group, p = 0.12). The rate of major bleeding was low and similar in both groups (at 1 year, 2 episodes in the DEB group and 1 in the EES group; after the first year, 2 additional bleeding episodes occurred in the EES arm). No episodes of very late stent thrombosis occurred in any group.

## DISCUSSION

This is the first study comparing the very long-term results obtained with DEB and EES in patients with ISR. Our findings suggest that in patients with BMS ISR, both strategies are safe and effective at 3-year clinical follow-up. Indeed, episodes of target lesion and target vessel revascularization were very low and comparable in both groups. In the landmark analyses, the rates of late (>1 year) target vessel and target lesion revascularization were also low and similar in the 2 arms. The sustained clinical efficacy of these therapeutic modalities strongly argues against the presence of a late catch-up phenomenon. Overall, there was a nonsignificant lower need for target vessel revascularization in the EES arm. Importantly, however, at late follow-up, there was a significant reduction in the need for target lesion revascularization in the EES arm. This clinical benefit appears to be mainly a result of the superior late angiographic results obtained in the EES arm. Regarding safety, both therapies proved to be safe at 3 years, with absence of episodes of stent thrombosis after the first year.

**PREVIOUS STUDIES ASSESSING LONG-TERM CLINICAL OUTCOMES IN PATIENTS WITH ISR.** There are few studies assessing the late clinical results of patients with ISR treated with modern therapeutic modalities. Specifically, scarce information exists on the long-term value of DEB in these patients. Scheller et al. (25) reported the very long-term clinical follow-up of a pivotal randomized study comparing DEB with balloon angioplasty in patients with BMS ISR. Patients allocated to DEB maintained a sustained clinical benefit at 5.4 ± 1.2 years of follow-up. Notably, the DEB group obtained a significant reduction in major adverse cardiovascular events (59.3% vs. 27.8%), driven mainly by a significant reduction in target lesion revascularization (from 38.9% to 9.3%). Beyond the first year, 3 patients in the DEB group and 1 in the conventional balloon group required target lesion revascularization. No episodes of very late stent thrombosis were documented (25). Kufner et al. (26) reported 3-year clinical follow-up of the ISAR-DESIRE-III (Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches) trial. In that study, 402 patients with limus-eluting stent ISR were randomly allocated to DEB, paclitaxel-eluting stents, or conventional balloon angioplasty. At late follow-up, the risk for target lesion revascularization was comparable with DEB versus paclitaxel-eluting stents but significantly lower with DEB than with balloon angioplasty. In addition, the rates of late (>1 year) target lesion revascularization was 14.5%, 12.4%, and 13.4% and those of "clinically indicated" late target lesion revascularization 12%, 8.2%, and 5.1% for the DEB, paclitaxel-eluting stent, and balloon angioplasty groups, respectively (all differences not significant). Interestingly, the risk for death or myocardial infarction was numerically lower with DEB versus paclitaxel-eluting stents, driven mainly by significantly lower risk for death. The 2-year follow-up of the PEPCAD China (A Safety and Efficacy Study of Paclitaxel-Eluting Balloon to Paclitaxel-Eluting Stent) randomized trial (220 patients with DES ISR randomized to DEB or paclitaxel-eluting stents) was recently reported (27). Clinical and angiographic results at 1 year were similar in both arms. No adverse ischemic events occurred between 1 and 2 years in the DEB group except for 1 episode of non-target vessel revascularization. Notably, at 2 years, the rate of all-cause death was statistically lower in the DEB group compared with the paclitaxel-eluting stent group (0% vs. 4.9%; $p < 0.03$) (27). Likewise, the 3-year follow-up of the PEPCAD-DES randomized study in patients with DES ISR demonstrated significantly lower rates of target lesion revascularization (19.4% vs. 36.8%) and major cardiac events (20.8% vs. 52.6%) in the DEB group compared with the conventional balloon group (28). Finally, the 3-year results of the PEPCAD-II ISR study have been recently reported (29). In this study, 131 patients with BMS ISR were randomly allocated to either paclitaxel-eluting stents or DEB, with similar clinical results at 1 year. From 12 to 36 months, only 1 DEB patient (1.5%) experienced a myocardial infarction, while neither target lesion revascularization nor death occurred in any patient (29). Altogether, information from these previous controlled studies (25-29) strongly argues against the presence

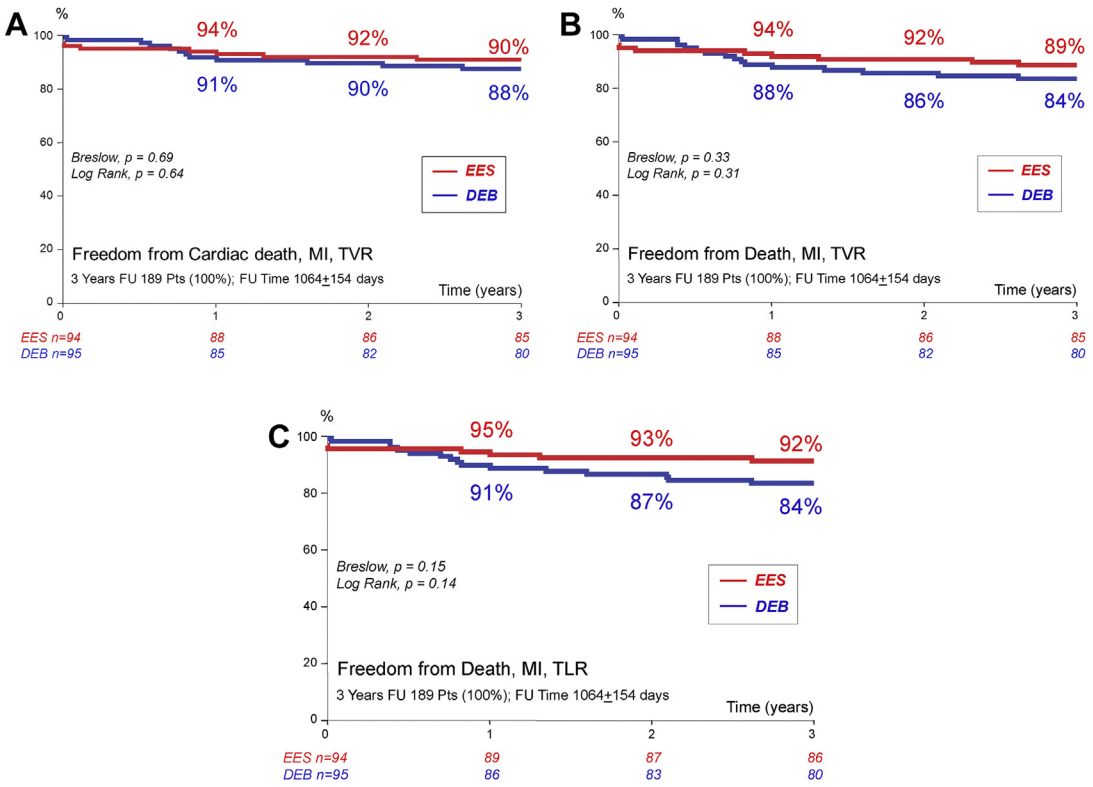
**TABLE 3 Major Adverse Clinical Events**

| Event | DEB (n = 95) | EES (n = 94) | p Value | HR (95% CI) |
|---|---|---|---|---|
| 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 | – |
| 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) |
| Definite/probable stent thrombosis | 1 (1) | 0 (0) | 0.61 | – |
| Events at 2 yrs | | | | |
| Death | 6 (6) | 1 (1) | 0.04 | 0.16 (0.02-0.98) |
| Cardiac death | 2 (2) | 1 (1) | 0.54 | 0.49 (0.04-5.36) |
| Myocardial infarction | 4 (4) | 5 (5) | 0.72 | 1.27 (0.34-4.74) |
| Target lesion revascularization | 6 (6) | 2 (2) | 0.13 | 0.32 (0.06-1.56) |
| Target vessel revascularization | 7 (7) | 3 (3) | 0.17 | 0.41 (0.11-1.58) |
| Coronary angioplasty | 6 (6) | 3 (3) | 0.28 | 0.48 (0.12-1.92) |
| Coronary surgery | 1 (1) | 0 (0) | 0.61 | – |
| Composite MAE | 13 (14) | 8 (8) | 0.28 | 0.62 (0.26-1.49) |
| Composite MACE | 9 (10) | 8 (8) | 0.81 | 0.88 (0.34-2.30) |
| Definite/probable stent thrombosis | 1 (1) | 0 (0) | 0.61 | – |
| Events at 3 yrs | | | | |
| Death | 7 (7) | 2 (2) | 0.08 | 0.28 (0.06-1.34) |
| Cardiac death | 2 (2) | 1 (1) | 0.54 | 0.49 (0.04-5.36) |
| Myocardial infarction | 4 (4) | 5 (5) | 0.72 | 1.27 (0.34-4.74) |
| Target lesion revascularization | 8 (8) | 2 (2) | 0.04 | 0.23 (0.06-0.93) |
| Target vessel revascularization | 9 (9) | 5 (5) | 0.24 | 0.52 (0.18-1.56) |
| Coronary angioplasty | 8 (8) | 5 (5) | 0.35 | 0.59 (0.19-1.81) |
| Coronary surgery | 1 (1) | 0 (0) | 0.61 | – |
| Composite MAE | 15 (16) | 10 (11) | 0.31 | 0.66 (0.30-1.48) |
| Composite MACE | 11 (12) | 9 (10) | 0.64 | 0.81 (0.34-1.96) |
| Definite/probable stent thrombosis | 1 (1) | 0 (0) | 0.61 | – |

Values are n (%). Patients with more than 1 event were counted only once for the composite clinical endpoint, although each event is listed separately in the corresponding category. P values from bootstrap Cox analysis.

CI = confidence interval; HR = hazard ratio (events at follow-up); MACE = major adverse cardiac event (cardiac death, myocardial infarction, target vessel revascularization); MAE = major adverse event (death, myocardial infarction, target vessel revascularization); other abbreviations as in Table 1.

**FIGURE 2 Freedom From Events**



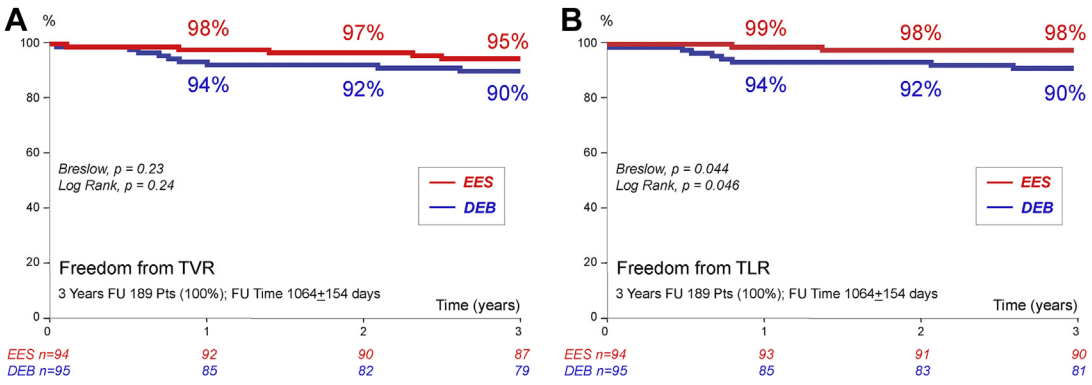

**(A)** Freedom from major adverse cardiac events (MACE) (cardiac death, myocardial infarction [MI], and target vessel revascularization [TVR]) at 3 years. **(B)** Freedom from death, MI, and TVR. **(C)** Freedom from death, MI, and target lesion revascularization (TLR). DEB = drug-eluting balloon(s); EES = everolimus-eluting stent(s); FU = follow-up.

of a significant late catch-up phenomenon in patients treated with DEB for either BMS ISR or DES ISR.

Conversely, in a recent large observational study, Habara et al. (30) suggested that the occurrence of "late ISR" was significantly higher in patients treated with DEB for DES ISR. In that study, which included 468 patients treated for ISR, 2 sequential late angiographic follow-up studies (at 6 and 18 months after the procedure) were routinely scheduled. Late ISR was defined as the appearance of ISR at 18 months in patients without ISR at 6-month angiographic follow-up. Late ISR was found in only 2 lesions (2.5%) treated with DEB for BMS ISR, whereas this phenomenon occurred in 50 lesions (16.8%) treated with DEB for DES ISR. Likewise, delayed (from 6 to 18 months) late luminal loss was significantly larger in the DES ISR group. Eventually, these findings translated into a higher need for target lesion revascularization after DEB implantation in patients with DES ISR, not only at 6 months but also later on (30).

**IMPLICATIONS OF THE PRESENT STUDY.** To the best of our knowledge, no previous study has assessed the long-term (>1-year) results of EES in patients with ISR. Assessing the long-term performance of currently competing interventions (namely, DEB and new-generation DES) is critical to establish their comparative efficacy. Our findings suggest that patients with BMS ISR treated with modern therapeutic strategies have favorable clinical outcomes and that clinical events after the first year are rare. The durability of effects suggest the stability of the treated lesions. Close clinical surveillance was obtained by protocol in all patients included in this prospective controlled study, thus excluding the possibility of undertreatment in patients with recurrent symptoms. Therefore, our findings confirm the absence of a late

**FIGURE 3** Freedom From Revascularization




**(A)** Freedom from target vessel revascularization (TVR). **(B)** Freedom from target lesion revascularization (TLR). DEB = drug-eluting balloon(s); EES = everolimus-eluting stent(s); FU = follow-up.

catch-up phenomenon in patients with BMS ISR treated with DEB. Whether this remains a significant clinical problem in patients treated with DEB for DES ISR warrants prospective assessment. In this regard, the very late clinical follow-up of patients with DES ISR included in the RIBS IV trial (currently ongoing) will shed additional light on this issue.

Importantly, although the long-term clinical outcomes obtained with both strategies in patients with BMS ISR were favorable, a significant reduction in the rate of target lesion revascularization was demonstrated at late follow-up in patients treated with EES compared with those allocated to DEB. This novel information should be considered in the clinical decision-making process involved in the treatment of these challenging patients.

**STUDY LIMITATIONS.** Only a specific paclitaxel DEB was used in this study, so its results may not be extrapolated to other DEB. This is of relevance because the antirestenotic efficacy of DEB appears to be related, at least in part, to the coating selected (iopromide, urea, shellac), as suggested by preclinical and clinical observations (31). Likewise, only EES were used in this study. Whether similar results can be obtained with other new-generation DES remains to be established. Despite randomization, there were some imbalances in the baseline characteristics. In addition, most patients included in this study had relatively small vessels. It remains possible that the results of these interventions would be more favorable in patients with larger vessels. Moreover, the protocol-mandated late angiographic surveillance could inflate the rate of revascularization beyond that seen in routine clinical care. Likewise, the different duration of the mandated dual-antiplatelet regimen remains a potential confounder in the comparison of clinical results. Finally, although the analysis of clinical follow-up at 3 years was prespecified, our study had a relatively small sample size and was not powered for individual clinical events. This could explain why only numerically lower rates (differences not statistically significant) of target vessel revascularization and the combined clinical outcome measures were found in the EES arm. Along the same lines, the significant reduction in target lesion revascularization seen at late follow-up with the use of EES should be confirmed in larger studies.

## CONCLUSIONS

The long-term clinical follow-up of this randomized clinical study demonstrates the sustained clinical efficacy and safety of EES and DEB in patients with BMS ISR. In this setting, however, the use of EES is associated with a significant reduction of target lesion revascularization at 3-year clinical follow-up.

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## PERSPECTIVES

**WHAT IS KNOWN?** EES and DEB are well-accepted interventional strategies in patients with BMS ISR. However, the long-term relative safety and efficacy of these interventions in this setting remain unknown.

**WHAT IS NEW?** At 3-year follow-up, both EES and DEB provide excellent similar clinical results, although EES reduced the rate of target lesion revascularization.

**WHAT IS NEXT?** Larger studies with longer clinical follow-up are still required to assess potential differences between these interventions in patients with BMS ISR. Additional studies are warranted in patients with DES ISR.

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**KEY WORDS** drug-eluting balloon(s), drug-eluting stent(s), everolimus-eluting stent(s), in-stent restenosis

**APPENDIX** For a supplemental figure and its legend and a list of RIBS V study investigators, coordinators, and sites, please see the online version of this article.