JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 12, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.03.037

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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Manuscript received March 22, 2016; accepted March 24, 2016.

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