RIBS IV: EES Superior to Paclitaxel-Eluting Balloon for Treating DES Restenosis

Written by Maria Vinall

Treatment of drug-eluting stent in-stent restenosis (DES-ISR) is challenging. Results from the Restenosis Intra-Stent of Drug-Eluting Stents: Paclitaxel-Eluting Balloon vs Everolimus-Eluting Stent trial [RIBS IV; NCT01239940], presented by Fernando Alfonso, MD, PhD, Hospital Universitario "La Princesa," Madrid, Spain, indicate that DES provide superior late angiographic clinical outcomes compared with drug-eluting balloons (DEBs).

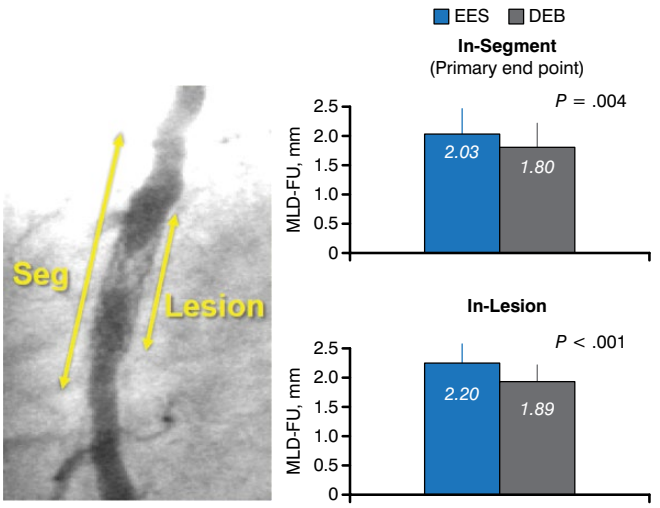
The objective of this multicenter (23 sites in Spain), prospective, randomized phase 4 study was to compare the efficacy of a paclitaxel DEB with an everolimus-eluting stent (EES) in patients with DES-ISR. The study included patients (n = 309; mean age, 66 years) with DES-ISR > 50% stenosis, angina or silent ischemia, and ISR suitable for conventional balloon angioplasty and stenting were randomized to EES (n = 155) or DEB (n = 154). Patients with an undefined stent location, ISR < 1 month, vessel diameter < 2 mm, ISR length > 30 mm, or ISR outside the stent were excluded. The primary end point was minimal lumen diameter (MLD) at late angiographic follow up (6-9 months) based on quantitative coronary angiography. Secondary outcome measures were a composite of clinical (including cardiac death, myocardial infarction [MI], and revascularization), and angiographic (eg, percentage of diameter stenosis, angiographic late lumen loss, and binary restenosis) end points at 6 to 9 months and 1 and 3 years. The design of this study has been published [Alfonso F et al. *EuroIntervention.* 2014].

Approximately 49% of participants had a history of MI and 11% had prior bypass surgery. Unstable angina was present in 52% of subjects; stable angina in 48%. Mean left ventricular ejection fraction (LVEF) was 58%. The mean number of diseased vessels was 1.65 with the most common (48%) target vessel being the left anterior descending coronary artery. Mean length of initial stent was 21 ± 7 mm and maximal pressure was 16 ± 3 atm. Mean time to ISR was 547 days.

At 9 months, in-segment MLD was larger with EES compared with DEB (2.03 vs 1.80, respectively; $P = .004$). In-lesion MLD was also larger (2.20 vs 1.89 EES and DEB, respectively; $P < .001$; Figure 1) as were the cumulative frequency distribution curves for in-segment MLD ($P = .004$ at 9 months; $P = .04$ post procedure). Further analysis of MLD using 10 prespecified clinical and angiographic variables revealed consistent results favoring EES. Trends favored EES for both binary restenosis and late lumen loss.

After 1 year, subjects receiving an EES had higher rates of freedom from target lesion revascularization (96% vs 87%; $P = .008$) and freedom from major adverse coronary events, including cardiac death, MI, and target vessel revascularization (90% vs 82%; $P = .044$; Figure 2). There were 1 definite, 1 probable, and 2 possible thromboses in the EES arm and 2 definitive, 1 probable, and 1 possible thrombosis in the DEB arm. Five patients in the DEB group crossed over to stenting.

Figure 1. In-Segment and In-Lesion MLD Larger With EES Compared With DEB



DEB, drug-eluting balloon; EES, everolimus-eluting stent.
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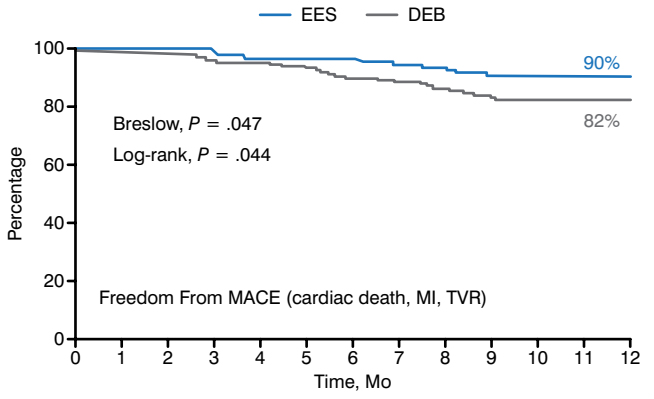
Figure 2. MACE Outcomes at 1 Year in EES and DEB Groups



DEB, drug-eluting balloon; EES, everolimus-eluting stent, MACE, major cardiac adverse events.
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In this first randomized trial of EES vs DEB in patients with DES-ISR, EES provided superior late angiographic results than DEB. In these patients EES also provided better late clinical results, driven by a significant reduction in the rate of target vessel revascularization. Further studies with more patients and longer follow-up are warranted in this setting.

Low 2-Year All-Cause Mortality and Major Stroke Rates After CoreValve Implantation

Written by Toni Rizzo

The Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High-Risk and Very High-Risk Subjects Who Need Aortic Valve Replacement [CoreValve; NCT01240902] evaluated transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. Extreme-risk patients were randomized to CoreValve implantation by iliofemoral (n = 489) or noniliofemoral (n = 150) access [Popma JJ et al. *J Am Coll Cardiol*. 2014]. At 1 year, the primary end point of all-cause mortality or major stroke rate was 26.0% (95% CI, 22.1% to 29.9%) compared with the objective performance goal (OPG) of 43.0% ($P < .0001$).

Steven J. Yakubov, MD, Riverside Methodist Hospital Columbus, Ohio, USA, presented the 2-year results of the CoreValve trial. At 2 years, 305 patients who received an implant by iliofemoral access remained in the study. The primary analysis cohort consisted of the "attempted implant" by iliofemoral access population (n = 489). The attempted implant population was defined as patients brought into the procedure room with anesthesia administration, transesophageal echocardiography, vascular line placement, or any other monitoring line placement. The OPG comparator for all-cause mortality was the calculated rate for 117 events in 179 patients (65.4%, lower confidence bound of 57.9% by Exact method).

The rate of all-cause mortality or major stroke (at risk n = 489) at 2 years was 38.0% (95% CI, 33.6% to 42.3%) vs the OPG of 57.9%.

All-cause mortality and cardiovascular mortality at 1 year were 24.3% and 18.3%, respectively, and at 2 years were 36.5% and 26.5%, respectively. All-cause mortality and cardiovascular mortality from 1 to 2 years were 16.1% and 10.0%. The 1-year, 2-year, and 1- to 2-year major stroke rates were 4.3%, 5.1%, and 0.9%, respectively.

Table 1. Secondary End Points at 1 and 2 Years

Events, %[a]	1 Year	2 Years
Any stroke	7.0	8.7
Major	4.3	5.1
Minor	3.2	4.1
Myocardial infarction	2.0	2.8
Reintervention	1.8	1.8
VARC bleeding	42.8	45.3
Life-threatening or disabling	18.0	20.8
Major	28.3	29.1
Major vascular complications	8.4	8.4
Permanent pacemaker implant	26.4	28.9
Per ACC guidelines	19.5	22.0

ACC, American College of Cardiology; VARC, Valve Academic Research Consortium.
[a]Percentages obtained from Kaplan-Meier estimates.

The secondary end point rates are shown in Table 1.

At 2 years, 92% of patients improved at least 1 NYHA class and 58% improved at least 2 NYHA classes. The effective orifice area increased from 0.73 cm^2 at baseline to 1.85 cm^2 at 2 years. The mean gradient decreased from 47.31 mm Hg at baseline to 8.66 mm Hg at 2 years. At 2 years, paravalvular regurgitation was absent or trivial in 64.8%, mild in 30.8%, moderate in 4.4%, and severe in 0.0% of patients.

Among patients with all-cause mortality, paravalvular leak (PVL) was absent or trivial in 30.3%, mild in 38.2%, moderate in 35.9%, and severe in 85.7%. Only severe PVL affected mortality ($P < .001$). Among patients with all-cause mortality, 38.7% had received a new pacemaker and 35% had not received a new pacemaker. Pacemaker implantation did not affect mortality ($P = .534$). A subgroup analysis showed that a Society of Thoracic Surgeons (STS) risk score > 15% ($P = .0120$), coronary artery disease (CAD; $P = .0019$), and assisted living ($P < .0001$) were associated with 2-year all-cause mortality or major stroke.

The CoreValve 2-year results demonstrated low rates of all-cause mortality, major stroke, and moderate or severe aortic insufficiency. Patients experienced improvement in NYHA classification and durable improvement in hemodynamic valve performance. There was no association between mild or moderate paravalvular regurgitation and mortality. The 2-year results confirm the improved survival benefit in patients with severe aortic stenosis at extreme risk for surgery.