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Randomized Comparison of Cost-Saving and Effectiveness of Oral Rapamycin Plus Bare-Metal Stents With Drug-Eluting Stents: Three-Year Outcome From the Randomized Oral Rapamycin in Argentina (ORAR) III Trial

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Objectives: The Oral Rapamycin in ARgentina (ORAR) III trial is a randomized study comparing a strategy of oral rapamycin (OR) plus bare-metal stent (BMS) versus a strategy of drug-eluting stents (DES) in patients with de novo coronary lesions. The purpose of this study was to assess the 3 years cost-effectiveness outcome of each strategy. Background: OR after BMS has been associated with reduction of target vessel revascularization (TVR) although its value in long-term efficacy in comparison with DES is unknown. Methods: In three hospitals in Buenos Aires, Argentina, 200 patients were randomized to OR plus BMS (n = 100) or DES (n = 100). Primary objectives were costs and effectiveness. Cost analysis included in-hospital and follow-up costs. Safety was defined as the composite of death, myocardial infarction (MI), and stroke. Efficacy was defined as TVR. Results: Baseline characteristics between groups were similar. The 3-year follow-up rate was 99%. Cardiac mortality was 2% and 5% in OR group and DES group, respectively (P = 0.44). The composite of death, MI and stroke rate was 11% in OR group and 20% in DES group (P = 0.078). TVR rate was 14.5% in OR group and 17.6% in DES group (P = 0.50), respectively. Three year cumulative costs were significantly lower in the OR arm as compared to the DES arm (P = 0.0001) and DES strategy did not result cost-effective according to the non-inferiority test. Conclusions: At 3 years follow-up, there were no differences in effectiveness between the two strategies, and DES strategy was not more cost-effective as compared to OR plus BMS.

Key words: restenosis; percutaneous coronary interventions; drug delivery; thrombosis; complications

INTRODUCTION

In the last years, drug-eluting stents (DES) have become the standard procedure to reduce restenosis and improve clinical outcome after percutaneous coronary interventions (PCI) [1–5]. Simultaneously with the introduction of DES, a strategy of systemic immunosuppressive therapy in conjunction with bare-metal stents (BMS) was tested in clinical studies to reduce restenosis and improve outcome. Oral administration of rapamycin and prednisone after PCI with BMS

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implantation were reported in observational and randomized studies [6–12].

The Oral Rapamycin in Argentina (ORAR) III trial is a randomized trial that aimed to assess the cost-effectiveness of oral rapamycin (OR) plus BMS versus DES in patients with de novo coronary lesions [13]. Here, we report the 3-year outcome and the cost analysis of the study.

METHODS

Study Design

From January 2006 to September 2007, patients undergoing coronary stent implantation at the catheterization laboratories of three centers in Buenos Aires, Argentina (Sanatorio Otamendi, Las Lomas, and Clinica IMA) were evaluated and those who met the study clinical inclusion criteria were asked to consent to the study.

The study design and the 1-year follow-up results were previously described [13].

Patients were eligible for the study if they had a de novo $>$ 70% stenosis in a coronary vessel with a reference diameter $\geq$ 2.5 mm on visual assessment. Patients with acute myocardial infarction, in-stent restenosis, previous PCI in the last 6 months, chronic total occlusion of the target vessel, rapamycin allergy, clopidogrel or aspirin intolerance, significant bleeding in the last 6 months, stroke or transient ischemic attack in the last 12 months, major blood dyscrasia including thrombocytopenia, poorly controlled dyslipidemia, short life expectancy, or infectious diseases were excluded from the study (Fig. 1).

The protocol of the study was approved by the Ethics Committee of the participating centers and by the Argentinean National Regulatory Agency for Drug, Food and Medical Technology (ANMAT). The study was monitored by an Independent Safety Clinical Events Committee whose members were blinded to the patient's assigned treatment group. The study was conducted according to the principles of the Declaration of Helsinki and all patients signed a written informed consent for participation in this trial.

The trial was registered in ClinicalTrials.gov Registry (NCT00552669).

Medication and Coronary Procedures

In the OR arm, patients received a sirolimus-loading dose of 10 mg the day before stent implantation followed by 3 mg per day for a total of 14 days. During the first 14 days, 180 mg a day of diltiazem sustained release were added to the sirolimus regimen to achieve higher sirolimus blood concentrations [9,10]; beta-blockers were withdrawn during this period. The administration of sirolimus and diltiazem was stopped simultaneously. All patients received 325 mg a day of aspirin indefinitely. OR patients received clopidogrel 75 mg a day for 1 month, and DES patients for at least 1 year. Statins were given to all patients indefinitely.

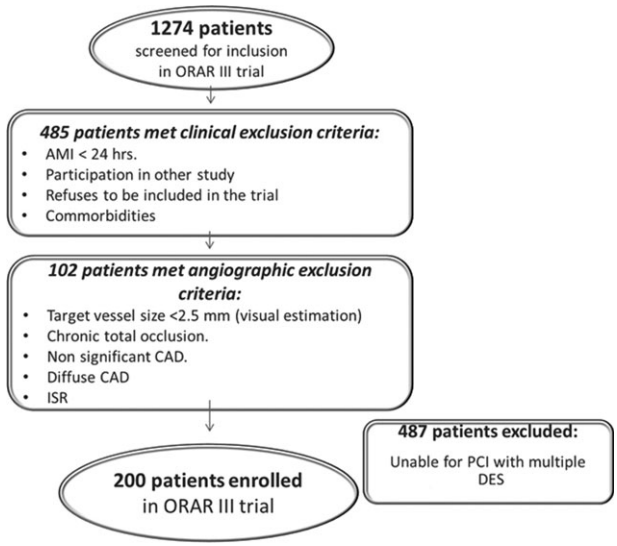

Fig. 1. Study design and patient recruitment.

After the first year, a clinical interview was required with intervals of 6 months. The interviews were conducted by trained staff from the coordinating center. Follow-up coronary angiography after PCI was performed only if clinically indicated.

Percutaneous Coronary Intervention and Stent Procedure

PCI was performed using standard techniques [10]. In the BMS group, patients received any of the following stents: Multilink (Abbott Vascular, Santa Clara, CA), Driver (Medtronic Vascular, Santa Rosa, CA), Liberté (Boston Scientific, Natick, MA), or Eucastsflex (Eucatech AG, Rheinfelden, Germany). In the DES group, patients received one of the four commercially available stents: Taxus (Paclitaxel-eluting stents [PES], Boston Scientific), Endeavor (Zotarolimus-eluting stents [ZES], Medtronic Vascular), Cypher (Sirolimus-eluting stents [SES], Cordis, Warren, NJ), and EucaTax (PES, Eucatech AG). In the DES group, a BMS was allowed if it was implanted as a second stent in a side branch.

End Points

The primary end point of the study was to compare overall costs (in-hospital and follow-up costs of the

two revascularization strategies (OR and DES) at 1, 3, and 5 years follow-up. This end point was selected on the hypothesis that both strategies would have similar efficacy.

Costs (expressed in US dollars) included hospitalization, medications (procedural and follow-up), and procedural resources (initial and follow-up). Professional fees during PCI procedures were estimated according to the national fees [14]. All costs, procedural, in hospital, and follow-up, were calculated from the perspective of third party payers based on the Argentinean medical tariff. All direct costs were actualized by the Argentinean inflation rate and converted to US dollars on December 2010. Specific costing was done for each patient. The same stent list prices were used in all patients. The cost of oral sirolimus treatment was added to the initial procedure costs. Costs associated with new adverse events during follow-up were added if related to the initial procedure or to progression of the coronary artery disease.

The secondary end points included safety end points defined by a composite of death from any cause, myocardial infarction (MI) or stroke. Only these three major adverse cardiovascular events were included in major adverse cardiovascular events (MACE) definition according to end point definition requirements in recent randomized trials comparing different revascularization strategies [15]. Target vessel failure (TVF) was defined as cardiac death, MI, and target vessel revascularization (TVR).

TVR and target lesion revascularization (TLR) were analyzed separately as efficacy end points and were not included as part of the MACE definition. TVR and TLR were considered only if clinically indicated. At 3 years, the incidence of malignancies and cancer-related death was analyzed in both groups. All end points were examined by the intention to treat principle. Stent thrombosis was defined according to a previous definition, which was consistent with the category of definite, probable or possible stent thrombosis by the Academic Research Consortium [16,17].

The diagnosis of MI was based on typical chest pain combined with either new pathological Q waves or an increase of creatine kinase to more than three times the upper limit of normal, with a concomitant increase in the MB isoenzyme. Oral sirolimus treatment compliance and adverse side effects were also recorded.

Statistical Analysis

The sample size of the study was calculated on the basis of a test for a trend analysis. Based on previous data with oral sirolimus and DES, we predicted that the incidence of TVR would be between 8 and 9% with both revascularization therapies [10,18–20].

A two-sided test for differences in independent binomial proportions with an alpha error of 0.05 was used to determine the power to detect a significant difference in the primary end point of overall cost between treatment groups at 1 year. We determined that at least 100 patients needed to be treated to provide adequate numbers of patients with similar demographic, clinical, and angiographic baseline characteristics in both groups and guarantee a power of 90%. Taking into account that both revascularization procedures share indirect costs, we only analyzed direct costs and cost differences between the two strategies using the microcosting method.

A one-tailed noninferiority test was performed using a predetermined noninferiority threshold level of 15% with an overall alpha ≤ 0.05. A noninferiority test was selected under the hypothesis of equivalence in clinical efficacy between both strategies of OR and DES. The hypothesis was that the average DES cost minus the average cost of OR plus BMS was greater than the prespecified noninferiority threshold level, and as a consequence, DES would not be cost-effective compared to the OR plus BMS [14]. A bootstrap method was used to validate the noninferiority cost test and was also applied to patients having adverse events at follow up.

Cost analysis was performed by the staff of the Economic Department of the Ministry of Health of Argentina.

Continuous variables were expressed as mean $\pm$ SD and categorical variables as percentage (%). Continuous variables were compared using ANOVA with Bonferroni correction. Categorical variables were compared using chi square analysis or Fisher's exact test. Freedom from adverse end points at follow-up was obtained using Kaplan–Meier curves that were compared by the log-rank test. Cox regression curve was used to analyze the composite of death, MI, and stroke.

Univariate and multivariate Cox regression analysis were performed using SPSS v. 17.0 to determine independent predictors of outcome at follow-up. Variables of statistical significance after univariate analysis and clinically relevant covariates including all demographic, clinical, angiographic, and procedural variables were included into the model.

A P-value of <0.05 was considered significant.

RESULTS

Between January 2006 and September 30, 2007, 1,274 patients underwent coronary angiography at the three participating centers, from which 200 patients

(15.6% of the entire population) were randomized (Fig. 1). One hundred patients were included in OR plus BMS (131 vessels and 158 lesions) and 100 in the DES group (142 vessels and 170 lesions). A total of 347 stents were implanted, 171 in the OR and 176 in the DES group. Baseline demographic, clinical, and angiographic characteristics of the two groups were similar (Table I). In the DES group, Taxus (Boston Scientific) and Endeavor (Medtronic Vascular) stents were used in 90.8% of the cases. Detailed information of baseline characteristics, PCI strategy, hospital results, oral sirolimus therapy compliance and related adverse events were described elsewhere [13]. Briefly, in OR group 24% developed mild side adverse events [7] related to oral immunosuppressive therapy (gum sores and diarrhea in 14% and 12%, respectively) and only 4 patients discontinued the treatment.

None of these patients with undesirable side effects required hospitalization and they had complete relief of the symptoms when the drug was stopped.

No patient had adverse events linked to diltiazem.

Three Years Follow Up Clinical Results

The 3 years of follow-up rate in both groups was 99%. At 3 years, 55% of DES patients and 23% of the OR arm were still on clopidogrel treatment ($P = 0.003$).

Cumulative 1-year and 3-year adverse clinical events are described in Table II.

At 3 years, the incidence of death, cardiac death, MI, and stroke were similar in the two groups, whereas there was a trend towards higher MACE rate in the DES group (20%) as compared to the OR plus BMS group (11%) (RR 0.49, CI: 0.22–1.09, $P = 0.078$). After 1 year, there were two additional deaths in the OR group and four in the DES group ($P = 0.69$); cardiac death occurred in one patient in each group. Patients with new malignancies were four in the OR group and eight in the DES group ($P = 0.41$); cancer-related deaths were two and three in the OR group and DES group, respectively ($P = 0.69$).

Incidence of MI at 3 years was 6% in the OR group and 11% in the DES group, meaning that 2 patients of the DES arm developed a new MI after 1 year, whereas no patient in the OR arm suffered a new MI in the same period (RR: 0.51, CI: 0.18–1.45, $P = 0.20$). TVF rate was 25% in the OR group and 32% in the DES group (RR: 0.70; CI: 0.38–1.31, $P = 0.27$). TVR rate was 14.5% in the OR and 17.6% in the DES groups (RR: 0.80, CI: 0.41–1.53, $P = 0.50$), whereas TLR rate was 10.1% and 14.1% in OR and DES, respectively (RR: 0.68; CI: 0.35–1.34, $P = 0.27$). Compared to the first year, TVR rate increased to 3.9% and 7.1% in the OR group and the DES group, respectively ($P = 0.37$), and TLR increased to 3% and 5.9%, respectively ($P = 0.31$). Of interest, no differences between both groups were seen in patients with reference vessel size <2.5 mm, TVR was 6.3% (3/48) and 16.6% (6/36) in OR and DES groups, respectively, $P = 0.132$, whereas TLR was 5.3% (3/57) and 10.4% (5/48) in OR and DES groups, respectively, $P = 0.198$. Similarly, comparable results between both groups were seen if stent length was > 18 mm, TVR was 16.7% (7/42) in OR, and 15.5% (9/58) in DES group, $P = 0.877$, and TLR was 14.9% (7/47) and 11.7% (7/60) in OR and DES group respectively, $P = 0.562$.

Figures 2 and 3 show the Kaplan–Meier curves of freedom from TLR and TVR, and from MACE and TVF, respectively, in the two groups.

Any definition of stent thrombosis was reached in 2% and 6% of patients (RR: 0.32, CI: 0.06–1.62, $P = 0.14$) in the OR group and the DES group, respectively. Definite stent thrombosis occurred in 1 and 3 patients in the OR and the DES groups, respectively; 1 patient in each group suffered very late stent thrombosis (Table II).

Three Years Cumulative Costs

Table III summarizes the in-hospital, follow-up, and cumulative costs per patient in each group.

At 3 years, out-of-hospital costs and cumulative costs were higher in the DES group as compared to the OR group (US$ 11202.52 ± 6422.58 and 6998.15 ± 3385.96, respectively; $P = 0.0001$), (Table III). Higher follow-up costs in patients with DES were explained by similar TVR rates in the two groups during the entire follow-up and by an increased use of clopidogrel therapy in the DES arm ($P = 0.003$).

One tailed noninferiority testing showed that DES therapy was not cost-effective as compared to OR in all possible cost scenarios (hospital and/or follow-up). To be cost effective, DES strategy should be associated with a 16.6% decrease in the cost of the initial procedure, a 42% cost decrease during follow-up and a 27.2% cost decrease at 3 years. Cost differences between treatment strategies reflect the initial differences between the cost of DES and BMS and the similar incidence of TVR and TLR in both groups (Tables II and III).

In addition, the average follow-up cost per patient with adverse cardiac events was significantly higher in the DES group than the OR group (7.686 ± 4,491 US$ vs. 4.751 ± 4,098 US$, respectively, $P < 0.047$). Figure 4 shows the results of factoring in the costs of patients with new adverse cardiac events and generating 100 samples costs of patients with reposition using the bootstrap method; at 3 years follow-up, the DES patients with complications developed significantly higher in-hospital costs than the OR patients.

TABLE I. Baseline, Demographic, Clinical, Angiographic, and Procedural Characteristics

Characteristics *n* (%)	OR+BMS ($n = 100$ pts)	DES ($n = 100$ pts)	*P* value
Age (years)	62.1 ± 10.1	63.4 ± 10.6	0.30
Age > 65 years	40%	48%	0.31
Male gender	83 (83.0%)	81 (81.0%)	1.00
Hypertension	69 (69.0%)	72 (72.0%)	0.93
Dyslipemia	71 (71.0%)	81 (81.0%)	0.61
Current smokers	21 (21.0%)	17 (17.0%)	0.67
Diabetes mellitus	24 (24.0%)	33 (33.0%)	0.36
LV ejection fraction < 50%	11 (11.0%)	6 (6%)	0.20
CRF	4 (4%)	6 (6%)	0.74
BMI > 25	25 (25%)	30 (30%)	0.42
COPD	3 (3%)	5 (5%)	0.71
Previous CVA	2 (2.0%)	2 (2.0%)	1.00
Previous MI	26 (26.0%)	33 (33.0%)	0.51
EUROSCORE (Arithmetic)	3.63 ± 2.7	3.41 ± 2.6	0.56
Previous coronary revascularization	12 (12.0%)	13 (13.0%)	1.00
MVD	48 (48%)	51 (51%)	0.90
LMD	10 (10%)	7 (7%)	0.44
Unstable angina[a]	62 (62.0%)	56 (56.0%)	0.74
AI and IIB	27 (27%)	25 (25%)	0.74
IIIB and C	35 (25%)	31 (31%)	0.54
Angiographic characteristics			
No. of treated vessels	131	142	0.70
No. of treated lesions	158	170	0.75
No. of stents per patient	1.71	1.76	0.91
Reference diameter < 2.5 mm	36.1%	28.2%	0.32
Lesion length > 18 mm	29.7%	35.3%	0.51
Overlapping stents per vessel	24.4% (32/131)	14.8% (21/142)	0.28
Stent length (mm)	19.1 ± 4.3	21.4 ± 5.2	0.001
Stent diameter (mm)	2.78 ± 0.4	2.76 ± 0.4	0.66
Stent design deployed			
Paclitaxel eluting stents	0%	92/176 (52.2%)	-
Sirolimus eluting stents	0%	9/176 (5.2%)	-
Zotarolimus eluting stents	0%	52/176 (29.6%)	-
Bare-metal stents	100%	23/176 (13.0%)	-
Treated vessel			
RCA	32 (20.3%)	39 (22.9%)	0.73
LAD	71 (44.9%)	82 (48.2%)	0.79
LCX	50 (31.6%)	44 (25.9%)	0.46
LM	5 (3.2%)	5 (2.9%)	0.83
Lesion type according to AHA class			
Plaque type A/B1	61 (38.8%)	55 (32.3%)	0.19
Plaque type B2	66 (41.7%)	71 (41.8%)	0.99
Plaque type C	31 (19.5%)	44 (25.9%)	0.14

PTS: patients; LV: left ventricle; CRF: chronic renal failure; BMI: body mass index; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; CVA: cerebrovascular accident; MI: myocardial infarction; # According to Braunwald Classification; MVD: Multiple Vessel Disease; LMD: Left Main Disease; ACS: Acute Coronary Syndromes; UA: Unstable Angina; NSTEMI: Non ST elevation Myocardial Infarction; ACC: American College of Cardiology; AHA: American Heart Association; RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; LCX: Left Circumflex Artery; LM: Left Main.DES: drug-eluting stents; OR plus BMS: Oral Rapamycin + bare-metal stents

Multivariable Predictors of Outcome

Multivariable Cox regression analysis did not identify any independent baseline demographic, clinical, or angiographic predictors of adverse outcome: MACE and TVR. The variables analyzed were sex, age, hypertension, diabetes, high cholesterolemia, renal failure, smoking, angina status, unstable angina, previous MI, previous PCI, previous stroke, left ventricular ejection fraction, multivessel disease, left anterior descending as the target vessel, left main as the target vessel,

TABLE II. Incidence of Clinical Endpoints at 1 and 3 Years of Follow Up

Event	OR + BMS (100, %)	DES (100, %)	RR	CI 95% Inferior	CI 95% Superior	*P* value
Death						
0–1 years	3 (3.0%)	7 (7.0%)	0.42	0.11	1.61	0.36
0–3 years	5 (5.0%)	11 (11.0%)	0.42	0.14	1.27	0.11
Cardiac death						
0–1 years	1 (1.0%)	4 (4.0%)	0.25	0.02	2.11	0.38
0–3 years	2 (2.0%)	5 (5.0%)	0.38	0.07	2.04	0.44
AMI						
0–1 years	6 (6.0%)	9 (9.0%)	0.66	0.24	1.80	0.63
0–3 years	6 (6.0%)	11 (11.0%)	0.51	0.18	1.45	0.20
Death, AMI, and stroke						
0–1 years	9 (9.0%)	15 (15.0%)	0.60	0.27	1.30	0.34
0–3 years	11 (11.0%)	20 (20.0%)	0.49	0.22	1.09	0.07
TVF						
0–1 years	21 (21.0%)	23 (23.0%)	0.89	0.45	0.17	0.73
0–3 years	25 (25.0%)	32 (32.0%)	0.70	0.38	1.31	0.27
TLR						
0–1 years	11 (7.0%)	14 (8.2%)	0.83	0.36	1.89	0.84
0–3 years	16 (10.1%)	24 (14.1%)	0.68	0.35	1.34	0.27
TVR						
0–1 years	14 (10.6%)	15 (10.5%)	1.01	0.50	2.01	0.86
0–3 years	19 (14.5%)	25 (17.6%)	0.80	0.41	1.53	0.50
Stent thrombosis (A.R.C.)						
Early (<30 days)	0 (0.0%)	1 (1.0%)	0.49	0.43	0.57	1.00
Late (30–365 days)	1 (1.0%)	4 (4.0%)	0.24	0.02	2.20	0.36
Very late (>365 days)	1 (1.0%)	1 (1.0%)	1.00	0.62	16.2	1.00
Overall	2 (2.0%)	6 (6.0%)	0.32	0.06	1.62	0.14

AMI: acute myocardial infarction; TVF: target vessel failure; TLR: target lesion revascularization; TVR: target vessel revascularization; ARC: Academic Research Consortium; DES: drug-eluting stents; OR plus BMS: Oral Rapamycin + bare-metal stents.

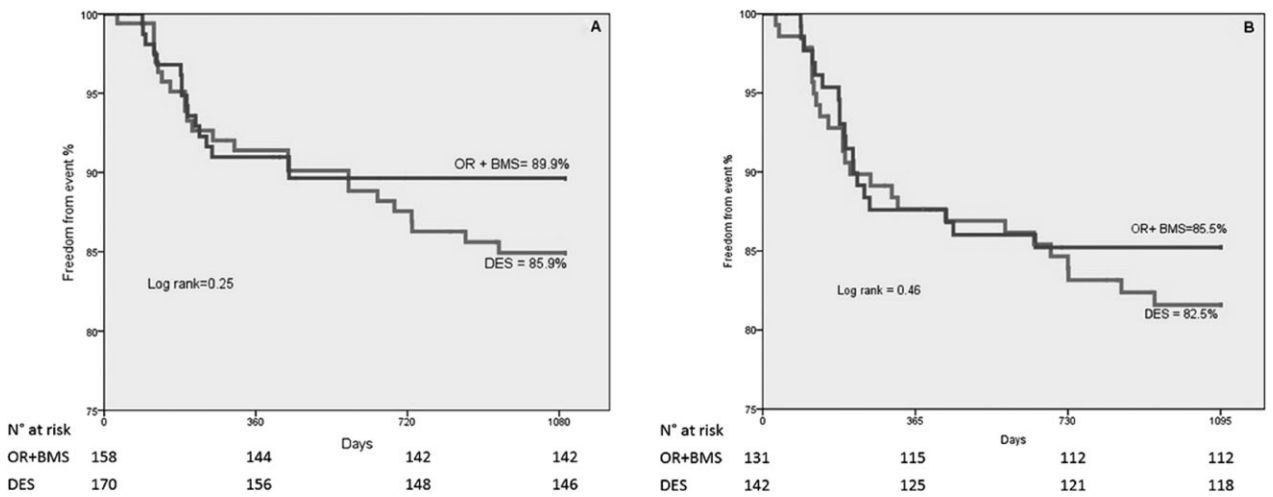

Fig. 2. Freedom from target lesion (A) and target vessel revascularization (B). DES: drug-eluting stents; OR plus BMS: Oral Rapamycin + bare-metal stents.

number of treated vessels, number of treated lesions, number of stents, stent length, overlapping stents, reference vessel diameter, and treatment assignment. We first performed univariate analysis using all listed variables to identified possible predictors of poor outcome; after univariate analysis only three variables could be introduced in the Cox regression model: multiple vessel disease, diabetes, and group assignment.

At 3 years, only DES assignment showed a trend towards poor outcome (RR: 2.01, CI 95: 0.95–4.22, $P = 0.065$), and no independent predictor of TVR was identified.

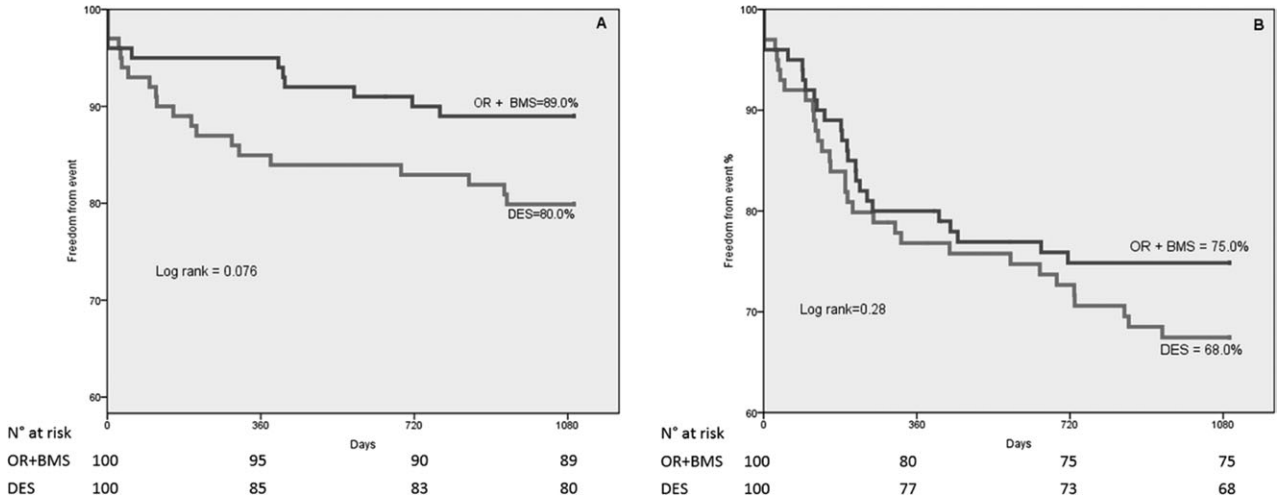

Fig. 3. Freedom from death, myocardial infarction, and stroke (A) and freedom from target vessel failure. DES: drug-eluting stents; OR plus BMS: Oral Rapamycin + bare-metal stents.

TABLE III. In-hospital, Follow-up, and Cumulative Costs per Patient in Both Groups

(US$)	OR + BMS (100 patients)	DES (100 patients)	*P* value[a]
Initial procedure			
PCI	970.5 ± 43.7	973.9 ± 52.9	0.35
Stents (BMS or DES)	596.3 ± 304.6	2623.7 ± 1397.4	<0.001
Drugs	761.0 ± 14.9	54.7 ± 1.2	<0.001
Professional fees	603.5 ± 17.2	605.2 ± 19.0	0.52
Hospital fees	1502.9 ± 637.0	1459.5 ± 1199.3	0.74
Overall initial costs	4434.3 ± 724.0	5720.3 ± 1860.7	<0.001
Overall initial costs plus taxes	5365.5 ± 876.0	6921.5 ± 2251.4	<0.001
Follow up			
Drugs	170.1 ± 427.1	1482.8 ± 630.3	<0.001
Events	1179.2 ± 2377.7	2054.3 ± 4436.9	0.083
Overall follow-up costs	1349.3 ± 2696.0	3537.2 ± 4621.4	<0.001
Overall follow-up costs plus taxes	1632.7 ± 3262.2	4280.0 ± 5591.9	<0.001
Overall costs	5783.6 ± 2798.0	9257.4 ± 5307.9	<0.001
Overall costs plus taxes	6998.1 ± 3385.6	11201.5 ± 6422.6	<0.001

Costs per patient respond to the moment were the original procedure and posterior events took place and there were analyzed by the existing December 31, 2010 values.
DES: drug eluting stents; BMS: bare-metal stents; OR: Oral rapamycin.
[a]ANOVA test.

DISCUSSION

This is the first study that reports the long-term safety, efficacy, and cost-effectiveness of OR plus BMS in the prevention of coronary restenosis and its value in comparison with DES.

At 3 years follow-up, patients randomized to OR plus BMS compared to those randomized to DES had a significant reduction of costs during the entire follow-up in all clinical scenarios, confirming the primary hypothesis. All clinical efficacy and safety end points such as TVR, TLR, TVF, death, MI, and stent thrombosis were similar using the two revascularization strategies. However, it should be outlined that a trend in favor of OR plus BMS was revealed for the composite end point of death, MI, and stroke ($P = 0.07$).

The final cost-effectiveness advantage of OR plus BMS is explained by the fact that the high procedural cost of DES and its requirements for long-term antiplatelet therapy were never counterbalanced, since repeat revascularization procedure rates during the entire follow-up were similar. Study design prescribing 1 month and 1 year of clopidogrel therapy in OR and DES, respectively, would contribute with higher follow-up cost in the DES group; however, if OR would have

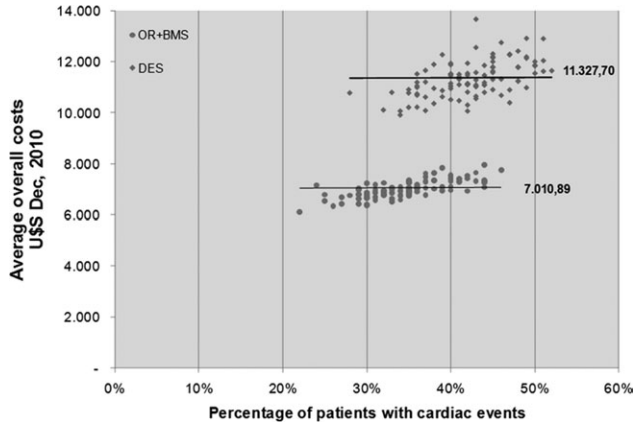

Fig. 4. Bootstrap analysis of costs of patients with adverse cardiac events. DES: drug-eluting stents; OR plus BMS: Oral Rapamycin + bare-metal stents.

significant high incidence in follow-up clinical events, these differences in clopidogrel therapy would be counterbalanced. That is the case of cost/effective comparison between DES versus BMS in first trials with Cypher and Taxus stents; the initial high costs of DES design were counterbalanced in high-risk subgroups during follow up by the greater rate of TVR in the BMS [21,22]. Moreover, the cumulative cost of the DES strategy was 37.5% higher than the OR strategy at 3 years, and 22.5% at the time of the initial procedure, meaning that in ORAR III trial, OR plus BMS strategy increased cost-saving over time. In addition, DES patients with complications developed significant higher follow-up costs than patients with complications in the OR group, suggesting different components in the adverse events for each revascularization strategy, and this finding is consistent with a recent report [23].

Recent data with OR at 4 years follow-up in patients with in-stent restenotic lesions [24] show a loss of initial TVR advantage and a trend of high incidence of new malignancies in the group taking high OR doses. However, the patient population of this trial is very different from the ORAR III population since in the latter only de novo lesions were included. Moreover, in the ORAR III low doses of OR were used and patients with previous malignancies were not included.

STUDY LIMITATIONS

First, the open-label design of the study may have the potential for bias. However, patient care was clinically driven and all adverse events were adjudicated by an independent committee blinded of assignments treatment group. The sample size of the study was powered for the primary end point of cost-saving analysis and was too small to ascertain differences in clinical events. Only 15.6% of the screened patients were randomized, which introduces another potential for bias. However, the patient population included in this study had several factors linked with high risk of recurrence after PCI such as diabetes in 28.5%, vessel size < 2.5 mm in 32%, overlapped stents in 19.4%, and older age in 44% [24–27]. The incidence of TVR, TLR, TVF, and stent thrombosis described in the DES arm is consistent with long-term data using similar DES designs in studies that included a population with complex patient/lesion subsets [28–30]. In addition, the DES used in this study were PES (Taxus, Boston Scientific) and ZES (Endeavor, Medtronic Vascular) in most patients, and DES results cannot be considered as class effect; therefore, we should not generalize these results to other DES designs including "best in class" DES available [30]. Finally, the health care system in Argentina differs significantly from the one of the US and this may be interpreted as a weakness of our study. However, cost-effective analysis between DES/BMS was also a concern in recent analysis from others worldwide health systems including US Medicare [31,32].

CONCLUSIONS AND CLINICAL IMPLICATIONS

At 3 years follow-up, there were no differences in effectiveness between the two revascularization strategies, OR plus BMS versus DES, and as a consequence, DES strategy failed to be cost effective as compared to OR plus BMS.

The findings of this study strengthen previous reports on effectiveness of oral sirolimus in the prevention of TVR and TLR after BMS implantation, although the definitive role of this strategy as alternative to DES is still pending for large randomized trials.

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