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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])

Fernando Alfonso, MD,* Maria J. Pérez-Vizcayno, MD,* Jaime Dutary, MD,* Javier Zueco, MD,† Angel Cequier, MD,‡ Arturo García-Touchard, MD,§ Vicens Martí, MD,‖ Iñigo Lozano, MD,¶ Juan Angel, MD,# José M. Hernández, MD,** José R. López-Mínguez, MD,†† Rafael Melgares, MD,‡‡ Raúl Moreno, MD,§§ Bernhard Seidelberger, MD,‖‖ Cristina Fernández, MD,* Rosana Hernandez, MD,* for the RIBS-III Study Investigators (under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology)

Madrid, Santander, Barcelona, Oviedo, Málaga, Badajoz, and Granada, Spain

Objectives This study sought to assess the effectiveness of a strategy of using drug-eluting stents (DES) with a different drug (switch) in patients with DES in-stent restenosis (ISR).

Background Treatment of patients with DES ISR remains a challenge.

Methods The RIBS-III (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent) study was a prospective, multicenter study that aimed to assess results of coronary interventions in patients with DES ISR. The use of a different DES was the recommended strategy. The main angiographic endpoint was minimal lumen diameter at 9-month follow-up. The main clinical outcome measure was a composite of cardiac death, myocardial infarction, and target lesion revascularization.

Results This study included 363 consecutive patients with DES ISR from 12 Spanish sites. The different-DES strategy was used in 274 patients (75%) and alternative therapeutic modalities (no switch) in 89 patients (25%). Baseline characteristics were similar in the 2 groups, although lesion length was longer in the switch group. At late angiographic follow-up (77% of eligible patients, median: 278 days) minimal lumen diameter was larger (1.86 ± 0.7 mm vs. 1.40 ± 0.8 mm, p = 0.003) and recurrent restenosis rate lower (22% vs. 40%, p = 0.008) in the different-DES group. At the last clinical follow-up (99% of patients, median: 771 days), the combined clinical endpoint occurred less frequently (23% vs. 35%, p = 0.039) in the different-DES group. After adjustment using propensity score analyses, restenosis rate (relative risk: 0.41, 95% confidence interval [CI]: 0.21 to 0.80, p = 0.01), minimal lumen diameter (difference: 0.41 mm, 95% CI: 0.19 to 0.62, p = 0.001), and the event-free survival (hazard ratio: 0.56, 95% CI: 0.33 to 0.96, p = 0.038) remained significantly improved in the switch group.

Conclusions In patients with DES ISR, the implantation of a different DES provides superior late clinical and angiographic results than do alternative interventional modalities. (J Am Coll Cardiol Intv 2012;5:728–37) © 2012 by the American College of Cardiology Foundation

From the *Clinico San Carlos University Hospital, Madrid, Spain; †Marqués de Valdecilla University Hospital, Santander, Spain; ‡Bellvitge University Hospital, Barcelona, Spain; §Puerta de Hierro-Mahalahonda University Hospital, Madrid, Spain; ‖San Pablo University Hospital, Barcelona, Spain; ¶Central Asturias University Hospital, Oviedo, Spain; #Valle de Hebrón University Hospital, Barcelona, Spain; **Virgen de la Victoria University Hospital, Málaga, Spain; ††Infanta Cristina University Hospital, Badajoz, Spain; ‡‡Virgen de las Nieves University Hospital, Granada, Spain; §§La Paz University Hospital, Madrid, Spain; and the ‖‖La Princesa University Hospital, Madrid, Spain. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Drug-eluting stents (DES) are widely used due to their dramatic antirestenosis efficacy (1). However, DES are not immune to in-stent restenosis (ISR), particularly when used with off-label indications in complex clinical and angiographic scenarios (2–4). In fact, treatment of DES ISR represents a growing clinical problem (2–4). Favorable early experiences have been reported in these patients using

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several coronary interventions, including conventional balloon angioplasty, cutting balloon angioplasty, bare-metal stents (BMS), and repeat DES implantation (5–16). However, most studies suggest that despite satisfactory initial results, patients with DES ISR have poorer long-term clinical and angiographic outcomes than those classically seen in patients with BMS ISR (7,8). Therefore, treatment of patients with DES ISR remains a technical and clinical challenge and the intervention of choice for these patients remains unsettled (2–4).

From a pathophysiological standpoint, the use of a different DES ("switch" strategy) is highly appealing and has been previously advocated for patients with DES ISR (11–16). The concept of drug resistance provides the foundation for this distinct therapeutic approach (17–19). However, early results of the switch strategy, mainly coming from observational studies but also from randomized clinical trials, remain controversial (11–16).

In this large prospective, multicenter study, we sought to assess the value of a different DES strategy in patients presenting with DES ISR.

Methods

Patient selection and study design. The RIBS-III (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent Implantation) study was designed as a prospective, multicenter study aimed to assess the results of coronary interventions in patients with DES ISR (Online Appendix). Specifically, the study sought to assess the value of the switch strategy (DES with a different drug) in this setting. DES with different drugs but within the same family (limus) were considered as different DES. However, as a secondary "exploratory" analysis, the switch to a different DES "family" (any limus DES to a nonlimus DES and vice versa) was also assessed. Inclusion and exclusion criteria were similar to those used in previous RIBS studies (20,21). Briefly, patients with ISR (>50% diameter stenosis on visual assessment) after DES implantation (any DES qualified) were eligible if they presented with angina or documented ischemia. In patients in whom the initial DES was implanted in another center, the original procedural report was obtained. When the type or location of the original stent remained unknown, the patient was not included in the study. Patients with DES ISR on small vessels (<2.0 mm) or very diffuse ISR (>32 mm) were excluded. Patients with early (<4 weeks) DES ISR, those presenting as an acute myocardial infarction, and those with intracoronary thrombus were also excluded (20,21). Patients with edge-ISR, affecting the 5-mm coronary segments adjacent to the previous DES, were only included if the stent border was involved. Where in doubt, the protocol suggested the use of intravascular ultrasound imaging to confirm the involvement of the stent edge. Additional exclusion criteria were current contraindications to aspirin or clopidogrel, severe renal failure, and major concomitant systemic diseases potentially interfering with clinical follow-up.

The use of a different DES was the recommended strategy. However, patients eventually treated with alternative strategies (at the discretion of local investigators) were also included. The main angiographic endpoint was the in-segment minimal lumen diameter (MLD) at 9-month follow-up as assessed by quantitative coronary angiography. The main clinical outcome measure was a composite of cardiac death, myocardial infarction, and target lesion revascularization (TLR).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
IQR = interquartile range
ISR = in-stent restenosis
MLD = minimal lumen diameter
PES = paclitaxel-eluting stent(s)
RR = relative risk
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

Twelve university hospitals from Spain participated in the trial (Online Appendix). Data collection, management, and analysis were performed at the coordinating center (Clínico San Carlos University Hospital, Madrid, Spain). The study was an investigators-driven initiative and was conducted under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology. All patients gave informed consent to the procedure. The study was performed according to the provisions of the Declaration of Helsinki regarding investigations with human subjects. Following current Spanish regulations for prospective multicenter studies, the protocol was approved by the Institutional Ethics Committee at the coordinating center.

Coronary interventions. All patients were pre-treated with aspirin and clopidogrel. A loading dose of clopidogrel (300 to 600 mg) was administered to clopidogrel-naive patients requiring ad hoc interventions. Before interventions, a bolus of unfractionated heparin (100 mg/kg) was given followed by subsequent boluses as required to maintain an activated clotting time >250 s.

The protocol suggested lesion pre-dilation with an undersized and relatively short balloon to avoid damaging the coronary vessel segment adjacent to the lesion site. Care was

taken to prevent balloon slippage phenomena. The importance of complete lesion coverage to prevent geographic-miss–related problems was emphasized (21). The use of a final 1.1/1 balloon-to-artery ratio and relatively high pressures (>14 bar) was recommended (21). Special emphasis was made to carefully seek, and aggressively treat, underlying underexpanded stents or residual underexpansion of the new stent. In this setting, the use of additional noncompliant balloons at high pressures was recommended. Although the value of intracoronary imaging techniques to assess DES expansion was explicitly described in the protocol, the use of these techniques was not mandated and remained a decision of the local investigators.

Serial serum creatine kinase levels (with myocardial band determinations when abnormal) and 12-lead electrocardiograms were routinely obtained for 24 h. After the procedure, all patients received aspirin indefinitely and clopidogrel (75 mg/day) for 1 year after repeat DES implantation and for only 1 month following other interventions.

Follow-up and definitions. Patients were followed-up at 1 month, 9 months, and 1 year and yearly thereafter. Angiographic follow-up was initially scheduled at 9 months but 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 reviewed for completeness and consistency checks were systematically performed. When required, specific queries were sent back to the sites. All data were entered into a dedicated, relational, database specifically designed for the RIBS studies. All major events were verified against source documentation. Clinical events (death, myocardial infarction, TLR) were adjudicated by an independent Clinical Events Committee that was unaware of the interventional strategy used. All deaths were considered as cardiac unless a clear noncardiac cause could be established. The diagnosis of myocardial infarction required at least 2 of the following: 1) >30 min of chest pain; 2) creatine kinase rise >2× the upper normal local value (with abnormal myocardial band fraction); and 3) development of pathological Q waves (21). The protocol indicated that all repeated interventions during follow-up had to be clinically justified (i.e., based on symptoms or objective evidence of ischemia). The Academic Research Consortium definition was used to assess the presence of stent thrombosis (22).

Angiographic analysis. Coronary angiograms were centrally analyzed at the angiographic core laboratory by trained personnel blinded to treatment allocation (20,21). The American College of Cardiology/American Heart Association (23) and the Mehran classifications (24) were used to qualitatively assess lesion morphology. Quantitative coronary angiography was performed with an automatic edge-detection system (CASS II System, Pie Medical, Maastricht, the Netherlands). Selected angiographic views that avoided vessel foreshortening and side-branch overlap were obtained after nitroglycerin administration. The same projections were repeated after intervention and at late follow-up. In-lesion and in-segment (treated segment plus 5-mm segments on both sides) analyses were performed (21). Reference vessel diameter, MLD, percentage of diameter stenosis, late loss, loss index, and net gain were measured. Binary restenosis was defined as >50% diameter stenosis at late angiography.

Statistical analysis. Categorical variables were compared with the chi-square test or Fisher exact test as required. Continuous data are presented as mean ± SD or median (interquartile range [IQR]) according to data distribution (Kolmogorov-Smirnov test). The Student *t* test or the Mann-Whitney tests were used for the comparison of continuous variables. Logistic regression analysis and multiple linear regression analysis were used to determine predictors of restenosis and MLD at follow-up, respectively. Kaplan-Meier analyses were performed to estimate event-free survival among different interventions that were compared with the log-rank and Breslow tests. Univariate and multivariate Cox regression analyses were used to determine predictors of events during follow-up. To avoid potential bias caused by confounding by indication, propensity score analyses were also performed. Variables selected for the propensity score were diabetes, time to restenosis, lesion length, vessel diameter (clinical criteria) and >1 restenosis, baseline MLD, edge-ISR, calcium, and ostial location (statistical criteria, $p < 0.2$ at the univariate analysis). Most of these variables, in addition to age, sex, and clinical presentation, were included in the different multivariate models. The propensity score was estimated using a multivariable logistic regression model and entered into the corresponding treatment effect models as a covariate to adjust for baseline differences. The C-index (area under the receiver-operating characteristic curve) was calculated to confirm adequate model fit. Relative risk [RR] and hazard ratio [HR] (95% confidence interval [CI]) were determined. The SPSS (version 15, IBM, Armonk, New York) statistical package was used. A value of $p < 0.05$ was considered statistically significant.

Results

From July 2004 to October 2009, 363 consecutive patients with ISR were prospectively enrolled in the study. Most patients (n = 274, 75%) were treated with the recommended different-DES strategy. However, alternative therapeutic strategies were selected by the local investigator in 89 patients (25%) (same-DES [n = 51], BMS [n = 9], balloon angioplasty [n = 29]) (Fig. 1). A significant number of patients were treated with limus-family DES (n = 225, 67%) or second-generation DES (n = 107, 32%). Table 1 summarizes baseline clinical and angiographic characteristics of the total patient cohort and compares results of patients treated with the different-DES approach and other strategies. Baseline clinical findings were similar in both groups with a high rate of

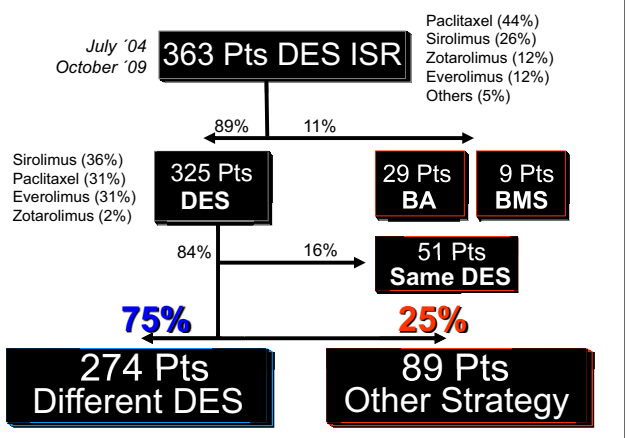

Figure 1. The RIBS III Study Flow Chart

BA = balloon angioplasty; BMS = bare-metal stent(s); DES = drug-eluting stent(s); ISR = in-stent restenosis; Pts = patients.

diabetics. Time to ISR tended to be shorter in the switch group. Results of the quantitative angiography analysis are shown in Table 2. In the switch group, lesions were longer and tended to be more severe. High dilation pressures were used in both groups. Angiographic success was obtained in all but 1 patient.

Late angiographic follow-up was obtained in 275 of 355 (77%) eligible patients (median: 278 days, IQR: 226 to 409 days). Either the remaining patients declined this late angiographic follow-up study, or the decision was made by the attending cardiologist after considering the clinical status. Baseline characteristics were similar in patients with and without late angiographic study. At late follow-up, MLD was larger (1.86 ± 0.7 mm vs. 1.40 ± 0.8 mm, p = 0.003) and recurrent restenosis rate lower (22% vs. 40%, p = 0.008) in the different-DES group (Table 2). Figure 2 depicts cumulative frequency distribution curves of MLD at all time points.

Clinical follow-up at 9 months was obtained in 360 patients (99%) and a clinical follow-up longer than 1 year in 349 patients (96%) (median: 771 days, IQR: 488 to 1,144 days). Time to follow-up was similar in both groups. Table 3 summarizes all major adverse clinical events, during hospitalization, at 1 year, and at last clinical follow-up. Of interest, a significant number of events occurred after the first year. The rate of definitive/probable stent thrombosis at last follow-up was very low and similar in both groups (2 [0.7%] vs. 1 [1.1%]). Estimates of event-free survival are presented in Figure 3. On actuarial analysis, the combined primary clinical endpoint occurred less frequently (23% vs. 35%, p = 0.039) in the different-DES group, because of a lower requirement for TLR.

Crude, adjusted by logistic regression or Cox multivariate analyses, and propensity sore adjusted (C-index: 0.75) clinical and angiographic results of both strategies are compared in Figure 4. All outcome estimates favored the switch strategy. After propensity score adjustment, the restenosis rate (RR: 0.41, 95% CI: 0.21 to 0.80, p = 0.01), the difference in late MLD (0.41 mm, 95% CI: 0.19 to 0.62, p = 0.001), and the event-free survival (HR: 0.56, 95% CI: 0.33 to 0.96, p = 0.038) remained significantly improved in the different-DES group.

When switch was assessed from a "family perspective" as a secondary analysis (limus to nonlimus DES and vice versa), the switch group obtained better late angiographic (MLD: 1.86 ± 0.8 mm vs. 1.67 ± 0.8 mm, p = 0.06; percentage of diameter stenosis: 29 ± 25% vs. 36 ± 27%, p = 0.04) and clinical (combined clinical endpoint: 17% vs. 25%, p = 0.04) outcomes.

Sensitivity analyses (first- vs. second-generation DES and limus vs. nonlimus DES) failed to detect significant interactions between specific DES types and main clinical

Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics

Characteristic	Different DES (n = 274)	Other Strategy (n = 89)	p Value
Age, yrs	66 ± 11	66 ± 10	0.78
Female	78 (29)	19 (21)	0.19
Risk factors			
Diabetes mellitus	143 (52)	43 (48)	0.53
Hyperlipidemia	178 (65)	51 (57)	0.19
Hypertension	198 (72)	65 (73)	0.88
Ever smoked	135 (49)	53 (60)	0.09
Clinical features			
Unstable angina	129 (47)	44 (50)	0.12
Stable angina	112 (41)	28 (31)	
Silent ischemia	33 (12)	17 (19)	
Previous myocardial infarction	108 (39)	33 (37)	0.69
Previous bypass surgery	45 (16)	10 (11)	0.24
>1 intervention on target lesion	15 (6)	9 (10)	0.12
Time to restenosis, days	279 (180–576)	334 (245–597)	0.07
Ejection fraction, %	61 ± 14	61 ± 15	0.99
Target artery			
Left anterior descending	136 (50)	48 (54)	0.57
Left circumflex	45 (16)	16 (18)	
Right coronary	79 (29)	22 (25)	
Saphenous vein graft	14 (5)	3 (3)	
Procedural characteristics			
Length of initial stent, mm	22 ± 13	22 ± 12	0.83
Length final stent, mm	21 ± 11	18 ± 11	0.07
IVUS/OCT	105 (37)	33 (38)	0.83
Second-/first-generation DES	96/178 (35)	11/40 (22)	0.07
Maximal pressure, atm	18 ± 3	17 ± 4	0.29
Balloon/artery ratio	1.33 ± 0.3	1.26 ± 0.3	0.07
Angiographic success	274 (100)	88 (99)	0.25

Values are mean ± SD, or n/N (%).

DES = drug-eluting stent(s); IVUS = intravascular ultrasound; OCT = optical coherence tomography.

Table 2. Angiographic Results

Variable	Different DES (n = 274)	Other Strategy (n = 89)	p Value
Qualitative features			
B2-C lesion	161 (59)	55 (62)	0.61
Mehran class I, II, III, IV	181 (66), 55 (20), 15 (6), 23 (8)	70 (79), 6 (7), 2 (2), 11 (12)	0.01
Edge-ISR	75 (27)	37 (42)	0.01
Ostial	34 (12)	17 (19)	0.10
Calcium	17 (6)	13 (15)	0.01
Quantitative findings			
Before the procedure	(n = 274)	(n = 89)	
Reference vessel diameter, mm	2.41 ± 0.5	2.46 ± 0.5	0.45
Minimal lumen diameter, mm	0.77 ± 0.4	0.87 ± 0.5	0.06
Stenosis, % of lumen diameter	68 ± 16	65 ± 17	0.13
Lesion length, mm	10.1 ± 9	8.1 ± 6	0.01
Diffuse lesions, >10 mm	96 (35)	19 (21)	0.01
After the procedure	(n = 274)	(n = 89)	
Reference vessel diameter, mm	2.41 ± 0.5	2.46 ± 0.5	0.45
Minimal lumen diameter, mm	2.26 ± 0.5	2.08 ± 0.6	0.007
Stenosis, % of lumen diameter	19 ± 10	22 ± 13	0.04
Acute gain, mm	1.61 ± 0.6	1.32 ± 0.6	<0.001
At follow-up: "in segment" analysis	(n = 210)	(n = 65)	
Reference vessel diameter, mm	2.62 ± 0.5	2.57 ± 0.5	0.47
Minimal lumen diameter, mm	1.86 ± 0.7	1.40 ± 0.8	0.003
Stenosis, % of lumen diameter	29 ± 24	42 ± 30	0.004
Restenosis	47 (22)	26 (40)	0.008
Late loss, mm	0.42 ± 0.6	0.63 ± 0.6	0.02
Loss index	0.27 ± 0.6	0.53 ± 1.4	0.18
Net gain, mm	1.08 ± 0.7	0.54 ± 0.8	<0.001
At follow-up: "in lesion" analysis	(n = 210)	(n = 65)	
Reference vessel diameter, mm	2.65 ± 0.5	2.57 ± 0.5	0.22
Minimal lumen diameter, mm	1.93 ± 0.7	1.60 ± 0.9	0.01
Stenosis, % of lumen diameter	28 ± 24	38 ± 30	0.02
Restenosis	41 (20)	22 (34)	0.016

Values are n (%) or mean ± SD.
DES = drug-eluting stent(s); ISR = in-stent restenosis.

outcome measures. However, limus-DES (restenosis: 21% vs. 36%, p = 0.006) and second-generation DES (restenosis: 16% vs. 31%, p = 0.009) provided better late angiographic results than alternative treatment modalities did. Likewise, in patients receiving DES (different or the same), late angiographic results were better when limus (restenosis: 21% vs. 32%, p = 0.07) or second-generation DES (restenosis rate: 16% vs. 28%, p = 0.04) were used. Finally, within the switch strategy, second-generation DES also obtained better late angiographic results than first-generation DES did (restenosis: 15% vs. 26%, p = 0.08).

A landmark analysis of the entire population "after" the first year demonstrated that the appearance of very late adverse clinical events was similar in both groups, although numerically lower in the different-DES arm (17% vs. 22%, p = 0.7). Finally, when the different-DES strategy was compared exclusively with the same-DES strategy, the switch strategy also achieved better angiographic results and a trend to better clinical outcomes (Fig. 5).

In this study, the use of intracoronary diagnostic techniques (37% of patients) was associated with larger initial angiographic acute gain (1.55 ± 0.6 mm vs. 1.35 ± 0.6 mm, p < 0.01) and MLD at follow-up (1.89 ± 0.8 mm vs. 1.68 ± 0.7 mm, p < 0.05) compared with patients not guided by these techniques, but these results did not translate into a reduction in target TLR or in the combined clinical endpoint (differences: p = NS).

Discussion

This study supports the value of a different DES (switch) strategy in patients suffering from DES ISR. Our study represents the first large multicenter study where the results of this strategy have been prospectively evaluated. In addi-

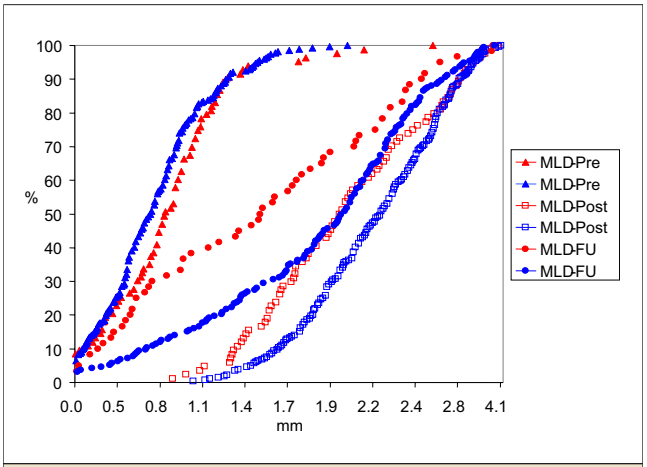

Figure 2. Cumulative Frequency Distribution Curves of MLD

Cumulative frequency distribution curves of minimal lumen diameters (MLD) before the procedure (Pre), after intervention (Post) and at late follow-up (FU). Different-drug-eluting-stent group **(blue curves),** other strategy **(red curves)** (p = 0.003 for difference of means in MLD at follow-up).

tion, the current report provides a uniquely long clinical follow-up and actually represents the longest clinical and angiographic follow-up currently available of the different-DES strategy (9). Our findings suggest that patients treated with this strategy obtain superior clinical and angiographic long-term results compared with those seen with alternative interventions. In particular, the switch strategy achieved a remarkable improvement in all late angiographic parameters, including MLD, percentage of diameter stenosis, late loss, net gain, and recurrent restenosis rate. These superior late angiographic findings translated into improved long-term clinical outcomes, mainly as the result of a reduction in the requirement for TLR. Furthermore, the superior clinical and angiographic results of the different-DES strategy were maintained despite careful adjustments for potential confounders using both classical multivariate models and propensity score analyses. The consistency of all these independent analyses supports the robustness of our findings. In addition, we also found that when the analysis was restricted to patients treated with a new DES, the use of a different DES provided better long-term angiographic results than the use of the same DES.

In contradistinction to prior studies that only analyzed the value of first-generation DES (11–16), in the current study, second-generation DES were used in 33% of patients treated for DES ISR. Strut thickness and polymer-mediated inflammatory reaction may act as a stimulus for recurrent neointimal growth and, therefore, newer-generation DES might be of particular value in this setting (4). In our study, the use of second-generation and limus-type DES were associated with better angiographic outcomes. This might help to explain the favorable results obtained by the switch strategy in our series (11–16). However, due to the post hoc nature of these subanalyses and the small sample sizes, further studies are required to confirm the superiority of second-generation DES in this setting.

Our findings also suggest that a low, but persistent, event rate accrues beyond the first year, emphasizing the importance of maintaining a close long-term clinical surveillance in these complex patients. We found that recurrences following treatment of DES ISR might occur after a longer time interval than those seen in historical series of BMS ISR (20,21). Finally, our results underscore the safety of repeat stent implantation in this challenging anatomic scenario. Indeed, the rate of stent thrombosis in the hetero-DES strategy at >2-year follow-up was only 0.7%.

Treatment of DES restenosis. Most previous studies consistently demonstrated relatively poor long-term clinical results in patients treated for DES ISR versus patients with BMS ISR (7,8). It has been proposed that although DES are dramatically effective at inhibiting the neointimal proliferative

Table 3. Major Adverse Clinical Events

Event	Different DES (n = 274)	Other Strategy (n = 89)	p Value	HR (95% CI)
Hospital events				
Death	0 (0)	0 (0)	1.00	—
Myocardial infarction	1 (0.4)	0 (0)	1.00	—
Target lesion revascularization	0 (0)	0 (0)	1.00	—
Coronary angioplasty	0 (0)	0 (0)	1.00	—
Coronary surgery	0 (0)	0 (0)	1.00	—
Any major hospital event	1 (0.4)	0 (0)	1.00	—
Events at 1 year				
Death	10 (3.7)	6 (6.7)	0.25	0.54 (0.20–1.50)
Cardiac death	6 (2.2)	5 (5.6)	0.13	0.39 (0.12–1.28)
Myocardial infarction	7 (2.6)	1 (1.1)	0.39	2.31 (0.28–18.7)
Target lesion revascularization	17 (6.3)	12 (13.5)	0.03	0.44 (0.21–0.91)
Coronary angioplasty	16 (5.9)	11 (12.4)	0.05	0.45 (0.21–0.98)
Coronary surgery	2 (0.7)	1 (1.1)	0.73	0.65 (0.06–7.1)
Any major event	28 (10.3)	17 (19.1)	0.04	0.51 (0.28–0.94)
Any major cardiac event	24 (8.9)	17 (19.1)	0.01	0.44 (0.24–0.82)
Events at last follow-up				
Death	19 (7.0)	11 (12.4)	0.33	0.68 (0.32–1.46)
Cardiac death	13 (4.8)	8 (9)	0.43	0.68 (0.27–1.71)
Myocardial infarction	10 (3.7)	2 (2.2)	0.46	1.72 (0.38–7.85)
Target lesion revascularization	37 (13.7)	19 (21.3)	0.08	0.60 (0.34–1.04)
Coronary angioplasty	33 (12.2)	18 (20.2)	0.06	0.57 (0.32–1.01)
Coronary surgery	8 (3.0)	2 (2.2)	0.26	2.83 (0.35–22.7)
Any major event	54 (19.9)	28 (31.5)	0.05	0.60 (0.37–0.99)
Any major cardiac event	48 (17.7)	26 (29.2)	0.04	0.61 (0.37–0.98)

Values are n (%). Patients with >1 event are counted only once for the composite clinical endpoints, although each event is listed separately in the corresponding category. p values from Cox analysis.

CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio; — = not estimable.

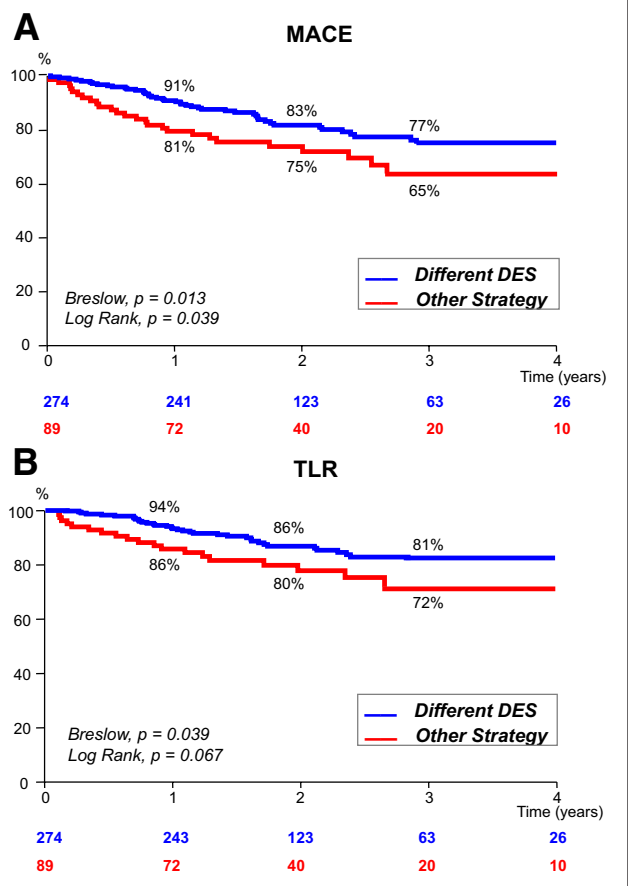

Figure 3. Kaplan-Meier Estimates of Event-Free Survival

(A) Freedom from major adverse cardiac events (MACE) (cardiac death, myocardial infarction, and target lesion revascularization [TLR]). **(B)** Freedom from TLR. The number of patients at risk in each time interval is presented at the bottom. DES = drug-eluting stent(s).

response, when they fail to achieve their aim, the elicited biologic response may actually be more difficult to tackle. Accordingly, treatment of DES ISR remains a pervasive technical and clinical challenge (2–4). Some reports suggest that focal DES ISR may be more likely the consequence of mechanical or technical factors, whereas diffuse DES ISR should raise the suspicion of drug failure (2–4). In some previous studies, this general concept has been empirically used to select and guide the repeated interventions.

In a pioneer study, Lemos et al. (5) demonstrated that treatment of patients with sirolimus-eluting stent (SES) ISR was associated with very high (43%) recurrence rates. The superiority of additional DES implantation, with a recurrent restenosis rate of only 29%, over alternative strategies, was already suggested in this preliminary report. Kim et al. (6) also suggested that the use of SES, compared with conventional strategies, for DES ISR was associated with a reduced rate of recurrences. More recently, larger studies with long-term clinical follow-up have confirmed that in patients with DES ISR, repeat DES implantation provide superior results to those obtained with balloon angioplasty, even after adjustment for potential confounders (9,10). Latib et al. (9) and Abe et al. (10) demonstrated that repeat SES implantation emerged as an independent predictor of absence of restenosis (9) and TLR (10) at follow-up. Interestingly, in these studies, the superiority of repeat DES implantation over balloon angioplasty was also demonstrated in patients with "focal" DES ISR (9,10). Notably, in all these studies, repeat DES implantation was found to be very safe and did not increase the risk of stent thrombosis at late follow-up (10).

Previous studies of the "switch" strategy. On theoretical grounds, the use of DES is highly appealing in patients with DES ISR considering, first, that restenting guarantees optimal early angiographic results and, second, the powerful antirestenosis properties of DES (7–16). Likewise, in this scenario, the rationale for a different-DES strategy stems from the concept of drug failure at an individual patient level. In fact, some previous studies have demonstrated that genetic factors may explain individual resistance to either sirolimus or paclitaxel (17–19). Considering the different mechanisms of action of drugs currently available in DES, the idea of trying a new drug has been considered as particularly attractive to tackle DES failures. Likewise, hypersensitivity reactions to metals (nickel and molybdenum) (25), different alloys, and even to specific durable polymers may elicit untoward proliferative responses (2–4). All these problems could be exacerbated if the same DES is used to manage recurrences but might be prevented using a different DES.

Five small observational and retrospective studies (11–15) have focused on the analysis of a switch strategy compared with other treatment modalities. Although highly heterogeneous in nature and design, these studies lumped together 487 patients with DES ISR (279 treated with the same DES and 208 with different DES). Most of these studies reported similar clinical and angiographic results with the 2 strategies; although, numerically, the rate of major adverse events always tended to be lower in the switch strategy (11–15). Only Mishkel et al. (13) explicitly suggested a potential benefit of the switch modality. At 1 year, the rate of TLR was 19% with a different DES; 29% with the same DES; and 37% after cutting-balloon, BMS, or brachytherapy. All these studies reported retrospective analyses of strategies selected by the investigators, baseline characteristics differed among therapeutic modalities, and no attempt was made to adjust for potential confounders (11–15). Indeed, most investigators favored the switch strategy in patients with diffuse DES ISR, whereas the same-DES strategy was more frequently used in focal DES ISR (9). Interestingly, in our study, the switch strategy also encompassed longer lesions. Furthermore, in these studies, the

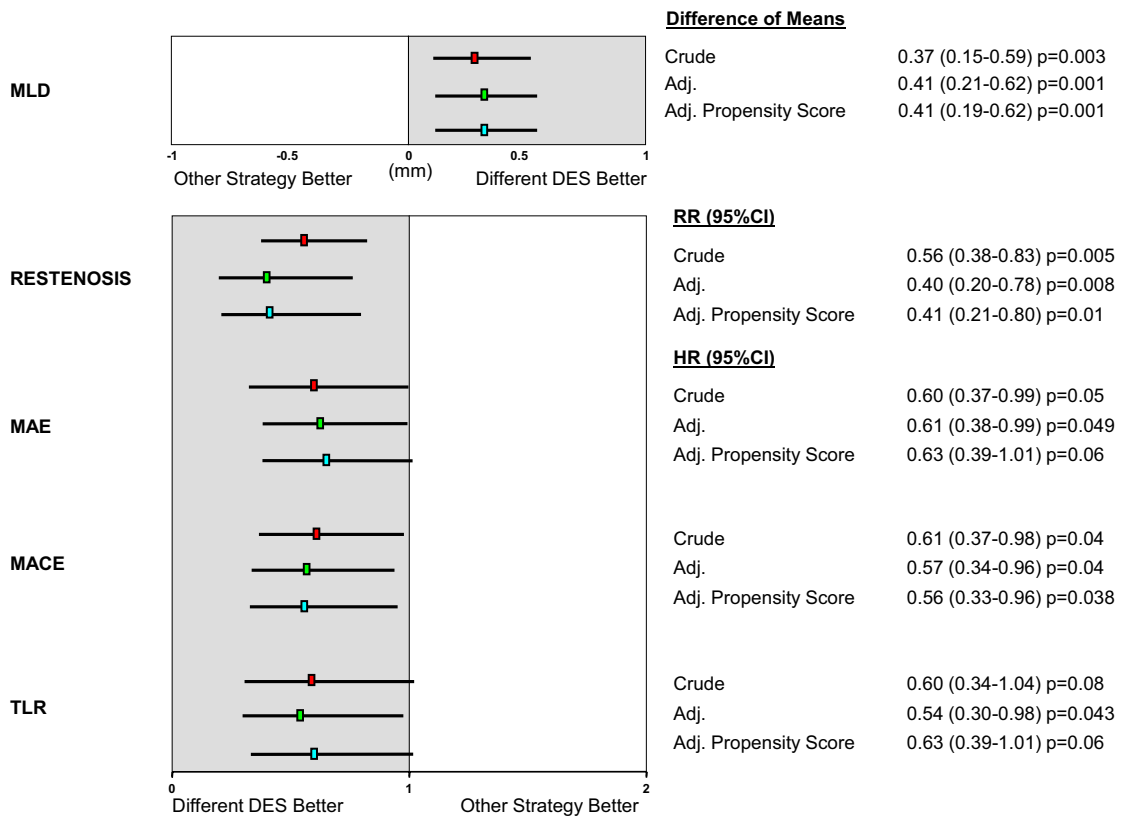

Figure 4. Comparison of Main Clinical and Angiographic Outcome Measures Between Treatment Strategies

Comparisons are presented as crude estimates, adjusted (Adj.) (logistic regression or Cox analysis), and propensity score adjusted. MAE = major adverse events; HR = hazard ratio; RR = relative risk; other abbreviations as in Figures 1 to 3.

number of patients included was small; follow-up duration was limited; late angiographic evaluation was not systematically obtained; and treatment modalities were highly diverse (11–15). Therefore, overall results do not allow drawing definitive conclusions on the potential value of the switch strategy.

Recently, Mehilli et al. (16) reported the ISAR-DESIRE-2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) randomized study. This trial allocated 450 patients with SES ISR to either repeat SES implantation (n = 225) or paclitaxel-eluting stent (PES) implantation (n = 225). Late lumen loss, MLD at follow-up (1.93 ± 0.73 mm vs. 1.94 ± 0.67 mm) and binary restenosis rate were similar following SES and PES. TVR rates were also similar in both arms. However, two-thirds of enrolled patients presented ISR of the polymer-free ISAR-SES, a stent not widely available (16). Moreover, the antiproliferative efficacy of SES and PES is different (16). Previous reports by the same group demonstrated that SES were more effective than PES to inhibit tissue proliferation (26). Therefore, it remains possible that the equivalent results obtained in the 2 arms were largely driven by the use of a less effective DES (PES) in the switch arm. Clinical and angiographic equipoise might have been the result of a superior ability of SES to suppress neointimal proliferation being counterbalanced by a potential resistance to sirolimus in patients suffering from SES ISR. Accordingly, the question regarding the potential value of a different DES strategy in patients with DES ISR remains open.

Study limitations. First, a wide array of DES with ISR were analyzed in this study, and patients were treated with diverse strategies (Fig. 1). Even in patients undergoing the recommended switch strategy, different DES were selected. This heterogeneity provides multiple small treatment subgroups, precluding a comprehensive analysis of the individual effectiveness of particular DES. However, this reinforces the primary hypothesis of the study, namely that the different-DES strategy (as a proof of concept) provides superior results than alternative treatment modalities do. This was also supported by the parallel findings of the switch strategy analyzed as a family strategy. Likewise, the number of patients treated with a same-DES strategy was limited, so when this strategy alone was used as the comparator, statistically significant superior results were only found in

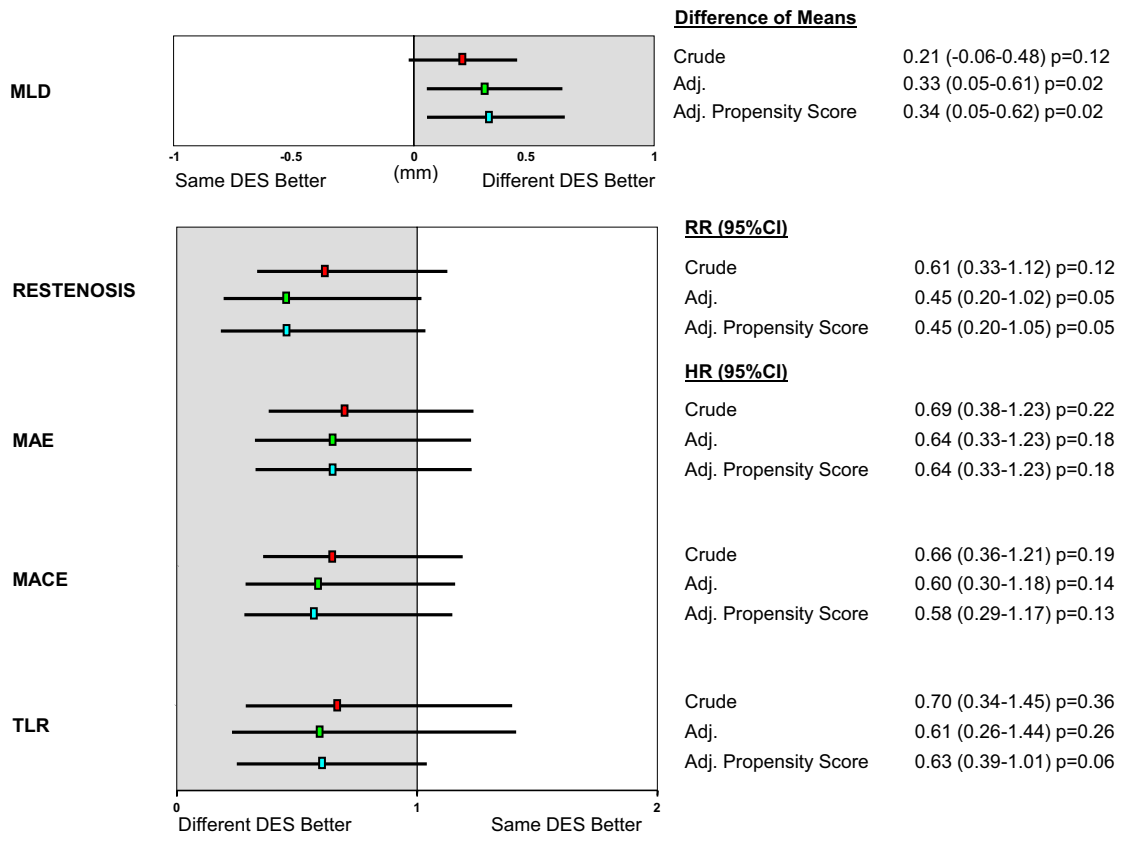

Figure 5. Main Outcome Measures Compared Only Between the Different-DES and Same-DES Strategies

Outcome measures are presented as crude estimates, adjusted with logistic regression or Cox analysis, and propensity adjusted. Abbreviations as in Figures 1 to 4.

angiographic outcomes. Second, this was a nonrandomized study and therefore has all the inherent limitations of observational studies. Precise patient-level reasons for not selecting the recommended strategy could not be fully elucidated. Thus, conventional and propensity score multivariate adjustments were used to address this issue providing consistent results, further suggesting the superiority of the switch approach. Nevertheless, the possibility that residual unmeasured confounders would have affected our findings cannot be discarded. In addition, the number of events of some outcome measures was relatively low and the potential for overfitting in some multivariate models must be considered. Third, angiographic follow-up (77%) was incomplete. Accordingly, our results should be only considered as hypothesis generating. Further studies with larger series of patients are warranted to definitively confirm these findings. Fourth, although intravascular ultrasound is a valuable technique in patients with ISR, this tool was not systematically used in the current series. Finally, the value of drug-eluting balloons has recently been demonstrated in patients with DES (27), yet these balloons were not available at the time of this study.

Conclusions

In patients with DES ISR, the use of a different DES provides superior long-term clinical and angiographic results compared with other therapeutic modalities.

Reprint requests and correspondence: Dr. Fernando Alfonso, Cardiología Intervencionista, Instituto Cardiovascular IdISSC, Hospital Universitario Clínico "San Carlos," Ciudad Universitaria, Plaza de Cristo Rey, Madrid 28040, 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. 20th official report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990–2010).] Rev Esp Cardiol 2011;64:1012–22.
2. 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.
3. Aminian A, Kabir T, Eeckhout E. Treatment of drug-eluting stent restenosis: an emerging challenge. Catheter Cardiovasc Interv 2009;74:108–16.

4. Alfonso F. Treatment of drug-eluting stent restenosis the new pilgrimage: quo vadis? J Am Coll Cardiol 2010;55:2717–20.
5. Lemos PA, van Mieghem CA, Arampatzis CA, et al. Post-sirolimus-eluting stent restenosis treated with repeat percutaneous intervention: late angiographic and clinical outcomes. Circulation 2004;109:2500–2.
6. Kim YH, Lee BK, Park DW, et al. Comparison with conventional therapies of repeated sirolimus-eluting stent implantation for the treatment of drug-eluting coronary stent restenosis. Am J Cardiol 2006;98:1451–4.
7. Whan Lee C, Kim SH, Suh J, et al. Long-term clinical outcomes after sirolimus-eluting stent implantation for treatment of restenosis within bare-metal versus drug-eluting stents. Catheter Cardiovasc Interv 2008; 71:594–8.
8. Steinberg DH, Gaglia MA Jr., Pinto Slottow TL, et al. Outcome differences with the use of drug-eluting stents for the treatment of in-stent restenosis of bare-metal stents versus drug-eluting stents. Am J Cardiol 2009;103:491–5.
9. Latib A, Mussardo M, Ielasi A, et al. Long-term outcomes after the percutaneous treatment of drug-eluting stent restenosis. J Am Coll Cardiol Intv 2011;4:155–64.
10. Abe M, Kimura T, Morimoto T, et al., for the j-Cypher Registry Investigators. Sirolimus-eluting stent versus balloon angioplasty for sirolimus-eluting stent restenosis: insights from the j-Cypher registry. Circulation 2010;122:42–51.
11. Cosgrave J, Melzi G, Corbett S, et al. Repeated drug-eluting stent implantation for drug-eluting stent restenosis: the same or a different stent. Am Heart J 2007;153:354–9.
12. Garg S, Smith K, Torguson R, et al. Treatment of drug-eluting stent restenosis with the same versus different drug-eluting stent. Catheter Cardiovasc Interv 2007;70:9–14.
13. Mishkel GJ, Moore AL, Markwell S, Shelton MC, Shelton ME. Long-term outcomes after management of restenosis or thrombosis of drug-eluting stents. J Am Coll Cardiol 2007;49:181–4.
14. Sardella G, Colantonio R, De Luca L, et al. Comparison between balloon angioplasty and additional coronary stent implantation for the treatment of drug-eluting stent restenosis: 18-month clinical outcomes. J Cardiovasc Med (Hagerstown) 2009;10:469–73.
15. Liistro F, Fineschi M, Grotti S, et al. Long-term clinical outcome of alternative treatment strategies for drug-eluting stents restenosis. EuroIntervention 2009;5:454–9.
16. Mehilli J, Byrne RA, Tiroch K, et al., for the ISAR-DESIRE 2 Investigators. 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.
17. Kurmasheva RT, Huang S, Houghton PJ. Predicted mechanisms of resistance to mTOR inhibitors. Br J Cancer 2006;95:955–60.
18. Huang S, Houghton PJ. Mechanisms of resistance to rapamycins. Drug Resist Update 2001;4:378–91.
19. Yusuf RZ, Duan Z, Lamendola DE, Penson RT, Seiden MV. Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation. Curr Cancer Drug Targets 2003;3:1–19.
20. Alfonso F, Zueco J, Cequier A, et al., for the RIBS Investigators. A randomized comparison of repeat stenting with balloon angioplasty in patients with restenosis after coronary stenting. J Am Coll Cardiol 2003;42:796–805.
21. Alfonso F, Pérez-Vizcayno MJ, Hernandez R, et al., for the RIBS-II Investigators. 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.
22. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
23. Alfonso F, Cequier A, Angel J, et al., for the RIBS Investigators. Value of the American College of Cardiology/American Heart Association angiographic classification of coronary lesion morphology in patients with in-stent restenosis. Insights from the Restenosis Intra-Stent Balloon Angioplasty Versus Elective Stenting (RIBS) randomized trial. Am Heart J 2006;151:681.e1–e9.
24. 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.
25. Köster R, Vieluf D, Kiehn M, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet 2000;356:1895–7.
26. 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.
27. 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.

Key Words: different stent ■ drug-eluting stents ■ in-stent restenosis ■ switch strategy.

APPENDIX

For a list of participating university hospitals, please see the online version of this article.