

# Predictors of recurrent restenosis after second-generation drug-eluting stent implantation for in-stent restenosis of drug-eluting stents



**Takenori Kanazawa\***, MD; Kazushige Kadota, MD, PhD; Seiji Habara, MD; Takeshi Tada, MD, PhD; Hiroyuki Tanaka, MD; Yasushi Fuku, MD; Tsuyoshi Goto, MD; Kazuaki Mitsudo, MD

*Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan*

## KEYWORDS

- calcified stenosis
- drug-eluting stent
- in-stent restenosis

## Abstract

**Aims:** The aim of the study was to evaluate predictors of recurrent restenosis after second-generation drug-eluting stent (DES) implantation for in-stent restenosis (ISR) of DES.

**Methods and results:** We retrospectively investigated 228 consecutive patients undergoing second-generation DES implantation for ISR of DES. There were 285 lesions in total and the implanted stents were as follows: biolimus-eluting stent, 71; everolimus-eluting stent, 214. We performed eight-month follow-up on 241 lesions (84.6%). The primary angiographic endpoint was binary restenosis, which was defined as  $\geq 50\%$  stenosis at follow-up angiography. Of the 241 lesions, recurrent restenosis was documented in 54 lesions (22.4%), and target lesion revascularisation was performed in 39 lesions (16.2%). Multivariate analysis showed that small vessel (odds ratio [OR] 2.21; 95% confidence interval [CI]: 1.12 to 4.40;  $p=0.02$ ) and non-focal type restenosis (OR 2.78; 95% CI: 1.36 to 5.78;  $p=0.0048$ ) were independent predictors of recurrent restenosis. The type of second-generation DES, whether a biolimus-eluting stent or an everolimus-eluting stent, did not affect the angiographic outcomes (OR 0.80; 95% CI: 0.37-1.78;  $p=0.58$ ).

**Conclusions:** Small vessel and non-focal type restenosis are predictors of recurrent restenosis after second-generation DES implantation for ISR of DES.

\*Corresponding author: Department of Cardiology, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, 710-8602, Japan.  
E-mail: minowaism79@yahoo.co.jp

## Abbreviations

<b>BES</b>	biolimus-eluting stent
<b>DES</b>	drug-eluting stent
<b>EES</b>	everolimus-eluting stent
<b>ISR</b>	in-stent restenosis

## Introduction

Drug-eluting stents (DES) have substantially reduced the revascularisation rate in *de novo* lesions, and outcomes have been further improved with the advent of second-generation DES. In-stent restenosis (ISR) remains a significant clinical issue after DES implantation. The treatment outcome of patients with ISR lesions is worse than that of patients with *de novo* lesions.

It has been reported that the rate of target lesion revascularisation is about 15% and that of target vessel revascularisation about 22% one year after treatment of ISR of DES<sup>1-5</sup>, and second-generation DES are superior to first-generation DES in the treatment of ISR of DES<sup>6,7</sup>. We sought to evaluate predictors of recurrent restenosis after second-generation DES implantation for ISR of DES.

## Methods

### ETHICS

The study was carried out in accordance with the provisions of the Declaration of Helsinki and the guidelines for epidemiological studies issued by the Ministry of Health, Labour, and Welfare of Japan, and has been approved by the institutional review board of Kurashiki Central Hospital. All patients provided informed consent for both the procedure and subsequent data collection and analysis for research purposes.

### PATIENT POPULATION

We retrospectively investigated 228 consecutive patients undergoing second-generation DES implantation for ISR of DES between January 2010 and November 2012 (285 lesions: biolimus-eluting stent [BES], 71; everolimus-eluting stent [EES], 214). We performed eight-month follow-up angiography on 241 lesions (84.6%). The 241 lesions were classified into two groups according to the presence or absence of recurrent restenosis. Fifty-four lesions had recurrent restenosis. We compared patient and lesion characteristics between the above-mentioned two groups.

### PROCEDURES

We performed predilatation on all ISR lesions. Two types of second-generation DES, BES (Nobori®; Terumo, Tokyo, Japan) and EES (XIENCE V® and XIENCE PRIME®, Abbott Vascular, Santa Clara, CA, USA), were used. Available BES were 8 to 28 mm in length and 2.5 to 3.5 mm in diameter. Available EES were 8 to 38 mm in length and 2.5 to 3.5 mm in diameter. The choice of stent type was at the operator's discretion. All patients were pretreated with aspirin (100 mg daily) and clopidogrel (75 mg daily). Aspirin treatment was maintained lifelong. Clopidogrel treatment was recommended for at least eight months.

## ANGIOGRAPHIC ANALYSIS

Coronary angiography was performed serially at baseline (before and after procedure) and at eight-month follow-up. Quantitative coronary angiography (QCA) analysis was performed with QCA-CMS (Medis medical imaging systems, Leiden, The Netherlands). All angiograms were analysed in a random sequence by two experienced observers who were blinded to the clinical characteristics of the patients. Coronary angiograms in multiple views were obtained after intracoronary nitrate injection. Reference diameter, minimal lumen diameter, percentage diameter stenosis, and lesion length were measured before and after procedure, and at eight-month follow-up.

## DEFINITIONS

Binary restenosis was defined as  $\geq 50\%$  stenosis inside the stent or within margins 5 mm proximal or distal to the stent at follow-up angiography. ISR was classified according to the Mehran classification<sup>8</sup>, and this study defined non-focal type as type ID, patterns II, III, and IV. Target lesion revascularisation was defined as repeat percutaneous coronary intervention or aortocoronary bypass surgery due to angiographic restenosis ( $>50\%$ ) associated with symptoms or objective signs of ischaemia. A bifurcation lesion was defined as a lesion in a branch whose vessel size was  $>2.0$  mm.

## STATISTICAL ANALYSIS

Data are expressed as mean $\pm$ standard deviation for continuous variables. We compared the differences between patients with and without recurrent restenosis using the t-test for continuous data and the  $\chi^2$  test for categorical data. Stepwise multivariable logistic regression analysis was applied to individuate the variables independently associated with recurrent restenosis. Multivariable analysis was selected if the variables were shown to affect dependent variables in a univariate analysis or if they were empirically known to have predictive values as follows: non-focal type restenosis, small vessel (reference diameter  $\leq 2.5$  mm), dialysis, bifurcation, acute coronary syndrome, chronic total occlusion, and diabetes mellitus. P-values of less than 0.05 were considered to be statistically significant. JMP 9 (SAS Institute Inc., Cary, NC, USA) was used for all statistical calculations.

## Results

### BASELINE AND PROCEDURAL DATA

**Table 1** shows baseline characteristics of the 228 patients including those with hypertension, 182 (63.9%); diabetes mellitus, 121 (42.5%); dyslipidaemia, 146 (51.2%); and dialysis, 41 (17.9%). The rates of the following two factors were significantly higher in the BES group: bifurcation lesion (45.1% vs. 17.3%,  $p<0.001$ ); reference diameter ( $3.30\pm 0.59$  mm vs.  $2.97\pm 0.50$  mm,  $p<0.001$ ). The rate of 2.5 mm stent use was significantly higher in the EES group (19.7% vs. 38.8%,  $p=0.004$ ).

**Figure 1** shows the lesion sites of ISR as follows: left main trunk, 35 (12.3%); left anterior descending, 79 (27.7%); left

**Table 1. Baseline characteristics.**

Lesion, number	Total (285)	BES (71)	EES (214)	p-value
Age, yrs	69.3±11.2	69.3±12.7	69.3±10.7	0.91
Men	234 (82.1)	60 (84.5)	174 (81.2)	0.60
Diabetes mellitus	121 (42.5)	34 (47.9)	87 (40.6)	0.33
Hypertension	182 (63.9)	49 (69.0)	133 (62.1)	0.32
Dyslipidaemia	146 (51.2)	38 (53.5)	108 (50.5)	0.68
Current smoker	11 (3.86)	2 (2.82)	9 (4.20)	0.74
Dialysis	41 (14.3)	10 (14.1)	31 (14.5)	1.00
Acute coronary syndrome	45 (16.0)	10 (14.5)	35 (16.8)	0.71
Bifurcation lesion	69 (24.2)	32 (45.1)	37 (17.3)	<0.001
Reference diameter, mm	3.06±0.54	3.30±0.59	2.97±0.50	<0.001
Lesion length, mm	18.4±15.8	16.6±16.6	19.0±15.5	0.28
Non-focal lesion	132 (46.3)	28 (39.4)	104 (48.6)	0.22
Chronic total occlusion	32 (11.2)	9 (12.7)	23 (10.7)	0.67
2.5 mm stent	97 (34)	14 (19.7)	83 (38.8)	0.004

Data are shown as n (%) unless otherwise indicated.

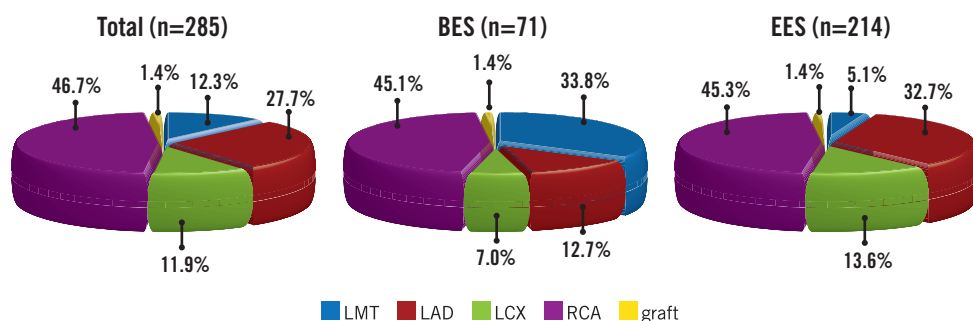
circumflex artery, 34 (11.9%); right coronary artery, 133 (46.7%); and graft, 4 (1.4%). The right coronary artery accounted for the major portion of the ISR sites.

**Figure 2** shows the previously deployed stent as follows: sirolimus-eluting stent, 164 (57.5%); paclitaxel-eluting stent, 51 (17.9%); zotarolimus-eluting stent, 13 (4.6%); BES, 22 (7.7%); and EES, 35 (12.3%). Sirolimus-eluting stents accounted for the major portion of the ISR sites. In treating ISR of EES, BES were more frequently deployed than EES.

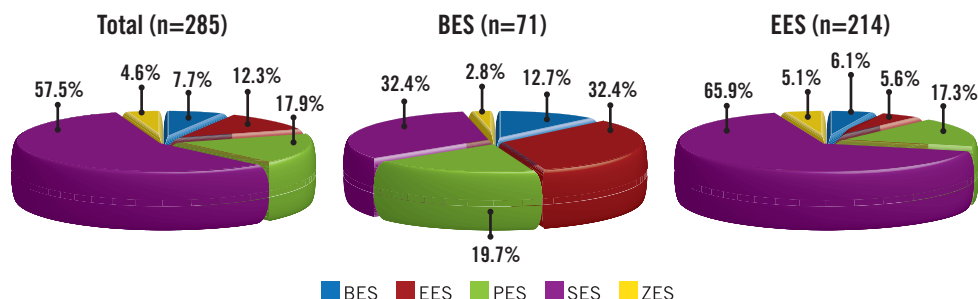
**Figure 3** shows the angiographic patterns of ISR as follows: focal type (55.8%) and non-focal type (30.5%). Focal body type IC was observed most frequently in both BES and EES.

### FOLLOW-UP AND RECURRENT RESTENOSIS

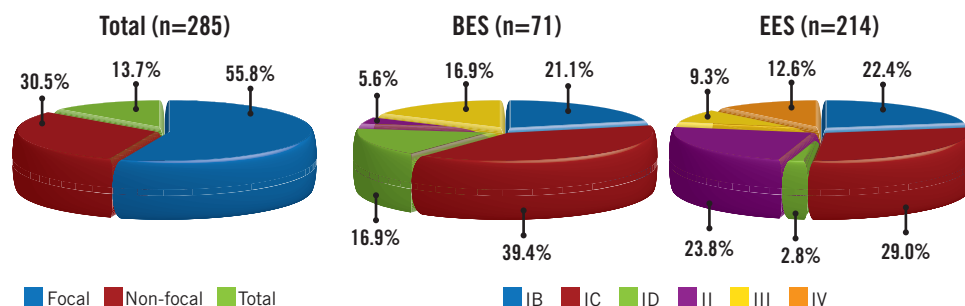
We performed eight-month follow-up angiography on 241 (84.6%) of the 285 lesions. Of the 241 lesions, recurrent restenosis was documented in 54 (22.4%): type IB, 6 (11.1%); type IC, 23 (42.6%); pattern II, 19 (35.2%); pattern III, 2 (3.7%); and pattern IV, 4 (7.4%), and angiographically driven target lesion revascularisation was performed in 39 lesions (16.2%).



**Figure 1.** Lesion sites of in-stent restenosis. The right coronary artery accounted for the largest portion of the in-stent restenosis sites. BES: biolimus-eluting stent; EES: everolimus-eluting stent; LAD: left anterior descending; LCX: left circumflex artery; LMT: left main trunk; RCA: right coronary artery



**Figure 2.** Stent types of in-stent restenosis. Sirolimus-eluting stents accounted for the largest portion of the in-stent restenosis sites. In treating in-stent restenosis of everolimus-eluting stents, biolimus-eluting stents were more frequently deployed than everolimus-eluting stents. BES: biolimus-eluting stent; EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent



**Figure 3.** Angiographic patterns of in-stent restenosis. The angiographic patterns are based on the Mehran classifications. Focal body type IC was observed most frequently in both biolimus-eluting and everolimus-eluting stents. BES: biolimus-eluting stent; EES: everolimus-eluting stent

## UNIVARIATE ANALYSIS

As shown in **Table 2**, the 241 lesions undergoing follow-up angiography were classified as recurrent restenosis (54 lesions) and non-recurrent restenosis (187 lesions). There were no significant differences in baseline characteristics such as hypertension, current smoker, dialysis, diabetes mellitus, and acute coronary syndrome between the two groups. The rates of the following three factors were significantly higher in the recurrent restenosis group: dyslipidaemia (68.5% vs. 48.2%,  $p=0.01$ ); non-focal type restenosis (61.1% vs. 41.7%,  $p=0.01$ ); and 2.5 mm stent (46.3% vs. 31.0%,  $p=0.048$ ).

## MULTIVARIATE ANALYSIS

As shown in **Table 3**, small vessel (odds ratio [OR] 2.21; 95% confidence interval [CI]: 1.12 to 4.40;  $p=0.02$ ) and non-focal type restenosis (OR 2.78; 95% CI: 1.36-5.78;  $p<0.05$ ) were independent predictors of recurrent restenosis. The type of second-generation DES, whether BES or EES, may make no difference to the

**Table 3.** Multivariate analysis.

	Odds ratio	95% confidence interval	p-value
Non-focal type restenosis	2.78	1.36-5.78	0.0048
Small vessel (stent length $\leq 2.5$ mm)	2.21	1.12-4.40	0.02
Dialysis	2.20	0.90-5.20	0.08
Bifurcation	1.86	0.89-3.82	0.09
Acute coronary syndrome	1.91	0.75-5.40	0.18
Chronic total occlusion	1.95	0.66-6.40	0.23
Everolimus-eluting stent	0.80	0.37-1.78	0.58
Diabetes mellitus	1.14	0.60-2.22	0.69

angiographic outcomes (OR 0.80; 95% CI: 0.37-1.78;  $p=0.58$ ). However, this result should be interpreted with caution because the available lengths of BES and EES were different.

## Discussion

Our results suggest that small vessel and non-focal type restenosis have a major impact on the risk of recurrent restenosis after second-generation DES implantation for ISR of DES. The type of second-generation DES, whether BES or EES, did not affect the angiographic outcomes. The ISR rate in *de novo* lesions has substantially decreased by using second-generation DES compared with first-generation DES. Byrne et al showed that the incidence of recurrent restenosis when using first-generation DES in the treatment of ISR of DES was 24.0%<sup>9</sup>, whereas that in the present study using second-generation DES was 22.4%, and the rate of target lesion revascularisation was 16.2%. Thus, the efficacy of DES implantation for ISR of DES may not be notably different between first- and second-generation DES. The prognosis of ISR is reported to be worse with DES than with BMS due to drug-specific factors such as hypersensitivity, inflammation, and neoatherosclerosis<sup>10</sup>.

In the present study, small vessel and non-focal type restenosis were independent predictors of recurrent restenosis, as described in the previous report on first-generation DES implantation for ISR of DES<sup>11</sup>. Patients with small vessels had several clinical

**Table 2.** Univariate analysis.

Lesion, number	Recurrent restenosis		
	Yes (187)	No (54)	p-value
Age, yrs	69.9 $\pm$ 10.6	67.0 $\pm$ 9.77	0.06
Men	149 (79.7)	45 (80.5)	0.69
Diabetes mellitus	77 (41.2)	23 (42.6)	0.88
Hypertension	137 (73.2)	38 (70.4)	0.73
Dyslipidaemia	128 (68.5)	26 (48.2)	0.01
Current smoker	5 (2.67)	2 (3.70)	0.20
Dialysis	22 (11.8)	11 (20.4)	0.12
Acute coronary syndrome	32 (17.1)	7 (13.0)	0.54
Bifurcation lesion	43 (23.0)	18 (33.3)	0.15
Reference diameter, mm	3.07 $\pm$ 0.52	2.98 $\pm$ 0.59	0.27
Non-focal lesion	78 (41.7)	33 (61.1)	0.01
Chronic total occlusion	18 (9.63)	6 (11.1)	0.80
2.5 mm stent	58 (31.0)	25 (46.3)	0.048

Data are shown as n (%) unless otherwise indicated.

characteristics such as a higher prevalence of diabetes mellitus, multivessel disease, and chronic occlusions, which are often associated with a poorer outcome after DES implantation. Stent overlap in a long lesion can easily cause inflammation and uneven drug distribution. An occluded lesion may result in stent mal-expansion due to organised thrombus. Because the struts of EES are thinner than those of BES, using EES seems to be more suitable for treating ISR lesions, especially for those with small vessels. Our study was unable to confirm that there were no significant differences between EES and BES because of the small numbers involved and the differences in the available stent lengths.

Recently, drug-coated balloons (DCB) have emerged as a potential alternative to the current treatment of ISR<sup>12</sup>. Although both DES and DCB are recommended for the treatment of ISR of DES, the RIBS IV study, a recent randomised controlled study based on relatively simple angiographic scenarios, demonstrated that EES implantation provided long-term clinical and angiographic results superior to DCB angioplasty<sup>13</sup>, whereas Habara et al reported the inferiority of DES implantation to DCB angioplasty in the treatment of non-focal type DES restenosis<sup>14</sup>. The strategy selection according to the lesion characteristics may be important.

## Limitations

First, this is a single-centre, small-scale, highly selective and retrospective study. However, this study is valuable because we included all consecutive patients undergoing second-generation DES implantation for ISR of DES, and serial clinical and angiographic outcomes with a high follow-up rate were obtained. Second, intravascular ultrasound was not used in any patient at the time of DES implantation. Finally, the available lengths of BES and EES were different. Hence, the results may be biased.

## Conclusion

Small vessel and non-focal type restenosis are predictors of recurrent restenosis after second-generation DES implantation for ISR of DES.

### Impact on daily practice

More attention should be paid to small vessel and non-focal type restenosis when performing second-generation DES implantation for ISR of DES to reduce the incidence of recurrent restenosis.

## Acknowledgements

We thank Miho Kobayashi for her writing assistance.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

## References

1. Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schömig A; ISAR-DESIRE Study Investigators. Sirolimus-eluting stent or paclitaxel-

eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA*. 2005;293:165-71.

2. Koizumi T, Fitzgerald PJ, Honda Y, Ellis SG, Kent K, Martin SL, Brown CL, Masud AR, Patterson JB, Greenberg J, Friedman M, Uchida T, Stone GW. Vascular responses to the multiple overlapped paclitaxel-eluting stents for the treatment of bare-metal in-stent restenotic lesions: angiographic and intravascular ultrasound analysis from the TAXUS-V ISR trial. *Cardiovasc Resusc Med*. 2010;11:140-8.

3. Steinberg DH, Gaglia MA Jr, Pinto Slottow TL, Roy P, Bonello L, De Labriolle A, Lemesle G, Torguson R, Kineshige K, Xue Z, Suddath WO, Kent KM, Satler LF, Pichard AD, Lindsay J, Waksman R. 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.

4. Mehilli J, Byrne RA, Tiroch K, Pinieck S, Schulz S, Kufner S, Massberg S, Laugwitz KL, Schömig A, Kastrati A; 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.

5. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner GS, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Boxberger M, Speck U, Degenhardt R, Scheller B. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119:2986-94.

6. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J*. 2006;151:1260-4.

7. Yamashita K, Ochiai M, Yakushiji T, Ebara S, Okabe T, Yamamoto MH, Saito S, Hoshimoto K, Isomura N, Araki H, Obara C. Repeat drug-eluting stent implantation for in-stent restenosis: first- or second-generation stent. *J Invasive Cardiol*. 2012;24:574-8.

8. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100:1872-8.

9. Byrne RA, Neumann FJ, Mehilli J, Pinieck S, Wolff B, Tiroch K, Schulz S, Fusaro M, Ott I, Ibrahim T, Hausleiter J, Valina C, Pache J, Laugwitz KL, Massberg S, Kastrati A; ISAR-DESIRE 3 investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet*. 2013;381:461-7.

10. Ge H, Zhang Q, Zhou W, He Q, Han ZH, He B. Efficacy and safety of drug-eluting stent implantation for the treatment of in-stent restenosis occurring within bare-metal stent and drug-eluting stent. *J Zhejiang Univ Sci B*. 2010;11:553-60.

11. Habara S, Mitsudo K, Goto T, Kadota K, Fujii S, Yamamoto H, Kato H, Takenaka S, Fuku Y, Hosogi S, Hirono A, Yamamoto K,

Tanaka H, Hasegawa D, Nakamura Y, Tasaka H, Otsuru S, Okamoto Y, Yamada C, Miyamoto M, Inoue K. The impact of lesion length and vessel size on outcomes after sirolimus-eluting stent implantation for in-stent restenosis. *Heart*. 2008;94:1162-5.

12. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541-619.

13. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García del Blanco B, García-Touchard A, López-Minguéz JR, Benedicto A, Masotti M, Zueco J, Iñiguez A, Velázquez M, Moreno R, Mainar V, Domínguez A, Pomar F, Melgares R, Rivero F, Jiménez-Quevedo P, Gonzalo N, Fernández C, Macaya C; RIBS IV Study Investigators (under auspices of Interventional Cardiology Working Group of Spanish Society of Cardiology). A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. *J Am Coll Cardiol*. 2015;66:23-33.

14. Habara S, Kadota K, Kanazawa T, Ichinohe T, Kubo S, Hyodo Y, Otsuru S, Hasegawa D, Tada T, Tanaka H, Fuku Y, Goto T, Mitsudo K. Paclitaxel-coated balloon catheter compared with drug-eluting stent for drug-eluting stent restenosis in routine clinical practice. *EuroIntervention*. 2016;11:1098-105.