EuroIntervention 2012;8:701-707

Angiographic and clinical outcome of percutaneous coronary intervention for in-stent restenosis of bifurcated lesions

Santiago Federico Coroleu[1], MD; Maria De Vita[2], MD, PhD; Francesco Burzotta[1]*, MD, PhD; Carlo Trani[1], MD; Italo Porto[1], MD, PhD; Giampaolo Niccoli[1], MD, PhD; Antonio Maria Leone[1], MD, PhD; Antonella Tommasino[1], MD; Giovanni Paolo Talarico[1], MD; Giovanni Schiavoni[1], MD; Filippo Crea[1], MD

1. Institute of Cardiology, Catholic University of Sacred Heart, Rome, Italy; 2. Cardiology Department, Morgagni Hospital, Forli, Italy

KEYWORDS

- bifurcated lesions
- in-stent restenosis
- percutaneous coronary intervention

Abstract

Aims: Restenosis and bifurcated lesions represent technically challenging lesions for percutaneous coronary interventions (PCI). Data regarding procedural and clinical outcome of re-PCI for restenosis of stented bifurcated lesions are lacking. Our aims were to evaluate angiographic and procedural results and one-year clinical outcome of PCI for restenosis of stented bifurcated lesions.

Methods and results: Consecutive patients undergoing PCI for restenosis of one bifurcated lesion previously treated by stent implantation at our centre entered the study. The primary endpoint was angiographic and procedural success, defined as final residual stenosis ≤30% in the main vessel with TIMI 3 flow in both MV and side branch, and stenosis ≤50% in the SB without death, myocardial infarction or target vessel revascularisation during hospitalisation. The secondary endpoint was the incidence of major adverse cardiac events at one-year clinical follow-up. The study population included 64 patients treated by PCI on a single restenotic bifurcated lesion. Angiographic and procedural success was achieved in 61 cases (95.3%) whereas the three cases of failure were due to SB residual stenosis >50%. At one year, MACE rate was 18.7% (12/64) with rates of cardiac death, MI and TVR of 1.6% (1/64), 6.2% (4/64) and 18.7% (12/64), respectively. No cases of stent thrombosis occurred. Patients treated by a single drug-eluting stent (DES) on main vessel (MV) had a significant lower rate of MACE at one year as compared to patients treated with balloon only PCI or by double-stenting technique or with a BMS, irrespective of the strategy adopted: 4/37 (10.8%) vs. 8/27 (29.6%); p=0.04.

Conclusions: PCI in restenotic bifurcated lesions can be a good treatment option with high rates of angiographic and procedural success and an acceptable rate of long-term MACE. The use of a single DES implantation may be a promising strategy as it is associated with lower rates of MACE in the long term.

**Corresponding author: Via Prati Fiscali 158, 00141 Rome, Italy.*
E-mail: f.burzotta@rm.unicatt.it

DOI: 10.4244/EIJV8I6A109

Introduction

Bifurcated lesions and in-stent restenosis (ISR) represent two of the most challenging issues in percutaneous coronary interventions (PCI)[1-5], both types of intervention being characterised by an increased technical complexity and higher risk of recurrence. Initially, balloon angioplasty was considered to be an effective treatment of ISR but it soon became evident that the recurrent ISR rate was high. Later, directional and rotational atherectomy[6], laser[7] and cutting balloon[8] failed to demonstrate superiority compared with balloon angioplasty. Coronary brachytherapy results proved to be highly effective in patients with diffuse ISR but this strategy was limited by logistic constraints[9,10]. In recent years, drug-eluting stents (DES) and drug-eluting balloons (DEB) have emerged as promising new alternatives for patients with ISR[11-13], but its optimal treatment remains controversial.

Bifurcation interventions, when compared with non-bifurcation interventions, have a lower rate of procedural success and a higher rate of restenosis[1-3]. Various techniques have been developed to optimise the treatment of this subset of lesions[14-19]. The introduction of DES has allowed the reduction of event rates, in particular the rate of main vessel (MV) restenosis[20].

Given such premises, treatment of restenosis of bifurcated lesions previously treated by stent implantation can be recognised as highly challenging. The aim of this study was to assess the angiographic and procedural results and the long-term clinical outcome of PCI for restenosis in a stented bifurcation.

Methods

Between March 2005 and December 2007, all consecutive patients treated by PCI for significant restenosis of a single bifurcated lesion previously treated by stent implantation at our institution were included in this study. Procedural, angiographic and clinical data were prospectively collected for all the study population and entered into an electronic database (Cardio-planet V.3.0.8, Ebit Aet S.p.A., Genoa, Italy). Patients aged <18 years or unable to give informed consent, with known hypersensitivity or contraindication to aspirin, clopidogrel, heparin, ticlopidine or contrast dye, with chronic total occlusion, ST-elevation myocardial infarction undergoing primary PCI, cardiogenic shock and bifurcation with MV and/or side branch (SB) diameter ≤ 2.0 mm were excluded.

PERCUTANEOUS CORONARY INTERVENTIONS

All procedures were performed by interventional cardiologists who met minimal proficiency criteria of performance of ≥100 interventional cases per year. PCI technique was left to the operator's discretion. Final kissing balloon was always attempted in the case of a double-stenting technique, while it was left to the operator's discretion in the case of single stent implantation.

All patients were pretreated with aspirin and clopidogrel. A 300 mg loading dose of clopidogrel before the index procedure was administered if patients were not pretreated. The double antiplatelet therapy was continued in all the patients for at least 12 months. During the procedure, patients received intravenous unfractionated heparin to maintain an activated clotting time between 250 and 300 seconds. The administration of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion.

After PCI, all patients underwent a post-PCI electrocardiogram (ECG) as well as six-hour and 24-hour assessment of creatine-kinase (CK) and creatine-kinase-MB (CK-MB) levels. Thereafter, additional ECGs and enzyme evaluations were performed if clinically indicated.

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS

Matched orthogonal views were used for three-dimensional quantitative coronary analysis (QCA) (CardioOp-B System; Paieon Medical Ltd, Park Afek, Israel)[21] before and after treatment. Angiograms were analysed off-line by two independent investigators blinded to patient identities and outcomes.

STUDY ENDPOINTS

Primary endpoints were angiographic and procedural success. Angiographic success was defined as final residual stenosis ≤30% in the MV with TIMI 3 flow in both MV and SB and stenosis ≤50% in the SB. Procedural success was defined as angiographic success without the occurrence of cardiac death, MI or TVR during hospitalisation.

The secondary endpoint was the incidence of major adverse cardiac events (MACE) defined as the composite of cardiac death, myocardial infarction (MI) and target vessel revascularisation (TVR) at one-year clinical follow-up and the incidence of stent thrombosis. In all cases, the one-year follow-up was performed by clinical visit or phone call. All deaths were considered cardiac unless otherwise documented.

MI was defined as recurrent chest pain or ischaemia equivalent, or the appearance of new pathological Q-waves in ≥2 ECG contiguous leads with post-procedure CK-MB levels above normal or as an elevation of post-procedural CK levels >2 times normal levels with elevated CK-MB in the absence of chest pain or ischaemia equivalent, or pathological Q-waves[22].

TVR was defined as clinically-driven revascularisation by either PCI or coronary artery bypass grafting (CABG) involving the treated vessel.

Stent thrombosis (ST) was classified by the Academic Research Consortium definition as definite, probable or possible, and as early (0-30 days), late (31-360 days) or very late (>360 days)[23].

Statistical analysis

Data were expressed as mean±SD for continuous variables and frequencies, and percentages for the categorical variables. For comparison of categorical data, χ^2 test or the Fisher exact test was performed. For comparison of continuous variables, a two-tailed paired Student's t-test was used. Statistical significance was declared if the two-sided p value was <0.05. All analyses were performed using SPSS version 14 (SPSS Inc, Chicago, IL, USA).

Results

STUDY POPULATION

The study population included 64 patients (49 men, age 68±8 years) treated by PCI on a single restenotic bifurcated lesion. Main clinical characteristics of the study population are summarised in **Table 1**.

Table 1. Baseline clinical characteristics.

Clinical characteristics and risk factors	n (%)
Age (mean±SD)	68.1±8.8
Male gender	49 (76)
Diabetes mellitus	20 (31)
Dyslipidaemia	42 (66)
Hypertension	50 (78)
Active smoking	8 (13)
EuroSCORE (mean±SD)	3.5±2.5
History of cardiovascular disease	
Previous CABG	9 (14)
Previous MI	26 (41)
Three-vessel disease	19 (30)
LMCA disease	7 (11)
Left ventricular function <50%	30 (47)
Clinical presentation	
Stable angina	27 (42)
Silent ischaemia	17 (27)
Unstable angina/non-ST-elevation myocardial infarction	20 (31)

CABG: coronary artery bypass graft; MI: myocardial infarction; LMCA: left main coronary artery

Table 2. Baseline angiographic characteristics and procedural characteristics.

Baseline angiographic and PCI characteristics	n (%)
Target bifurcation lesion	
Distal LMCA	5 (8)
Left anterior descending - diagonal	32 (50)
Left circumflex - marginal branch	23 (36)
Right coronary - posterior descending artery	4 (6)
Stent distribution after first PCI on target lesions	
MV stenting	46 (72)
SB stenting	4 (6)
MV and SB stenting	14 (22)
Restenotic bifurcation lesions	
MV restenosis (Medina 1,1,0 - 1,0,0 - 0,1,0)	24 (38)
SB restenosis (Medina 0,0,1)	6 (9)
MV and SB restenosis (Medina 1,1,1 - 1,0,1 - 0,1,1)	34 (53)
Angulation	
Y type (<70°)	40 (63)
T type (>70°)	24 (37)
Vascular access	
Radial	41 (64)
Femoral	23 (36)
Stenting technique	
Single stenting	41 (66)
Double stenting*	8 (12)
Balloon angioplasty	15 (22)
Stent implantation	
DES	44 (90)
BMS	5 (10)
Final kissing balloon	45 (70)

LMCA: left main coronary artery; MV: main vessel; SB: side branch; *T-stenting: 2; TAP-stenting: 4; crush stenting: 2

Briefly, 31% were diabetics, 31% were admitted for acute coronary syndrome and 47% had impaired left ventricular function. Left main coronary artery disease and three-vessel disease were present in 10.9% and 29.6%, respectively.

PRE-PCI ANGIOGRAPHIC CHARACTERISTICS AND PERCUTANEOUS CORONARY INTERVENTIONS

The angiographic characteristics of the study population are shown in **Table 2**. In all cases, the strategy selected was decided by the operator according to: 1) angiographic lesion characteristic; 2) complexity of the case; 3) personal preferences. The bifurcation most frequently involved was the left anterior descending artery-diagonal (50% of the cases). The stent distribution after the first PCI on target bifurcation lesions was: MV stenting only 72% (46/64), MV+SB stenting 22% (14/64) and SB stenting only 6% (4/64) **(Figure 1)**. The restenotic process involved both MV and SB in 53% (34/64) of the cases, MV only in 38% (24/64) and SB only in 9% (6/64) **(Figure 2)**.

Procedural data are are reported in **Table 2**. In particular, 66% (41/64) of patients received single stenting on MV, 12% (8/64) double stenting and 22% (15/64) balloon angioplasty only. A DES was implanted in 90% of patients receiving a stent (44/49). Final kissing balloon was performed in 70% (45/64) of cases (always in double-stenting technique and 56% in single-stenting cases).

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS

MV and SB three-dimensional QCA results at baseline and after procedure are summarised in **Table 3**. The CardioOp-B system[21] was able to provide automatic three-dimensional reconstructed analysis in 96.9% of cases (62 patients). Major improvements in diameter and area were documented in both MV and SB by 3-D-QCA analysis (main vessel MLA 1.22±0.7 vs. 4.43±2.26 mm^2; main vessel MLD 1.07±0.44 vs. 2.44±0.56 mm; side branch MLA 1.08±1.02 vs. 2.20±1.31 mm^2 and side branch MLD 1.10±0.67 vs. 1.75±0.65 mm). No significant differences in the QCA results were found according to the technique adopted.

ANGIOGRAPHIC, PROCEDURAL AND CLINICAL OUTCOMES

Angiographic success was achieved in 61 cases (95.3%). The three cases of failure were due to SB residual stenosis >50%. The rate of procedural success was 95.3%, as no in-hospital MACE occurred. Clinical follow-up was available in all patients at one year. Total MACE rate was 18.7% (12/64), with rates of cardiac death, MI and TVR of 1.6% (1/64), 6.2% (4/64) and 18.7% (12/64), respectively.

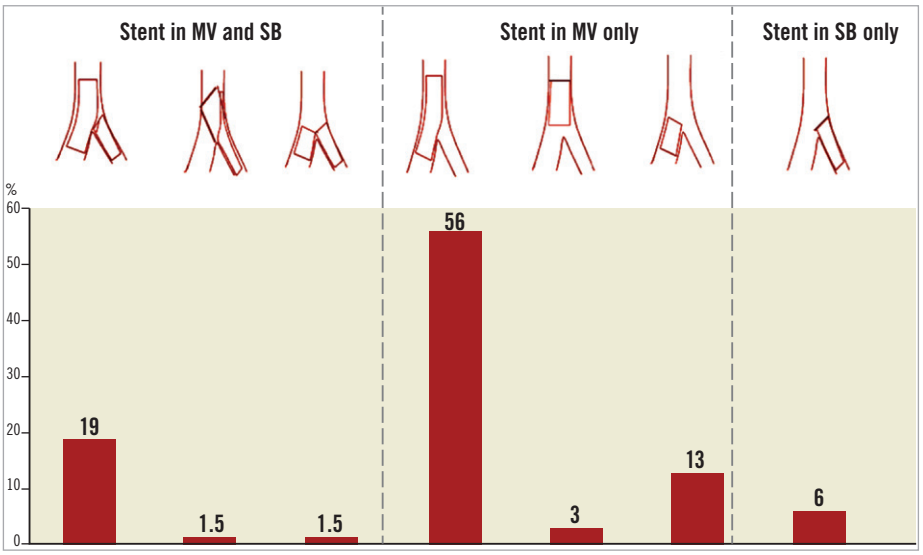

Figure 1. *Stent distribution after first PCI in target bifurcation lesions.*

The only cardiac death was observed in a patient who suffered NSTEMI due to repeated bifurcation ISR sent to cardiac surgery and who died in the postoperative period. Concerning the patients who presented with TVR at follow-up, nine (14%) were treated by re-PCI and three (4.7%) by CABG. There were no cases of stent thrombosis.

Patients treated with double-stenting techniques had a non-significant higher rate of MACE at one year as compared to patients treated by single stent on MV (2/8 [25%] vs. 6/41 [14%]; p=0.27). Kissing balloon (KB) technique was performed in 45 cases (100% in double-stenting techniques); in this group, MACE was present in 10/45 (22.2%) vs. 2/19 (10.5%) in cases without KB (p=0.23). Results and details about each strategy are shown in **Table 4**.

To evaluate MACE according to the stent used, we allocated patients to one of two groups: DES patients vs. non-DES patients (BMS or balloon angioplasty only). A trend was observed towards a lower incidence of MACE at one year in the DES group as compared to the non-DES group (4/44 [9%] vs. 4/19 [21%]; p=0.18). We then compared the rate of MACE at one year in the group of patients treated by a single DES on MV with the rate of MACE at one year in the group of patients treated with balloon only PCI or double-stenting technique or BMS, irrespective of the strategy adopted.

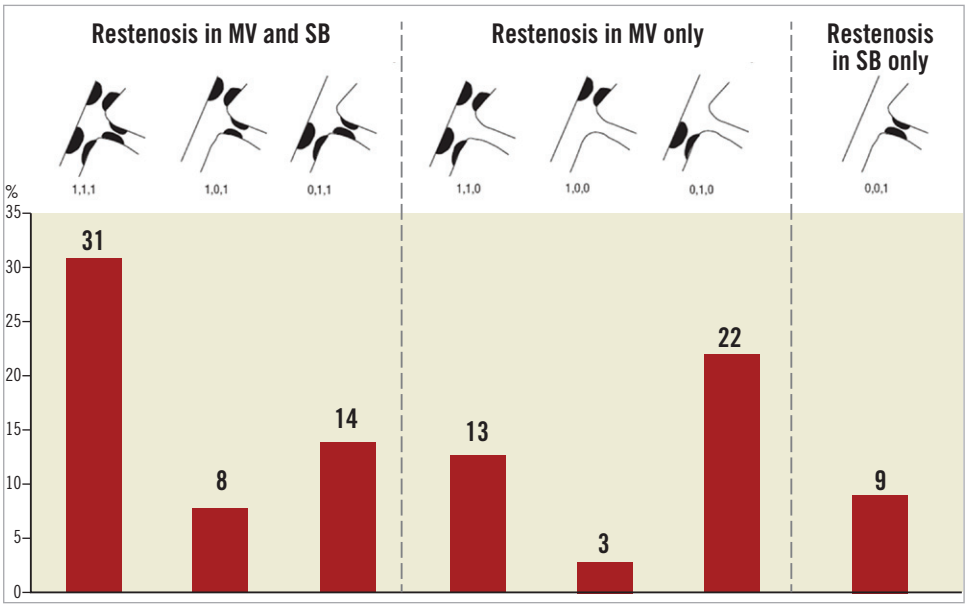

Figure 2. *Baseline angiographic characteristics of the restenotic bifurcation lesions.*

Table 3. Three-dimensional quantitative coronary angiographic analysis.

	Baseline	Post PCI
Main vessel		
RVD, mm	2.13±0.62	2.77±0.57
MLD, mm	1.07±0.44	2.44±0.56
MLA, mm^2	1.22±0.7	4.43±2.26
Diameter stenosis (%)	68.9±17.4	21.0±18.0
Lesion length, mm	12.7±3.0	–
Side branch		
RVD, mm	1.87±0.63	2.27±0.66
MLD, mm	1.10±0.67	1.75±0.65
MLA, mm^2	1.08±1.02	2.20±1.31
Diameter stenosis (%)	59.64±23.74	33.80±23.10
Lesion length, mm	12.29±3.48	–

The patients treated by a single DES had a significantly lower rate of MACE at one year as compared to the patients treated by all of the other strategies adopted (4/37 [10.8%] vs. 8/27 [29.6%]; p=0.04) **(Figure 3)**.

Interestingly, all the events at one year registered in the group of patients treated with a single DES were TVR, all treated by a re-PCI.

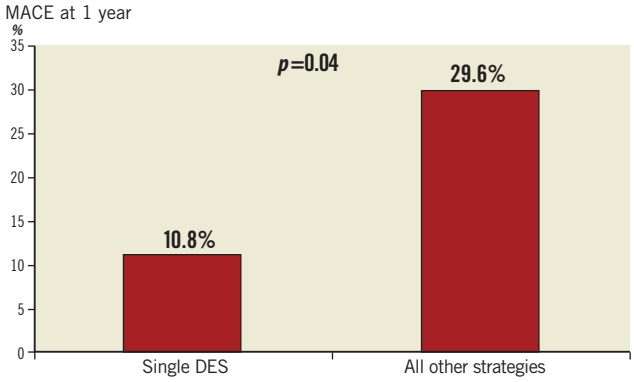

Figure 3. *MACE at 1 year in patients treated with a single DES strategy versus MACE at 1 year in patients treated with all other strategies.*

Discussion

Our study is one of the first specific reports on PCI treatment of in-stent restenosis in bifurcated lesions and focused on the angiographic success rate of such complex procedures as well as on their clinical efficacy in terms of in-hospital and long-term clinical outcome. To the best of our knowledge, there are only two studies analysing this issue: the study from Costa et al[24] which reported the outcomes of five patients treated with brachytherapy for bifurcation-ISR and the experience of Kim et al who reported DES treatment for specific LMCA BMS restenosis[25]. In the remaining studies which evaluated ISR, bifurcation restenoses were analysed along with other lesions, despite the known differences in terms of treatment techniques and outcomes.

Data from several studies show that MACE rates after treatment of ISR or bifurcated lesions is about 15% for each condition[1,2,26,27]. Interestingly, in our population the angiographic success rate was high with only three cases of failure due to SB residual stenosis >50%. Moreover, no coronary events occurred during hospitalisation after the procedure. Finally, MACE rate at one year was 18.7% and was principally driven by TVR.

The operator's decision to use DES in most of the patients corresponds with data coming from both ISR and bifurcation trials, where DES improved angiographic success and clinical outcome when compared with BMS and balloon angioplasty[5,12,20,28-30]. Likewise in our study, we found a non-significant trend to better clinical outcomes in patients treated by DES as opposed to BMS or balloon angioplasty only. Moreover, we found a significantly better outcome with single DES implantation as compared to all other strategies, showing concordance with previous studies on bifurcation lesions reporting clinical advantages of provisional stenting as compared to double-stenting techniques[31,32]. Interestingly, we found a trend towards a lesser incidence of MACE in patients in whom the KB technique was not performed: these finding can probably be explained by less complex bifurcation lesions and by the treatment technique.

Study limitations

The drawbacks of this study are typical of single-centre observational studies[33]. Thus, no definitive conclusions on the optimal technique for the treatment of ISR of bifurcated lesions can be derived

Table 4. Procedural characteristics and results according to different strategies.

	Balloon angioplasty only	Single stenting	T-stenting	TAP-stenting	Crush stenting
Total procedures	15	41	2	4	2
MACE	4	6	1	1	0
Final kissing balloon	14	23	2	4	2
Balloon - stent diameter	3.08±0.45	3.08±0.5	MV 3.5±0 SB 2.25±0	MV 3.12±0.47 SB 2.75±0.5	MV 3.12±0.5 SB 2.5±0
Stent length	NA	20.45±14.7	MV 21.5±9.1	MV 26.5±17.0	MV 22.5±13.4
			SB 17±1.4	SB 20±4.24	SB 15.5±3.5
NA: not available					

from our results. As the stenting technique was left to the operator's discretion, it is possible that more complex procedures were performed in more complex lesions, resulting in a potential bias of selection. Other limitations include the small study population and the lack of IVUS data, especially important in these complex lesions. During the study, drug-eluting balloons were not available in our institution; their role in this subset of lesions requires evaluation.

Conclusions

In an unselected population of patients with in-stent restenosis of bifurcated lesions, treatment with PCI appears to be safe and effective with high rates of angiographic and procedural success and acceptable rates of long-term MACE. Moreover, provisional single DES implantation appears to be the best option, as it is associated with a lower rate of MACE. Further studies are warranted to assess the best treatment strategy for this complex subset of lesions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Al Suwaidi J, Yeh W, Cohen HA, Detre KM, Williams DO, Holmes DR. Immediate and one-year outcome in patients with coronary bifurcation lesions in the modern era (NHLBI dynamic registry). *Am J Cardiol.* 2001;87:1139-44.

2. Garot P, Lefevre T, Savage M, Louvard Y, Bamlet WR, Willerson JT, Morice MC, Holmes DR. Nine-month outcome of patients treated by percutaneous coronary interventions for bifurcation lesions in the recent era: a report from the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial. *J Am Coll Cardiol.* 2005;46:606-12.

3. Yamashita T, Nishida T, Adamian MG, Briguori C, Vaghetti M, Corvaja N, Albiero R, Finci L, Di Mario C, Tobis JM, Colombo A. Bifurcation lesions: two stents versus one stent--immediate and follow-up results. *J Am Coll Cardiol.* 2000;35:1145-51.

4. Radke PW, Kaiser A, Frost C, Sigwart U. Outcome after treatment of coronary in-stent restenosis; results from a systematic review using meta-analysis techniques. *Eur Heart J.* 2003;24:266-73.

5. 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.

6. vom Dahl J, Dietz U, Haager PK, Silber S, Niccoli L, Buettner HJ, Schiele F, Thomas M, Commeau P, Ramsdale DR, Garcia E, Hamm CW, Hoffmann R, Reineke T, Klues HG. Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). *Circulation.* 2002;105:583-8.

7. Giri S, Ito S, Lansky AJ, Mehran R, Margolis J, Gilmore P, Garratt KN, Cummins F, Moses J, Rentrop P, Oesterle S, Power J, Kent KM, Satler LF, Pichard AD, Wu H, Greenberg A, Bucher TA, Kerker W, Abizaid AS, Saucedo J, Leon MB, Popma JJ. Clinical and angiographic outcome in the laser angioplasty for restenotic stents (LARS) multicenter registry. *Catheter Cardiovasc Interv.* 2001;52:24-34.

8. Albiero R, Silber S, Di Mario C, Cernigliaro C, Battaglia S, Reimers B, Frasheri A, Klauss V, Auge JM, Rubartelli P, Morice MC, Cremonesi A, Schofer J, Bortone A, Colombo A; RESCUT Investigators. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). *J Am Coll Cardiol.* 2004;43:943-9.

9. Waksman R, Ajani AE, White RL, Chan R, Bass B, Pichard D, Satler LF, Kent KM, Torguson R, Deible R, Pinnow E, Lindsay J. Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. *Circulation.* 2004;109:340-4.

10. Holmes DR Jr, Teirstein P, Satler L, Sketch M, O'Malley J, Popma JJ, Kuntz RE, Fitzgerald PJ, Wang H, Caramanica E, Cohen SA; SISR Investigators. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA.* 2006;295:1264-73.

11. Dibra A, Kastrati A, Alfonso F, Seyfarth M, Pérez-Vizcayno MJ, Mehilli J, Schömig A. Effectiveness of drug-eluting stents in patients with bare-metal in-stent restenosis: meta-analysis of randomized trials. *J Am Coll Cardiol.* 2007;49:616-23.

12. Alfonso F, Pérez-Vizcayno MJ, Hernandez R, Bethencourt A, Martí V, López-Mínguez JR, Angel J, Mantilla R, Morís C, Cequier A, Sabaté M, Escaned J, Moreno R, Bañuelos C, Suárez A, Macaya C; 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.

13. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, Böhm M, Speck U. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol*. 2008;97:773-81.

14. Brunel P, Lefevre T, Darremont O, Louvard Y. Provisional T-stenting and kissing balloon in the treatment of coronary bifurcation lesions: results of the French multicenter «TULIPE» study. *Catheter Cardiovasc Interv.* 2006;68:67-73.

15. Chevalier B, Glatt B, Royer T, Guyon P. Placement of coronary stents in bifurcation lesions by the "culotte" technique. *Am J Cardiol.* 1998;82:943-9.

16. Pan M, Suárez de Lezo J, Medina A, Romero M, Segura J, Ramírez A, Pavlovic D, Hernández E, Ojeda S, Adamuz C. A stepwise strategy for the stent treatment of bifurcated coronary lesions. *Catheter Cardiovasc Interv.* 2002;55:50-7.

17. Fort S, Lazzam C, Schwartz L. Coronary 'Y' stenting: a technique for angioplasty of bifurcation stenoses. *Can J Cardiol.* 1996;12:678-82.

18. Colombo A, Stankovic G, Orlic D, Corvaja N, Liistro F, Airoldi F, Chieffo A, Spanos V, Montorfano M, Di Mario C.

Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. *Catheter Cardiovasc Interv.* 2003;60:145-51.

19. Burzotta F, Gwon HC, Hahn JY, Romagnoli E, Choi JH, Trani C, Colombo A. Modified T-stenting with intentional protrusion of the side-branch stent within the main vessel stent to ensure ostial coverage and facilitate final kissing balloon: the T-stenting and small protrusion technique (TAP-stenting). Report of bench testing and first clinical Italian-Korean two-centre experience. *Catheter Cardiovasc Interv.* 2007;70:75-82.

20. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation.* 2004;109:1244-9.

21. Dvir D, Marom H, Assali A, Kornowski R. Bifurcation lesions in the coronary arteries: early experience with a novel 3-dimensional imaging and quantitative analysis before and after stenting. *EuroIntervention.* 2007;3:95-9.

22. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention.* 2010;5:871-4.

23. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

24. Costa R, Joyal M, Harel F, Fox T, Crocker I, Arsenault A, Gregoire J, Bonan R. Treatment of bifurcation in-stent restenotic lesions with beta radiation using strontium 90 and sequential positioning pullback technique: procedural details and clinical outcomes. *J Invasive Cardiol.* 2003;15:469-73.

25. Kim HS, Kim YH, Lee SW, Park DW, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. Safety and effectiveness of sirolimus-eluting stent implantation for in-stent restenosis of the unprotected left main coronary artery. *Int J Cardiol.* 2008;124:118-20.

26. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation.* 2004;109:190-5.

27. Sheiban I, Chiribiri A, Beninati S, Moretti C, Omede P, Sciuto F, Marra WG, Biondi-Zoccai G, Bollati M, Gambino A, Trevi GP. Sirolimus-eluting stents for the treatment of bare-metal in-stent restenosis: long-term clinical follow up. *J Invasive Cardiol.* 2007;19:174-80.

28. Thuesen L, Kelbaek H, Kløvgaard L, Helqvist S, Jørgensen E, Aljabbari S, Krusell LR, Jensen GV, Bøtker HE, Saunamäki K, Lassen JF, van Weert A; SCANDSTENT Investigators. Comparison of sirolimus-eluting and bare metal stents in coronary bifurcation lesions: subgroup analysis of the Stenting Coronary Arteries in Non-Stress/Benestent Disease Trial (SCANDSTENT). *Am Heart J.* 2006;152:1140-5.

29. Tanabe K, Serruys PW, Grube E, Smits PC, Selbach G, van der Giessen WJ, Staberock M, de Feyter P, Müller R, Regar E, Degertekin M, Ligthart JM, Disco C, Backx B, Russell ME. TAXUS III Trial: in-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. *Circulation.* 2003;107:559-64.

30. Alfonso F, Pérez-Vizcayno MJ, Hernández R, Bethencourt A, Martí V, López-Mínguez JR, Angel J, Iñiguez A, Morís C, Cequier A, Sabaté M, Escaned J, Jiménez-Quevedo P, Bañuelos C, Suárez A, Macaya C; RIBS-II Investigators. Long-term clinical benefit of sirolimus-eluting stents in patients with in-stent restenosis results of the RIBS-II (Restenosis Intra-stent: Balloon angioplasty vs. elective sirolimus-eluting Stenting) study. *J Am Coll Cardiol.* 2008;52:1621-7.

31. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, Niemelä M, Kervinen K, Jensen JS, Galløe A, Nikus K, Vikman S, Ravkilde J, James S, Aarøe J, Ylitalo A, Helqvist S, Sjögren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Lassen JF, Thuesen L; Nordic PCI Study Group. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation.* 2006;114:1955-61.

32. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, Maccarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation.* 2010;121:1235-43.

33. Biondi-Zoccai GGL, Agostoni P, Abbate A. Parallel hierarchy of scientific studies in cardiovascular medicine. *Ital Heart J.* 2003;4:819-20.