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Safety and Efficacy of Drug-Eluting Balloons in Percutaneous Treatment of Bifurcation Lesions: The DEBIUT (*D*rug-*E*luting *B*alloon in *BI*furcaton *UT*recht) Registry

James C. Fanggiday, MD, Pieter R. Stella,* MD, Siyrous Hoseyni Guyomi, MD, and Pieter A. Doevendans, MD, PhD

Objectives: To evaluate outcomes after percutaneous coronary intervention (PCI) with a drug-eluting balloon catheter (paclitaxel-coated) in patients with coronary artery bifurcation lesions. Background: The current practice of provisional stenting of the main branch (MB) is reasonable; however, long-term results of side-branch (SB) treatment are suboptimal. The use of drug-eluting stents has not improved these results, regardless of the implantation technique, and could potentially lead to a significant increase in (late) thrombotic events. To evaluate short-term safety and efficacy of a drug-eluting balloon (DEB) in patients with bifurcation lesions followed by provisional stenting of the main branch, we set up the DEBIUT Registry. Methods: This registry enrolled 20 eligible patients with coronary artery bifurcation lesions. Patients received a PCI with a paclitaxel-coated balloon catheter, followed by provisional stenting of the MB with a bare-metal stent. Acute angiographic and clinical follow-up were performed after 1 and 4 months. Results: The procedure was successful in all patients. The use of sequential predilatation with DEB was safe and well tolerated. No acute or subacute closure of side branches occurred after treating with DEB. All patients were treated according to the provisional stenting technique; no stents were placed in the SB. At 4-month follow-up no major acute coronary events and no subacute vessel closure were reported. Conclusion: The use of a drug-eluting balloon in patients with bifurcation lesions was effective and safe up to 4 months following PCI in patients with coronary artery bifurcation lesions. © 2008 Wiley-Liss, Inc.

Key words: drug delivery (DDEL); percutaneous coronary intervention (PCI); restenosis (RSTN)

INTRODUCTION

The treatment of bifurcated coronary artery stenosis remains one of the most difficult and challenging lesions. Percutaneous coronary intervention (PCI) in bifurcation lesions (BiF) is associated with lower immediate angiographic and clinical success and higher rates of restenosis, which furthermore, are more challenging to treat compared to non-bifurcated lesions. The introduction of the drug-eluting stents (DES) seems to have had less of an impact on PCI results [1,2] in bifurcation lesions. Furthermore, it has been reported recently that especially in complex lesions, rates of subacute thrombosis and even mortality are high in patients treated with drug-eluting stents [3].

The implementation of a variety of bifurcation-specific PCI techniques [4–14] has improved the acute angiographic and procedural success to acceptable rates (more than 95% and ~90%, respectively) [1,2,15]. Current knowledge and experience provide almost universal agreement that whenever possible, stenting only of the main branch with the jailed-wire technique and final kissing balloon should be the strategy of choice [16]. Thus the current practice of stenting only (whenever possible) the main branch with DES is reasonable,

Department of Heart and Lung, University Medical Center Utrecht, Utrecht, The Netherlands

*Correspondence to: P.R. Stella, MD, University Medical Center Utrecht, Heidelberglaan 100, Room E.01.207, 3584 CX, Utrecht, Netherlands. E-mail: p.stella@umcutrecht.nl

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but the results of side-branch treatment are suboptimal and there is room for improvement especially regarding long term side branch treatment.

Recently, nonstent-based local balloon delivery systems of antiproliferative drugs have been developed. These drug eluting balloons might improve the current results of side-branch treatment and overcome some of the late disadvantages of the drug-eluting stents. Such an approach would obviously not halt recoil, but it should efficiently diminish the component of restenosis due to proliferation/hyperplasia [17], especially in bifurcation lesions. If its side-branch-restenosis prevention capability is proved, the temptation to deploy a second stent in the side branch may be best resisted, simplifying the procedure and in turn may improve overall outcomes of PCI in bifurcation lesions with regard to restenosis and late-stent thrombosis.

The aim of this registry was to study the safety and efficacy of the use of drug-eluting balloons in bifurcation lesions with sequential predilatation of side branch and main branch, followed by provisional stenting of the main branch.

MATERIALS AND METHODS

Registry Setup

Patients with bifurcation lesions were enrolled and received PCI with the DIOR drug-eluting balloon catheter. The registry was notified and approved by the institutional ethics committee, and all patients provided written informed consent.

Inclusion/Exclusion Criteria

Patients with lesions involving a de novo coronary artery bifurcation lesion located at a side-branch point with a main vessel diameter of $\geq$2.5 mm and with a SB diameter of $\geq$2 mm were eligible for the study. See Table I for inclusion and exclusion criteria.

TABLE I. Inclusion/Exclusion Criteria

Inclusion criteria
- Stable angina pectoris (CCS class 1, 2, 3, 4) or unstable angina and documented ischemia or silent ischemia.
- Patients eligible for coronary revascularization.
- The target bifurcation lesion has a major native coronary artery ($\geq$2.5 mm) with a stenosis $\geq$50% (on visual assessment) located at a side branch ($\geq$2 mm).
- Patient must be acceptable for CABG.
- De novo lesion.
- The main vessel lesion can be covered by one stent (up to 32 mm).
- Only one target lesion can be included in the study: other lesions in different vessels are successfully treated before the treatment of the target lesion (residual stenosis <30%; stent well deployed; no residual dissection; normal TIMI flow; no chest pain; ECG unchanged compared to pre-procedural ECG).
- Signed informed consent.

Exclusion criteria
- Patient unable to give informed consent.
- Left ventricular ejection fraction $\leq$30%.
- Patients with a previous PCI in the target vessel.
- Patients with left main disease.
- Severe calcifications with an undilatable lesion during balloon predilatation.
- History of bleeding diathesis.
- Untreated significant lesion >50% diameter stenosis remaining proximal or distal to the target intervention.
- Acute myocardial infarction.
- Allergy to contrast and/or required anti-platelet medication.

CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

Dior™ Balloon

The Dior™ balloon has a paclitaxel-coated balloon surface, containing 3 μg paclitaxel/mm^2. The drug is contained within the nanoporous balloon surface, with paclitaxel microcrystals (following dimethylsulfate treatment). For protection of potential wash off effect of the drug during manipulation in the guide and vessel, the drug is hidden within the balloon folds. The preclinical findings revealed no concerns as per the pharmacological and toxicological properties. In acute experimental settings, the tissue concentration after deployment was found to be 0.3 to 0.5 μM [EuroCor GmbH Germany. Personal communication. 2007], which is well within the effective range for single-dose applications of paclitaxel without leading to unspecific apoptosis [1]. The recommended balloon inflation time is 45–60 sec at nominal balloon pressure, during which 30–45% of the paclitaxel is released to the vessel wall.

Interventional Procedure

All patients enrolled in the registry were treated with acetylsalicylic acid 325 mg and a 300 mg loading-dose of clopidogrel 12 and 2 hr before the procedure, respectively. Heparin was administered intravenously to maintain an activated clotting time $\geq$250 sec during the procedure. Administration of glycoprotein IIb/IIIa inhibitors was left to the physician's discretion.

The technique for the lesion treatment was a stepwise strategy according to the "provisional T-stenting" approach. Two 0.014-guide wires were placed in the main target vessel and the SB. Balloon predilatation with regular balloons of both vessels was performed first at low pressure (6–8 atm) as usual, followed by sequential drug eluting balloon inflations (8 atm for 60 sec) in the main and side branch, respectively. Special care was taken to record each balloon inflation to avoid too much of a balloon overlap in the main branch and potential geographical miss after stent placement in the main branch (see flow chart Fig. 1).

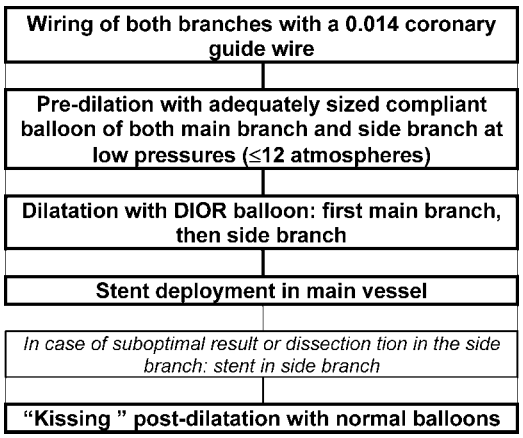

Fig. 1. Flow chart.

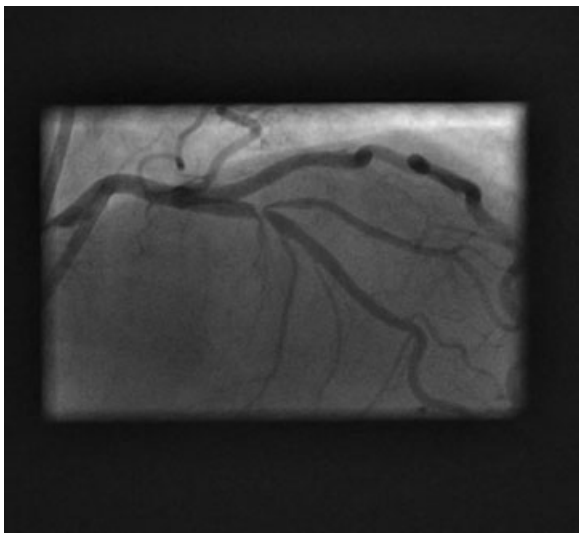

Fig. 2. Bifurcation LAD/D1.

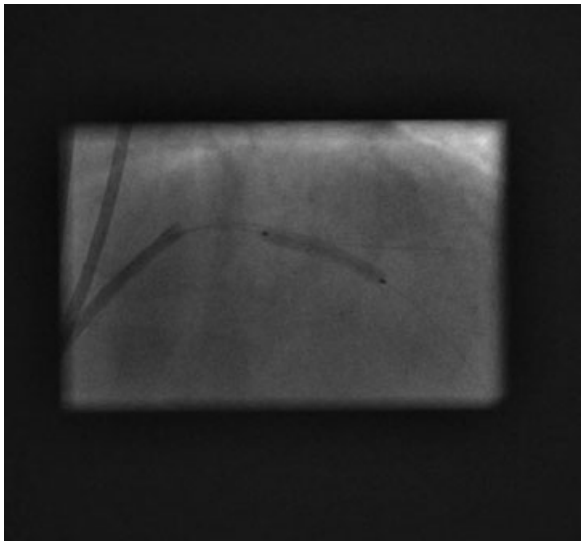

Fig. 3. After wiring and predilatation with regular balloons, dilatation with 3.0 × 25 mm^2 Dior^{TM}.

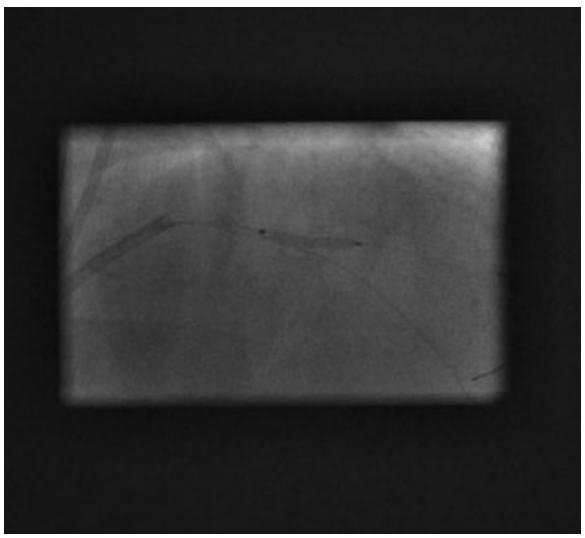

Fig. 4. Followed by dilatation of the sidebranch with 2.0 × 20 mm^2 Dior^{TM}.

Once satisfied with the angiographic result, the main branch was stented with a bare-metal stent (BMS) leaving the side branch wire in place ("jailed wire" technique). After recrossing with the wires, a final kissing-balloon inflation with regular balloons was performed according to routine practice. The procedure was completed when the result met the criteria of angiographic success (TIMI 3 flow in the main and side branch with a diameter stenosis $<10\%$ and $<40\%$, respectively). For an example of a successful procedure, see Figs. 2–8.

Acetylsalicylic acid was continued indefinitely after the procedure and clopidogrel (75 mg/day) for 3 months only.

Follow-Up and Endpoints

All patients were contacted by phone and interviewed on clinical status 1 month and 4 months after the procedure. Major acute coronary events (MACE) were defined as all cardiac deaths, Q-wave, and non-Q wave myocardial infarction, target-lesion failure (defined as both the MB and SB) including PCI and CABG.

Statistical Analysis

Descriptive statistical methods were used to describe the data. Continuous variables were presented as mean ± SD, categorical variables were presented as counts and percentages. No confirmatory analyses were performed.

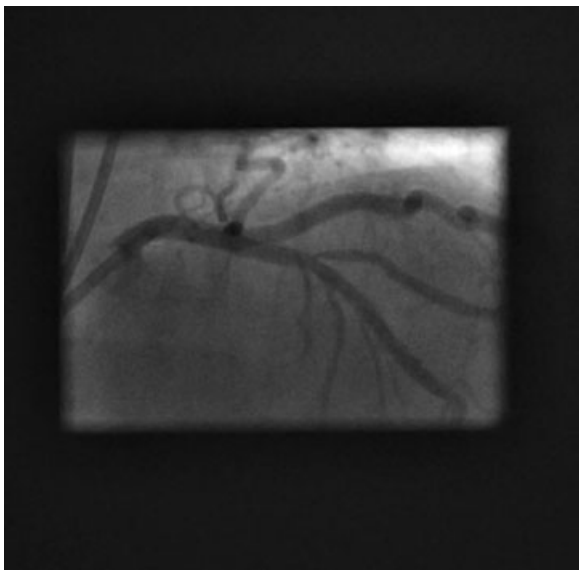

Fig. 5. Result after Dior™ dilatations.

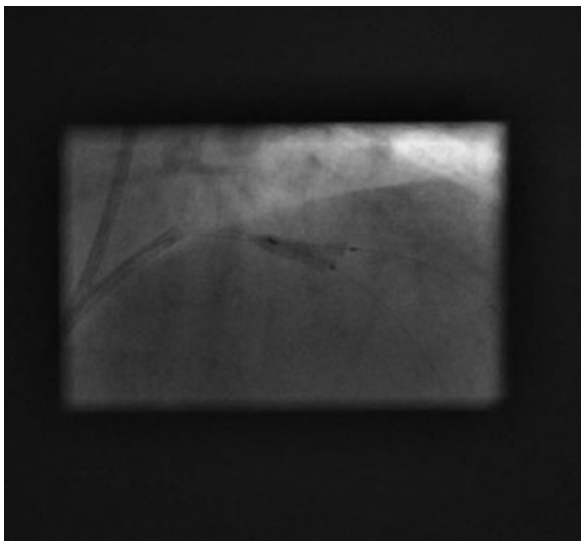

Fig. 7. "Kissing" postdilitation with regular balloons.

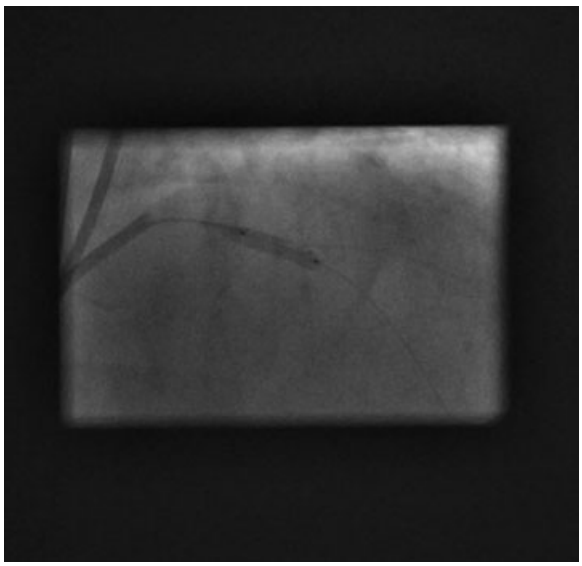

Fig. 6. Placement of 3.0 × 15 mm^2 Crono™ stent (bare metal).

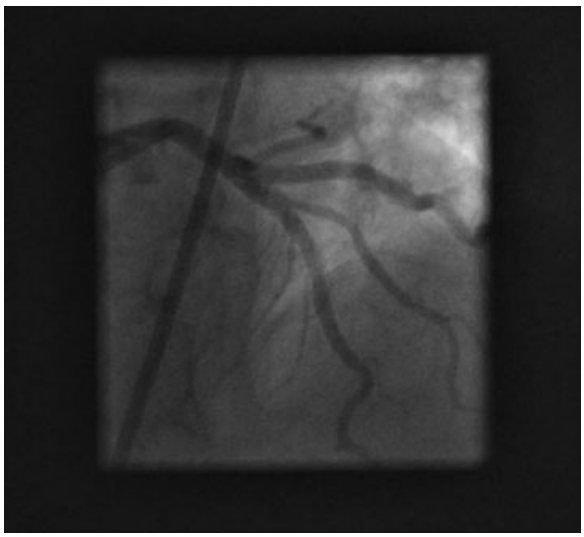

Fig. 8. Final result.

RESULTS

Patient Characteristics

Twenty patients with suitable bifurcation lesions were treated according to protocol between June and August 2007. Baseline patient characteristics are shown in Table II.

Most lesions were located at the left anterior descending artery/diagonal branch bifurcation. For baseline bifurcation anatomy (Medina classification [18]) see Table III. Quantitative coronary angiography (QCA) analysis results after the procedure are shown in Table IV. Because of the nature of this registry no follow-up QCA is reported.

The procedure was successful in all twenty patients. All side branches were treated with a 2.0 × 20 mm^2 DIOR balloon. Glycoprotein IIb/IIIa inhibitors were used in four procedures due to some haziness at the side branch ostium. However, no flow-limiting dissections or acute closure of sidebranches was observed for which additional stenting in the side branch was required. The balloons and stents used in the main branch are shown in Tables V and VI. Because safety and long-term data on the use of drug-eluting-balloon combined with drug-eluting stents are lacking, this combination was not used in this study.

TABLE II. Baseline Characteristics

Characteristics	Number of patients (n = 20)
Age (years [range])	68 (41–78)
Male sex, n (%)	14 (70)
Current or ex-smoker, n (%)	15 (75)
Hypercholesterolemia, n (%)	16 (80)
Hypertension, n (%)	14 (70)
Diabetes mellitus, n (%)	6 (30)
Previous myocardial infarction, n (%)	5 (25)
Previous CABG, n (%)	5 (25)
LVEF, percent	49
Glycoprotein IIb/IIIa inhibitor use, n (%)	4 (20)
Lesion characteristics	
LAD/diagonal, n (%)	17 (85)
LCX/OM, n (%)	1 (5)
LM/LAD/LCX, n (%)	0 (0)
RCA/RCA-PL/RCA-PD, n (%)	2 (10)

CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; OM, obtuse marginal; PD, posterior descending; PL, posterior lateral; RCA, right coronary artery; SD, standard deviation.

TABLE III. Baseline Bifurcation Anatomy—Medina Classification [18]

Medina classification type: (proximal main branch, distal main branch, and side branch involvement	Number of patients (n = 20) (n [%])
1.1.1	12 (60)
1.1.0	2 (10)
1.0.1	4 (20)
0.1.1	2 (10)

TABLE IV. Quantitative Coronary Angiography Analysis

	Main branch	Side branch
Lesion length (mm)	15.5 ± 5.0	4.2 ± 2.8
Stent length (mm)	19.0 ± 6.0	–
Reference vessel diameter (mm)	3.0 ± 0.6	2.4 ± 0.4

Angioplasty

The primary procedure was successful in all 20 patients. For baseline angiographic findings see Table II.

Follow-Up

Patients were contacted after 1 month and 4 months; all were symptom free at follow-up. No MACE or reintervention had occurred.

Adverse Events

No serious adverse events were reported during the 4-month follow-up period. Adverse events were reported in five patients (see Table VII for details). Phlebitis and small groin hematoma in three patients were considered related to the performed procedure, whereas a skin rash and paroxysmal atrial fibrillation were unrelated. Remarkably, no late thrombosis was reported so far, although all patients stopped Clopidogrel 3 months after the index procedure.

TABLE V. Drug-Eluting Balloons Used in the Study[a]

Location	Numbers	Size
Side branch	20	2.0 × 20 mm^2
Main branch	16	3.0 × 25 mm^2
	3	2.75 × 25 mm^2
	1	3.5 × 25 mm^2

[a]Inflation at 8 atmosphere for 1 min according to instructions for use.

TABLE VI. Stents Placed in Main Branches

Size in mm	Numbers
2.75 × 18	3
3.0 × 15	14
3.0 × 25	2

DISCUSSION

Despite the development in the treatment of bifurcation lesions, these lesions are still known to have a suboptimal clinical outcome, compared with straight single-lesion PCI, due to a lower acute success rate and a high risk of restenosis, especially in the SB.

In previous years, side branch lesions were mainly treated with balloon dilatation. However, later the use of bare-metal stents was considered necessary to reduce the rate of acute vessel closure, but this was accompanied with a higher rate of restenosis.

The introduction of DES showed in general a reduction in late in-stent restenosis compared with bare-metal stents. However, the initial promising results of DES were not reproducible in the special circumstances of bifurcation lesions as the rates of restenosis in the side branch remained high. Data from the Nordic Bifurcation Study show that the method of choice is stenting the main branch and only dilating the side branch, because double stenting appears not to lower the risk of restenosis [16].

At first the anatomical configuration of bifurcation lesions, with the consequence of an abnormal flow pattern within the bifurcation, is probably an important cause of restenosis. The second important factor is the inhomogeneous area of the stent struts which are not covering the full circumferential bifurcation ostium.

It should be noted that according to recent reports the rates of subacute thrombosis and even mortality might be higher in patients especially with complex lesions treated with DES [3].

Drug-eluting-stents were developed with the knowledge that the process of restenosis development is a

TABLE VII. Adverse Events

Patient number	Time and type of event	Relationship to procedure	Outcome
2	Day 1: Phlebitis in left hand due to intravenous line	Related	Complete recovery
6	Day 8: Skin rash possibly due to clopidogrel	Not related	Complete recovery
9	Day 1: Paroxysmal atrial fibrillation	Not related	Complete recovery
12	Day 1: Small groin hematoma	Related	Complete recovery
17	Day 1: Small groin hematoma	Related	Complete recovery

slow process. Therefore, drug release from the stent is deliberately prolonged with the use of special polymer coatings, providing a long-term and sustained drug release.

Surprisingly, laboratory results showed that even a short contact between taxane compounds and vascular smooth muscle cells can inhibit the proliferation of the cells for a long period, so a stent-driven sustained drug release does not seem to be necessary at all [19,20].

This was confirmed in animal experiments, where paclitaxel was delivered into coronary arteries using a contrast medium or a paclitaxel-coated balloon catheter. Both methods significantly reduced neointimal proliferation with a more pronounced reduction in the paclitaxel-coated balloon group [17].

In addition, about 85% of the stented coronary artery area is not covered by the stent struts, resulting in inhomogeneous drug distribution. This may yield a less effective result than initially thought. Balloon-catheter drug delivery on the other hand, makes a direct effective homogeneous intracoronary drug delivery possible without the disadvantages of the DES. The Paccocath ISR trial [21] was the first to demonstrate a significant reduction in the incidence of restenosis by using the paclitaxel-coated balloon compared with PCI with an uncoated balloon. The lesions-to-treat were restenotic lesions in a stented coronary artery.

The potential advantages of the use of DEB in bifurcation lesions are (1) homogeneous administration of the drug, whereas the DES only delivers paclitaxel in the proximity of the struts; (2) delivery of high drug concentrations at the vessel wall at the moment of injury; (3) avoidance of potential late stent thrombosis; and (4) respecting the original anatomy of the bifurcation carina, leaving no stent scaffold and hence diminish abnormal flow patterns within the bifurcation.

This registry investigated the short-term safety and efficacy of a drug-eluting balloon for PCI in coronary bifurcation lesions after sequential dilatation and final placement of a stent in the main branch. The procedure is easy and safe to perform and yielded excellent short-term results with an acute success rate of 100%. To our knowledge this is the first report on the use of the drug-eluting-balloon in patients with bifurcation lesions.

The major limitation of this registry is the short clinical follow-up period. However, the main purpose of this study was to show the safety and efficacy of the drug-eluting-balloon under the special circumstances of the bifurcation lesions.

CONCLUSIONS

The use of paclitaxel-coated balloon catheters is effective and safe in PCI for coronary artery bifurcation lesions, without clinical signs of restenosis at 4 months follow up. Although all patients stopped Clopidogrel at 3 months after the index procedure so far no late thrombosis was reported.

This registry provides encouraging results with respect to the safety and efficacy of the drug-eluting balloon. Stenting of the side branch does not lower the rate of restenosis, while the placement of two stents in BiF makes the procedure more difficult to perform. The drug-eluting-balloon makes the procedure easier and may even lower long-term restenosis rates in the side branch.

Future randomized studies need to compare the use of the drug-eluting-balloons and drug-eluting-stents in Bifurcation lesions and assess the long-term efficacy and safety of the drug-eluting balloon.

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