



Effect of Drug-Coated Balloons in Native Coronary Artery Disease Left With a Dissection

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ABSTRACT

OBJECTIVES The authors sought to understand the clinical and angiographic outcomes of dissections left after drug-coated balloon (DCB) angioplasty.

BACKGROUND Second-generation DCB may be an alternative to stents in selected populations for the treatment of native coronary lesions. However, the use of these devices may be hampered by a certain risk of acute vessel recoil or residual coronary dissection. Moreover, stenting after DCB has shown limited efficacy. Little is known about when a non-flow-limiting dissection is left after DCB angioplasty.

METHODS This was a prospective observational study whose aim was to investigate the outcome of a consecutive series of patients with native coronary artery disease treated with second-generation DCB and residual coronary dissection at 2 Italian centers. We evaluated patient clinical conditions at 1 and 9 months, and angiographic follow up was undertaken at 6 months.

RESULTS Between July 2012 and July 2014, 156 patients were treated with DCB for native coronary artery disease. Fifty-two patients had a final dissection, 4 of which underwent prosthesis implantation and 48 were left untreated and underwent angiographic follow-up after 201 days (interquartile range: 161 to 250 days). The dissections were all type A to C, and none determined an impaired distal flow. Complete vessel healing at angiography was observed in 45 patients (93.8%), whereas 3 patients had persistent but uncomplicated dissections, and 3 had binary restenosis (6.2%). Late lumen loss was 0.14 mm (−0.14 to 0.42). Major adverse cardiovascular events occurred in 11 patients in the entire cohort and in 4 of the dissection cohort (7.2% vs. 8.1%; $p = 0.48$). We observed 8 and 3 target lesion revascularizations, respectively (5.3% vs. 6.2%; $p = 0.37$).

CONCLUSIONS In this cohort of consecutive patients treated with new-generation DCB and left with a final dissection, this strategy of revascularization seemed associated with the sealing of most of dissections and without significant neo-intimal hyperplasia. (J Am Coll Cardiol Intv 2015;8:2003-9) © 2015 by the American College of Cardiology Foundation.

Drug-coated balloons (DCB) were developed to overcome neointimal hyperplasia and have been widely tested for the treatment of in-stent restenosis, in which setting they have shown an efficacy comparable to drug-eluting stents (DES) in terms of target lesion revascularization (TLR) (1-4). For this indication, DCB gained a Class I, Level of Evidence: A in the latest European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for myocardial revascularization (5).

However, from the mechanical point of view, DCB behave just like simple balloons, thus they share

some of the main limitations of these devices after angioplasty, namely coronary dissection and acute recoil.

Very preliminary observations seem to show how new-generation DCB could be associated with a faster spontaneous healing of an arterial dissection left after balloon angioplasty, especially in case of angioplasties of the femoropopliteal region and for the treatment of in-stent restenosis (6,7). The aim of this study was to test this hypothesis in a consecutive series of patients with native coronary vessel disease.

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**ABBREVIATIONS
AND ACRONYMS**

- DCB** = drug-coated balloon(s)
- DES** = drug-eluting stent(s)
- LLL** = late lumen loss
- MACE** = major adverse cardiac event(s)
- MLD** = minimal lumen diameter
- PCI** = percutaneous coronary intervention
- RVD** = reference vessel diameter
- TLR** = target lesion revascularization

METHODS

This is an observational study conducted at 2 centers expert in DCB angioplasty. The aim of the study was to investigate the outcome of consecutive coronary dissections left after DCB angioplasty in native vessels.

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Inclusion criterion was any percutaneous coronary intervention (PCI) performed with DCB in native coronary vessels. Exclusion criteria were any use of DCB for reasons different from the aforementioned (e.g., for in-stent restenosis); ST-segment elevation myocardial infarction that occurred in the previous 48 h; or life expectancy <1 year. Other clinical indications for PCI, unstable hemodynamics at presentation, and the presence of renal insufficiency were not exclusion criteria. We had a restrictive use of DCB in case of big vessel size (e.g., >3 mm in diameter) or in case of very calcific vessels, especially when we feared possible vessel recoil.

In the current study, the following devices were used: Restore (Cardionovum, Milano, Italy) and Elutax SV (Aachen Resonance, Lainate, Italy) DCB. These 2 devices, both eluting paclitaxel, may be considered a second-generation DCB because of a more efficient

delivery of paclitaxel to the vessel wall, which results in a longer persistence of the drug. Restore DCB has a concentration of paclitaxel of 3.0 µg/mm² of balloon surface, and shellac is used as a carrier. Elutax SV DCB has a concentration of paclitaxel of 2.2 µg/mm² of balloon surface, and is embedded in a 3-layer matrix. Available measures for both devices used in this study included diameters of 2.0, 2.5, and 3.0 mm, and lengths of 15, 20, 25, and 30 mm.

The intervention was performed according to international guidelines and the recent Italian position paper on DCB PCI (8). Specifically, pre-dilation with an undersized semicompliant balloon was mandatory (the recommended size was 0.9:1 of DCB). In case of flow-limiting dissection after pre-dilation, we recommended considering conversion to a stent PCI without using a DCB. The DCB was inflated for 30 to 45 s at nominal pressure, according to the morphological characteristics of the lesion (e.g., degree of calcification, length, tortuosity). After DCB use, final assessment was undertaken after at least 5 min, in order to catch early vessel recoil. In this event, bailout stent implantation was considered. The type of stent or scaffold was left to the operator's discretion.

Patients with any residual coronary dissection after DCB use entered the current analysis. It is our habit not to stent coronary dissections of type A to C (National Heart, Lung, and Blood Institute [NHBLI] classification system for intimal tears, developed by the Coronary Angioplasty Registry) with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. In case of coronary dissections of type D or higher and/or impaired distal flow, it is our habit to implant a stent.

After sheath insertion, all patients were administered unfractionated heparin (single bolus of 5,000 IU, then adjunctive boluses following activated clotting time) or bivalirudin (bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure). A bailout glycoprotein IIb/IIIa receptor inhibitor strategy was allowed in case of high thrombus burden. All patients received aspirin (either 100 mg/day for at least 3 days before PCI or with a pre-PCI 300-mg intravenous bolus), and clopidogrel (300 or 600 mg as a loading dose, followed by 75 mg daily) or prasugrel (60 mg as a loading dose, followed by 10 mg daily) or ticagrelor (180 mg as a loading dose, followed by 90 mg twice a day) following clinical indication. The duration of prescribed dual antiplatelet treatment was 1 month, or 6 months in case of stent implantation; after this time, patients were prescribed only aspirin.

Angiographic success was defined as a final residual stenosis <50% by visual estimate, with TIMI flow

TABLE 1 Patients' Clinical Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Age, yrs	61 (54-67)	59 (51-64)	60 (54-66)	0.18
Female	50 (32.0)	31 (29.8)	19 (36.5)	0.31
Hypertension	91 (58.3)	59 (56.7)	32 (63.5)	0.21
Hypercholesterolemia	95 (60.9)	65 (62.5)	30 (57.7)	0.32
Diabetes	55 (35.2)	37 (35.6)	18 (34.6)	0.86
Prior MI	14 (9.3)	10 (9.6)	4 (8.4)	0.48
Prior revascularization	17 (10.9)	9 (8.7)	8 (13.5)	0.16
Multivessel coronary disease	78 (50)	52 (50)	26 (50)	0.91
Stable angina	82 (52.6)	55 (52.9)	27 (51.9)	0.84
Unstable angina	31 (19.9)	19 (18.3)	12 (23.0)	0.33
Non-ST-segment elevation MI	43 (27.6)	30 (28.8)	13 (25)	0.75
Culprit vessel				
Left anterior descending artery	88 (56.4)	52 (50)	35 (67.0)	0.02
Left circumflex artery	13 (8.3)	10 (9.6)	3 (5.8)	0.06
Right coronary artery	55 (35.2)	42 (40.4)	14 (26.9)	0.842

Values are median (interquartile range) or n (%). p Value in **bold** have reached statistical significance.
DCB = drug-coated balloon; MI = myocardial infarction.

grade 3. Procedural success was defined as angiographic success without the occurrence of in-hospital major adverse cardiac events (MACE) (defined as any occurrence of ST-segment elevation acute myocardial infarction, target vessel revascularization, TLR, or death). Periprocedural myocardial infarction was defined as a post-procedural increase in cardiac troponin T >5 × 99th percentile of the upper reference limit.

All patients underwent clinical follow-up after 1 and 9 months; all patients in the dissection cohort underwent angiographic follow-up with quantitative coronary assessment after 6 months, in order to assess the degree of coronary dissection healing. All measurements were performed on cineangiograms recorded after 200 mg of intracoronary nitroglycerin administration. Identical projections were used for each comparison. Quantitative analysis of angiographic data were initially assessed by a single experienced investigator, and afterwards validated by an internal committee of experts, using the CAAS II research system (Pie Medical Imaging, Maastricht, the Netherlands). The following parameters were analyzed: reference vessel diameter (RVD), minimal lumen diameter (MLD), percent diameter stenosis (the difference between RVD and MLD divided by RVD), late lumen loss (LLL) (defined as the difference between MLD after index PCI and MLD at angiographic follow up), lesion length, binary restenosis, and persistence of dissection (NHBLI classification). Measurements included the whole segment treated plus 5 mm proximally and distally. Binary restenosis was defined as stenosis of at least 50% of the luminal diameter at angiographic follow-up.

Primary endpoint of this study was the percentage of dissection healing detected at angiographic follow-up. Secondary endpoints included TLR, binary restenosis, LLL, and the occurrence of MACE.

Data are presented as mean ± SD or median (interquartile range) as appropriate for continuous variables, and as proportions (%) for dichotomous variables. The differences between groups were assessed by chi-square test or Fisher exact test for categorical data, and paired Student *t* test for continuous data. The relative risk and its 95% confidence interval were calculated for each study endpoint. A 2-sided *p* value <0.05 was considered statistically significant.

RESULTS

The study population consisted of 156 consecutive patients treated between July 2012 and July 2014 at 2 centers with second-generation DCB for native

TABLE 2 Procedural Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Radial approach	144 (92.3)	96 (92.3)	48 (92.3)	0.95
Total occlusion	18 (11.5)	9 (8.7)	9 (17.3)	0.47
Reference vessel diameter, mm	2.83 (2.12-3.01)	2.87 (2.15-3.0)	2.80 (2.07-2.97)	0.21
Minimal lumen diameter, mm	0.4 (0.0-0.73)	0.37 (0.03-0.65)	0.41 (0.00-0.79)	0.11
Stenosis severity, %	83 (72-100)	82 (71-100)	84 (70-100)	0.18
Lesion length, mm	21 (10-33)	19 (10-28)	22 (12-33)	0.10
Severe-moderate calcification (visual estimation)	100 (64.1)	60 (57.7)	40 (76.9)	0.01
Pre-dilation balloon diameter, mm	2.45 (2.0-3.0)	2.35 (2.0-3.0)	2.5 (2.0-3.0)	0.04
DCB diameter, mm	2.55 (2.0-3.0)	2.50 (2.0-3.0)	2.60 (2.0-3.0)	0.035
DCB length, mm	25 (15-30)	24 (15-30)	25 (15-30)	0.37
Max pressure during DCB angioplasty, atm	12 (8-14)	11 (9-14)	12 (8-15)	0.49
DCB inflation duration, s	35 (30-45)	37 (32-45)	34 (30-42)	0.33
OCT/IVUS guidance	15 (9.6)	11 (10.6)	4 (7.7)	0.13
Minimal lumen diameter after PCI, mm	2.21 (1.75-2.67)	2.17 (1.75-2.58)	2.24 (1.84-2.67)	0.22
Procedural success	156 (100)	104 (100)	52 (100)	0.87
Periprocedural myocardial infarction	21 (13.5)	13 (12.5)	8 (15.4)	0.42
Bivalirudin	15 (9.6)	9 (8.7)	6 (11.5)	0.23
Dual antiplatelet therapy				
ASA + clopidogrel	130 (83.3)	85 (81.7)	45 (86.5)	0.24
ASA + ticagrelor/prasugrel	26 (16.7)	19 (18.3)	7 (13.5)	0.36

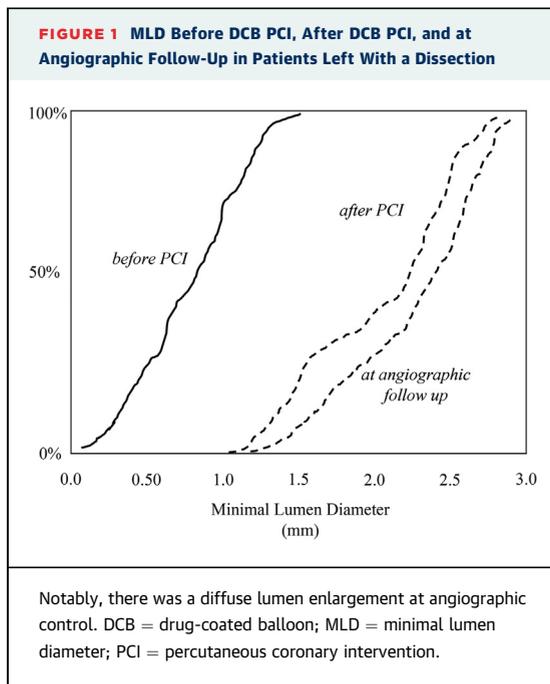
Values are n (%) or median (interquartile range). Values in **bold** have reached statistical significance.
ASA = acetylsalicylic acid; DCB = drug-coated balloon; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.

coronary artery disease (87 with Restore and 69 with Elutax SV), that were prospectively entered in the database. Thirty-five percent of patients had diabetes, and clinical indication was stable angina in 82, unstable angina in 31, and non-ST-segment elevation myocardial infarction in 43 patients. Procedural success was achieved in all patients.

TABLE 3 Angiographic Follow-Up of Patients With Dissection After DCB PCI

	Dissection Cohort (n = 48)
Reference vessel diameter, mm	2.87 (2.11 to 2.98)
Minimal lumen diameter, mm	2.42 (2.22 to 2.66)
Diameter stenosis, %	12 (8 to 20)
LLL, mm	0.14 (-0.14 to 0.42)
Complete vessel healing	45 (93.8)
Binary restenosis	3 (6.2)

Values are median (interquartile range) or n (%). Follow-up was at 201 days (interquartile range 161 to 250 days).
LLL = late lumen loss; other abbreviations as in Table 2.



For the purpose of this analysis, we studied the 52 patients that had an angiographically detectable dissection after DCB angioplasty. All patients of this cohort underwent programmed coronary angiography after 6 to 9 months. Baseline clinical characteristics and clinical indication to PCI of the entire population and of the 2 cohorts are shown in [Table 1](#). The dissection study group did not differ significantly from the entire DCB group, if we exclude a higher incidence of left anterior descending artery as the culprit vessel, the degree of calcification of the culprit lesion, the size of balloon used for predilation, and the size of the DCB ([Table 2](#)). Baseline angiographic characteristics are shown in [Table 2](#). Of note, the vessel diameter was 2.83 mm in the entire population, and 2.80 mm in the dissection population.

Of the 52 patients with residual dissection after DCB PCI, 4 had a prosthesis implanted (2 a bare-metal stent, 1 a DES, and 1 a biovascular scaffold). The reason for implanting a stent/scaffold was impairment of distal flow in 3 patients, and the presence of a spiral, type D dissection in 1.

All patients with a final dissection underwent scheduled angiographic follow-up with quantitative coronary assessment, that was undertaken after 201 days (interquartile range 161 to 250 days). Angiographic outcome is presented in [Table 3](#). Of note, LLL was as low as 0.14 ± 0.28 mm in this group. We also observed a late lumen enlargement in the treated segments ([Figure 1](#)).

Complete vessel healing at angiography was observed in 45 of 48 patients (93.8%) ([Figure 2](#)). The 3 patients that had an unhealed dissection had, respectively, a type A, type B, and type C coronary dissection after the index PCI. TLR occurred in 3 patients (6.2%) in the dissection cohort and in 8 patients (5.3%) in the entire DCB population ($p = 0.49$) ([Figure 3](#)). Of the 3 patients that underwent TLR in the dissection cohort, the first 2 had recurrence of angina after 4 and 6 months, respectively; angiography showed subocclusive coronary stenoses (of 85% and 90%, respectively) at the site of the previous PCI that were successfully treated with DES implantation. The third patient was asymptomatic but had a persisting, chronic coronary dissection discovered at angiographic follow-up that was sealed with DES implantation.

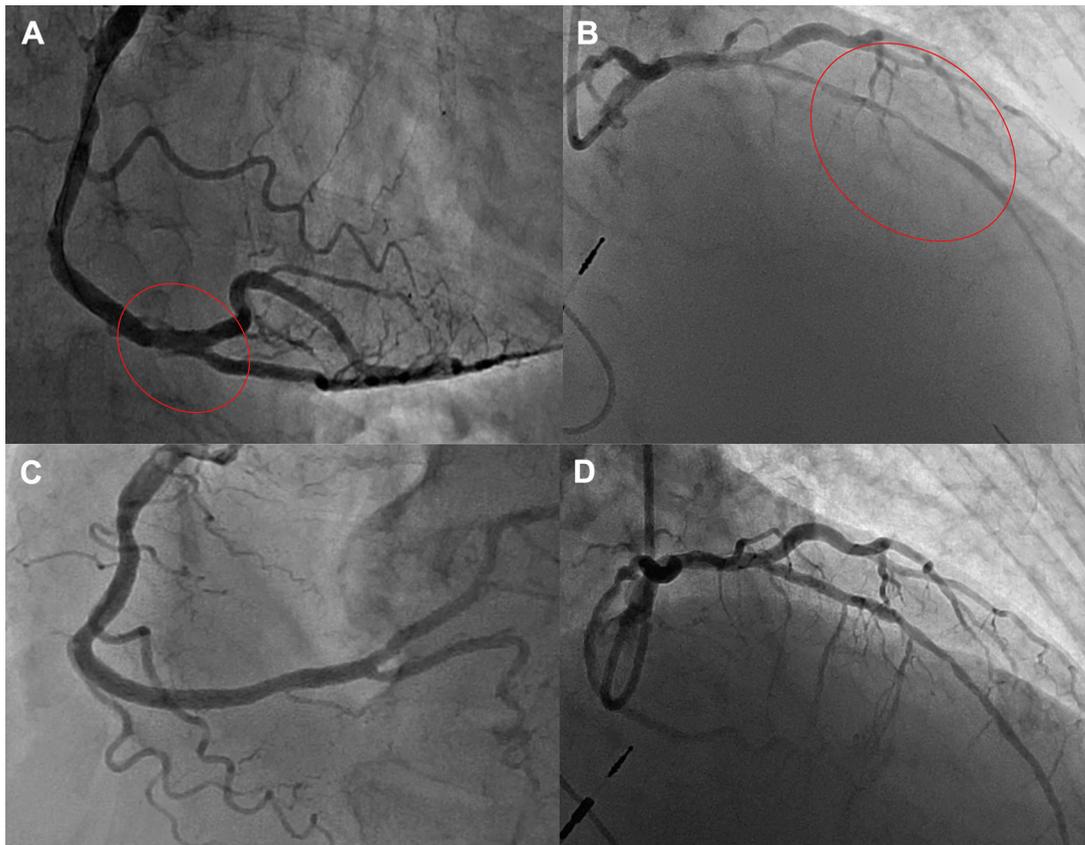
The other clinical endpoints showed no significant differences between the whole group and the groups with and without dissection ([Figure 3](#)). Interestingly, we did not observe cases of target vessel myocardial infarction during the entire clinical follow-up (average length 9 ± 3 months). Finally, there were no significant differences between the 2 devices tested in terms of clinical and angiographic endpoints.

DISCUSSION

This prospective observational study describes the first consecutive series of patients treated with DCB for native coronary artery disease and with final dissection left “unsealed” with prosthesis. Our results confirm that leaving a non-flow-limiting dissection untreated after DCB PCI is safe and not associated with an increase in myocardial infarction and TLR, despite the short-term (1 month) dual antiplatelet treatment. Notably, we did not observe a correlation between the type of dissection at baseline (type A, B, or C) and the propensity to healing ([Figure 4](#)).

DCB were developed to overcome neointimal hyperplasia and have been first tested in the in-stent restenosis setting with good results maintained for years ([3,9](#)). However, the use of DCB for the treatment of native vessels seems particularly encouraging, especially in the case of small vessels and distal lesions, where the encumbrance of a stent may limit its potential and is associated with increased rates of restenosis and stent thrombosis. However, the application of this technology as standalone procedure in de novo lesions has resulted in conflicting results. After some early mistakes, such as the ones depicted in the PICCOLETO (Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small

FIGURE 2 Angiographic Outcome of Dissections Left After DCB Angioplasty



A and B show the final dissections (respectively, a type C and a long type A dissection, red circles); after 6 months, both dissections were healed (**C and D**). DCB = drug-coated balloon.

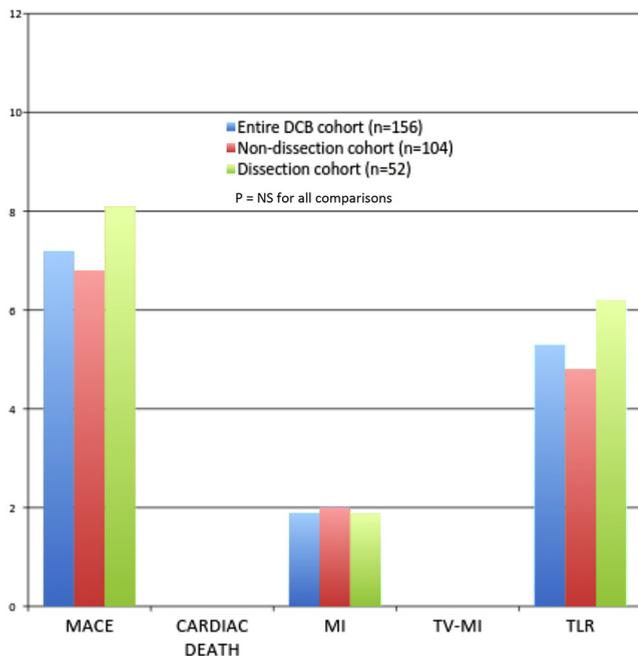
Coronary Artery Diseases) study (10,11), a newer generation of DCB has been tested in the BELLO (Balloon Elution and Late Loss Optimization) study for the treatment of native coronary vessels. Here, DCB overcame Taxus DES for the treatment of small vessel disease in terms of the primary endpoint of LLL (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; 95% confidence interval: -0.34 to -0.09 ; $p = 0.001$) (12). Recently, the 2-year follow up of the BELLO study, that showed persisting good results of DCB in terms of clinical endpoints, has been published. (13) Similar encouraging results for this technology in native coronary vessels were shown in large registries with different, new-generation DCB (14,15).

This study was performed with 2 devices of the latest available technology, that provides optimal paclitaxel delivery to the vessel wall and contemporarily allows its longer persistence.

The central point of our findings is the safety of leaving a dissection after DCB angioplasty. Early

experiences have shown how leaving a dissection after plain old balloon angioplasty was associated with increased rates of thrombotic events, early reocclusion, and recurrence of restenosis, and this was one of the main indications for the use of stents in an earlier era (16). The widespread use of more potent antiplatelet regimens (e.g., the association of aspirin with a P2Y₁₂ receptor inhibitor) has undoubtedly improved the early outcome of this type of patient. In the early stent era, a previous series of patients treated consecutively with plain angioplasty and with a final dissection, despite a very low occurrence of thrombotic events and an acceptable rate of restenosis (12%), 36.7% of dissections left were still visible at 6-month angiographic follow-up (17). With this current study, we have opened the hypothesis that the effect of paclitaxel, when correctly delivered to the vessel wall, may have a role in facilitating the healing of coronary vessels.

FIGURE 3 Clinical Follow-Up After 9 Months in the Entire Population and in the Dissection and No-Dissection Cohorts



p Values are not significant for all comparisons. DCB = drug-coated balloon; MACE = major cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization; TV = target vessel.

FIGURE 4 The Fate of Dissections After DCB Angioplasty

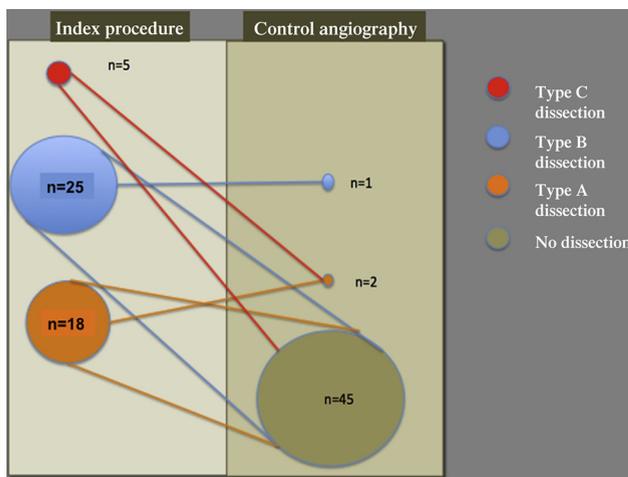


Figure shows what happened to dissections at 6-month angiography: 45 were healed and 3 were chronic. There was not an apparent correlation between the type of initial dissection left after DCB angioplasty and its fate. We followed the NHLBI classification for coronary dissections. DCB = drug-coated balloon; NHLBI = National Heart, Lung, and Blood Institute.

This effect was already described in a post-hoc analysis of the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) study (6), where patients with femoropopliteal disease were randomized to simple angioplasty or DCB. In this analysis, patients treated with DCB resulting in final dissection of any grade had significantly lower LLL than patients with dissection after simple angioplasty (0.4 vs. 1.9 mm; $p = 0.001$), especially if the dissection grade was severe (type C to E) (0.4 vs 2.4 mm; $p = 0.05$). This result was maintained for all the duration of the 2-year follow-up, with a TLR of 10% versus 56% respectively ($p = 0.002$) (6). In another study, Agostoni et al. (18) have found how leaving small dissections after DCB angioplasty for in-stent restenosis resulted in complete dissection healing at optical coherence tomography after 6 months. In addition to this information, we also found that our patients, who did not have a “caged” coronary artery because they did not have in-stent restenosis, also had an improved late lumen gain, as already described in another series of patients treated with DCB for native coronary vessel disease (19). This late lumen enlargement (Figure 1) is another interesting effect of DCB that needs further, dedicated analysis.

In this study, we decided to limit the degree of dissections left to a low-medium grade (type A to C) because of ethical reasons (the eventual vessel occlusion would result in myocardial infarction). Now with our results, if the dissection is of low-medium grade, it seems safe to leave it untreated. In fact, data from the literature show how any stent strategy associated with DCB use is unsafe or yields unsatisfactory results (20,21). There are some initial data on the use of DES after DCB, but such data are limited in number and are without angiographic follow-up (22), thus the contemporary use of 2 different antirestenotic drugs with stent metal layers needs to be better understood before recommending this strategy. Moreover, in this case, the advantages of using a DCB are immediately lost (23).

STUDY LIMITATIONS. First, the population is limited and derives from 2 centers expert in this type of PCI, thus it may not be reproducible everywhere without an adequate learning curve. Moreover, we have to disclose an initial bias at the time of decision of leaving the dissection untreated. So far, these results are not easily reproducible in all settings. Our findings, although a confirmation of other previous studies, are the first assessment of this property of new-generation DCB in native coronary lesions, and need to be validated in other ad hoc clinical studies.

CONCLUSIONS

In a consecutive series of patients treated with new-generation DCB for native coronary artery disease and with a final non-flow-limiting dissection, these lesions tended to heal despite their initial severity. After DCB angioplasty, a strategy of bailout stenting should be reserved to more severe, flow-limiting dissections.

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PERSPECTIVES

WHAT IS KNOWN? DCB are a useful tool for the treatment of small coronary arteries. However, little is known regarding the fate of dissections left unsealed after DCB PCI.

WHAT IS NEW? With this study, for the first time in the coronary tree, we showed a pro-healing effect of DCB when a final dissection was left at the end of PCI.

WHAT IS NEXT? We now need an adequately powered study (e.g., a randomized controlled study) to test this preliminary report in a broader population of coronary artery disease patients.

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