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The Role of Drug-Eluting Balloons Alone or in Combination With Drug-Eluting Stents in the Treatment of De Novo Diffuse Coronary Disease

Charis Costopoulos, MD,*†‡ Azeem Latib, MD,*† Toru Naganuma, MD,*† Alessandro Sticchi, MD,* Filippo Figini, MD,* Sandeep Basavarajaiah, MD,*†‡ Mauro Carlino, MD,* Alaide Chieffo, MD,* Matteo Montorfano, MD,* Charbel Naim, MD,* Masanori Kawaguchi, MD,*† Francesco Giannini, MD,* Antonio Colombo, MD*†

Milan, Italy; and London, United Kingdom

Objectives This study sought to investigate the role of drug-eluting balloons (DEB) alone or in combination with drug-eluting stents (DES) in the treatment of diffuse de novo coronary artery disease (CAD) (>25 mm).

Background The use of DEB in diffuse CAD, either alone or in combination with DES, offers an alternative to stenting alone. Data regarding DEB in this context are limited.

Methods We retrospectively evaluated all patients treated with DEB for diffuse CAD between June 2009 and October 2012. Endpoints analyzed were major adverse cardiac events, defined as all-cause death, myocardial infarction, and target vessel revascularization (TVR), as well as TVR and target lesion revascularization separately. Results were compared with those obtained from a cohort of patients with similar characteristics treated with DES alone.

Results A total of 69 patients (93 lesions) were treated with DEB ± DES, and 93 patients with DES alone (93 lesions). A high proportion of patients were diabetic (46.4% vs. 44.1%, p = 0.77). Of the DEB-treated lesions, 56.0% were treated with DEB alone, 7.4% with DEB and DES as bail out, and 36.6% with DES and DEB as part of a hybrid approach for very long disease. Outcome rates with DEB ± DES were comparable to those with DES alone at 2-year follow-up (major adverse cardiac events = 20.8% vs. 22.7%, p = 0.74; TVR = 14.8% vs. 11.5%, p = 0.44; target lesion revascularization = 9.6% vs. 9.3%, p = 0.84).

Conclusions DEB may have a role in the treatment of diffuse de novo CAD, either alone in smaller vessels or in combination with DES in very long disease. (J Am Coll Cardiol Intv 2013;6:1153–9)

From the *Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy; †Interventional Cardiology Unit, EMO-GVM Centro Cuore Columbus, Milan, Italy; and the ‡Imperial College London, London, United Kingdom. Dr. Latib is on the Medtronic Advisory Board. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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The use of paclitaxel drug-eluting balloons (DEB) is an emerging approach to the treatment of de novo coronary disease and in-stent restenosis (1–4). Apart from the mechanical treatment of underlying disease after balloon inflation, it allows the local release of an antirestenotic drug without the use of a polymer or metal scaffold. This limits cellular proliferation and restenosis associated with conventional balloon angioplasty while at the same time overcomes some of the limitations associated with drug-eluting stent (DES) implantation such as the need for prolonged dual antiplatelet therapy (DAPT) (5), the risk of late and very late stent thrombosis (ST) (6), and the absence of a permanent metal prosthesis within the vessel wall (7). In addition, the implantation of long metal devices in coronary vessels may impair restoration of vasomotion in the stented segment, promote neoatherosclerosis, and limit access for coronary artery bypass graft (CABG) (8).

Abbreviations and Acronyms

CABG = coronary artery bypass graft
DAPT = dual antiplatelet therapy
DEB = drug-eluting balloon
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis
TVR = target vessel revascularization
TLR = target lesion revascularization

Stent length is known to independently predict in-stent restenosis and thrombosis (9,10). We previously demonstrated that treatment with ≥60-mm overlapping DES, although associated with acceptable mortality and ST rates, can lead to high target lesion revascularization (TLR) rates, approximating 24% (11). Thus, the possibility of using DEB alone or as part of a hybrid procedure combining DEB and DES to limit stent length in vessels with diffuse disease may be an alternative and useful approach.

Here we report the data and clinical outcomes from 2 high-volume centers in Milan, Italy, of patients who underwent treatment with DEB alone or in combination with DES for diffuse coronary artery disease (CAD) and compare them with those of a cohort of patients with similar characteristics treated over the same period with DES alone.

Methods

We examined all DEB procedures performed at San Raffaele Scientific Institute and EMG-GVM Cento Cuore Columbus in Milan from June 2009 until October 2012. Each procedure was entered into a percutaneous coronary intervention (PCI) database at the time of the procedure and subsequently, all clinical parameters were verified by inspecting the case records. Exclusion criteria included DEB PCI for in-stent restenosis and de novo lesions <25 mm. Using these criteria, 69 patients with 93 lesions were identified. A separate cohort of 93 patients treated over the same period with second-generation DES alone was selected as a comparison group after matching for clinically important characteristics such as diabetes, age, ejection fraction, prevalence of multivessel disease, device diameter, and treated lesion length. All patients provided informed consent for both the procedure and subsequent data collection and analysis. Patients received standard DAPT before the procedure and continued this for 1 month after a DEB-only approach and for 12 months in cases of DES implantation. Interventional approach, intravascular ultrasound use, and administration of glycoprotein IIb/IIIa receptor inhibitors during the procedure were left to the discretion of the operator. In the DEB group, bail-out stenting in cases of dissection or residual stenosis was also left to the discretion of the operator. Stent implantation in the DEB group was undertaken either as part of a hybrid approach incorporating DEB and DES to treat very long disease or to treat a dissection with signs of lumen compromise or reduced flow or when the residual stenosis was evaluated to be greater than 50%.

Clinical follow-up and definitions. Clinical follow-up was achieved for all recruited subjects by clinic visit or telephone interview. Angiographic follow-up was not encouraged unless clinically indicated or as part of a separate revascularization procedure. Clinical outcomes reported represent patient-specific data unless otherwise stated. The measured endpoints were major adverse cardiac events (MACE) defined as a composite of all-cause death, myocardial infarction (MI) (including periprocedural) and target vessel revascularization (TVR). Death was considered cardiac in origin unless obvious noncardiac causes were identified. We defined post-procedural non–Q-wave MI as a creatine kinase-myocardial band increase of >3 times the upper limit of normal (12). Creatine kinase was routinely measured after PCI in all patients at both centers. Nonprocedural or spontaneous MI was defined as an increase in troponin above the upper range limit in combination with at least 1 of the following: symptoms of ischemia; electrocardiographic changes indicative of new ischemia; or the development of pathological Q waves on electrocardiography. TVR was defined as repeat PCI or CABG of the target vessel. TLR was defined as repeat PCI or CABG for the lesion in the previously treated segment or within the 5 mm proximal or distal to the stent edge or site of DEB inflation. The occurrence of ST was defined on the basis of the Academic Research Consortium definitions (13). Chronic total occlusion was defined as complete occlusion with Thrombolysis In Myocardial Infarction flow grade of 0 lasting at least 3 months. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) (14) and the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) scores were calculated (15). Diffuse disease was defined as de novo CAD >25

mm. Procedural success was defined as completion of the procedure with no in-lab complications, final Thrombolysis In Myocardial Infarction flow of 3 with residual stenosis <50%.

Quantitative coronary angiographic measurements. Matched orthogonal views were used for quantitative analysis before and after treatment. Angiography was performed after intracoronary injection of nitroglycerin (100 to 200 μg). Angiograms were analyzed by means of the Clinical Measurements Solutions system (QCA-CMS version 5.1, Medis Medical Imaging Systems, Leiden, the Netherlands). Quantitative coronary analysis measurements were performed at baseline and after device inflation. Minimal lumen diameter, diameter stenosis, acute gain, and reference vessel diameter of the treated segment were measured.

Statistical analysis. Values are presented as mean ± SD or median (interquartile range) for continuous variables or as count and percentage for categorical variables. Continuous variables were compared by the independent sample Student *t* or Mann-Whitney *U* tests. Categorical variables were compared by the chi-square statistic or Fisher exact test. A p value <0.05 was considered to be statistically significant, and all reported p values were 2 sided. Time-to-event curves were generated using the Kaplan-Meier method. Analyses were carried out using SPSS for Windows, version 19.0 (SPSS Inc., Chicago, Illinois).

Results

Baseline patient characteristics. During the study period, 262 patients were treated with DEB, 69 of whom for diffuse de novo CAD >25 mm. In these 69 patients, 93 lesions were treated. Baseline patient demographic characteristics for the patients treated with DEB ± DES or DES alone are demonstrated in Table 1. Mean age was similar in both groups (66.5 ± 10.4 years vs. 66.1 ± 8.4 years, p = 0.73) as was ejection fraction (54.3 ± 9.4% vs. 56.3 ± 9.4%, p = 0.88). A high proportion of patients were diabetic in both groups (46.4% vs. 44.1%, p = 0.77). Multivessel disease was present in the majority of the patients (71.0% vs. 73.1%, p = 0.77).

Angiographic and procedural details. Average treated lesion length was similar between the DEB ± DES and DES-alone groups (47.3 ± 18.1 mm vs. 47.6 ± 18.6 mm, p = 0.88). Other angiographic and procedural characteristics are summarized in Tables 2 and 3. With regard to the DEB type used, the IN.PACT Falcon (Medtronic Inc., Santa Rosa, California) was used in the majority of cases (n = 81, 87.1%) with the Pantera Lux (Biotronik SE, Berlin, Germany) being used in the remaining lesions. As expected, the mean DES diameter was greater in the DEB ± DES group compared with the DES-alone group (2.95 ± 0.42 mm vs. 2.79 ± 0.25 mm, p < 0.01) as DES use in the former was in general at the more proximal part of

Table 1. Baseline Clinical Characteristics

	DEB ± DES Strategy (n = 69)	DES-Alone Strategy (n = 93)	p Value
Age, yrs	66.5 ± 10.4	66.1 ± 8.4	0.73
Male	63 (91.3)	77 (82.8)	0.12
Ejection fraction, %	54.3 ± 9.4	56.3 ± 9.4	0.77
Previous myocardial infarction	37 (53.6)	45 (48.4)	0.51
Previous percutaneous intervention	40 (58.0)	42 (45.2)	0.11
Previous coronary artery bypass graft	13 (18.8)	19 (20.4)	0.80
Risk factors			
Family history of ischemic heart disease	28 (40.6)	34 (36.6)	0.60
Hypertension	50 (72.5)	64 (68.9)	0.62
Hypercholesterolemia	47 (68.1)	65 (69.9)	0.81
Current smoker	9 (13.01)	14 (15.1)	0.72
Ex-smoker	39 (56.5)	38 (40.9)	0.05
Diabetes	32 (46.4)	41 (44.1)	0.77
Diet controlled	1 (1.4)	3 (3.2)	0.47
Oral hypoglycemics or insulin dependent	31 (44.9)	38 (40.9)	0.60
Acute coronary syndrome	11 (15.9)	12 (12.9)	0.58
Multivessel disease	49 (71.0)	68 (73.1)	0.77
EuroSCORE	3.23 ± 2.28	3.11 ± 1.94	0.69
SYNTAX score	23.7 ± 10.3	21.5 ± 8.7	0.14

Values are mean ± SD or n (%).
DEB = drug-eluting balloon; DES = drug-eluting stent; EuroSCORE = European System for Cardiac Operative Risk Evaluation; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

Table 2. Lesion and Procedural Characteristics

Characteristic	DEB ± DES Strategy (n = 93)	DES-Alone Strategy (n = 93)	p Value
Vessel treated			0.48
Left anterior descending artery	37 (39.8)	43 (46.2)	
Circumflex artery	16 (17.2)	18 (19.4)	
Right coronary artery	40 (43.0)	32 (34.4)	
Location of lesion in treated vessel			0.10
Proximal	4 (4.3)	10 (10.8)	
Mid/distal	89 (95.7)	83 (89.2)	
Balloon pre-dilation	80 (86.0)	84 (90.3)	0.36
Procedural adjuncts			
IVUS	37 (39.8)	30 (32.3)	0.28
Rotablation	3 (3.2)	4 (4.3)	0.70
Device characteristics			
DEB diameter, mm	2.52 ± 0.29	NA	
DES diameter, mm	2.95 ± 0.42	2.79 ± 0.25	<0.01
Total stent length,* mm	29.0 ± 9.1	50.2 ± 18.2	<0.01

Values are n (%) or mean ± SD. *DEB ± DES (n = 41), DES alone (n = 93).
IVUS = intravascular ultrasound; NA = not applicable; other abbreviations as in Table 1.

the lesion, with the exception of bail-out stenting. Of the DEB-treated cases, bail-out stenting was required in 7.4% of cases. A hybrid approach, using the combination of a DES and a DEB, for treating very long disease (67.7 ± 13.4 mm) was used in 34 lesions (36.6%). In these cases, a DEB was used more distally compared with a DES, with an overall DEB/DES ratio of 1.24, suggesting that a DEB rather than a DES treated a greater lesion length. Quantitative coronary angiography measurements at baseline and at the end of the procedure for the 2 groups are reported in Table 4. The acute post-procedural result was better after stenting alone compared with balloon angioplasty, with less residual stenosis and a greater acute gain in the DES alone group.

Clinical follow-up. Clinical outcomes over the entire follow-up period (median, 26.1 months; interquartile range, 13.4 to 31.5 months) are summarized in Table 5. Aside from the cases of periprocedural MI, there were no other in-hospital events recorded in the DEB ± DES group. There was 1 case

Table 3. Strategies Used in the Treatment of Diffuse Disease Using DEB

Treatment Strategy	Lesion (n = 93)	Lesion Length, mm	% Lesion Length Covered by DES	DEB/DES Length Ratio in Treated Segment
DEB alone	52 (56.0)	35.4 ± 5.7	NA	NA
Sequential (hybrid) DEB and DES	34 (36.6)	67.7 ± 13.4	44.6 ± 15.3	1.24
DEB with DES bail out	7 (7.4)	36.7 ± 5.2	39.9 ± 8.8	1.51

Values are n (%) or mean ± SD.
Abbreviations as in Table 2.

Table 4. Quantitative Coronary Angiography Measurements in the Treated Segment at Baseline and After the Procedure

Characteristic	DEB ± DES Strategy (n = 93)	DES-Alone Strategy (n = 93)	p Value
Baseline			
Reference vessel diameter, mm	2.44 ± 0.37	2.58 ± 0.29	<0.01
Minimal lumen diameter, mm	0.66 ± 0.30	0.67 ± 0.26	0.68
Diameter stenosis, %	72.9 ± 11.3	73.9 ± 10.7	0.58
Length, mm	47.3 ± 18.1	47.6 ± 18.6	0.88
Final			
Minimal lumen diameter, mm	1.78 ± 0.41	2.19 ± 0.37	<0.01
Diameter stenosis, %	26.5 ± 7.93	15.6 ± 4.98	<0.01
Acute gain, mm	1.12 ± 0.45	1.52 ± 0.44	<0.01

Values are mean ± SD.
Abbreviations as in Table 1.

of acute ST in the DES-alone group that occurred in a patient who received a 3.0 × 38-mm everolimus-eluting stent (EES) for a mid left anterior descending artery lesion. Estimated MACE and TVR rates at 2-year follow-up (Figs. 1 and 2) were similar and not significantly different between the DEB ± DES and DES-alone groups (20.8 ± 6.1% vs. 22.7 ± 4.5%, p = 0.74 and 14.8 ± 5.7% vs. 11.5 ± 3.4%, p = 0.44). Estimated TLR rates per patient and per lesion were also comparable over the same follow-up period (9.6 ± 4.6% vs. 9.3 ± 3.2%, p = 0.836 and 8.0 ± 3.9% vs. 9.3 ± 3.2%, p = 0.858). With regard to the TLR cases observed in the DEB ± DES group, 3 of these occurred in patients who received both a DEB and DES as part of a hybrid strategy (2 in the DES-treated segment and 1 in the DEB-treated segment) to treat very long disease and 2 in patients treated with DEB alone. There were no cases of vessel thrombosis in the DEB-treated group.

Discussion

The main finding of our study is that DEB use, either alone in smaller diameter vessels or in combination with DES for very long disease, is an acceptable approach for the treatment of diffuse CAD, associated with MACE, TVR, and TLR rates similar to those seen with a DES-alone approach at long-term follow-up.

DEB are becoming increasingly used in the treatment of CAD, especially in the setting of in-stent restenosis (16). Recent studies have also evaluated the role of DEB in the treatment of de novo CAD. The Pilot Long Lesion Study examining optimal balloon angioplasty followed by DEB and spot bare-metal stenting on an as-needed basis reported reasonable TLR rates, although only 12 patients were recruited (17). The STARDUST (Spot Bare-Metal Stenting Provisional Implantation plus Drug-Eluting Balloon Against Drug-Eluting Stenting) trial, currently recruiting,

Table 5. Cumulative Clinical Events

Clinical Outcomes	DEB ± DES Strategy (n = 69)	DES-Alone Strategy (n = 93)
In-hospital events		
MI	3 (4.3)	5 (5.4)
ST (definite/probable)	0	1 (1.1)
Death	0	0
Follow-up events		
Death	4 (5.8)	6 (6.5)
Cardiac cause	2 (2.9)	2 (2.2)
Noncardiac cause	2 (2.9)	4 (4.3)
TVR	8 (11.6)	13 (14.0)
TLR	5 (7.2)	10 (10.8)
MI	0	1 (1.1)
ST (definite/probable)	0	0
MACE*	13 (18.8)	23 (24.7)
TLR (per lesion)	5/93 (5.4)	10/93 (10.8)

Values are n (%) or n/N (%). *MACE is defined as all-cause death, TVR, and MI (including periprocedural).

MACE = major adverse cardiac events; MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

is examining this further. The prospective randomized BELLO (Balloon Elution and Late Loss Optimization) study examining the role of DEB in small coronary vessels with visual reference diameter <2.8 mm and lesion length <25 mm demonstrated similar MACE rates between paclitaxel-eluting stents and DEB at 6-month follow-up (16.3% vs. 10%, p = 0.21) (4). Reference vessel diameter of the DEB treated vessels in our study was as expected, similar to that observed in the BELLO study (2.25 mm vs. 2.15 mm) and reflects the interventionist's tendency toward DEB use in small coronary vessels, especially in the context of diffuse disease. A hybrid approach, using both DES and DEB, was used in patients with very long lesions, which comprised approximately a third of the lesions treated. In these cases, DES were used in the larger, more proximal lesion site and DEB in the more distal, smaller part. Advantages of such a hybrid approach include the reduction of overall stent length, a predictor of in-stent restenosis and ST while maintaining access for a future CABG if required. A decrease in metal stent length may also preserve the vessel's response to vasomotion stimuli and reduce the risk of neoatherosclerosis (7). The procedural efficacy of a DEB strategy in our study is evident by the acceptable residual percentage of diameter stenosis and bail-out stent rate, both of which are comparable with previous DEB studies (4,18). The differences in procedural efficacy with regard to acute gain and percentage of diameter stenosis between a DES-alone strategy and a strategy using a DEB should be expected in view of the absence of a permanent metal scaffold where a DEB has been used. Similar results had been reported in previous studies comparing balloon angioplasty with bare-metal stent implantation (19).

With regard to the clinical outcomes observed with a strategy using a DEB, these were not dissimilar to those reported by the BELLO study (MACE = 10%, TVR = 7.8% at 6 months) and the Valentines II registry (MACE = 8.7%, TVR = 6.9% at 8 months), despite differences in lesion length (lesions >25 mm were excluded in both of these studies) (4,18). More importantly, the clinical outcomes observed with a DEB ± DES approach were similar to those seen in patients with a similar risk factor profile and lesion length who were treated with a DES alone. In agreement with this, the incidence of MACE at 1 year (10.4%) in the DEB ± DES group does not appear to differ significantly from that observed in the prospective LONG-DES III (Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-III) trial in which patients with lesion length >25 mm experienced MACE rates of 14.3% and 10.2%

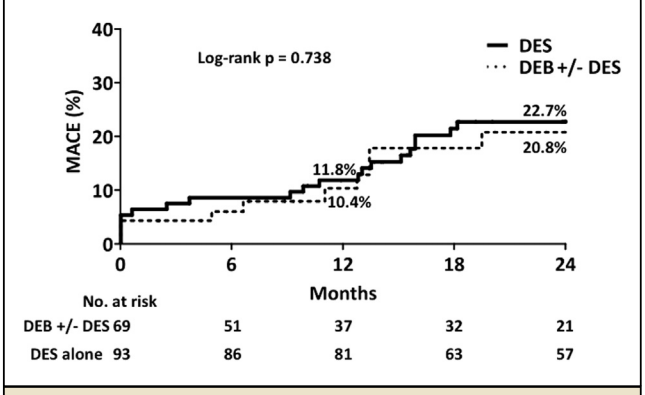

Figure 1. Kaplan-Meier Time-to-Event Curve for MACE

Kaplan-Meier curves for MACE according to strategy used. DEB = drug-eluting balloon(s); DES = drug-eluting stent(s); MACE = major adverse cardiac events.

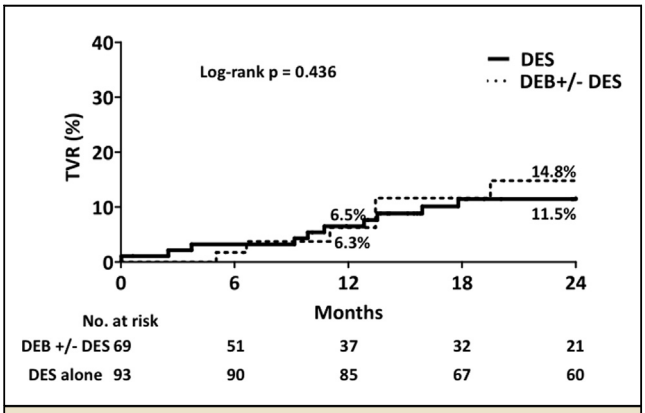

Figure 2. Kaplan-Meier Time-to-Event Curve for TVR

Kaplan-Meier curves for TVR according to strategy used. TVR = target vessel revascularization; other abbreviations as in Figure 1.

at 1-year follow-up with EESs and sirolimus-eluting stents, respectively (20). Although TVR rates in this study were lower, at 4% with EES and 2.7% with sirolimus-eluting stents, than those observed in our study over the same time interval, it is important to note that in the LONG-DES III trial, larger vessels were treated and the prevalence of diabetes mellitus was lower. Moreover, a pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) randomized trials demonstrated MACE and TLR rates at 2 years in a subgroup of patients treated with either EESs or paclitaxel-eluting stents for disease in vessels with a lesion length >13.4 mm and a reference lumen diameter <2.65 mm of 5.5% and 7.6%, respectively (21). Although these are lower than the ones we have observed, treated length was much shorter in this analysis (mean length, 28.7 mm), and MACE definition was less liberal compared with our study. Furthermore, as was the case with the LONG DES III trial, the prevalence of diabetes mellitus was also much lower.

Our study suggests that DEB use can be an alternative approach to the use of DES for the treatment of diffuse coronary disease, either alone in the smaller coronary vessels or in combination with DES in very long lesions. Use of DEB in such circumstances can reduce overall stent length and stent use in small vessels, both of which are predictors of ST and TLR, while treating the underlying disease and maintaining access for a future CABG if required. It is also an attractive option when used alone for patients who cannot tolerate prolonged DAPT. Further studies are required to fully evaluate the role of DEB in this setting.

Study limitations. First, this was a retrospective observational study with a small number of patients, with not all patients completing the 2-year follow-up. Second, the lack of systematic angiographic follow-up did not allow us to assess the angiographic efficacy of DEB in the DEB-treated segments. Third, some patients in our cohort had already experienced in-stent restenosis in a different coronary vessel, and, thus, it may be that part of our cohort was "inherently" predisposed to restenosis, which could have led to higher TLR rates. Finally, angina burden, an important clinical parameter, was not included in the follow-up data.

Conclusions

Our data suggest that DEB may have a role in the treatment of diffuse coronary disease, either alone in smaller vessels or in combination with DES, in very long disease. Such an approach is associated with acceptable long-term clinical outcomes, similar to those seen with a DES-alone strategy. Further studies are required to evaluate the role of DEB in this setting.

Reprint requests and correspondence: Dr. Antonio Colombo, EMO-GVM Centro Cuore Columbus, 48 Via M. Buonarroti, 20145 Milan, Italy. E-mail: info@emocolumbus.it.

REFERENCES

1. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med 2006;355:2113–24.
2. Scheller B, Hehrlein C, Bocksch W, et al. Two-year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. Clin Res Cardiol 2008;97:773–81.
3. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol 2012;59:1377–82.
4. Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. J Am Coll Cardiol 2012;60:2473–80.
5. Bhatt DL. Intensifying platelet inhibition—navigating between Scylla and Charybdis. N Engl J Med 2007;357:2078–81.
6. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55.
7. Colombo A, Latib A. Can long-term results following balloon angioplasty be the "crystal ball" to predict outcome following bioresorbable vascular scaffolds? J Am Heart Assoc 2012;1:e005272.
8. Hofma SH, van der Giessen WJ, et al. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. Eur Heart J 2006;27:166–7.
9. Lee CW, Park DW, Lee BK, et al. Predictors of restenosis after placement of drug-eluting stents in one or more coronary arteries. Am J Cardiol 2006;97:506–11.
10. D'Ascenzo F, Bollati M, Clementi F, et al. Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. Int J Cardiol 2013;167:575–84.
11. Sharp AS, Latib A, Ielasi A, et al. Long-term follow-up on a large cohort of "full-metal jacket" percutaneous coronary intervention procedures. Circ Cardiovasc Interv 2009;2:416–22.
12. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
14. Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
15. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
16. Basavarajaiah S, Latib A. Drug elution without the need for stent struts and polymers: a promising technology? Interv Cardiol 2012;4:291–5.
17. Sangiorgi G. Drug eluting balloons in very long and diffuse coronary artery disease. Paper presented at: EuroPCR; May 19, 2011; Paris, France.
18. Serra A. The Valentines II trial. Paper presented at: Cardiovascular Research Technologies; February 7, 2012; Washington, DC.
19. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489–95.

20. Park DW, Kim YH, Song HG, et al. Comparison of everolimus- and sirolimus-eluting stents in patients with long coronary artery lesions: a randomized LONG-DES-III (Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-III) Trial. J Am Coll Cardiol Intv 2011;4:1096–103.
21. Claessen BE, Smits PC, Kereiakes DJ, et al. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) Randomized Trials. J Am Coll Cardiol Intv 2011;4:1209–15.

Key Words: diffuse coronary artery disease ■ drug-eluting balloon(s) ■ drug-eluting stent(s) ■ target lesion revascularization.