IMR Press

Review

Back to the future: the role of DCB for the treatment of coronary bifurcation

Andrea Buono[1,2], Diego Maffeo[2], Mariano Pellicano[1], Giuseppe De Blasio[3], Maurizio Tespili[1], Alfonso Ielasi[1,*]

[1]*Clinical and Interventional Cardiology Unit, Sant'Ambrogio Cardio-Thoracic Center, 20149 Milan, Italy*

[2]*Interventional Cardiology Unit, Fondazione Poliambulanza, 25124 Brescia, Italy*

[3]*Cardiology Unit, IRCCS Istituto Ortopedico Galeazzi, 20161 Milan, Italy*

*Correspondence: alielasi@hotmail.com (Alfonso Ielasi)

DOI:10.31083/j.rcm2204147

Submitted: 6 September 2021 Revised: 9 November 2021 Accepted: 17 November 2021 Published: 22 December 2021

Coronary bifurcation lesion (CBL) is a common but challenging scenario in percutaneous coronary interventions. Drug-coated balloons (DCBs) are modern devices with attractive perspective in CBL treatment. In-stent restenosis, small vessel and diffuse de-novo coronary artery disease have been, so far, considered the ideal scenario for DCBs application. Studies assessing DCBs in de-novo CBL demonstrated the safety and efficacy of this strategy. However, the heterogeneity of the study populations and the presence of methodological limitations prevent from drawing definite recommendations. Considering that the best treatment of bifurcations has not yet been defined, the "leaving nothing behind" philosophy will be the topic of future studies.

Keywords

Coronary bifurcation lesion; Drug-coated balloon; Percutaneous coronary intervention; De-novo coronary artery disease

1. Introduction

Coronary bifurcation lesion (CBL) is a common finding in daily practice, being encountered in up to 20% of percutaneous coronary interventions (PCI) [1]. Despite the common occurrence, CBL treatment still remains a challenging scenario because of its technical complexity and the not always favorable clinical outcomes. In fact, coronary bifurcation is a complex anatomical structure composed of three different vessel segments: proximal main vessel (MV), distal MV and side branch (SB). Adequate angiographic result in all segments has to be pursued, even if the definition of optimal SB result has yet to be established [2]. Drug-coated balloons (DCBs) are modern devices able to guarantee a fast and homogenous transfer of anti-proliferative drugs into the vessel, without the permanent implant of metallic struts. This "leaving nothing behind" philosophy re-proposes some of the advantages related to the bioresorbable scaffold use [3]. On this premise, in-stent restenosis, small vessel and diffuse de-novo coronary artery disease have been, so far, considered the ideal scenario for DCBs application.

2. Why could we treat CBLs with DCBs?

The European Bifurcation Club (EBC) has recently recommended that PCI on bifurcation stenting should adhere to the "keep it simple and safe" principle, trying to limit the number of stents [2]. On this basis, a one-stent strategy is usually the preferred approach for the vast majority of CBLs (the so-called "provisional strategy"), whereas a two-stent approach should be selected in patients with complex lesions involving large and diseased SBs (especially unprotected left main). These recommendations go hand in hand with the "leaving nothing behind" philosophy, making the DCB very attractive in the CBL setting for several reasons. First of all, DCB can dramatically increase the rate of provisional strategy, reducing the incidence of device-related failure (in-stent restenosis and stent thrombosis) associated with a wide application of two-stent strategies. Moreover, DCB can reduce the PCI complexity, since two-stent strategies require extensive knowledge of technical steps. Secondly, treating diseased SBs with anti-proliferative drug can provide better results in comparison with a conventional dilation, mitigating the limits of the current SB plain angioplasty recommended among provisional strategy steps. Lastly, CBL SBs are often small vessels (with a diameter $\leq$2.75 mm) but subtending a not negligible area of myocardium. Taken together, these aspects represent the rationale of different studies investigating the efficacy and safety of DCB application in CBL setting. In this review, we provide a contemporary overview on the topic, discussing the available evidence; articles were searched on the online library Pubmed.gov on the basis of the following keywords: "drug-coated balloon; drug-eluting balloon; coronary bifurcation lesions". All the articles including CBLs patients treated with DCB were included.

3. Studies assessing DCBs in de-novo coronary artery disease scenario

In several trials, DCBs have been proved to be a safe and effective therapeutic option in the context of de-novo coronary artery disease [4–27]. Despite hundreds of patients

have been enrolled in these trials, no definite conclusions can be formulated concerning the role of DCB in CBL setting. In fact, in most of the above-named trials the percentage and the number of CBL patients have not been reported [5, 6, 8, 10, 11, 13–15, 22, 24, 27] or CBL has represented an exclusion criteria [7, 12, 16, 17, 21]. Thus, the remaining of the afore mentioned studies enrolled a small number of CBL patients [4, 9, 18–20, 23, 25], suggesting conflicting results (Table 1, Ref. [4, 9, 18–20, 23, 25]): in the DEBUT trial [23], DCBs have been associated with a better outcome (composite of cardiovascular mortality, nonfatal myocardial infarction, or ischemia-driven target lesion revascularization at 9 months) in comparison with bare-metal stent (BMS), whereas in the BASKET-SMALL 2 trial [20] no difference has been emerged between DCB and drug-eluting stent (DES) at the 1-year assessment. Recently, Iannopollo *et al.* [26], described a multicenter registry with the main aim to assess the performance of the Agent DCB (Boston Scientific) in all PCI settings, including 97 patients with 117 CBLs treated. In this CBL subgroup, the treated bifurcations were mainly true bifurcations (84%) and the adopted stent strategy was provisional, with DES implantation in the MV and DCB in the SB. Authors reported optimal procedural outcomes (92% of success defined as completion of the procedure with no in-lab complications, final Thrombolysis in Myocardial Infarction flow 3, and residual stenosis $<$30%) and favorable 1-year clinical outcomes (3.7% rate of major adverse cardiac events, all of them consisting in target-lesion revascularization [TLR]).

4. Studies assessing DCBs in de-novo CBL scenario

Considering the small number of CBL patients enrolled in the main trials assessing the use of DCBs in the context of de-novo coronary artery disease, the need of drawing focused studies was primary. On this premise, several studies have been so far conducted. However, the available studies, focused on the topic, are characterized by heterogeneous designs, especially considering the type of bifurcation studied (according to Medina classification), the applied strategy and the step in which DCB was delivered. Not all bifurcations are equal in complexity, being classifiable in three major types: CBLs involving only the SB (Medina 0.0.1), CBLs involving only the MV (Medina 1.0.0 or 0.1.0 or 1.1.0) and CBLs involving both MV and SB (true bifurcation; Medina 1.0.1 or 0.1.1 or 1.1.1). Briefly, two strategies are possible: (1) MV stenting plus DCB application (in SB only or in both segments); (2) DCB-only (both in SB and MV). Different combinations of these approaches have been described in the available trials. Yet, also the timing of DCB application can introduce variability. In fact, when a DCB is used to treat SBs can be inflated before MV stenting (then avoiding SB rewiring and final kissing-balloon inflation), during the kissing-balloon inflation (after MV stenting) and even after kissing-balloon inflation (as final SB dilation). Different theoretical advantages and disadvantages can influence the result: pre-dilating the SB with DCB application may results in SB dissection; on the other hand, applying DCB after MB stenting could result in partial disruption of the coating caused by the stent strut, taking into account the profile of such balloons. Despite the best timing is still unknown, some Authors suggest that DCB should be applied as the final step and not as an intermediate one [28]. Lastly, a wide variety of different DCBs have been used in the different studies: interaction among doses, formulations, and release kinetics of the drugs used play an important role in determining no evidence of a "class effect" among different platforms [29].

On these premises, an overview of the available studies is reported in Table 2 (Ref. [30–42]).

Despite the first studies [30–32] documented the safety and the efficacy of the strategy consisting in DCB application followed by MV stenting, their main limitation consisted in the use of BMS, nowadays considered an outdated tool. In fact, the randomized controlled trials (RCTs) comparing DCB inflation plus BMS with standard PCI performed with BMS or DES, showed the absence of angiographic and clinical superiority of the first strategy over conventional BMS and the inferiority compared with DES [33, 35].

Three observational studies [36–38] assessed the feasibility of the hybrid approach (DES implantation in MV and DCB inflation in SB). In the multicenter BIOLUX-trial [36] 35 CBL patients deemed appropriate for provisional stenting technique were treated with DCB (Pantera Lux, Biotronik AG, Buelach, Switzerland) inflation in SB before DES implantation in MV. Authors reported a 60% device success (defined as procedural absence of residual SB diameter stenosis $\geq$30%), a low 9-month late lumen loss (LLL) and a 5.9% rate of 12-month major adverse cardiovascular events (MACE). Despite the mandatory final kissing-balloon inflation which represents a strength of this study, major limitation consists in the exclusion of major anatomical bifurcations (LM and very proximal CBLs). The French DEBSIDE trial [36] treated 50 CBL patients with DCB inflation (DANUBIO, Minvasys, Gennevilliers, France) in SB, after the systematic implantation of DES (Nile PAX, Minvasys, Gennevilliers, France) in MV. Procedural success was 100%. 6-month ostial SB LLL was the pre-specified primary endpoint and resulted in a very low value (-0.04 ± 0.34 mm). One of the main limitations of this study is the monobrand nature of the used devices, that are not anymore available on the market. The third observational study, named SARPEDON trial [38], enrolled 58 CBL patients in which a final DCB (Pantera Lux, Biotronik AG, Buelach, Switzerland) application in SB followed MV stenting. The 6-month angiographic follow-up showed a low rate of SB LLL with a total 10% rate of restenosis (6% in the MV and 4% in the SB), whereas MACE occurred in 19% of the patients at 1-year follow-up. Taken together, despite the absence of a control group and the limited number of enrolled patients, the results provided by the afore mentioned three trials showed a good performance of the hybrid strategy.

Table 1. Study assessing DCBs in de-novo coronary artery disease.

First author/Study	Year	Study	CBL patients enrolled (n)	CBL patients enrolled treated with DCB (n)	Main findings	Comments
Cortese B *et al.* [4] PICCOLETO	2010	DCB vs DES	13	6	Subgroup analysis of CBL patients not performed	
Poerner TC *et al.* [9]	2014	DCB + BMS vs DES	21	12	Subgroup analysis of CBL patients not performed	
Cortese B *et al.* [18] FASICO	2017	DCB-only	7	32	Subgroup analysis of CBL patients not performed	
Cortese B *et al.* [19] DCB-RISE	2018	DCB-only	96	544	Subgroup analysis of CBL patients not performed	CBL is not an independent predictor of TLR at follow-up
Jeger RV *et al.* [20] BASKET-SMALL 2	2018	DCB vs DES	51	22	No difference in terms of composite of cardiac death, non-fatal MI, and TVR at 1 year (9% DCB vs 17% DES, HR 0.45 (0.08–2.39).	
Rissanen TT *et al.* [23] DEBUT	2019	DCB vs BMS	36	21	Difference in terms of composite of cardiovascular mortality, nonfatal MI, or ischemia driven TLR at 9 months (0% DCB vs 20% BMS, OR not applicable).	CBL needing a two-stent technique represented an exclusion criteria
Cortese B *et al.* [25] PICCOLETO II	2020	DCB vs DES	29	15	Subgroup analysis of CBL patients not performed	Major bifurcation represented an exclusion criteria

BMS, bare-metal stent; CBL, coronary bifurcation lesion; DCB, drug-coated balloon; DES, drug-eluting stent; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; TLR, target-lesion revascularization; TVR, target-vessel revascularization.

In the last years, the concept to treat de-novo CBLs only with DCB avoiding stent implantation (DCB-only strategy) has quickly developed. To confirm this trend, the last evidence available in the literature has been focused on DCB-only strategy [39–42]. In the PEPCAD-BIF trial [39] 64 CBL patients were randomized to plain angioplasty (POBA) or DCB-only strategy. Left main bifurcation as well all bifurcations with proximal MV involvement (Medina 1.X.X) were excluded. The main study finding was a lower 9-month LLL and binary restenosis incidence in the DCB subgroup when compared with POBA subgroup. The main limitation of this study is intuitive and consists of the outdated strategy adopted for the control group (POBA). To overcome this drawback, Bruch *et al.* [40] compared a DCB-only strategy to a DCB plus stenting strategy, showing no differences in terms of MACE and TLR after 9 months. Nevertheless, once again, the control study group does not represent the contemporary standard-of-care, since the MV stenting was performed using BMS. In 2016, Vaquerizo *et al.* [41] applied a DCB-only strategy for 49 patients affected by Medina 0.0.1 CBLs. After a mandatory SB lesion preparation (as confirmed by a 59% use of cutting balloon), paclitaxel DCB (Dior, Eurocor GmbH, Bonn, Germany) was inflated for a minimum of 45 seconds. Angiographic success was 86% (in the remaining 14% a BMS was implanted), 7-month angiographic follow-up revealed 22.5% of binary restenosis whereas at 1-year follow-up MACE were 14.3%. Recently, Kitani S *et al.* [42] enrolled in the DCA/DCB Registry 129 patients affected by major CBLs in which DCB application in the SB was performed after lesion preparation with directional atherectomy: authors reported a low rate of TLR (3.1%) at 1-year follow-up.

Taken these data together, two meta-analyses concluded that DCB is superior to plain angioplasty for SB treatment in bifurcations [43, 44]. In the first one [43], 349 patients were included: the angiographic follow-up performed after a mean of 9 months demonstrated that DCB was associated with a lower SB LLL compared to POBA [mean difference, –0.19 mm; 95% confidence interval (CI), –0.37 to –0.01; $p = 0.04$] but without difference in terms of risk of SB binary restenosis [odds ratio (OR), 0.52; 95% CI, 0.18 to 1.47; $p = 0.22$] and 15-month MACE (OR, 0.76; 95% CI, 0.4 to 1.4; $p = 0.40$) and TLR (OR, 0.85; 95% CI, 0.3 to 2.4; $p = 0.76$). The second meta-analysis [44] is focused on comparison of DCB versus POBA for SB-only treatment in terms of LLL: including 281 CBLs, Authors showed a statistically significant difference favoring DCB over POBA [mean difference –0.24 mm; 95% CI, –0.44 to –0.05; $p = 0.01$].

To date, no robust data coming from RCTs and comparing DCB-only strategy versus contemporary gold-standard approach (DES) are available.

5. Available recommendations on the use of DCB in the setting of CBL

Despite DCB use in the SB is an attractive approach, according to the last EBC consensus document [3], many questions, including the appropriate SB selection, technique (DCB with or without final kissing ballooning or repeat proximal optimization technique) and actual impact on meaningful clinical endpoints are still unanswered. Studies, so far available, exploring DCB efficacy in de novo CBL had major limitations and to date have provided no conclusive evidence. Contrariwise, DCB use in bifurcation restenosis (especially after 2-stent techniques) is highly encouraged: the strategy proved to be feasible and able to minimize metal within the bifurcation [45].

Whenever a DCB strategy is chosen, a meticulous lesions preparation is suggested. The choice of DCB size can be difficult for MV treatment because of caliper change: in such case, using the distal MV reference diameter is reasonable when the distal-to-proximal MV ratio is in the range of 0.75:1 to 1:1 [29]. In the case of a DCB-only strategy, all the steps can be performed in a sequential manner, reserving kissing balloon inflation (with DCBs) in selected cases.

In our opinion, a case by case evaluation is strongly recommended: DCB can represent a valuable tool to treat SBs, especially when the amount of the disease is limited in extension (e.g., ostial stenosis), the bifurcation have disfavoring anatomical characteristics (e.g., prohibitive angle and relevant difference in branches diameters), and the subtended myocardium is relatively limited. Application of a complete DCB-only strategy (for both SB and MV) needs further investigations.

6. Future perspectives

Nowadays, the best treatment of bifurcations has not yet been defined. The available studies included heterogeneous populations and specific subgroups (diabetic patients, major CBLs) have been frequently excluded. A clear definition of procedural steps in case of DCB application should be explored. RCTs comparing a strategy of DCB application versus the gold-standard treatment (DES) for SB have not been conducted. Furthermore, the optimal antiplatelet regimen and duration after DCB application are unknown. Future studies are called to answer to these unresolved questions: results are awaited from the Hyper Pilot study [46], in which a hybrid approach (DCB plus DES) has been applied to treat diffuse de-novo coronary artery disease, including bifurcation lesion (with reference diameter of the SB $\geq$2 mm and $<$2.75 mm). However, to the best of our knowledge no specific RCTs focused on CBLs treatment comparing DCB and DES are in pipeline, making the ongoing gaps of knowledge a relevant issue.

7. Conclusions

The "leaving nothing behind" philosophy associated with the use of DCB is an attractive therapeutic option for CBLs. Limited data have demonstrated the safety and the feasibility of this approach. However, larger RCTs with homogeneous populations and procedural steps, comparing DCB strategies to the gold standard treatment (DES implantation) are strongly needed.

Table 2. Study assessing DCBs in de-novo coronary bifurcation lesions.

First author/Study	Year	Study type	DCB	Study strategy	Patient enrolled (n)	Follow-up	Main findings	Comments
Fanggiday *et al.* [30] DEBIUT Registry	2008	Observational Registry	DIOR-I	Sequential DCB inflation in MV and SB, followed by BMS in MV and KBI	20	4 months	100% procedural success No cardiac deaths, MI or TLF	
Mathey *et al.* [31] PEPCAD V	2011	Observational Registry	Sequent Please	Sequential DCB inflation in MV and SB, followed by BMS in MV	88	9 months	100% procedural success LLL: 0.38 ± 0.46 mm (MV); 0.21 ± 0.48 mm (SB) 3 restenosis with 1 TLR; 2 ST	
Sgueglia *et al.* [32]	2011	Observational case series	Various	MV stented with BMS, followed by KBI with DCBs	14	234 ± 81 days	100% procedural success No cardiac death, non fatal myocardial infarction or target bifurcation revascularization	
Stella PR *et al.* [33] DEBIUT	2012	RCT	DIOR-I	Sequential DCB inflation in MV and SB, followed by BMS in MV vs standard provisional stenting with BMS vs standard provisional stenting with DES	117	12 months	Absence of angiographic and clinical superiority over conventional BMS DES showed superior angiographic results than DCB and BMS	
Schulz *et al.* [34]	2014	Observational Registry	Sequent Please In.Pact Falcon	Sequential DCB inflation in MV and SB (with bail-out stenting)	38	4 months	7.7% of MACE, all consisting in TLR	
López Mínguez JR *et al.* [35] BABILON	2014	RCT	Sequent Please (B Braun)	Sequential DCB inflation in MV and SB, followed by BMS in MV vs standard provisional MV T-stenting with DES	108	9 months (angiographic follow-up) 24 months (clinical follow-up)	Angiographic results: better performance of DES in terms of MV in-segment restenosis No significant differences were found in MACE (17.3% in the DCB group vs 7.1% in the DES group) but significantly higher incidence of TLR and TVR in the DCB group	
Berland J *et al.* [36] DEBSIDE	2015	Observational Registry	Danubio (Mynvasis)	MV stenting with DES, followed by KBI and finally DCB inflation in SB	50	6 months	SB MLD increase (from 1.36 ± 0.38 mm to 1.55 ± 0.35 mm) with ostial LLL of 0.04 ± 0.34 mm 10% of TLR (of those 6% not clinically-driven); 2% of TVR	LM bifurcation excluded

Table 2. Continued.

First author/Study	Year	Study type	DCB	Study strategy	Patient enrolled (n)	Follow-up	Main findings	Comments
Worthley S *et al.* [37] BIOLUX-I	2015	Observational Registry	Pantera Lux (Biotronik)	Sequential DCB inflation in SB and MV stenting with DES, followed by final KBI	35	9 months (angiographic and IVUS); 12 months (clinical assessment)	60% of post-procedural device success rate SB LLL: 0.10 ± 0.43 mm (per QCA) and –0.03 ± 0.22 mm (per IVUS) 5.9% of composite endpoint of cardiac death, TV-MI and clinically driven TVR	LM, severely calcified and bifurcation near to ostial LAD, LCx and RCA origin excluded
Jim MH J *et al.* [38] SARPEDON	2015	Observational registry	Pantera Lux (Biotronik)	DES implantation in MV, followed by SB dilation and DCB inflation, final KBI	58	6 months (angiographic follow-up) 12 months (clinical follow-up)	MV LLL 0.21 ± 0.35; SB LLL 0.09 ± 0.21 mm; 10% restenosis (6% in MV, 4% in SB) 1-year MACE (any death, non-fatal MI, TVR): 19%	DCB applied only in case of residual SB stenosis <50% after KBI
Kleber FX *et al.* [39] PEPCAD-BIF	2015	RCT	Sequent Please (B Braun)	DCB-only strategy vs POBA	64 (32 vs 32)	9 months (angiographic follow-up)	LLL: 0.13 ± 0.31 in DCB group vs 0.51 ± 0.66 in POBA group ($p = 0.013$) Binary restenosis: 5.9% vs 25.7%, $p = 0.045$)	LM bifurcations and bifurcations with proximal MV involvement were excluded (Medina 1.0.0)
Bruch *et al.* [40]	2016	Observational Registry	Sequent Please (B Braun)	DCB-only strategy vs DCB + stenting	127 (70 vs 57)	9 months	No difference between the two groups in terms of MACE (6.1% DCB-only vs 7.3%) and TLR (4.5% DCB-only vs 3.6%)	
Vaquerizo B *et al.* [41]	2016	Observational Registry	DIOR (Eurocor GmbH)	DCB-only strategy for SB	49	7-months (angio-) graphic follow-up 1 year (clinical follow-up)	86% of angiographic success 22.5% of binary restenosis 14.3% of MACE	Only Medina 0.0.1 included; LM CBL excluded
Kitani S *et al.* [42] DCA/DCB Registry	2021	Observational Registry	Sequent Please (B Braun)	DCB-only strategy with lesion preparation with directional coronary atherectomy followed by DCB inflation	129	6-15 months (angiographic follow-up) 12 months (clinical follow-up)	3.1% of TLR 10.9% of TVF (with 1 clinically-driven TVR) 0.8% non TV-MI	Only major bifurcation included

BMS, bare metal stent; CBL, coronary bifurcation lesion; DCB, drug-coated balloon; KBI, kissing balloon inflation; IVUS, intravascular ultrasound; LAD, left descending artery; LCx, left circumflex; LLL, late lumen loss; LM, left main; MACE, major adverse cardiac events; MI, myocardial infarction; MLD, minimal lumen diameter; MV, main vessel; POBA, plain old balloon angioplasty; QCA, quantitative coronary angiography; RCA, right coronary artery; RCT, randomized controlled trial; SB, side branch; ST, stent thrombosis; TLF, target-lesion failure; TVF, target-vessel failure; TV-MI, target-vessel myocardial infarction; TVR, target-vessel revascularization.

Author contributions

Conceptualization—AI, AB, DM, MP, GDB, MT; Writing - original draft preparation—AI, AB, DM, MP, GDB, MT; Writing - review and editing—AI, AB, DM, MP, GDB, MT; Supervision—AI.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Sawaya FJ, Lefèvre T, Chevalier B, Garot P, Hovasse T, Morice M, *et al.* Contemporary Approach to Coronary Bifurcation Lesion Treatment. JACC: Cardiovascular Interventions. 2016; 9: 1861–1878.

[2] Burzotta F, Lassen JF, Lefèvre T, Banning AP, Chatzizisis YS, Johnson TW, *et al.* Percutaneous coronary intervention for bifurcation coronary lesions: the 15th consensus document from the European Bifurcation Club. EuroIntervention. 2021; 16: 1307–1317.

[3] Buono A, Ielasi A, Colombo A. Latest generation stents: is it time to revive the bioresorbable scaffold? Minerva Cardioangiologica. 2020; 68: 415–435.

[4] Cortese B, Micheli A, Picchi A, Coppolaro A, Bandinelli L, Severi S, *et al.* Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. Heart. 2010; 96: 1291–1296.

[5] Ali RM, Degenhardt R, Zambahari R, Tresukosol D, Ahmad WAW, Kamar HBH, *et al.* Paclitaxel-eluting balloon angioplasty and cobalt-chromium stents versus conventional angioplasty and paclitaxel-eluting stents in the treatment of native coronary artery stenoses in patients with diabetes mellitus. EuroIntervention. 2011; 7: K83–K92.

[6] Belkacemi A, Agostoni P, Nathoe HM, Voskuil M, Shao C, Van Belle E, *et al.* First results of the DEB-AMI (Drug Eluting Balloon in Acute ST-Segment Elevation Myocardial Infarction) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug- eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intra- vascular, functional, and clinical outcomes. Journal of the American College of Cardiology. 2012; 59: 2327–2337.

[7] Liistro F, Porto I, Angioli P, Grotti S, Ducci K, Falsini G, *et al.* Elutax paclitaxel-eluting balloon followed by bare-metal stent compared with Xience V drug-eluting stent in the treatment of de novo coronary stenosis: a randomized trial. American Heart Journal. 2013; 166: 920–926.

[8] Clever YP, Cremers B, Speck U, Dietz U, Böhm M, Scheller B. Influence of a paclitaxel coated balloon in combination with a bare metal stent on restenosis and endothelial function: comparison with a drug eluting stent and a bare metal stent. Catheterization and Cardiovascular Interventions. 2014; 84: 323–331.

[9] Poerner TC, Otto S, Gassdorf J, Nitsche K, Janiak F, Scheller B, *et al.* Stent coverage and neointimal proliferation in bare metal stents postdilated with a Paclitaxel-eluting balloon versus everolimus-eluting stents: prospective randomized study using optical coherence tomography at 6-month follow-up. Circulation: Cardiovascular Interventions. 2014; 7: 760–767.

[10] Naganuma T, Latib A, Sgueglia GA, Menozzi A, Castriota F, Micari A, *et al.* A 2-year follow-up of a randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels the BELLO study. International Journal of Cardiology. 2015; 184: 17–21.

[11] Żurakowski A, Buszman PP, Milewski KP, Janas A, Gorycki B, Kondys M, *et al.* Stenting and Adjunctive Delivery of Paclitaxel via Balloon Coating Versus Durable Polymeric Matrix for De Novo Coronary Lesions: Clinical and Angiographic Results from the Prospective Randomized Trial. Journal of Interventional Cardiology. 2015; 28: 348–357.

[12] Seeger J, Markovic S, Birkemeyer R, Rittger H, Jung W, Brachmann J, *et al.* Paclitaxel-coated balloon plus bare-metal stent for de-novo coronary artery disease: final 5-year results of a randomized prospective multicenter trial. Coronary Artery Disease. 2016; 27: 84–88.

[13] Besic KM, Strozzi M, Margetic E, Bulum J, Kolaric B. Drug-eluting balloons in patients with non-ST elevation acute coronary syndrome. Journal of Cardiology. 2015; 65: 203–207.

[14] Nishiyama N, Komatsu T, Kuroyanagi T, Fujikake A, Komatsu S, Nakamura H, *et al.* Clinical value of drug-coated balloon angioplasty for de novo lesions in patients with coronary artery disease. International Journal of Cardiology. 2016; 222: 113–118.

[15] Gobić D, Tomulić V, Lulić D, Židan D, Brusich S, Jakljević T, *et al.* Drug-Coated Balloon Versus Drug-Eluting Stent in Primary Percutaneous Coronary Intervention: A Feasibility Study. The American Journal of the Medical Sciences. 2017; 354: 553–560.

[16] Chae IH, Yoon CH, Park JJ, Oh IY, Suh JW, Cho YS, *et al.* Comparison of Drug-Eluting Balloon Followed by Bare Metal Stent with Drug-Eluting Stent for Treatment of de Novo Lesions: Randomized, Controlled, Single-Center Clinical Trial. Journal of Korean Medical Science. 2017; 32: 933–941.

[17] García-Touchard A, Goicolea J, Sabaté M, Alfonso F, Ruiz-Salmerón R, Bethencourt A, *et al.* A randomised trial of paclitaxel-eluting balloon after bare metal stent implantation vs. bare metal stent in ST-elevation myocardial infarction (the PEBSI study). EuroIntervention. 2017; 12: 1587–1594.

[18] Cortese B, di Palma G, Latini RA, Elwany M, Orrego PS, Seregni RG. Immediate and short-term performance of a novel sirolimus-coated balloon during complex percutaneous coronary interventions. The FAtebenefratelli SIrolimus COated-balloon (FASICO) registry. Cardiovascular Revascularization Medicine. 2017; 18: 487–491.

[19] Cortese B, D'Ascenzo F, Fetiveau R, Balian V, Blengino S, Fineschi M, *et al.* Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE. Journal of Cardiovascular Medicine. 2018; 19: 247–252.

[20] Jeger RV, Farah A, Ohlow M, Mangner N, Möbius-Winkler S, Leibundgut G, *et al.* Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. Lancet. 2018; 392: 849–856.

[21] Tang Y, Qiao S, Su X, Chen Y, Jin Z, Chen H, *et al.* Drug-Coated Balloon Versus Drug-Eluting Stent for Small-Vessel Disease: The RESTORE SVD China Randomized Trial. JACC: Cardiovascular Interventions. 2018; 11: 2381–2392.

[22] Vos NS, Fagel ND, Amoroso G, Herrman JR, Patterson MS, Piers LH, *et al.* Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction: The REVELATION Randomized Trial. JACC: Cardiovascular Interventions. 2019; 12: 1691–1699.

[23] Rissanen TT, Uskela S, Eränen J, Mäntylä P, Olli A, Romppanen H, *et al.* Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a

single-blind, randomised, non-inferiority trial. The Lancet. 2019; 394: 230–239.
[24] Shin E, Lee JM, Her A, Chung J, Eun Lee K, Garg S, *et al.* Prospective randomized trial of paclitaxel-coated balloon versus bare-metal stent in high bleeding risk patients with de novo coronary artery lesions. Coronary Artery Disease. 2019; 30: 425–431.
[25] Cortese B, Di Palma G, Guimaraes MG, Piraino D, Orrego PS, Buccheri D, *et al.* Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease: PICCOLETO II Randomized Clinical Trial. JACC: Cardiovascular Interventions. 2020; 13: 2840–2849.
[26] Iannopollo G, Giannini F, Ponticelli F, Pagliaro B, Tzanis G, Gallone G, *et al.* Percutaneous Coronary Intervention With the Agent Paclitaxel-Coated Balloon: A Real-World Multicenter Experience. Journal of Invasive Cardiology. 2020; 32: 117–122.
[27] Cortese B, Testa L, Di Palma G, Heang TM, Bossi I, Nuruddin AA, *et al.* Clinical performance of a novel sirolimus-coated balloon in coronary artery disease: EASTBOURNE registry. Journal of Cardiovascular Medicine. 2021; 22: 94–100.
[28] Zuin M, Rigatelli G. Treatment of de novo coronary artery bifurcation lesions with drug coated balloons: a reappraisal according to the available scientific data. Cardiovascular Revascularization Medicine. 2018; 19: 57–64.
[29] Jeger RV, Eccleshall S, Wan Ahmad WA, Ge J, Poerner TC, Shin E, *et al.* Drug-Coated Balloons for Coronary Artery Disease: Third Report of the International DCB Consensus Group. JACC: Cardiovascular Interventions. 2020; 13: 1391–1402.
[30] Fanggiday JC, Stella PR, Guyomi SH, Doevendans PA. Safety and efficacy of drug-eluting balloons in percutaneous treatment of bifurcation lesions: the DEBIUT (drug-eluting balloon in bifurcation Utrecht) registry. Catheterization and Cardiovascular Interventions. 2008; 71: 629–635.
[31] Mathey DG, Wendig I, Boxberger M, Bonaventura K, Kleber FX. Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial. EuroIntervention. 2011; 7: K61–K65.
[32] Sgueglia GA, Todaro D, Bisciglia A, Conte M, Stipo A, Pucci E. Kissing inflation is feasible with all second-generation drug-eluting balloons. Cardiovascular Revascularization Medicine. 2011; 12: 280–285.
[33] Stella PR, Belkacemi A, Dubois C, Nathoe H, Dens J, Naber C, *et al.* A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. Catheterization and Cardiovascular Interventions. 2012; 80: 1138–1146.
[34] Schulz A, Hauschild T, Kleber FX. Treatment of coronary de novo bifurcation lesions with DCB only strategy. Clinical Research in Cardiology. 2014; 103: 451–456.
[35] López Mínguez JR, Nogales Asensio JM, Doncel Vecino LJ, Sandoval J, Romany S, Martínez Romero P, *et al.* A prospective randomised study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results. EuroIntervention. 2014; 10: 50–57.
[36] Berland J, Lefèvre T, Brenot P, Fajadet J, Motreff P, Guerin P, *et al.* DANUBIO—a new drug-eluting balloon for the treatment of side branches in bifurcation lesions: six-month angiographic follow-up results of the DEBSIDE trial. EuroIntervention. 2015; 11: 868–876.
[37] Worthley S, Hendriks R, Worthley M, Whelan A, Walters DL, Whitbourn R, *et al.* Paclitaxel-eluting balloon and everolimus-eluting stent for provisional stenting of coronary bifurcations: 12-month results of the multicenter BIOLUX-I study. Cardiovascular Revascularization Medicine. 2015; 16: 413–417.
[38] Jim M, Lee MK, Fung RC, Chan AK, Chan K, Yiu K. Six month angiographic result of supplementary paclitaxel-eluting balloon deployment to treat side branch ostium narrowing (SARPEDON). International Journal of Cardiology. 2015; 187: 594–597.
[39] Kleber FX, Rittger H, Ludwig J, Schulz A, Mathey DG, Boxberger M, *et al.* Drug eluting balloons as stand alone procedure for coronary bifurcational lesions: results of the randomized multicenter PEPCAD-BIF trial. Clinical Research in Cardiology. 2016; 105: 613–621.
[40] Bruch L, Zadura M, Waliszewski M, Platonic Z, Eränen J, Scheller B, *et al.* Results from the International Drug Coated Balloon Registry for the Treatment of Bifurcations. can a Bifurcation be Treated without Stents? Journal of Interventional Cardiology. 2016; 29: 348–356.
[41] Vaquerizo B, Fernández-Nofreiras E, Oategui I, Suarez de Lezo J, Rumoroso JR, Martín P, *et al.* Second-Generation Drug-Eluting Balloon for Ostial Side Branch Lesions (001-Bifurcations): Mid-Term Clinical and Angiographic Results. Journal of Interventional Cardiology. 2016; 29: 285–292.
[42] Kitani S, Igarashi Y, Tsuchikane E, Nakamura S, Seino Y, Habara M, *et al.* Efficacy of drug-coated balloon angioplasty after directional coronary atherectomy for coronary bifurcation lesions (DCA/DCB registry). Catheterization and Cardiovascular Interventions. 2021; 97: E614–E623.
[43] Megaly M, Rofael M, Saad M, Shishehbor M, Brilakis ES. Outcomes with Drug-Coated Balloons for Treating the Side Branch of Coronary Bifurcation Lesions. The Journal of Invasive Cardiology. 2018; 30: 393–399.
[44] Corballis NH, Paddock S, Gunawardena T, Merinopoulos I, Vassiliou VS, Eccleshall SC. Drug coated balloons for coronary artery bifurcation lesions: A systematic review and focused meta-analysis. PLoS ONE. 2021; 16: e0251986.
[45] Harada Y, Colleran R, Pinieck S, Giacoppo D, Michel J, Kufner S, *et al.* Angiographic and clinical outcomes of patients treated with drug-coated balloon angioplasty for in-stent restenosis after coronary bifurcation stenting with a two-stent technique. EuroIntervention. 2017; 12: 2132–2139.
[46] Ielasi A, Buono A, Pellicano M, Tedeschi D, Loffi M, Donahue M, *et al.* A HYbrid APproach Evaluating a DRug-Coated Balloon in Combination with a New-Generation Drug-Eluting Stent in the Treatment of De Novo Diffuse Coronary Artery Disease: The HYPER Pilot Study. Cardiovascular Revascularization Medicine. 2021; 28: 14–19.