

Review

Treatment of bifurcation lesions with drug-coated balloons: A review of currently available scientific data



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ABSTRACT

Bifurcation lesion management still represents a challenge for interventional cardiologists and currently there is a number of different approaches/techniques involving coronary stents. The use of a drug-coated balloon for native coronary vessel management is emerging as an alternative treatment, although in selected patient populations only. In particular, this technology has been tested for the treatment of bifurcations, both for the main vessel and the side branches. Several studies have evaluated this treatment as an alternative or as a therapeutic option complementary to stents, with conflicting and debatable results. However, the perspective of leaving lower metallic burden in this type of lesions is highly appealing and should be deeply investigated. We review here the currently available scientific data and future perspectives on drug-coated balloon use for bifurcation lesions.

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1. Introduction

Coronary lesions involving a bifurcation with mid-large size side-branch account for 15–20% of percutaneous coronary interventions (PCI) and may represent a challenge for interventional cardiologists [1]. The introduction of the latest generation drug eluting stents (DES) has improved the outcome of this complex lesion subset, but some issues including stent thrombosis (ST) and in-stent restenosis (ISR) are still considerable and higher than in non-bifurcation subsets [2].

Provisional stenting is usually the preferred approach for these lesions, but the rate of side branch (SB) stenosis/occlusion, with or without a final kissing balloon inflation, still accounts for approximately 17–19% of cases [3].

Drug coated-balloon (DCB) represents a relative new technology that consists in the deployment of an antirestenotic drug without the implantation of a permanent prosthesis [4] and has already shown to be an effective alternative to DES in other lesion subsets such as ISR [5] and small coronary vessel disease [6].

With these premises, in this paper we review the available literature data regarding the use of DCB for bifurcation coronary lesions.

2. Coronary artery disease involving a bifurcation

The European Bifurcation Club established a common terminology for the description of bifurcation lesions and their treatment. A typical bifurcation was first described as “a lesion occurring at, or adjacent to, a significant division of a major epicardial coronary artery” and was divided into three components: the proximal and distal main branch (MB) and the SB [7].

A univocal definition and classification is the start point to understand the most adequate treatment, especially in relation to the SB and its importance, too often left to the judgment of operators rather than to an objective assessment. Probably, the most widely used classification of bifurcations was first described by Medina et al. with a simple and intuitive method. This classification takes into consideration the three segments and the presence of a $\geq 50\%$ stenosis in each part (indicated with 1 or 0 in the presence or absence of the stenosis). However, other relevant information is not provided by this classification: lesion length of both MB and SB, plaque characteristics, Thrombolysis In Myocardial Infarction (TIMI) flow, and the presence and degree of calcification [8].

Another important parameter is the measurement of angles between the three segments involved, which has a certain impact on prognosis and should be assessed in at least two angiographic projections (Fig. 1). It has been suggested to identify the angle between the proximal MB and the SB as Angle A. Angle B is the angle between the two distal branches, and impacts on the risk of SB occlusion during MB stenting. Finally, Angle C is the angle between the proximal and distal MB.

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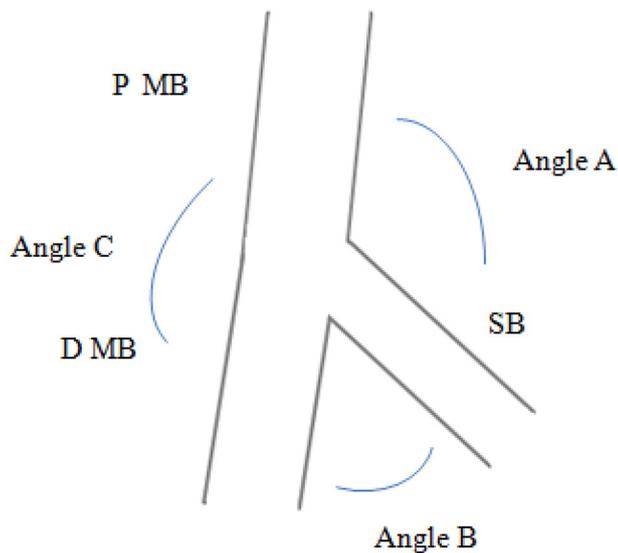


Fig. 1. Type of angles in bifurcation lesions, between proximal and distal main branch, and side branch.

Measurement of angles A and B seems to be relevant according to the treatment technique and the final angiographic result after revascularization [9].

Several bench test studies showed that the position of the stent struts with respect to the anatomy of the bifurcation has a specific role in determining local hemodynamics, thus potentially affecting long-term complications such as ST and ISR [10].

All this information allow to understand the lesion bifurcation type and branch involvement, that remain crucial to select the most adequate revascularization technique.

3. Treatment options for bifurcation lesions

Bifurcation lesion treatment involves the use of various revascularization techniques/steps, for which it was coined the acronym MADS [7].

All these techniques present several variants according to the sequence used during bifurcation treatment and the decision to use one or more stents, the predilatation, postdilatation and initial/final kissing balloon inflation. Among these variables, the main matter probably regards the decision to stent one or both branches. The most widely used approach is currently provisional stenting, that consists in stenting the MB alone, leaving SB stenting only in case of unsatisfactory result (residual stenosis >50% or lesion limiting blood flow) [12,13]. In fact, a SB stent may be associated with inadequate SB ostium coverage or excessive struts protrusion into the MB; moreover, recrossing MB stent struts with a guidewire/balloon/stent may be challenging and time-consuming. Several studies have shown how the presence of two or more stents at bifurcation sites was associated with an increase in the risk of ISR and ST [1,14]. Moreover, SB stent implantation has not proven to achieve improved angiographic or clinical results as compared to single MB stenting. In the Nordic bifurcation study, a randomized multicenter trial that enrolled 413 patients treated with a simple (single stent implantation) or complex (2-stent implantation) strategy in bifurcation lesions, the combined endpoint of cardiac death, myocardial infarction and TVR after 5-year follow-up was 15.8% vs. 21.8% respectively ($p = 0.15$). The rates of TLR and TVR were numerically lower in the simple strategy group (respectively 11.3% vs. 15.3%, $p = 0.24$, and 13.4% vs. 18.3%, $p = 0.14$) and if only patients with true bifurcation lesions were included, MACE rates resulted significantly higher in the 2-stent group (19.9% vs. 30.1% respectively, $p = 0.044$) [14].

In a recent meta-analysis Gao et al. analyzed the outcome of 2569 patients from 9 randomized clinical trials treated with one or 2 stents

in complex bifurcation lesions. Both strategies were found safe and effective in terms of ST, TVR and TLR without significant differences, however the complex strategy was associated with a higher risk of short and long term occurrence of myocardial infarction. One possible explanation for this finding was that high-pressure final kissing balloon inflation, that was required in case of 2-stent technique, could determine an increase in periprocedural myocardial infarction [15].

Park et al. recently reported the results of the COBIS-II registry, that analyzed 1502 patients with “true” bifurcation lesions (types 1,1,1 or 1,0,1 or 0,1,1 according to the Medina classification) and compared them with 1395 patients with “non-true” bifurcation lesions. In their analysis the authors assessed both the angiographic and the clinical outcome of these different groups of patients. Patients with “true” bifurcation lesions had a worse outcome in terms of:

- probable or definite stent thrombosis (1.4% vs. 0.4%; $p = 0.007$);
- TLR (9.1% vs. 6.7%; $p = 0.01$);
- MACE (12.1% vs. 8.2%; $p < 0.001$, unadjusted HR 1.51, 1.2–1.92) (Fig. 2) [16].

Until now, given the very variable anatomical subsets of bifurcation disease, there is not a clear and univocal indication for any type of lesions. Over the years, according to the KISSS principle (Keep it simple, swift and safe), the EBC consensus group indicated the provisional stent technique the first choice for bifurcation treatment, despite the relevant incidence of SB recurrent disease. Thereafter, a 2-stent technique is indicated only in case of large SB caliber with diffuse disease or difficult access of a large SB. Moreover, it should be emphasized that the total coverage of SB ostium with a stent, without protrusion in the MV is not easily achievable (Fig. 3). On this background, a strategy of treatment of the SB ostium with DCB seems a valuable alternative.

4. Studies involving drug-coated balloons for the treatment of bifurcation lesions

The first study that aimed at assessing the potential role of DCB for bifurcation lesions was the PEPCAD V registry, a prospective, multicenter, single arm trial that enrolled 28 patients with coronary bifurcation lesions treated with sequential first generation DCB (Sequent Please, B. Braun, Germany) inflation in both branches followed by BMS implantation in the MB alone (4 patients received bailout stenting of SB). Nine-month angiographic follow-up showed a rate of binary restenosis of 3.8% and 7.7% in the MB and SB respectively. Late lumen loss (LLL) was 0.38 ± 0.46 mm in the MB and 0.21 ± 0.48 mm in the SB. Three patients had SB restenosis, of which only one underwent TLR. There were also two episodes of ST [17]. This study proved the feasibility of DCB use in the SB of complex bifurcation coronary lesions, however the limited population enrolled, the lack of a control group and the inadequate lesion preparation before DCB use were its major drawbacks.

Later, the DEBIUT Study randomized 120 patients to 3 different strategies: 40 patients received a predilatation of both branches with DCB (Dior I generation, Eurocor, Germany) followed by BMS implantation in the MB; 37 patients received a predilatation of both branches with a semicompliant balloon followed by BMS implantation in the MB, and 40 received a predilatation of both branches with a semicompliant balloon followed by paclitaxel-eluting stent implantation. At 6-month angiographic follow-up, LLL was not significantly different in the BMS and DCB + BMS groups (0.49 vs. 0.41, $p = \text{NS}$), while DES treatment was associated with a superior angiographic outcome (LLL 0.19 mm, $p = 0.001$ vs. both the other treatment allocations). Twelve-month clinical follow-up showed a similar rate of MACE (20%, 29.7% and 17.5%, respectively; $p = 0.40$ for all comparisons), however the study was not powered enough to detect a clinical difference among treatments [18]. The results of the DEBIUT Study, that tested a BMS + DCB strategy for SB treatment, showed that this association does not warrant

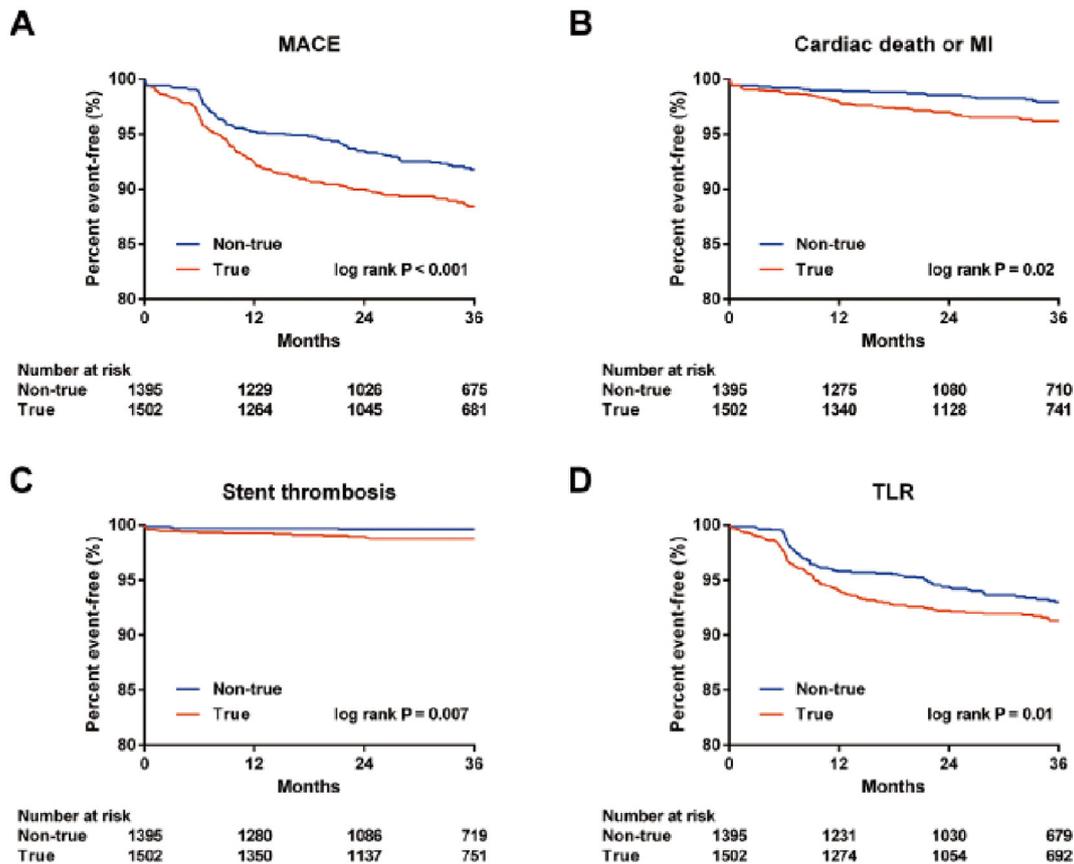


Fig. 2. Kaplan–Meier curves for clinical outcomes in patients with true bifurcation lesions vs. those with non-true bifurcation lesions. (A) Major adverse cardiac events (MACE), (B) cardiac death or myocardial infarction (MI), (C) definite or probable stent thrombosis, and (D) target lesion revascularization (TLR). Permissions obtained by Park TK et al., *Circulation J*, 2014;79:1954.

any advantage over a DES strategy, with a lower angiographic performance.

Schulz et al. reported the use of a DCB-only strategy in 39 consecutive patients with de-novo bifurcation lesions. All the lesions were predilated by a noncompliant balloon followed by DCB (Sequent Please or In.Pact Falcon, Medtronic, USA) dilatation of both branches with no stent implantation except for 5 patients that had either a high grade dissection or acute elastic recoil. After 4 months, angiographic follow-up showed a TLR and MACE rates of 7.7%. Despite the short follow-up and the limited information regarding the lesions type (degree of calcification, SB lesion length and MB–SB angle), DCB use in this setting was shown feasible [19].

The BABILON trial was a multicenter study that randomized patients with bifurcation lesions to MB and SB sequential dilation with the Sequent Please DCB (56 patients) or DES implantation in the MB and provisional SB stenting with the T-stent technique (56 patients) after predilation. Dual antiplatelet treatment was prescribed for 3 and 12 months, respectively. This study enrolled patients with complex bifurcation lesions, given that lesions Medina type 1,1,1 were 57.4% overall. Final kissing balloon inflation rate was 15.7% in the DCB and 35.7% in the DES group ($p = 0.019$). SB bailout stenting was respectively 7.8% vs. 8.9% ($p = 1$). The primary endpoint, in-segment LLL at 9-month angiographic follow-up, adjudicated in 86 patients, was 0.31 ± 0.48 and 0.16 ± 0.38 respectively ($p = 0.15$). SB LLL was respectively 0.04 ± 0.76 and 0.03 ± 0.51 ($p = 0.98$). After the 24-month clinical follow-up, the 2 strategies were found safe, with no deaths registered. On the other hand, the co-primary endpoint, 24-month MACE, and the secondary endpoint of TLR were higher in the DCB group (17.3% vs. 7.1%; $p = 0.105$, and 15.4% vs. 3.6%; $p = 0.045$). Interestingly, MB restenosis was significantly higher in the DCB group (13.5% vs. 1.8%;

$p = 0.027$), but SB restenosis was not significantly different (5.8% vs. 3.6%, $p = 0.67$) [20].

The main informations that can be summarized from this study show how the DCB tested was inferior to DES when used in medium-to-large caliber MB vessels, with a high safety and efficacy profile when used in the SB, where LLL and TLR were low and similar to the other strategy tested.

The BIOLUX-I study was a prospective, single arm multicenter study which investigated the efficacy of the Pantera Lux (Biotronik AG, Switzerland) DCB for SB treatment only. The 35 patients enrolled received direct SB treatment with DCB, followed by MB DES implantation. Nine-month angiographic and intravascular ultra-sound follow-up showed a SB LLL of 0.10 ± 0.43 mm (primary endpoint) with no cases of binary restenosis. Twelve-month clinical follow-up showed a total rate of MACE of 5.9%, with a rate of TLR of 2.9% and no stent thrombosis (Table 1) [20].

Recently, the DEBSIDE study analyzed the treatment of 50 patients treated with DES in the MB (Nile PAX) and DCB on the SB (Danubio balloon). The 6-month angiographic follow-up showed a SB LLL of -0.04 ± 0.33 , with a MLD of 1.55 ± 0.35 mm. At the clinical follow-up of 12 months, the incidence of TLR in the MB and SB was 10% and 2% respectively (Berland J et al. The DEBSIDE study: systematic treatment of the side branch in a bifurcation lesion with a new drug-eluting balloon, one-year results. Study presented at the EuroPCR 2015 meeting).

Another study lead by Sarpedon assessed the role of DCB for SB ostium treatment after DES implantation in the MB followed by kissing balloon. Angiographic follow-up showed a LLL of MV and SB of 0.21 ± 0.35 mm and 0.09 ± 0.21 mm respectively, with a restenosis rate of 4.0% and 6.0% (interestingly, in all cases SB restenosis involved the

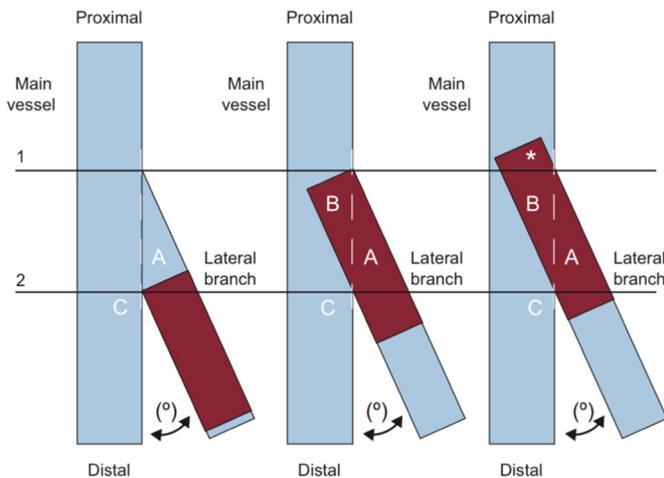


Fig. 3. Coronary bifurcation with angulation between branches illustrating the problems arising from stent implantation in the most proximal portion of the lateral branch. The horizontal line 1 represents the initial exit (proximal) of the lateral branch, while the horizontal line 2 represents the location of the carina (C). In the left image, the stent (red) fits the carina perfectly without protruding into the main branch. The disadvantage of this approach is that any disease existing in the proximal part of the lateral branch (blue triangle A) will not be covered by the stent. In contrast, in the central image, the stent fits the origin of the lateral branch and perfectly covers the entire proximal disease of this branch (red triangle A). The disadvantage of this strategy is that the medial part of this stent protrudes over the main vessel (red triangle B). In routine clinical practice (right image), the most proximal part of the stent (*) can even be above the origin of the lateral branch. In these latter 2 situations, it is necessary to crush the entire medial and proximal part of the stent implanted in the lateral branch with another stent in the main vessel (not shown). Thus, the lateral branch ends up double-caged and, also, the area immediately proximal to the exit of the lateral branch has three metal layers in the main vessel wall. Permissions requested to Alfonso F and Pan M, *Rev Esp Cardiol* 2014;67:790.

ostium). One-year clinical follow-up showed a rate of MACE of 19%, including 3 TVR and 2 deaths [21].

Table shows the main findings of the available studies that tested DCB for bifurcation lesions.

5. Limitations of drug-coated balloons in bifurcation lesions and future perspectives

Lacking dedicated international guidelines from scientific societies, two European Position Papers of expert users give the

following advertisements about the correct use of DCB in this setting of patients:

- The Italian Interventional Cardiology Society (SICI-GISE) Position Paper gives an indication of Class IIb, Level of Evidence C for the use of DCB plus BMS implantation in the MB. Moreover, DCB dilatation in both branches is suggested as safe and effective, recommending the TAP technique (T stenting plus small protrusion) in case of SB stenting [22].
- The German Consensus Group recommends the use of DCB alone after predilatation of both branches and final satisfactory result. In case of need for stent implantation (e.g., for residual major dissection after predilatation), the association of DCB plus BMS is indicated as a valid alternative to traditional DES implantation in the MB [23].

As previously shown, currently available literature on DCB for bifurcation lesions is scarce, and may be summarized as follows: MB treatment with DES should be left as the preferred option unless there are main contraindications to stenting; the use of DCB + BMS in this setting, as already shown in other settings, should not be considered as the first-choice line of treatment; SB treatment with DCB is feasible and safe, and warrants good angiographic and clinical outcome.

However, there are several technical issues that have not been addressed yet by current scientific evidence:

- There is no available data regarding SB vessel size, e.g. vessels with a diameter >2.75 mm have not yet been included in clinical studies;
- There is no clear information regarding the most effective bifurcation technique: MB stenting first and final kissing balloon with DCB; DCB use prior or after kissing balloon inflation; DCB use prior to MB stent implantation;
- There is no data on what degree of stenosis left after DCB is safe;
- Currently, a number of DCB is available on the market, with different technologies ahead determining different device deliverability and drug uptake, and no direct comparison is available yet.

Another potential advantage of DCB use for the SB is that preliminary scientific data seem to show how a dissection left has a great chance to heal after a few months, without jeopardizing the safety of this procedure [24]. This preliminary finding could be translated into fewer stents deployed in SB in case of not flow-limiting and minor residual dissections.

Some final considerations on the role of DCB for bifurcation lesions are the following. A sirolimus-coated balloon has recently obtained the CE mark for coronary interventions; this device uses a

Table 1
Available studies on DCB use for bifurcation lesion management.

Study name	RCT	Population	Treatment	DCB type	Angiographic results	Clinical results
PEPCAD V	No	28 patients	DCB in both branches + BMS in MB	Sequent Please (B. Braun Melsungen AG, Germany)	LLL: 0.38 ± 0.46 mm (MB) and 0.21 ± 0.48 mm (SB)	-3 angiographic restenosis, 1 TLR -2 late ST
DEBIUT	Yes	117 patients	-BMS in MB (37 patients) -DCB in both branches + BMS in MB (40 patients) -DES in MB (40 patients)	Dior I (Eurocor GmbH, Germany)	In-segment LLL: -0.49 ± 0.85 mm -0.41 ± 0.60 mm -0.19 ± 0.64 mm respectively (p = 0.001)	-MACE: 29.7%, 20% and 17.5% respectively (p = 0.40) -TLR: 27%, 20% and 15%, respectively (p = 0.4) -ST: 0%, 0%, 2.5% (p n/a)
BABILON	Yes	108 patients	-DCB in both branches + BMS in MB (52 patients) -DES in MB (56 patients)	Sequent Please (B. Braun Melsungen AG, Germany)	In-segment LLL: -0.31 ± 0.48 mm -0.16 ± 0.38 mm, (p = 0.150)	-MACE: 17.3% vs. 7.1%; p = 0.105 -TLR: 15.4% vs. 3.6%; p = 0.045 -ST: 1.9% vs. 1.8%, p = 0.958
BIOLUX-I	No	35 patients	DES in MB and DCB in SB	Pantera Lux (Biotronik AG, Switzerland)	SB LLL 0.10 ± 0.43 mm	-MACE: 5.7% (2/35) -TLR: 2.9% (1/35) -ST: 0%
DEBSIDE	No	50 patients	DES in MB and DCB in SB	Danubio (Minvasys, France)	SB LLL -0.04 ± 0.33 mm	MB TLR: 6 and 10% at 6 and 12 months. SB TLR: 2% at 6 and 12 months
SARPEDON	No	58 patients	DES in MB and DCB in SB	Pantera Lux (Biotronik AG, Switzerland)	MV and SB LLL were 0.21 ± 0.35 mm, and 0.09 ± 0.21 mm, respectively	-MACE: 19.0% (11) -TVR: 3% (5.2) -Any death: 2% (3.4)

Legend: BMS = bare metal stent; MB = main branch; RCT = randomized controlled trial; SB = side branch.

nanotechnology for the deposition and subsequent delivery of the much less lipophilic drug sirolimus. Preliminary animal data in a porcine model of ISR are promising, but data on humans are still scarce [25].

In case of doubt on the severity of SB lesions, a useful tool could be the fractional flow reserve, that would give valuable information on the functional severity of the stenosis. In this light, an FFR-guided revascularization approach may be considered instead of the only angiographically-driven [26].

Finally, bioresorbable vascular scaffolds (BVS) could be an interesting solution for bifurcation lesions treatment. An extensive analysis of these devices goes far beyond the purposes of this review, but some data are available for the use of BVS in the MB [27]. In line with these findings, some Experts that were interviewed on the topic expressed a certain confidence on their role for the management of challenging lesions such as bifurcations [28–29]. It is possible that a fully “biodegradable model” for bifurcations, with the use of BVS along with DCB, will become a valid alternative to current DES use [30–31].

6. Conclusions

DCB use for bifurcation lesion management remains very attractive indeed as a complement of a provisional stenting strategy. However, currently available scientific evidence remains scarce and we still require additional data to refine its real clinical value. However, an indiscriminate use of stents in this setting (complex stenting or any 2-stent technique) is associated with suboptimal clinical and angiographic results. The use of a novel generation DES in the MB remains the strategy of choice for most patients that can be managed with a provisional stenting strategy. It is possible that newer technologies such as DCB and biovascular scaffolds might improve the short and long-term outcome of bifurcation lesions, allowing a limited use of permanent prosthesis, especially at the SB.

Conflict of interest

No conflicts of interest or financial interests for current manuscript.

References

- [1] G. Niccoli, G. Ferrante, I. Porto, F. Burzotta, A.M. Leone, R. Mongiardo, M.A. Mazzari, C. Trani, A.G. Rebuzzi, F. Crea, Coronary bifurcation lesions: to stent one branch or both? A meta-analysis of patients treated with drug eluting stents, *Int. J. Cardiol.* 139 (2010) 80–91.
- [2] J.B. Hermiller, R.J. Applegate, C. Baird, M.M. Butler, D. Rutledge, J. Wang, K. Kakarala, M.W. Krucoff, K. Sudhir, Clinical outcomes in real-world patients with bifurcation lesions receiving Xience V everolimus-eluting stents: four-year results from the Xience V USA study, *Catheter. Cardiovasc. Interv.* (2015) (in press).
- [3] K. Nasu, Y. Oikawa, R. Yoshikawa, M. Kadotani, Y. Takeda, H. Ota, H. Kamiya, M. Muto, A. Okamura, M. Yamaki, S. Usui, S. Tohara, J. Yamashita, M. Suzuki, R. Kawaguchi, K. Kawajiri, Y. Nakatsu, Y. Uchida, Y. Kashima, N. Kawashima, T. Ozaki, T. Ogawa, T. Aizawa, T. Suzuki, SKT investigator. A randomized comparison of sirolimus- vs. paclitaxel-eluting stents for treatment of bifurcation lesions by single stent and kissing balloon: results of the SINGLE KISS trial, *Int. J. Cardiol.* 166 (2013) 187–192.
- [4] B. Cortese, A. Bertoletti, Paclitaxel coated balloons for coronary artery interventions: a comprehensive review of preclinical and clinical data, *Int. J. Cardiol.* 161 (2012) 4–12.
- [5] H. Rittger, J. Brachmann, A.-M. Sinha, R. Birkemeyer, V. Kurowski, O.A. Breithardt, M. Schmidt, S. Zimmermann, S. Lonke, M. von Cranach, T.V. Nguyen, W.G. Daniel, J. Wöhrle, 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.* 59 (2012) 1377–1382.
- [6] A. Latib, A. Colombo, F. Castriota, A. Micari, A. Cremonesi, F. De Felice, A. Marchese, M. Tespili, P. Presbitero, G.A. Sgueglia, F. Buffoli, C. Tamburino, F. Verbella, A. Menozzi, 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.* 60 (2012) 2473–2480.
- [7] J.F. Lassen, N.R. Holm, G. Stankovic, T. Lefèvre, A. Chieffo, D. Hildick-Smith, M. Pan, O. Darremont, R. Albiero, M. Ferenc, Y. Louvard, Percutaneous coronary intervention for coronary bifurcation disease: consensus from the first 10 years of the European Bifurcation Club meetings, *EuroIntervention* 10 (2014) 545–560.
- [8] A. Medina, J. Suárez de Lezo, M. Pan, A new classification of coronary bifurcation lesions, *Rev. Esp. Cardiol.* 59 (2006) 183.
- [9] Y. Louvard, M. Thomas, V. Džavík, D. Hildick-Smith, A.R. Galassi, M. Pan, F. Burzotta, M. Zelizko, D. Dudek, P. Ludman, I. Sheiban, J.F. Lassen, O. Darremont, A. Kastrati, J. Ludwig, I. Iakovou, P. Brunel, A. Lansky, D. Meerkin, V. Legrand, A. Medina, T. Lefevre, Classification of coronary artery bifurcation lesions and treatments: time for a consensus! *Catheter. Cardiovasc. Interv.* 71 (2008) 175–183.
- [10] G. Nakazawa, S.K. Yazdani, A.V. Finn, M. Vorpahl, F.D. Kolodgie, R. Virmani, Pathological findings at bifurcation lesions: the impact of flow distribution on atherosclerosis and arterial healing after stent implantation, *J. Am. Coll. Cardiol.* 55 (2010) 1679–1687.
- [11] T.K. Steigen, M. Maeng, R. Wiseth, A. Erglis, I. Kumsars, I. Narbutė, P. Gunnes, J. Mannsverk, O. Meyerdiereks, S. Rotevatn, M. Niemelä, K. Kervinen, J.S. Jensen, A. Galloë, K. Nikus, S. Vikman, J. Ravkilde, S. James, J. Aarøe, A. Ylitalo, S. Helqvist, I. Sjögren, P. Thayssen, K. Virtanen, M. Puhakka, J. Airaksinen, J.F. Lassen, L. Thuesen, Nordic PCI Study Group, Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study, *Circulation* 114 (2006) 1955–1961.
- [12] M. Maeng, N.R. Holm, A. Erglis, I. Kumsars, M. Niemelä, K. Kervinen, J.S. Jensen, A. Galloë, T.K. Steigen, R. Wiseth, I. Narbutė, P. Gunnes, J. Mannsverk, O. Meyerdiereks, S. Rotevatn, K. Nikus, S. Vikman, J. Ravkilde, S. James, J. Aarøe, A. Ylitalo, S. Helqvist, I. Sjögren, P. Thayssen, K. Virtanen, M. Puhakka, J. Airaksinen, E.H. Christiansen, J.F. Lassen, L. Thuesen, For the Nordic-Baltic Percutaneous Coronary Intervention Study Group, Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results, *J. Am. Coll. Cardiol.* 62 (2013) 30–34.
- [13] X.-F. Gao, Y.-J. Zhang, N.-L. Tian, W. Wu, M.-H. Li, C.V. Bourantas, X.-M. Jiang, Z.-M. Wang, B. Li, W.-X. Mao, J.-J. Zhang, S.-L. Chen, Stenting strategy for coronary artery bifurcation with drug-eluting stents: a meta-analysis of nine randomised trials and systematic review, *EuroIntervention* 10 (2014) 561–569.
- [14] T.K. Park, Y.H. Park, Y.B. Song, J.H. Oh, W.J. Chun, G.H. Kang, W.J. Jang, J.Y. Hahn, J.H. Yang, S.H. Choi, J.H. Choi, S.H. Lee, M.H. Jeong, H.S. Kim, J.H. Lee, C.W. Yu, S.W. Rha, Y. Jang, J.H. Yoon, S.J. Tahk, K.B. Seung, J.S. Park, H.C. Gwon, Long-term clinical outcomes of true and non-true bifurcation lesions according to Medina classification — results from the COBIS (COronary Bifurcation Stent) II registry, *Circ. J.* 79 (2015) 1954–1962.
- [15] D.G. Mathey, I. Wendig, M. Boxberger, K. Bonaventura, F.X. Kleber, Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial, *EuroIntervention* 7 Suppl K (2011) K61–K65.
- [16] P.R. Stella, A. Belkacemi, C. Dubois, H. Nathoe, J. Dens, C. Naber, T. Adriaenssens, E. van Belle, P. Doevendans, P. Agostoni, 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, *Catheter. Cardiovasc. Interv.* 80 (2012) 1138–1146.
- [17] A. Schulz, T. Hauschild, F.X. Kleber, Treatment of coronary de novo bifurcation lesions with DCB only strategy, *Clin. Res. Cardiol.* 103 (2014) 451–456.
- [18] J.R. López Mínguez, J.M. Nogales Asensio, L.J. Doncel Vecino, J. Sandoval, S. Romany, P. Martínez Romero, J.A. Fernández Díaz, J. Fernández Portales, R. González Fernández, G. Martínez Cáceres, A. Merchán Herrera, Manterola F2 on behalf of the BABILON Investigators. A prospective randomised study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results, *EuroIntervention* 10 (2014) 50–57.
- [19] S. Worthley, R. Hendriks, M. Worthley, A. Whelan, D.L. Walters, R. Whitbourn, I. Meredith, Paclitaxel-eluting balloon and everolimus-eluting stent for provisional stenting of coronary bifurcations: 12-month results of the multicenter BIOLUX-I study, *Cardiovasc. Revasc. Med.* 16 (2015) 413–417.
- [20] M.H. Jim, M.K. Lee, R.C. Fung, A.K. Chan, K.T. Chan, K.H. Yiu, Six month angiographic result of supplementary paclitaxel-eluting balloon deployment to treat side branch ostium narrowing (SARPEDON), *Int. J. Cardiol.* 187 (2015) 594–597.
- [21] B. Cortese, S. Berti, G. Biondi-Zoccai, A. Colombo, U. Limbruno, F. Bedogni, A. Cremonesi, P. Leon Silva, G.A. Sgueglia, Drug-coated balloon treatment of coronary artery disease: a position paper of the Italian Society of Interventional Cardiology, *Catheter. Cardiovasc. Interv.* 83 (2014) 427–435.
- [22] F.X. Kleber, D.G. Mathey, H. Rittger, B. Scheller, German Drug-eluting Balloon Consensus Group, How to use the drug-eluting balloon: recommendations by the German consensus group, *EuroIntervention* 7 Suppl K (2011) K125–K128.
- [23] B. Cortese, P. Silva-Orrego, P. Agostoni, D. Buccheri, D. Piraino, G. Andolina, R.G. Seregni, Effect of drug-coated balloons in native coronary artery disease left with a dissection, *JACC Cardiovasc. Interv.* 8 (2015) 2003–2009.
- [24] Y.P. Clever, D. Peters, J. Calisse, S. Bettink, M.C. Berg, C. Sperling, M. Stoeber, B. Cremers, B. Kelsch, M. Böhm, U. Speck, B. Scheller, Novel sirolimus-coated balloon catheter: in vivo evaluation in a porcine coronary model, *Circ. Cardiovasc. Interv.* (2016) (Epub ahead of print).
- [25] B.K. Koo, The present and future of fractional flow reserve, *Circ. J.* 78 (2014) 1048–1054.
- [26] R. Diletti, D. Tchetché, E. Barbato, A. Latib, B. Farah, R.J. van Geuns, A. Colombo, J. Fajadet, N.M. van Mieghem, Bioresorbable scaffolds for treatment of coronary bifurcation lesions: critical appraisal and future perspectives, *Catheter. Cardiovasc. Interv.* (2016) (Epub ahead of print).
- [27] D. Buccheri, M. Valgimigli, B. Cortese, Current-era biovascular scaffolds seen by experts: an experience-based survey, *Int. J. Cardiol.* 188 (2015) 16–18.

- [29] B. Cortese, D. Buccheri, G.G. Stefanini, R. Mehran, The contemporary pulse of biovascular-scaffold thrombosis among expert operators: a European survey, *J. Am. Coll. Cardiol.* (2016) (in press).
- [30] D. Piraino, D. Buccheri, G. Andolina, Coronary bifurcation lesions: some questions need an answer to make bioresorbable vascular scaffold technology more “coronary bifurcation-friendly”, *Int. J. Cardiol.* 215 (2016) 80–83.
- [31] D. Buccheri, D. Piraino, G. Andolina, Bioresorbable scaffold with drug-coated balloon: a “biodegradable” model for bifurcation lesions treatment. The new intriguing chapter of the “leaving nothing behind” Saga, *Am. J. Cardiol.* (2016) (Epub ahead of print).