International Journal of Cardiology 220 (2016) 589–594

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

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

Bernardo Cortese [a,b,*], Davide Piraino [c], Dario Buccheri [a,c], Fernando Alfonso [d]

[a] Interventional Cardiology, Fatebenefratelli Hospital, Milan, Italy
[b] Fondazione Monasterio CNR-Regione Toscana, Italy
[c] Interventional Cardiology, "P.Giaccone" Universitary Hospital of Palermo, Italy
[d] Interventional Cardiology, Hospital Universitario de La Princesa, Spain

ARTICLE INFO

Article history:
Received 26 February 2016
Received in revised form 11 June 2016
Accepted 21 June 2016
Available online 28 June 2016

Keywords:
Drug-coated balloon
Bifurcation lesions
Side branch

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.

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 ≥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.

* Corresponding author at: Interventional Cardiology, A.O. Fatebenefratelli Milano, Bastioni di Porta Nuova 21, 20100 Milano, Italy.
E-mail address: bcortese@gmail.com (B. Cortese).

http://dx.doi.org/10.1016/j.ijcard.2016.06.079
0167-5273/

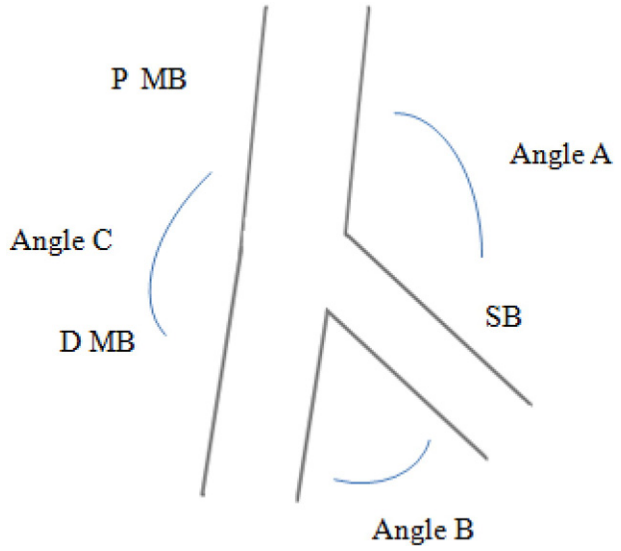

Fig. 1. Type of angles in bifurcation lesions, between proximal and distal main branch, and side branch.

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 = 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