Mini Review

Interventional Cardiology

Bail-out stenting: An overcoming problem in drug coating balloon percutaneous coronary intervention era

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Abstract

Drug Coated Balloons (DCB) Percutaneous Coronary Angioplasty (PCI) demonstrated great results especially in small vessels disease without leaving permanent metallic device and restoring vaso motricity. Although the risk of bail-out stent implantation is not a neglectable issue considering the higher risk of major adverse clinical event in comparison to DCB-only PCI. Some anatomical features and advance intracoronary assessment data are emerging as helpful tools in borderline angiographic aspects.

Keywords: Drug coated balloon • Bail-out stent • *De novo* coronary stenosis •Small vessels percutaneous coronary intervention • Optical coherence tomography •Fractional f low reserve

Introduction

In the last two decades Drug Coated Balloons (DCB) Percutaneous Coronary Angioplasty (PCI) have been exponentially applied to more patients and various settings with satisfying results. The idea of "leaving nothing behind" after a percutaneous coronary angioplasty is fascinating due to restoring native vasomotricity and to reduce late and very late stent thrombosis and stent restenosis in absence of permanent metallic device without the elevated thrombotic risk seen with bioresorbable scaffolds [1-3].

Recent improvements in device features, procedural techniques and operators' skills have limited acute complications such as recoil and high-grade dissections requiring a Bail-Out Stent (BOS) strategy, which remains the main issue related to DCB angioplasty.

Literature Review

What is a drug coated balloon?

DCBs are semi-compliant balloons coated with an ant proliferative drug and a matrix in order to reduce the drug loss into the blood flow and facilitate the drug delivery into vessel wall without permanent or semi-permanent scaffold implantation [4]. The DCB efficacy relies on the interplay between balloon designs, matrix formulations, drug, and its dose and release kinetics. The available DCBs differ in terms of the above characteristics so that a "class effect" may not be assumed [5].

The most used drugs are Paclitaxel and Sirolimus. Paclitaxel is an antimitotic agent that acts promoting the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization, so it inhibits neointima formation. Furthermore, it is a lipophilic substance that needs a short contact-time to pass in a significate concentration into the vessel wall and lasting for several weeks [6]. However, some studies have suggested that Paclitaxel may have a small therapeutic window since high deses have been associated with higher mortality in patients undergoing lower

limb revascularization with Paclitaxel DCB than those treated with Plain Old Balloon (POBA) [7]. Although these data have not been confirmed in subsequent studies and in coronary setting [8]. This theoretically drawback along with the fact that Paclitaxel drug eluting stent has resulted in worse clinical outcome as compared to current-limus drug eluting stents have prompted to develop new DCBs with the most studied one being the Sirolimus DCB.

When drug coated balloon can be used?

Primarily, DCB PCI demonstrated the same efficacy of Drug Eluting Stent (DES) in In-Stent Restenosis (ISR) [9]. In the last years, *de novo* small vessels DCB PCI resulted non inferior to DES at one-year and superior to DES at long follow-up in terms of Major Adverse Cardiac Events (MACE) [10-14]. These results could be related to the late lumen gain due to anti proliferative drug effect without the permanent inflammatory stimulus of a metallic platform [15]. Differently, DCB use in bifurcation treatment and in large vessels is still debated [16-18]. Promising evidences have been reported also in ST-Elevation Myocardial Infarction (STEMI) setting [19,20] and in high bleeding risk patient [21].

Drug coated balloon percutaneous coronary intervention step-by-step

The DCB is a device intended to delivery drug therapy into the vessel wall, not to properly do PCI. For this reason, a careful lesion preparation is recommended. There is not a predilatation tool of choice, but it should be calibrated on the kind of coronary stenosis and to the angiographic response. A balloon-to-artery ratio of 1:1 is recommended and in more complex stenosis it is reasonable to start with smaller balloons and subsequently reassess vessel size [22,23]. Any kind of predilatation tool can be used (semi-compliant, non-compliant, cutting or scoring balloon, intracoronary lithotripsy, calcium-ablator systems). The lesion preparation is to be considered successful if, at least 5 minutes after intracoronary nitro derivate administration, all the following points are met: 1) ≤ 30% residual angiographic stenosis; 2) Thrombolysis In Myocardial Infarction (TIMI) flow grade 3; the absence of a flow-limiting dissection. Then, a 0.8 or 1:1 DCB-to-artery ratio should be applied. The device should be two millimeters longer both side of the predilated lesion and inflated at nominal pressure. A single DCB must be used only for one coronary lesion. Referring to pre-stent era data, type A and B dissections are considered safe, and healing is always expected. Differently there is still debate on type C dissections [24], but at the moment the international recommendations suggest stent implantation in case of type C or worse coronary dissection. So, in case of high-grade dissections or important recoil BOS should be implanted (Figure 1).

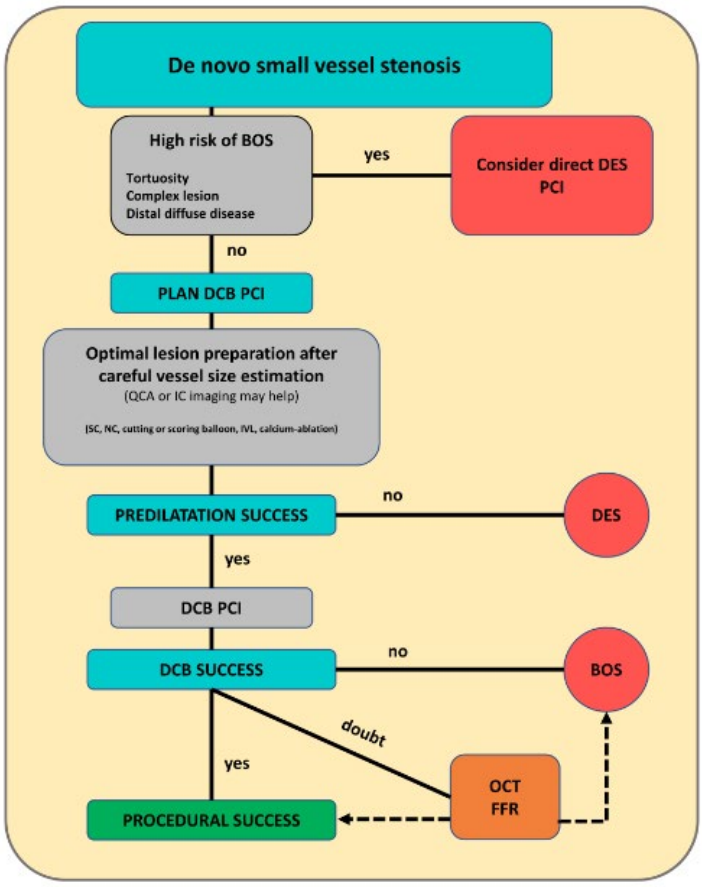

Figure 1: Flow chart of *de novo* small vessels DCB PCI step-by-step.

Bail-out stent

Bail-out stent is the term used for stent placement to treat a coronary artery with iatrogenic complication (e.g. high grade dissection) or ineffective balloon angioplasty [25]. During a planned DCB PCI, the need of stent implantation can occur both after lesion preparation, and after DCB inflation. In the first case the operator should change is mind due to the presence of high-grade dissection or in case of important vessel recoil. BOS after DCB inflation is generally secondary to a worsening pre-existing coronary dissection. The risk of BOS should be bear in mind especially in case of a planned DCB PCI for *de novo* lesions in small vessel disease. Indeed, stent of small diameter needs long dual antiplatelet therapy and are affected by a higher risk of restenosis and thrombosis [26]. In the first small vessels randomized studies the rate of BOS was very high (more than 30%) owing to the first technology of DCB and low rate of lesion predilation [27]; but in recent trials the number of stents implanted during DCB angioplasty has been drastically reduced, although it is still not neglectable (Table 1). The need of BOS has been constantly associated with a trend in worse outcome both in the BMS and DES era [28]. In the most recent trials DCB were not inferior to DES in small vessels PCI, but despite the use of second generation DES in case of bail-out, the BOS group showed two times higher, even not statistically significant, rate of MACE (Table 2). The rates of MACE at 12 months in the BOS group were 15.8 in the BASKET SMALL 2 and 12.5% in PICCOLETO 2 trial, as compared to 7.0% and 4.9% of the only-DCB group, respectively.

The link between the use of BOS and the higher risk of MACE is not still clearly understood. Failure in lesion preparation could be associated with the use of longer stents that in small vessels are correlated to higher risk of failure during follow-up even with second-generation DES. Moreover, stenting a longer coronary segment is not free from the risk of bifurcation involvement making the procedure more complex.

Table 1: Main clinical randomized trials comparing DCB and DES in *de novo* percutaneous coronary angioplasty.

	Year	Design	Pts (n)	Setting	DCB arm	DES arm	Stent before DCB protocol deviation (n, %)	BOS (n, %)
PICCOLETO27	2010	RCT	57	SVD	Dior	Taxus Libertè	nr	10 (36)
BELLO28	2012	RCT	182	SVD	IN.PACT Falcon	Taxus Libertè	nr	19 (20)
Nishiyama et al.18	2016	RCT	60	SVD	SeQuent Please	Xience	3 (10)	0 (0)
Gobic et al.20	2017	RCT	75	STEMI	SeQuent	Biomime	nr	3 (7)
BASKET SMALL 210	2018	RCT	758	SVD	SeQuent Please	Taxus or Xience	125 (14)	19 (5)
RESTORE SVD12	2019	RCT	230	SVD	Restore	Resolute	nr	6 (5)
DEBUT21	2019	RCT	208	HBR	SeQuent Please	Integrity	23 (10)	5 (5)
REVELATION19	2019	RCT	120	STEMI	Pantera Lux	Orsiro or Xience	nr	11 (18)
PEPCAD NSTEMI17	2020	RCT	210	NSTEMI	SeQuent Please	BMS or DES	nr	18 (17)
PICCOLETO 211	2020	RCT	232	< 2.75	Elutax SV/ Emperor	Xience	nr	8 (7)

Table 2: Main clinical randomized trials reporting BOS adverse events at follow-up.

	Year	Design	Pts (n)	BOS (n, %)	MACE DCB (%)	MACE DES (%)	MACE BOS (%)	Restenosis DCB (n, %)	Restenosis DES (n, %)	Restenosis BOS (n, %)
Piccoleto27	2010	RCT	57	10 (36)	nr	nr	nr	9 (32)	3 (10)	3 (30)
BELLO28	2012	RCT	182	19 (20)	10	16	nr	8 (10)	10 (12)	3 (16)
Nishiyama et al.18	2016	RCT	60	3 (10)	0	0	0	0 (0)	2 (6.1)	0 (0)
BASKET SMALL 210	2018	RCT	758	19 (5.1)	7	5.7	15.8	nr	nr	nr
PICCOLETO 211	2020	RCT	232	8 (6.7)	5.6	7.5	12.5	6.3	6.5	nr

Note: The table shows the main comparative studies between DCB and DES reporting major adverse clinical events or restenosis of BOS group at follow-up. Three of them reported the rate of restenosis and two of them the rate of MACE in DCB, DES or BOS group. BOS: bail-out stent; DCB: drug coated balloons; DES: drug eluting stents; Pts: number of patients; MACE: major adverse cardiac events; RCT: randomized controlled trial.

Discussion

How to reduce bail-out stent rate

In planning and performing a DCB PCI, therefore, the need to achieve good angiographic results should be balanced with the risk of BOS. In a recent study, enrolling 168 consecutive patients treated with DCB, Ghetti, et al have demonstred that both lesion and procedural characteristics may be associated with the risk of BOS. In particular, vessel tortuosity, distal diffuse disease without a good landing zone for the device and very complex lesion-grade C according to American Heart Association/American College of Cardiology (AHA/ACC) classification-are strongly correlate to BOS [29]. Secondly, in small vessels PCI and in severe or diffuse disease, an accurate evaluation of vessel diameter is extremely important in order to avoid device oversizing (Figure 2). This is one of the operator-dependent BOS risk factors. Precisely, per each 0.1 incremental in DCB-to-artery ratio more than 1.0, there is four times higher risk of BOS. Experts' consensuses suggest a gentle inflation with an under-dimensioned balloon or imaging assessment of vessel sizing and plaque morphology in case of visual estimation doubts. Ongoing randomized studies are applying imaging assessment, particularly Optical Coherence Tomography (OCT), to reduce the bail-out stent rate [30]. The advantages of imaging are: better sizing, identification of safe landing zones and plaque morphology assessment. Moreover, drug coated balloon inflation time should be as longer as can be tolerated. First, because longer balloon-artery contact leads to higher drug dose delivery into vessel wall. Secondly, long inflation can practice scaffold-like effect and reduce iatrogenic dissection, like in peripheral percutaneous treatment [31].

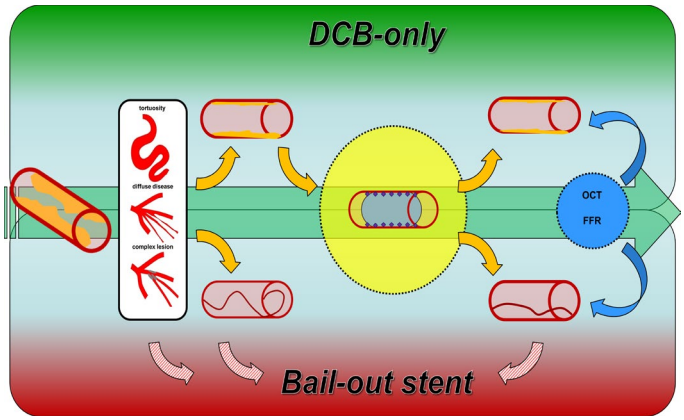

Figure 2: Bail-out stent

Post-DCB assessment

International Expert Consensuses suggest angiographic visual assessment in at least two orthogonal projections to evaluate DCB PCI results. In case of absence of type C or worse dissection and no more than 30% of residual stenosis, the procedure can be considered successful. The objective of *de novo* DCB PCI is not a "stent-like" acute result because the complete effect of this therapy can be seen at long follow-up with delayed acute gain. On the contrary, the main goal of the procedure is not to cage coronary artery with a metallic permanent platform but return coronary vaso motricity. When angiographic result is dubitative, further invasive assessment have been proposed. OCT is the best tool to analyze anatomical coronary changes during PCI and OCT post-DCB PCI evaluations have been advocated to predict acute vessel closure. As in stent PCI, the presence of medial dissection is considered a sign of abrupt coronary closure, so BOS is required [32]. Some small studies report that post DCB-PCI intimal limited dissection as assessed by OCT is safe and linked to late lumen enlargement. On the opposite, medial dissections correlate with angiographic dissection progression after 15 minutes [33]. Recently, it has been suggested that physiological assessment-both hyperemic and not hyperemic indices-after DCB may have prognostic implications [34-36], however the optimal cut-off of functional test post-PCI it is not still clear. Finally a recent small observational study has suggested that dynamic changes of functional tests during 15 min after DCB may be associated with the risk of abrupt vessel closure due to severe dissections. However larger studies are warranted to confirm the efficacy and safety of this latter approach.

Conclusion

De novo vessels drug coated balloon percutaneous coronary angioplasty is a real attractive procedure and has shown better results compared to drug eluting stent PCI. However, bail-out stent is a relevant issue that should be bear in mind when a DCB PCI is planned. Indeed, BOS patients are affected by higher rate of 1-year MACE compared to DCB or DES only small vessels patients. Anatomical features, like vessel tortuosity, distal diffuse disease, and complex coronary stenosis are correlate to the risk of addictive stent implantation, as well as DCB oversizing. OCT and physiological assessment can be helpful to thoroughly assess the DCB PCI results.

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