Clin Res Cardiol (2013) 102:785–797
DOI 10.1007/s00392-013-0609-7

REVIEW

Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group

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Received: 19 April 2013 / Accepted: 14 August 2013 / Published online: 28 August 2013

Abstract
Aims Drug-coated balloon catheters (DCB) are a new clinical treatment modality for coronary and peripheral artery disease. The goal of the consensus group is to develop recommendations for the clinical use of DCB based on randomized clinical trials and the best available clinical evidence. The present paper gives an update on the recommendations against the background of a variety of new data published since the first paper was presented.
Methods and results The general concept of our recommendations for the coronary use of DCB includes the preparation of the lesion to facilitate drug delivery and to estimate the need for stent implantation, especially after relevant dissections. Lesion preparation includes conventional angioplasty. In more complex lesions, additional treatments and imaging or functional measurements are helpful. In case of no flow-limiting dissection and an acceptable but not stent-like primary result, DCB use without additional stent implantation may be considered. The proposed advantages of the DCB only concept over a direct stent approach include reduced restenosis rates in indications where DES show limited efficacy, the reduction of DAPT especially in patients with contraindications for prolonged DAPT, and the option of leaving no foreign object behind resulting in vascular restoration with potentially plaque regression instead of neo-atherosclerosis.

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Conclusions DCB allow for local drug delivery in endovascular therapy leaving no permanent implant behind.

Keywords Drug-coated balloon · DCB only · In-stent restenosis · Dual antiplatelet therapy

Introduction

The pioneering work of Grüntzig [1] in the seventies was the beginning of the unprecedented success of percutaneous transluminal coronary angioplasty (PTCA). Later on, the introduction of stents allowed the control of elastic recoil and flow-limiting dissections [2]. However, this technology created two new diseases: in-stent restenosis (ISR) and stent thrombosis. Furthermore, a caged vessel excludes late lumen enlargement and advantageous vascular remodeling. About 10 years ago, local intravascular drug delivery by drug-eluting stents (DES) seemed to solve the problem of restenosis [3]. Despite a reduction of restenosis, DES therapy is limited by delayed healing, late acquired malapposition [4], and neo-atherosclerosis [5] leading to an increased but low risk for late stent thrombosis and late restenosis. Thus the challenge for new technologies is to reduce the need for permanent implants in percutaneous vascular treatment.

Drug-coated balloon catheters (DCB) are a new clinical treatment modality for coronary and peripheral artery disease [6, 7]. Proposed advantages of this approach are a homogeneous drug delivery to the vessel wall, an immediate drug release without the use of a polymer, the potential of reducing the intensity and duration of antiplatelet therapy, a lower restenosis rate in some indications, and finally the option of leaving no foreign object behind in the body. A variety of DCBs are available for clinical use in Europe and in other countries outside of the US [8]. By far, the largest clinical evidence in coronary artery disease has been reported for DCB coated with paclitaxel-iopromide; >3,500 patients have been studied in randomized clinical trials (RCT) and large registries [9–22]. Despite this rapidly growing data base, there still exist open questions that are not fully covered by clinical evidence from large randomized clinical trials.

The goal of the consensus group is to develop recommendations for the clinical use of DCB based on randomized clinical trials and the best available clinical evidence. The present paper gives an update on the recommendations against the background of a variety of new data published since the first paper was presented [23].

Lesion preparation

The increase in vessel lumen after conventional angioplasty is achieved by compression of soft atheromatous material, stretching the arterial wall, and finally disruption of intima and often media. Such intimal angiographic visible dissections occur in about 20–40 % of PTCA procedures [24]. Early experiences identified a relevant post-PTCA stenosis, intimal tear or dissection, and a post-PTCA gradient of 20 mmHg or more as risk factors for acute vessel closure [25]. Grüntzig's and other groups reported that uncomplicated, non-flow-limiting dissections are associated with favorable clinical outcomes, especially if there was no relevant trans-stenotic gradient [26, 27]. It could be demonstrated that dissections type A and B categorized according to the National Heart, Lung, and Blood Institute classification system [28] (NHLBI classification) had no increase in morbidity and mortality when compared with patients without dissection. However, dissections of types C to F result in a significant increase in short- and long-term complications after balloon angioplasty alone [28].

Coronary stents were developed for emergency treatment of acute vessel closure after balloon angioplasty, especially in the case of flow-limiting dissections [2, 29]. Randomized trials in simple lesions showed a reduction of restenosis and repeated revascularization by stents compared to angioplasty but no reduction of the hard endpoints death and myocardial infarction. Interestingly, cross-over rates to provisional stent implantation in the angioplasty groups varied between 5 and 17 % [30–32]. A major step forward was the reduction of stent thrombosis rates by dual antiplatelet therapy (DAPT) [33, 34] resulting in the ongoing enthusiasm for stent implantation [25, 32]. The paradigm that stent implantation would be essential to avoid vessel closure was created. However, the role of DAPT in angioplasty alone was never investigated systematically. Interestingly, the rate of thrombotic vessel closure after standalone DCB and contemporary adjunctive medical therapy seems to be quite low [22, 35].

Lesion preparation is considered the mandatory first treatment step for our approach [23]. The main goals of pretreatment are to identify patients with procedure-related flow-limiting dissections type C–F [28] and to facilitate homogeneous drug delivery. The simplest form of lesion preparation is conventional angioplasty with an uncoated semi-compliant balloon with a balloon-to-vessel ratio of 0.8–1.0 and an inflation pressure higher than nominal. In more complex lesions, the use of non-compliant high-pressure balloons, cutting or scoring balloon, or even rotablation might be considered as well as additional intravascular imaging (IVUS, OCT) or functional measurements (FFR).

Treatment of in-stent restenosis

Treatment of ISR with conventional balloon angioplasty (POBA) is limited by high repeat restenosis rates of ≥50 %

[9, 17, 36]. Intracoronary vascular brachytherapy (VBT) was found to be effective in this setting [37]; however, both high rates of restenosis (edge and late catch-up) and the unbridled enthusiasm for DES resulted in the banishment of VBT as the therapy of choice [38]. In the ISAR-DESIRE trial, treatment of bare metal stent (BMS)-ISR by POBA or the implantation of a Taxus™ or Cypher™ stent resulted in angiographic restenosis rates of 45, 22, and 14 %, respectively [22]. For the treatment of DES-ISR by a second DES, repeat restenosis rates of 20–40 % have been reported [39, 40]. There are justifiable doubts as to whether the stent-in-stent approach is the best solution for the ISR problem. DES use in the treatment of ISR may be associated with increased long-term stent thrombosis rates [38, 41, 42]. Therefore, non-stent based alternatives that avoid additional layers of metal in a native coronary artery may be the better alternative.

Scientific evidence

The Paccocath ISR-I trial compared the Paccocath™ DCB with POBA for the treatment of BMS-ISR. Patients in the DCB group had significantly better angiographic results (in-segment late luminal loss, LLL 0.74 ± 0.86 mm vs. 0.03 ± 0.48 mm; $p = 0.002$) and concomitant 12-month clinical outcomes [9]. The subsequent Paccocath ISR-II trial extended the initial findings [10]. During long-term follow-up, advantages of the DCB over POBA remained stable [11]. In the PEPCAD II trial, 131 patients with ISR after bare metal stent (BMS) implantation were randomized to either receive the SeQuent™ Please DCB (B. Braun, Germany) or a Taxus™ stent. LLL at 6 months, the primary endpoint of the study, was significantly smaller, 0.17 mm in the DCB group as compared to 0.38 mm in the Taxus group. MACE at 12 months was 9 % in the DCB group an 22 % in the Taxus group, mainly driven by a TLR of 6 % in the DCB group and 22 % in the Taxus group. These results show that the DCB was superior to a DES in the treatment of ISR. It is for this reason that the ESC has given the DCB a class IIa/B recommendation for the treatment of ISR [43]. Habara et al. [17] evaluated the efficacy of the DCB in patients with ISR of sirolimus-eluting stents. At 6 months follow-up LLL was 0.18 mm in the DCB group vs. 0.72 mm in the POBA group ($p = 0.001$). In PEPCAD-DES 110 patients with ISR of either -limus or paclitaxel-eluting stents were randomized to POBA or DCB. Including patients with multiple stent layers as well as patients with a second, third or even fourth ISR, late lumen loss was 0.44 mm in the DCB vs. 1.04 mm in the POBA group ($p = 0.001$)[18]. Patients with several layers of metal did not show an increase in TLR (Rittger, DGK 2013). Furthermore, long-term data of patients with repeated ISR and several layers of metal presented with excellent outcome after DCB (Clever 2013, submitted for publication).

The ISAR-DESIRE III-trial compared the use of DCB vs. DES vs. POBA in Limus-DES-ISR. The primary endpoint diameter stenosis at 8 months did not differ between DCB and DES and was significantly reduced compared to POBA. It was concluded that "by obviating the need for additional stent implantation, treatment with drug-eluting balloon therapy should be the treatment of choice in patients presenting with limus-eluting stent restenosis" [44].

From a health care payer perspective, DCB angioplasty seems to be cost-effective in the treatment of coronary BMS- and DES-ISR [45, 46]. The broadest evidence is provided for the SeQuent™ Please DCB (B. Braun; Melsungen, Germany), although there is favorable but not randomized data also for other balloons [47, 48]. But to date, data show no class effects for different types of balloons [49] (Table 1).

Treatment recommendations

Lesion preparation is considered mandatory in all cases. To avoid balloon slippage, scoring or cutting balloons might be considered. A non- or semi-compliant balloon with a balloon-to-vessel ratio of 0.8–1.0 is recommended, particularly, if incomplete stent expansion is still visible. The use of cutting balloons, scoring balloons or non-compliant high-pressure balloons is also strongly encouraged to provide a complete expansion of the restenosed stent. The use of IVUS or OCT for better evaluation of morphological reasons of the ISR (e.g., angiographically not apparent incomplete stent expansion) can also be taken into consideration.

After pre-dilatation, the operator has to decide whether to proceed with a DCB or to implant a DES in case of an extensive or flow-limiting dissection (NHLBI classification grade C–F [28]) or a significant residual stenosis. In case of acceptable angiographic results, a DCB may be used. It should extend beyond the pre-dilated area by 2–3 mm on each side. It should also have a balloon-to-vessel ratio of 0.8–1.0 and be inflated for at least 30 s at nominal pressure (about 8 atm) to avoid dissection outside the stent. In general, the DCB should be used for final angioplasty of in-stent restenosis and drug delivery after optimal lesion preparation (Fig. 1).

Small coronary vessels (SVD)

Scientific evidence

In small native vessels usually defined as a diameter between 2.0 and 2.8 mm, target lesion restenosis after

Table 1 Summary of clinical evidence for different drug-coated balloons (DCB) in coronary arteries with CE-mark and available commercially in Europe

DCB	Coating	Non-RCT, registry	RCT	No of patients published in peer-reviewed journals
SeQuent Please	Paclitaxel-iopromide (B.Braun)	ISR and de novo: WWW registry [22], SCAAR [49] SVD: PEPCAD I [13] BIF: PEPCAD V [14] DCB + BMS: PEPCAD CTO [64], (DEB-AMI presented at EuroPCR 2011)	ISR: Paccocath ISR I/II [9, 11], PEPCAD II [12], Habara [17], PEPCAD-DES [18], ISAR-DESIRE III [44], SEDUCE [65] DCB + BMS: PEPCAD IV[58], PERfEKT [15], OCTOPUS [66], INDICOR (presented at AsiaPCR 2012)	4,354
Dior I Dior II	Paclitaxel Paclitaxel-shellac (Eurocor)	BIF: DEBIUT [67] registry ISR: Valentines I [68], Spanish registry [69] De novo: DEAR [70], (Valentines II presented at CRT meeting 2012)	SVD: Piccoletto [53] (negative RCT) BIF: DEBIUT [57] (negative RCT) DCB + BMS: DEB-AMI [60] (negative RCT)	662
In.Pact Falcon	Paclitaxel-urea (Medtronic)	ISR: In.Pact FIM [47]	SVD: BELLO [35]	205
Pantera Lux	Paclitaxel-BTHC (Biotronik)	ISR: PEPPER [48]	–	81
Moxy	Paclitaxel-polysorbate (Bard)	(ISR: registry presented at TCT 2010)	DCB + BMS: Gutiérrez-Chico [71]	26
Elutax	Paclitaxel (Aachen Resonance)	ISR and de novo: SCAAR [49] (inferior to SeQuent Please)	(DCB + BMS: Liistro; negative RCT, presented at TCT 2011)	217
Protégé NC	Paclitaxel-BTHC (Blue Medical)	–	–	–
Danubio	Paclitaxel-BTHC (Minvasys)	–	–	–

Only prospective trials published in peer-reviewed journals are listed. Negative RCT did not reach their primary endpoint. Non-RCT prospective, non-randomized clinical trial

RCT randomized controlled clinical trial, *ISR* in-stent restenosis, *BMS* bare metal stent, *DES* drug-eluting stent, *SVD* small vessel disease, *BIF* bifurcation, *CTO* chronic total occlusion

percutaneous coronary intervention (PCI) remains an unresolved issue. It is a relevant clinical problem because lumen loss after stent implantation comprises a larger percentage of the total lumen diameter in small than large vessels. Although stent implantation after angioplasty reduced restenosis rates considerably compared with angioplasty alone, they still lay at 25 % for BMS and between 5 and 25 % with somewhat better results for sirolimus-eluting than paclitaxel-eluting stents [50–52]. Therefore, the use of DCB may be an attractive option in SVD. However, with just one non-randomized feasibility trial and two controlled randomized trials (RCT) adding up to less than 250 patients, published evidence for the treatment of SVD with DCB is limited (Tables 1, 2).

In PEPCAD 1, 120 patients with SVD (lesions 2.25–2.8 < 22 mm length) were intended to be treated with a DCB (SeQuent™ Please, B. Braun Melsungen AG, Germany) [13], with lesion crossing not successful in 4 cases, and protocol violations occurring in 2 cases (5 %). Out of the remaining 114 subjects, 82 (72 %) were treated with DCB only, while additional BMS implantation was necessary in the remaining 32 cases (28 %) due to dissections or unfavorable recoil. In patients treated with DCB only, LLL was 0.18 ± 0.38 mm. However, when combined with a bail out BMS, LLL increased significantly to 0.73 ± 0.74 mm ($p < 0.0001$). Accordingly, binary restenosis rate was 44.8 % in DCB combined with BMS vs. 5.5 % in DCB only ($p < 0.0001$). This result was ascribed to the geographic mismatch phenomenon, i.e., an overshooting neointimal growth if the BMS is longer than the DCB or the BMS is implanted outside the 'medicated vessel' segment, i.e., the DCB landing zone. These results highlight the importance of covering the whole dilated segment with the DCB and to avoid geographic mismatch.

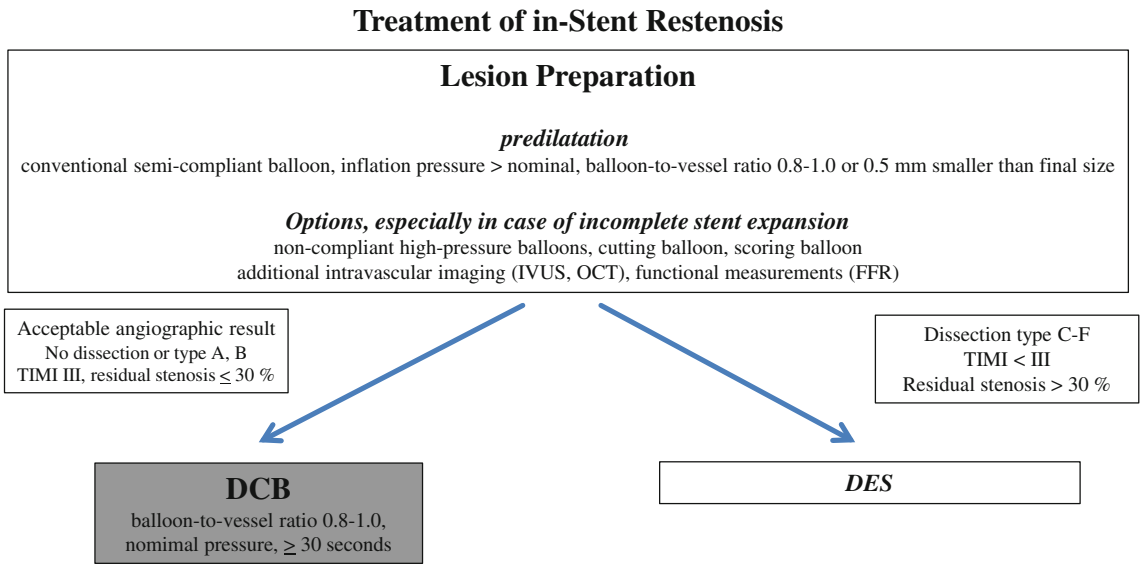

Fig. 1 Scheme to treat ISR lesions using a drug-coated balloon (DCB)

Only two randomized trials have been published in the field so far. The PICCOLETTO study failed to show non-inferiority of the Dior™ DCB (Eurocor GmbH, Bonn, Germany) vs. a DES in patients with SVD [53]. In total, 57 patients with SVD (<2.8 mm) were randomized to the Dior DCB or the drug-eluting TAXUS Liberté stent (Boston Scientific Corp, Natick, MA, USA). The primary endpoint was the percent diameter stenosis at 6 month follow-up, and was 43.6 % with the Dior DCB and 24.3 % with the TAXUS Liberté DES ($p = 0.02$). The hitherto largest randomized trial comparing DCB and DES is the BELLO study [35]. A total of 182 patients with de novo lesions in SVD (<2.8 mm) were randomized in a 1:1 fashion to DCB (In. Pact Falcon™, Medtronic Invatec, Roncadelle, Italy) or TAXUS. As expected, primary result immediately after the procedure was in favor of the stent approach. However, the primary endpoint LLL was assessed in 84 % of the patients, and showed superiority of the DCB (0.09 ± 0.38 mm) over the TAXUS stent (0.30 ± 0.44 mm, $p = 0.001$). LLL was similar to the DES in patients treated with a combination of DCB and BMS ($n = 15$, 0.37 ± 0.51 mm, $p = 0.59$ vs. DES) and lowest in the group with DCB only (0.03 mm). The binary restenosis and the MACE rates were both 10 % with DCB and 16 % with TAXUS ($p = 0.25$).

Based on these studies, DCB might represent a valid option in SVD, depending on the balloon type used. Geographic mismatch was not assessed in these trials, but might have been responsible for unfavorable results since rates of additional BMS implantation with DCB and restenosis show a strong association (Fig. 2). Currently, positive results for the use of DCB in SVD are published for the In. PACT Falcon and the SeQuent Please DCB, but not for other devices (Table 1).

Treatment recommendations

In SVD, i.e., native coronary arteries with a vessel diameter of 2.0–2.75 mm, the lesion should be pre-dilated with an uncoated balloon catheter (POBA). The suggested balloon-to-vessel ratio is 0.8–1.0 (≥12 atm). In the absence of major dissection or severe recoil subsequently, the DCB, which should be longer than the POBA balloon by 2–3 mm on each side, is inflated at nominal pressure for a minimum of 30 s. In case of a flow-limiting dissection (NHLBI classification grade C–F [28]) and/or a residual stenosis of ≥30 % after POBA pre-dilation, alternatively DES

Table 2 Prospective trials with drug-coated balloons (DCB) in coronary small vessel disease (SVD)

Trial	*n* (DCB)	Additional BMS (%)	Late lumen loss (mm)	Restenosis (%)	TLR (%)
PEPCAD I [13]	114	26.7	0.32 ± 0.41	17.3	12.8
PICCOLETTO [53]	28	34.5	1.37 ± 0.62	32.1	32.1
BELLO [35]	90	21.1	0.08 ± 0.38	10.0	7.8

TLR target lesion revascularization. *BMS* bare metal stent

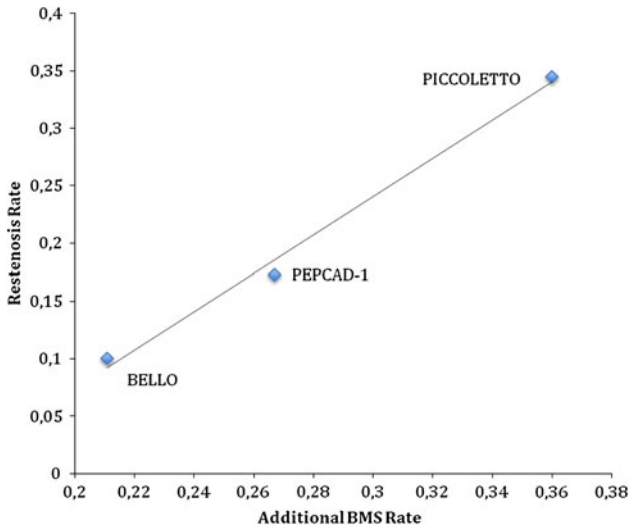

Fig. 2 Relationship between the rate of additional BMS implantation and binary restenosis rate in prospective studies with drug-coated balloons (DCB) in coronary small vessel disease (SVD)

implantation or a BMS spot stenting followed by a DCB inflation avoiding geographic mismatch may be performed (Fig. 3).

Bifurcations

Scientific evidence

Approximately 15 % of all PCI lesions involve bifurcations with important side branches. The treatment of these lesions is subject to a wide spectrum of proposed strategies, including relatively simple stent solutions without addressing the side branch as well as most complex interventions like crush stenting and its various modifications. As a result of the NORDIC and the BBC studies [54, 55] provisional T-stenting is the current most widely accepted approach. Side branch dilation followed by kissing balloon application improves the acute and the chronic clinical outcome (NORDIC III) [54, 56]. However, MACE and side branch restenosis rates still amount up to 15-20 %, depending on the complexity of lesions and interventions. Stenting of bifurcations is theoretically accompanied with disadvantages in terms of distal vessel overstretching up to the proximal vessel diameter and of straightening the vessel, both leading to carina shift into the side branch. In contrast, balloon angioplasty goes along with the preservation of bifurcation anatomy and flow physiology. However, restenosis and thrombosis rates have to be managed.

In 13 % of PCIs conducted within the World Wide DCB Registry[22] bifurcations were involved, reflecting the expected advantages of DCBs for the treatment of bifurcation lesions in all-day clinical practice. The DEBIUT trial, a randomized bifurcation study, comparing a DCB without carrier matrix (Dior^{TM}, 80 % first generation) with BMS and DES showed no superiority of the DCB to BMS in terms of late loss or clinical outcome [57]. PEPCAD V, a small observational study by Mathey et al. [14] investigating the efficacy and safety of DCB with SeQuent^{TM} Please revealed a very low in-lesion late loss of 0.21 mm (in-segment 0.12 mm) in the side branches treated mostly without stents. In the lesions treated with DCB only the in-lesion and in-segment LLL were 0.12 mm and 0.04 mm respectively.

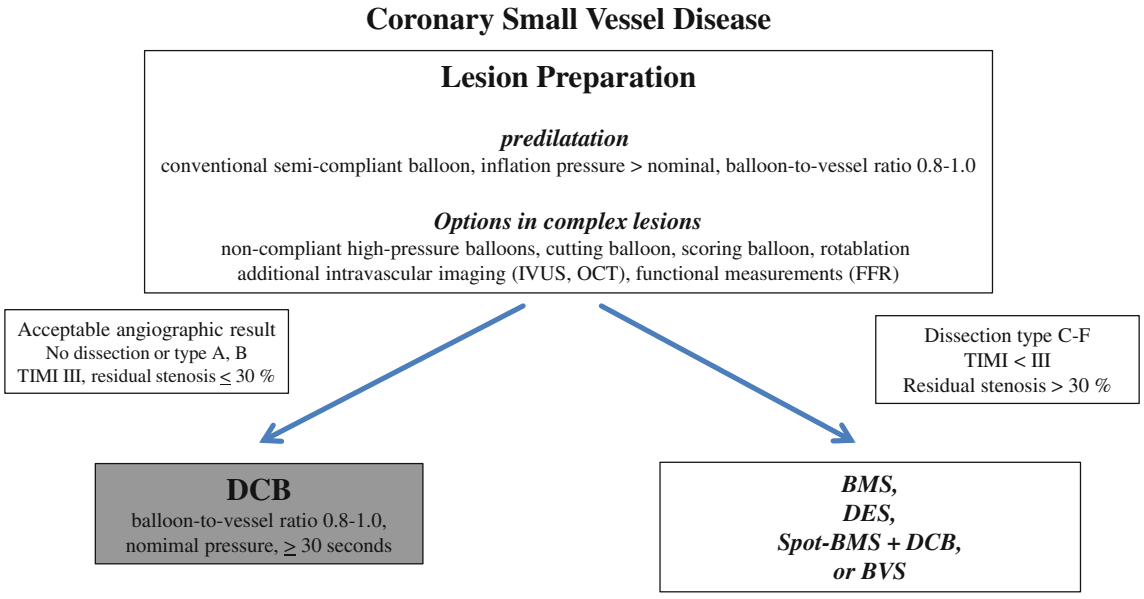

Fig. 3 Scheme to treat SVD lesions using a drug-coated balloon (DCB)

However, late and very late stent thrombosis occurred in three PEPCAD V patients at 6, 8, and 30 months, who had been treated with BMS after DCB application in the main branch. Based on the PEPCAD V results [14] regarding the side branches, affirmed by the BELLO study findings [35], a DCB only approach may be a promising option for the treatment of small vessel bifurcations.

Treatment recommendations

In case of main- and side branch involvement, a sequential pre-dilation of the main and the side branch with a balloon-to-vessel ratio of 0.8–1.0 should be followed by a sequential application of DCBs in both branches, overlapping the pre-dilated areas by 2–3 mm at both ends. In case of Medina X,X,0 or 0,0,1 solely the main branch respectively the side branch needs to be treated.

In the event of a major dissection (NHLBI classification grade C–F [28]) or a reduced TIMI flow <III as well as a major recoil (residual stenosis >30 % in main branch and >75 % in side branch) after pre-dilation a standard approach with insertion of a DES is recommended. No data are available concerning the combination of DCB and DES in bifurcation lesions to date. However, the application of a DES in the main branch and a DCB in the side branch seems reasonable and has been shown to be effective in individual patients. Because of a concern of loss of drug and matrix the DCB should not be applied through the stent struts. A scientific evaluation is needed. If the side branch result is inappropriate a provisional side branch stenting followed by kissing balloon angioplasty with conventional balloons finishes the procedure Fig. 4).

DCB plus BMS

Scientific evidence

Several trials investigated the combination of SeQuent™ Please DCB with bailout and elective stent implantation. In PEPCAD I de novo lesions in small coronary arteries were treated with SeQuent™ Please DCB [13]. An additional

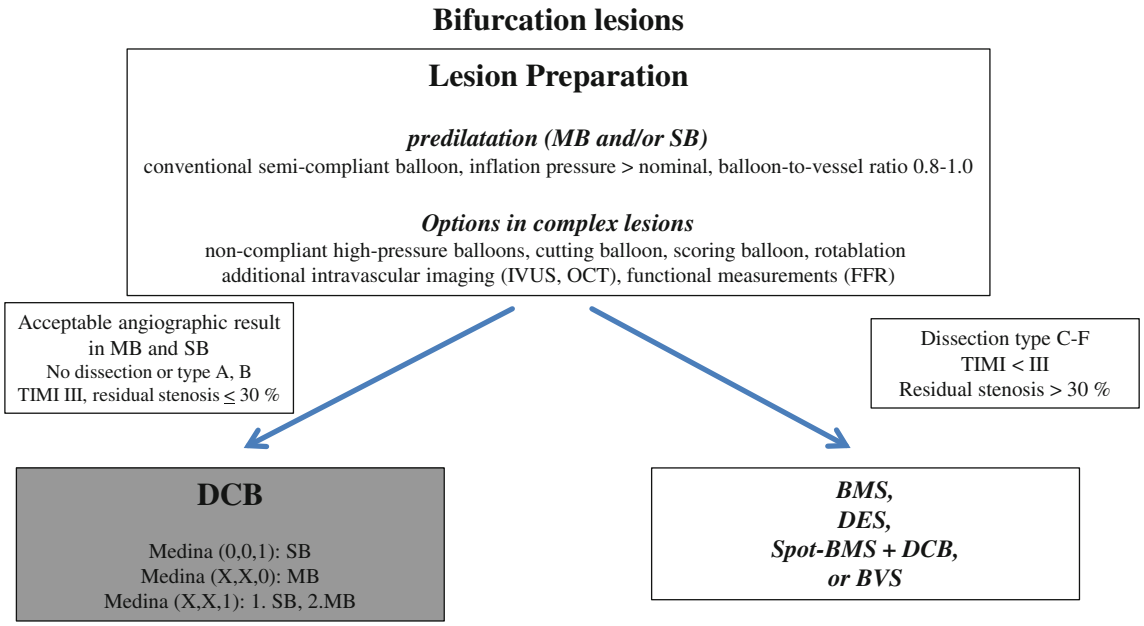

Fig. 4 Proposed treatment of bifurcation lesions with a drug-coated balloon (DCB) only approach. Step 1: pre-dilatation of main branch (MB) and/or side branch (SB) with conventional balloons. Choose a balloon-to-vessel ratio of 0.8–1.0 and nominal pressure or, in case of residual stenosis, high pressure (16–20 atm), length of the Balloon has to be corresponding to the length of the stenosis. Avoid oversizing. Step 2: evaluate the result. If dissection is absent or class A or B according to NHLBI classification, if residual stenosis is <30 % in the MB and <75 % in the SB and if TIMI flow is III, continue with step A, if not continue with step B. Step A: apply DCB to SB, DCB extending 4–5 mm into MB and distally 2–3 mm beyond pre-dilated area, balloon-to-vessel size ratio 0.8–1.0, apply 8–10 atm, at minimum for 30 s. Now sequentially apply the DCB to the MB in the same way extending balloon covered length 2–3 mm on both sides each beyond pre-dilated area. Step B: in case the result in the SB and the MB is unsatisfactory, use a DES for the main branch and provisional stenting for the side branch. If the result is unsatisfactory in the SB only and you have to stent the SB, usually a stent in the main branch cannot be avoided. In cases were the SB stent does not inflict the MB, a DCB only in the MB is an option. If the result is unsatisfactory in the MB only, use a DES in the MB and the standard approach for the SB, possibly with a DCB before stenting of the MB. If after stenting the MB a side branch access deems necessary finalize the procedure with kissing balloon dilatation. However, if the SB is not touched after stenting and the result is acceptable according to the criteria in step 2 side branch dilatation is not needed

BMS implantation was performed in case of elastic recoil or severe dissection. An additional DCB to completely cover the stented segment with the paclitaxel-coated balloon was not required. Therefore, the combination of DCB plus BMS resulted in a higher restenosis rate compared to a DCB only approach. The multivariate analysis revealed geographical mismatch as independent predictor for the incidence of restenosis. In the SeQuent™ Please worldwide registry 572 patients with de novo lesions were treated with a DCB and in case of dissection or recoil with additional stent implantation ($n = 101$) [22]. The treatment strategy was to use an additional DCB to completely cover the stented segment with a paclitaxel-coated balloon. With this approach rates of MACEs, TLR, and TVR were low in both groups with clinical 9 months follow-up and did not differ in patients with vs. patients without additional BMS implantation.

PEPCAD IV and the PERfECT Stent study investigated the combination of DCB plus BMS or endothelial capturing stent (EPC stent) implantation as routine treatment strategy for de novo coronary artery disease. In PEPCAD IV trial [58] the efficacy of the SeQuent™ Please DCB followed by cobalt-chromium stent (Coroflex™ Blue) implantation vs. Paclitaxel-eluting stenting (TAXUS™ Liberté™) in the treatment of de novo lesions in patients with diabetes mellitus. Clinical as well as angiographic results did not differ between both groups. LLL was 0.51 mm vs. 0.53 mm. In PERfECT stent study, the role of SeQuent™ Please DCB in patients treated with endothelial progenitor cell (EPC) capturing stents (Genous™ stent) was studied [15]. The use of a paclitaxel-coated balloon in EPC stents significantly reduced angiographic LLL and translated clinically in a reduced need for repeat revascularization. There was no stent thrombosis within 24 months follow-up. The largest trial is the PEPCAD-III study investigating the safety and efficacy of a commercially not available fixed combination of Coroflex BMS mounted on the DCB for treatment of de novo lesions compared to a sirolimus-eluting stent. The DCB + BMS system did not meet the non-inferiority criteria vs. sirolimus-eluting stents and showed a significant higher LLL. This finding may be explained by a variety of different factors, especially a not yet fully understood influence of the crimped BMS on DCB drug delivery. Therefore, standalone use of DCB is the preferred application.

Treatment recommendations

Based on these data a dissection or recoil after paclitaxel balloon angioplasty for treatment of de novo coronary artery disease can be safely and efficaciously treated by an additional implantation of a BMS or EPC stent and use of a DCB. For reduction of restenosis geographic mismatch has to be avoided. Therefore, the total stented segment should be covered by the paclitaxel-coated balloon. The preferred treatment sequence would be BMS first (as short as possible) followed by the DCB.

DCB in acute coronary syndromes

Scientific evidence

The clinical and angiographic presentation of patients with acute coronary syndromes (ACS) varies. Different clinical scenarios of DCB application in ACS may be discussed. Frequently, thrombosis in the ACS-related lesion plays a major role. Patients in hemodynamic critical situations under catecholamine therapy may present with too small vessel diameters. Another clinically relevant scenario represents ISR which is frequently associated with ACS [59]. The DEB-AMI study compared treatment with DCB plus BMS vs. BMS alone vs. DES for ST-segment elevated acute myocardial infarction (STEMI). DCB plus BMS was not superior to BMS alone [60]. This failure may be explained by the DCB used in this trial, the defined combination with a BMS, and possibly a limited drug transfer in the presence of thrombus.

Treatment recommendations

Based on this limited experience, the use of DCB plus BMS in STEMI patients cannot be recommended.

Dual antiplatelet therapy

The goal of dual antiplatelet therapy (DAPT) after PCI is to provide maximal protection against thrombosis without increasing the risk of bleeding. According to the ESC guidelines for myocardial revascularisation, every patient scheduled for PCI should be considered for pre-treatment with clopidogrel, regardless of whether stenting or DCB is intended or not. To ensure full antiplatelet activity, clopidogrel should be initiated at least 6–16 h prior to the procedure with a loading dose of 300 mg, ideally administered the day before a planned PCI. If this is not possible, a loading dose of 600 mg should be administered at least 2 h before PCI. In case of an acute coronary syndrome the loading dose of the ADP-receptor blocker (600 mg clopidogrel or 60 mg prasugrel or 180 mg ticagrelor) should be given as soon as possible [43].

The duration of DAPT after DCB depends on the indication for the DCB:

Treatment of ISR In case of treatment of an ISR patient should receive ASA 100 mg long-term and clopidogrel 75 mg for 4 weeks after PCI in BMS and at least 4 weeks or the duration defined by the DES implantation date.

Treatment of small vessel disease After treatment of de novo coronary lesions with reference diameters from 2.0 to

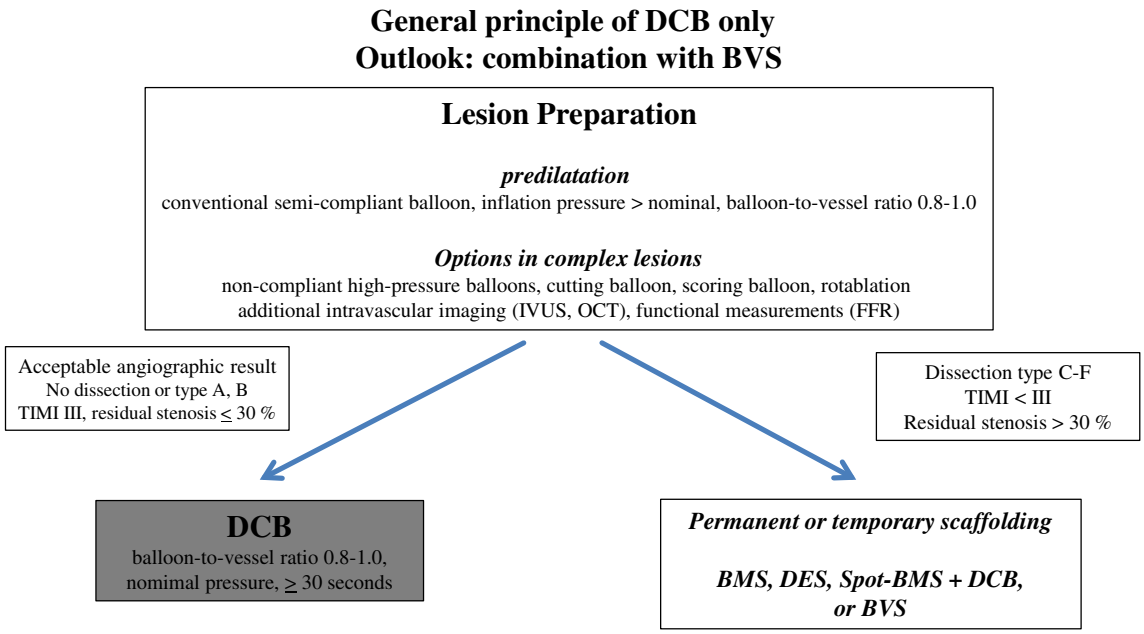

Fig. 5 Potential further development of DCB only to treat ISR and de novo lesions using a drug-coated balloon (DCB) or a bioabsorbable stent (BVS)

2.75 mm ASA 100 mg should be given long-term and additional clopidogrel 75 mg is recommended for 4 weeks after PCI with DCB alone and for 3 months after DCB with additional spot BMS.

Treatment of bifurcation stenosis If only DCB without stenting is used for the treatment of a bifurcation lesion, 4 weeks DAPT is recommended. In case stents are used before or after the DCB procedure, DAPT is recommended for 6–12 months due to the elevated stent thrombosis risk in bifurcation lesions.

According to the guidelines for acute coronary syndrome, the recommended duration of DAPT is 12 months independent of the use of a BMS, DES or DCB. Prasugrel or ticagrelor can be used instead of clopidogrel if the intervention with DCB was performed in an acute coronary syndrome.

Beside the proven efficacy, the possible reduction in the duration of DAPT after DCB represents an additional advantage regarding safety and patient compliance especially in patients with increased bleeding risk. Furthermore, economic analyses have shown that the duration of DAPT is a major driver of the overall procedure costs and the higher initial costs of DCB are more than offset by reduced medication costs [45].

Conclusion and outlook

The general concept of our recommendations for the coronary use of DCB includes the preparation of the lesion to facilitate drug delivery and to estimate the need for stent implantation, especially after relevant dissections. Lesion preparation includes conventional angioplasty. In more complex lesions, additional treatments and imaging or functional measurements are helpful. In case of no flow-limiting dissection and an acceptable but not stent-like primary result, DCB use without additional stent implantation may be considered. We assume that this strategy representing an expert opinion will be applicable in up to 75 % of lesions depending on the complexity of coronary disease (Fig. 5).

In peripheral DCB use patients with suboptimal initial angioplasty result showed lumen gain at follow-up [61]. Furthermore, angiographic analysis of patients with DCB only treatment (SeQuent™ Please) in coronary de novo lesions according to our recommendations show adaptive lumen enlargement over time compared to the primary result after angioplasty (Kleber FX, personal communication). These findings question the paradigm of the need for an optimal primary result after angioplasty.

Drug-coated balloons appear to be attractive in different vascular territories. Positive data from randomized trials or well done registries have been reported for lesions in the superficial femoral artery [19, 20, 61], below the knee [62], in dialysis shunts, in pediatric interventions, and cerebrovascular applications [21]. In the coronary arteries, the most appealing indications are the treatment of restenosis in BMS and DES, treatment of de novo lesions in SVD, the post-dilatation of short uncoated stents, in patients with indication for chronic anticoagulation therapy (like patients

Table 3 Current and potential indications for coronary use of DCBs

Accepted indications
In-stent—Restenosis (established diagnosis in several randomized trials, class IIa indication in the 2010 ESC PCI guidelines)
Patients with small vessel disease less suitable for stenting
Patients on oral anticoagulation or at high risk for initiation of oral anticoagulation, like atrial fibrillation, artificial heart valves etc.
Patients with high bleeding risks, or HAS-BLED score >3, or other need for reduced time of dual antiplatelet therapy like planned or likely surgical intervention or recent major surgery
Patients with bleeding disorders or increased bleeding risks like hemophilia, earlier bleeding history, gastric ulcer, severe renal failure
Potential indications
Patients with endothelial dysfunction/vasospastic angina
Patients with bifurcation lesions less suitable for stenting
Patients with former subacute stent thrombosis
Patients who refuse foreign body implantation

with atrial fibrillation and with artificial heart valves), in patients with bleeding disorders including moderate and severe renal failure, in patients with former subacute stent thrombosis (after excluding stent underexpansion), in patients with recent major or with planned or likely surgical interventions, in patients with high bleeding risks like HAS-BLED score $\geq$3, in bifurcations (especially side branch), and long diffuse lesions to avoid full-metal jacket (Table 3). To date, best clinical evidence in coronary arteries is available for ISR whereas it remains controversial in other settings.

The transfer of our recommendations into clinical practice seems to be promising. The results of the randomized BELLO trial in SVD [35] compare well with the SeQuent Please World Wide registry (2,095 patients, 2,234 lesions). In this large international DCB registry 491 patients were treated for de novo lesions (80 % DCB only); TLR rate after almost 10 months was only 1 % (2.4 % in patients with additional stent implantation) [22]. Ongoing trials with primary clinical endpoints comparing the DCB only concept with a conventional stent approach (e.g., BASKET SMALL 2, PEPCAD NSTEMI) will give further answers on its applicability.

The proposed advantages of the DCB only concept over a direct stent approach include reduced restenosis rates in indications where DES show limited efficacy, the reduction of DAPT especially in patients with contraindications for prolonged DAPT, and the option of leaving no foreign object behind resulting in vascular restoration with potentially plaque regression instead of neo-atherosclerosis.

DCB and bioresorbable vascular scaffold (BVS) are complementary technologies. Both have made it their goal to avoid permanent implants. For both technologies, lesion preparation is considered the mandatory first treatment step [23, 63]. When fulfilling the criteria for DCB only, DCB as standalone therapy is proposed. In case of relevant flow-limiting dissection, a BVS might be preferred. We are now in the beginning of a new age of vascular therapy of leaving nothing behind. The technologies are DCB for the majority of patients and BVS if temporarily scaffolding is needed.

Acknowledgments Franz X. Kleber has received lecture fees and study grants from B. Braun. Harald Rittger has received speaker honoraria and study grants from B. Braun. Klaus Bonaventura has received lecture fees from B. Braun. Jochen Wöhrle has received lecture fees and study grants from B. Braun. Raban Jeger has received study grants from B. Braun and travel support from Medtronic, Biotronik, and B. Braun. Dieter Fischer has received lecture fees from B. Braun. Bruno Scheller has received lecture fees from B. Braun and Medtronic, travel support from Medtronic and B. Braun; he was named on a patent application of Charite university hospital, Berlin and is a shareholder of InnoRa GmbH, Berlin.

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