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Application of drug-coated balloon in coronary artery intervention: challenges and opportunities

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Abstract

In recent decades, the outcomes of coronary heart disease (CHD) have markedly improved, which can be partly attributed to the use of novel drugs (especially statins and antiplatelet drugs) and partly to the evolution of percutaneous coronary intervention (PCI). From percutaneous transluminal coronary angioplasty to bare-metal stent and then to drug-eluting stent, every step of PCI is attractive to interventional cardiologist, great progress has been made for patients with CHD. In the past few years, some successor devices for treating CHD have emerged. Undoubtedly, drug-coated balloon (DCB), which was recommended by 2014 ESC Guidelines on myocardial revascularization, is a "shining star" among them. DCB involves a semi-compliant angioplasty balloon coated with an anti-proliferative agent that can exert antirestenotic efficacy by permeating into the vessel wall during balloon contact. This review discusses the conception and merits, preclinical data, emerging clinical indications, and results from clinical trials of this novel interventional technology. Although DCB has shown authentic efficacy in the treatment of in-stent restenosis, its use in de novo coronary lesions is still in dispute. Hence, concerns and the future direction of DCB are also covered in this paper.

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1 Introduction

Drug-coated balloon (DCB) is a novel device for percutaneous coronary intervention (PCI), which has demonstrated favorable outcome due to its peculiar characteristic of a high-concentration, rapid local delivery of an antirestenotic drug without the use of a durable polymer or metal stent.[1] The concept of DCB depends on rapid healing of the vessel wall due to the fast release of the drug. Furthermore, smooth muscle cells exposed to the drug in a short time could lead to a sustained effect in the first hours to days after angioplasty.[2] DCB, first proved to be effective in the inhibition of restenosis by Scheller in 2004,[3] is designed to have the same antirestenotic effects as a drug-eluting stent (DES) with additional flexibility and nothing remaining in the vessel.

Essentially, DCB is a semi-compliant angioplasty balloon coated with an antiproliferative agent that can exert antirestenotic efficacy by permeating into the vessel wall via balloon contact (Figure 1). Unlike the long-term drug release of DES, DCB transiently releases the drug in 30–60 s. Hence, the coated drug of DCB must be more lipophilic than that of DES; almost all of the coating drug currently available for DCB is paclitaxel.[4]

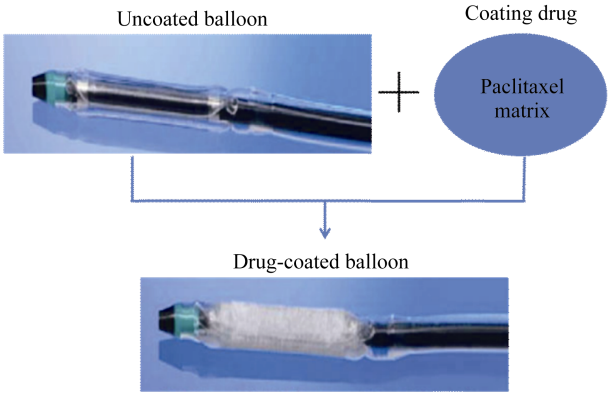

Figure 1. The structure of DCB. The balloon rapidly delivers antiproliferative drug into the vessel wall while expanding and then exert anti-restenotic efficacy. DCB: drug-coated balloon.

Nowadays, DES is regarded as the optimal treatment for coronary lesions. However, DES exhibits some device-associated features and shortcomings only solved in part by newer brands and new generations. The advantages of DCB

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over DES available at present are as follows: prevention of permanent implant scaffold, uniform drug distribution on the vessel wall, quick and transient drug elution, total drug dose released, avoidance of polymeric matrix, and reduced dual antiplatelet therapy (DAPT) course.[2]

2 Current clinical application of DCB

2.1 Treatment of coronary in-stent restenosis

Current evidence supports the use of paclitaxel DCB. Compared with plain old balloon angioplasty (POBA), DCB shows superiority in both bare metal stent (BMS) in-stent restenosis (ISR) and DES-ISR patients. In China, several DCB products have been or will be available for clinical application, and a few clinical trials have been completed in the Chinese population. PEPCAD (a safety and efficacy study of paclitaxel-eluting balloon to paclitaxel-eluting stent) China ISR compared DCB with paclitaxel-eluting stent for the treatment of DES-ISR in 215 patients. The DCB proved to be non-inferior to paclitaxel-eluting stent for in-device late lumen loss (LLL; 0.46 ± 0.51 mm *vs.* 0.55 ± 0.61 mm; CI 95%: 0.23 to 0.10; noninferiority P = 0.0005). The study also demonstrated that there was no difference in target lesion failure (TLF) at 12 months between the two groups.[5] The results of PEPCAD China ISR is consistent with that of PEPCAD II, which was carried out in German.[6] An alternative strategy for DES-ISR is repeated DES implantation; first-generation paclitaxel DES has been shown similar efficacy to DCB. However, there is limited data evaluating the role of second-generation DES, and long-term outcome data beyond one year are completely lacking. Alfonso, *et al*.[7] reported the results of the RIBS IV (Restenosis Intra-Stent: Drug-Eluting Balloon *vs.* Everolimus-Eluting Stent) study, in which the investigators evaluated the role of second-generation everolimus-eluting stents (EES) versus paclitaxel DCB for the treatment of DES-ISR. At follow-up angiography (median 247 days; 90% of eligible patients), when compared with patients in the DCB group, patients in the EES group had a significantly larger minimal lumen diameter (MLD; 2.03 ± 0.7 mm *vs.* 1.80 ± 0.6 mm; $P < 0.01$), net lumen gain (1.28 ± 0.7 mm *vs.* 1.01 ± 0.7 mm; $P < 0.01$), lower percent diameter stenosis (23% ± 22% *vs.* 30% ± 22%; $P < 0.01$), and binary restenosis rate (11% *vs.* 19%; $P = 0.06$). At the 1-year clinical follow-up (100% of patients), the main clinical endpoints (composite of cardiac death, myocardial infarction, and target vessel revascularization [TVR]) were significantly reduced in the EES group (10% *vs.* 18%; $P = 0.04$; hazard ratio: 0.58; 95% CI: 0.35 to 0.98), mainly driven by a lower need for TVR (8% *vs.* 16%; $P = 0.035$). Although the study demonstrated that EES is superior to DCB in long-term clinical and angiographic outcomes, confirmation of the clinical superiority of EES over DCB in these patients is required through further large-scale studies with a broad range patients and longer follow-up. Secondly, DCB are equivalent or possibly even superior to new-generation DES in specific patient subsets; further studies are absolutely warranted to address this intriguing possibility.

DCB has been proved to be effective for ISR lesions, the clinical trials are summarized in Table 1. Based on the solid evidence, the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines on myocardial revascularization recommended the DCB for treatment of various ISRs, including BMS-ISR and DES-ISR, with an A level of evidence.[18]

2.2 Coronary small vessel disease

Coronary procedures in small vessel disease represent 30%–50% of all coronary artery interventions performed worldwide each year, with small vessel size being the strongest predictor of restenosis. To date, several studies have demonstrated the efficacy of DCB for coronary small vessel disease (Table 2). The PEPCAD I study was the first trial to assess the performance of a DCB (SeQuent Please) in small vessels. In 114 patients with lesions < 2.8 mm, In-segment LLL at 6 months was 0.28 ± 0.53 mm, with a binary restenosis rate of 18%. When bailout stenting with a BMS was necessary, LLL was 0.62 ± 0.73 mm. In contrast, LLL was 0.16 ± 0.38 mm in DCB-only treated patients. At 12 months, the rate of MACE was 15%, which was mainly due to the need for target lesion revascularization (TLR).[19] The results of the PEPCAD I after 36 months follow-up demonstrated the excellent clinical outcome in the DCB-only group.[20] In the BELLO trial, 182 patients with lesions < 2.8 mm were randomized to two arms to treat with an In.Pact Falcon balloon and the TAXUS DES; 97% of the patients in the DCB-arm and 81% in the DES-arm underwent lesion preparation. LLL after 6 months was significantly lower in the DCB-arm than in DES-arm (0.08 ± 0.38 mm *vs.* 0.29 ± 0.44 mm; $P = 0.001$).[21] This was the first randomized trial to demonstrate the superiority of the DCB over DES in terms of angiographic end points. The most exciting implications were that the angiographic superiority translated ultimately into the clinical superiority after three years; MACE rates in the DCB group were significantly lower than in the DES group (14.4% *vs.* 30.4%; P = 0.015).[22,23] In the SeQuent SVD Registry study, a total of 479 patients (66.1 ± 10.9 years; 36.7% diabetics) with de novo lesions of small reference diameters (≥ 2.0 mm,

Table 1. Summary of major clinical trials of DCB in ISR.

Study	Study design	Primary endpoints	Secondary endpoints
PACCOCATH-ISR I/II[8,9]	Paccocath *vs.* ordinary balloon 54 cases: 54 cases Follow up: 6,24 and 60 months	LLL at 6 months: 0.11 ± 0.44 mm *vs.* 0.8 ± 0.79 mm (P < 0.001)	Rate of restenosis at 6 months: 6% *vs.* 51% (P < 0.001) MACE at 24 months: 11% *vs.* 46% (P = 0.001); MACE at 60 months: 27.8% *vs.* 59.3% (P = 0.009)
PEPCAD II[6]	SeQuent Please *vs.* TAXUS stent 66 cases: 65 cases Follow up: 6 and 12 months	LLL at 6 months: 0.17 ± 0.42 mm *vs.* 0.38 ± 0.61 mm (P = 0.03)	Rate of restenosis at 6 months:7% *vs.* 20% (P = 0.06); MACE at 12 months: 9% *vs.* 22% (P = 0.08)
PEPCAD-DES[10]	SeQuent Please *vs.* ordinary balloon 72 cases: 38 cases Follow up: 6 months	LLL at 6 months: 0.43 ± 0.61 mm *vs.* 1.03 ± 0.77 mm (P < 0.001)	MACE at 6 months: 16.7% *vs.* 50.0% (P < 0.001); Rate of restenosis at 6 months: 17.2% *vs.* 58.1% (P < 0.001)
ISAR-DESIRE-3[11]	SeQuent Please *vs.* TAXUS stent *vs.* ordinary balloon 137 cases: 131 cases: 134 cases Follow up: 9 months	Diameter stenosis at 9 months: 38% *vs.* 37.4 % *vs.* 54.1% ($P_{noninferiority}$ = 0.007)	TLR at 9 months: 22.1% *vs.* 13.5% *vs.* 43.5%;
SeQuent Please worldwide registry[12]	SeQuent Please (DES-ISR *vs.* BMS-ISR) 464 cases: 763 cases Follow up: 9 months	TLR at 9 months: 9.6% *vs.* 3.8% (P < 0.001)	MACE at 9 months: 11.6% *vs.* 5.3% (P < 0.001)
Spanish multicentre registry[13]	DIOR I/II DES n = 126 cases Follow up: 12 months	MACE at 12 months: 16.7%	TLR at 12 months: 9% (BMS-ISR), 15 % (DES-ISR)
Valentines I[14]	DIOR II DCB (Paclitaxel-DES-ISR *vs.* Everolimus-DES-ISR) 34 cases: 42 cases Follow up: 8 months	MACE at 8 months: 0 *vs.* 23.8% (P = 0.002)	TLR at 8 months: 0% *vs.* 16.7% (P = 0.015)
PEPPER[15]	Pantera Lux DES (BMS-ISR *vs.* DES-ISR) 43 cases: 38 cases Follow up: 6 and 12 months	LLL at 6 months: 0.07 ± 0.31 mm (–0.05 ± 0.28 mm *vs.* 0.19 ± 0.29 mm) (P = 0.001)	MACE at 6 months: 6.5%; MACE at 12 months: 11.8%
DELUX registry[16]	Pantera Lux DCB n = 1064 cases Follow up: 6 and 12 months	MACE at 6 months: 8.5%; MACE at 12 months: 15.1%	--
PEPCAD China-ISR[5,17]	SeQuent Please *vs.* TAXUS 110 cases:110 cases Follow up: 9 and 24 months	LLL at 9 months: 0.46 ± 0.51 mm *vs.* 0.55 ± 0.61 mm ($P_{noninferiority}$ = 0.0005)	TLR at 24 months: 14.8%
RIBS IV[7]	DCB *vs*. EES 154 cases: 155 cases follow up:	MLD at 9 months: 1.80 ± 0.6 mm *vs.* 2.03 ± 0.7 mm (P < 0.01)	MACE at 12 months: 18% *vs.* 10% (P = 0.04)

BMS: bare metal stent; DCB: drug coated balloon; DES: drug eluting stent; ISR: in-stent restenosis; LLL: late lumen loss; MACE: major adverse cardiovascular event; MLD: minimal lumen diameter; TLR: target lesion revascularization.

Table 2. Summary of major clinical trials of DCB in small vessel lesions.

Study	Study design	Primary endpoints	Secondary endpoints
PEPCAD I[19,20]	SeQuent Please *vs.* SeQuent Please + BMS 82 cases: 32 cases Follow up: 6, 12 and 36 months	LLL at 6 months: 0.16 ± 0.38 mm *vs.* 0.63 ± 0.73 mm (P < 0.0001)	MACE at 12 months: 6.1% *vs.* 37.5%; TLR at 12 months: 4.9% *vs.* 28.1%; 3 MACE at 6 months: 7.3% *vs.* 40.6%; TLR at 36 months: 4.9% *vs.* 34.4%;
BELLO[21]	Paclitaxel DCB *vs.* Paclitaxel DES 90 cases: 92 cases Follow up: 6 months	LLL at 6 months: 0.08 ± 0.38 mm *vs.* 0.29 ± 0.44 mm ($P_{noninferiority}$ = 0.001, $P_{superiority}$ = 0.001)	Rate of restenosis at 6 months: 10% *vs.* 14.6% (P = 0.35); TLR at 6 months: 4.4% *vs.* 7.6% (P = 0.37); MACE at 6 months:10% *vs.* 16.3% (P = 0.21)
SeQuent SVD Registry[24]	DCB only *vs.* DCB/DES n = 479 Follow up: 9 months	TLR at 9 months: 3.6% *vs.* 4.0% (P = 0.922)	MACE at 9 months: 4.7% *vs.* 4.0% (P = 0.866)

BMS: bare metal stent; DCB: drug coated balloon; DES: drug eluting stent; LLL: late lumen loss; MACE: major adverse cardiovascular event; TLR: target lesion revascularization.

≤ 2.75 mm) were enrolled. This is the largest prospective study of DCB in small vessel de novo lesions in unselected patients to date. TLR and MACE rates at 9 months (4.7% and 3.6%, respectively) were low, supporting DCB to be an alternative treatment option to DES in small vessel disease.[24]

2.3 Coronary bifurcation disease

Coronary bifurcation lesions are still a challenge for PCI due to unsatisfactory clinical outcomes, mostly in the side branch (SB). Even treated with DES, intolerable high risks of restenosis still remain, particularly when more complex techniques are used. Implanting a stent in the main branch (MB) combined with a provisional stent in the SB has become the preferred approach based on recent trial results. DCB treatment in the SB may be superior when compared with POBA.[25] With these hypotheses, several studies have evaluated the role of DCB in bifurcation lesions. The DEBIUT randomized 117 patients into three arms: DCB pretreatment + BMS; BMS with uncoated balloon; and paclitaxel DES with uncoated balloon.[26] Despite achieving good results with DCB + BMS, it failed to prove superiority over BMS, mostly due to unexpected good results of the POBA-treated SB in both BMS and DES arms. The multicenter randomized BABILON trial compared angiographic and clinical outcomes of DCB with BMS versus everolimus DES in 108 patients with de novo bifurcated lesions.[27] Although angiographic outcomes were significantly different between the two groups (LLL in MB: 0.31 mm vs 0.16 mm, $P = 0.15$; LLL in SB: −0.04 mm *vs.* −0.03 mm, $P = 0.983$), MACE and TLR rates were higher in the DCB group than the DES group (17.3% *vs.* 7.1%; $P = 0.105$ and 15.4 *vs.* 3.6%; $P = 0.045$). The author concluded that DCB bifurcation pretreatment with BMS implantation in MB showed greater and non-significant LLL and increased incidence of MACE compared with everolimus DES.

The DCB-only strategy has been considered by some investigators as the ideal coronary application for bifurcation lesions. The PEPCAD BIF trial, which is a multicenter, randomized, controlled trial, compared the DCB-only strategy with POBA in 64 patients with coronary bifurcation lesions. After 9 months of follow-up, the restenosis rate was 6% in the DCB-only group *vs.* 26% in the POBA group ($P = 0.045$). The results demonstrated that the DCB-only strategy would be a sound strategy for bifurcation lesions with acceptable angiographic results after careful lesion preparation.[28]

As a new type of interventional device, DCB has been compared with other treatments in many trials (Table 3). Although the optimal strategy and the role of DCB in treatment bifurcation lesions are not yet explicit, there is no doubt that DCB can be an alternative treatment option for bifurcation lesions.[30]

Table 3. Summary of major clinical trials of DCB in bifurcation lesions.

Study	Study design	Primary endpoints	Secondary endpoints
DCB bifurcation Study[25]	SeQuent Please *vs* ordinary balloon 50 cases: 50 cases Follow up: 12 months	LLL at 12 months: 0.09 ± 0.4 mm *vs.* 0.40 ± 0.5 mm ($P = 0.01$)	MACE at 12 months: 11% *vs.* 24% ($P = 0.11$); 12 months TLR: 12% *vs.* 22% ($P = 0.16$); Branch restenosis at 12 months: 7% *vs.* 20% ($P = 0.08$)
DEBIUT[26]	DCB *vs.* BMS *vs.* Paclitaxel DES $n = 117$cases Follow up: 6 and 12 months	LLL in proximal MB, distal MB and SB in DEB group and BMS + pDES group at 6 months ($P = 0.001$): 0.58 ± 0.65, 0.41 ± 0.6 and 0.19 ± 0.66 mm; 0.60 ± 0.6, 0.49 ± 0.85 and 0.21 ± 0.57 mm; 0.13 ± 0.45, 0.19 ± 0.64 and 0.11 ± 0.43 mm	Rate of binary restenosis in proximal MB, distal MB and SB at 6 months: 24.2%, 28.6% and 15% ($P = 0.45$); MACE in proximal MB, distal MB and SB at 12 months: 20%, 29.7% and 17.5% ($P = 0.40$)
BABILON[27]	pDEB + BMS *vs.* DES $n = 108$ cases Follow up: 9 months	Main coronary artery LLL at 9 months: 0.31 ± 0.48 mm *vs.* 0.16 ± 0.38 mm ($P = 0.15$); Branch LLL at 9 months:−0.04 ± 0.76 mm *vs.* −0.03 ± 0.51 mm ($P = 0.983$)	MACE at 9 months: 17.3% *vs.* 7.1% ($P = 0.105$); TLR at 9 months: 15.4% *vs.* 3.6% ($P = 0.045$)
PEPCAD BIF[28]	DCB-only *vs.* POBA 32 cases: 32 cases Follow up: 9 months	LLL at 9 months: 0.13 mm *vs.* 0.51 mm ($P = 0.013$)	Restenosis rate at 9 months: 6% *vs.* 26% ($P = 0.045$)
PEPCAD V[29]	SeQuent Please + BMS $n = 28$ cases Follow up: 9 months	LLL at 9 months: 0.38 ± 0.46 mm (main artery); 0.21 ± 0.48 mm (branch)	TLR at 9 months: 3.6% MACE at 9 months: 0 Stent thrombosis at 9 months: 7.1%

BMS: bare metal stent; DCB: drug coated balloon; DES: drug eluting stent; LLL: late lumen loss; MACE: major adverse cardiovascular event; MB: main branch; POBA: plain old balloon angioplasty; SB: side branch; TLR: target lesion revascularization.

Based on the evidence mentioned above, several guidelines or consensuses have recommended DCB to treat patients with ISR, small vessel de novo lesions, or de novo bifurcation lesions (Table 4). Patients with ST-segment elevation myocardial infarction (STEMI), high risk of bleeding, or who are unsuitable for, or are reluctant to receive, a stent could also be treated with DCB if appropriate.

3. Uncertain issues

3.1 Dual antiplatelet therapy duration after DCB angioplasty

Open questions, such as the long-term clinical outcomes of DCB and optimal duration of DAPT, still confuse the users of DCB. No explicit research or professional society guidelines are available regarding the need for, or optimal duration of, DAPT after DCB therapy. A German group,the Italian Society of Intervention Cardiology and China expert group recommend that DAPT is necessary and should be used for one month at least after DCB only, and for 3–12 months after DCB angioplasty with adjunctive stenting, based on the different stent.[31–33] Given the preclinical data showing markers of impaired vessel healing after DCB therapy, Byrne, *et al*.[34] suggested a DAPT duration of 6 months. More randomized trials are required to investigate this issue. According to the clinical guideline, when treated with DCB, patients with acute coronary syndrome should use DAPT for 12 months. ADP- receptor antagonist should be chosen depend on clinical presentation.[18]

3.2 Late lumen enlargement after DCB intervention

The immediate angiographic outcome after DCB therapy is inferior to that of stenting. Interestingly, late lumen enlargement has been observed in DCB treated patients while all other forms of PCI result in late catch-up. The angiographic outcome from 58 lesions treated with DCB-only were retrospectively assessed by quantitative coronary angiography (QCA).[35] Target lesion MLD increased significantly from 1.75 ± 0.55 mm to 1.91 ± 0.55 mm after 4.1 months of follow-up ($P < 0.001$), while diameter stenosis percentage decreased from 33.8% ± 12.3% to 26.9% ± 13.8% ($P < 0.001$), with 69% patients showed luminal enlargement. After exploring the mechanism of the phenomenon, the author suggested that positive vessel remodeling may be the main cause, as well as the possibility of plaque regression and vascular healing being partly responsible. Other studied using more precise imaging technology to verify and better understand the phenomenon is expected in the future.

3.3 DCB in patients with STEMI

An interesting application of DCB is in the setting of STEMI. First results of the DEB-AMI (drug eluting balloon in acute STEMI) trial showed that DCB followed by BMS implantation failed to show angiographic superiority to BMS-only, and angiographic results of DES were superior to both BMS and DCB.[36] The non-randomized fourth arm of the DEB-AMI trial aimed to compare DCB-only with the three other treatments in the same situation as the DEB-AMI trial. Primary PCI with DCB-only yielded an angiographic outcome comparable to BMS alone and DCB followed by BMS. Therefore, the author considered DCB- only to be a potential treatment alternative during primary PCI in patients with contra-indications to DES.[37] Although the aforementioned trials could not prove that DCB-only was equivalent to DES, the prospective, single center, randomized REVELATION trial study is ongoing.[38] In view of delayed healing and endothelial dysfunction induced by DES and the concept that local drug delivery to the culprit plaque at the moment of highest inflammation, DCB seems still to be an attractive treatment opportunity in STEMI patients.

Table 4. Indications of DCB and recommendations of guidelines or consensuses.

	ISR	Small vessel lesions	Bifurcation
German consensus[31]	√*	√	√
SICI-GISE consensus[32]	BMS-ISR: Class I indication, level of evidence: A DES-ISR: Class IIa indication, level of evidence: B	Class IIa indication, Level of evidence: B	Class IIb indication, Level of evidence: C
China consensus[33]	√	√	√
ESC guideline 2014[18]	BMS-ISR or DES-ISR: Class of recommendation: I, Level of evidence: A	—#	—

*: represent to recommended indication; #: represent to no recommendation. BMS: bare metal stent; DCB: drug-coated balloon; DES: drug eluting stent; ESC: European Society of Cardiology; ISR: in-stent restenosis; SICI-GISE: Italian Society of Intervention Cardiology.

3.4 DCB in patients with a high risk of bleeding

Due to the shortened duration of DAPT, DCB is an alternative choice to DES in patients with a high risk of bleeding. Recently, Miglionico, *et al*.[39] published an interesting prospective observational study of 82 randomized patients with high-risk bleeding [48 BMS-ISR patients (59%) and 34 DES-ISR patients (41%)]. DAPT with aspirin and clopidogrel was maintained for 4 weeks after the procedure. The result showed that the use of DCB for the treatment of ISR in high-risk patients was effective. At angiographic follow-up, overall LLL was 0.24 ± 0.32 mm, with no significant difference between BMS-ISR and DES-ISR (0.25 ± 0.35 *vs*. 0.22 ± 0.30 mm; $P = 0.714$). The Kaplan–Meier estimate for major adverse clinical events-free survival at three years was 81.4%, and no stent thrombosis has been recorded. Furthermore, contemporary clinical studies of DCB showed that a DAPT duration of 4 weeks was appropriate; however, further research is needed on whether such a short DAPT duration after treatment of DES-ISR with DCB is safe.

3.5 Multi-layered ISR

The treatment of multi-layered ISR is of great interest and frequently poses a clinical dilemma. A non-randomized study of recurrent ISR treated with at least three prior stents aimed to evaluate the role of DCB. A total of 171 lesions are analyzed; 82 lesions in the second-generation DES group, the others in the DCB group. After two years follow-up, there was no significant difference between DES and DCB treatment, although the DCB group had obvious higher rates of MACE (43.5 *vs.* 28.8%; $P = 0.21$).[40] Additional, well-designed clinical trials must be carried out to clarify the impact of DCB in the treatment of multi-layered ISR.

4 Perspective developments

Attributing to the characteristic of high lipophilicity and favorable tissue kinetics, currently available DCB devices use paclitaxel as the antiproliferative drug.[4] However, the development of limus-coated DCB catheters attract some attention due to the successful results with such drugs in DES. Cremers, *et al*.[41] reported encouraging data with a novel zotarolimus-coated balloon. In another study, the drug was proved to be effective; it transferred as rapidly as 5 min after angioplasty from a zotarolimus-coated balloon into femoral artery tissue and maintained a significant drug concentration in a hypercholesterolemic swine model up to the 28-day follow-up.[42] Long-term inhibition of neointimal growth still needs to be tested with these devices and, considering the transfer effectiveness of balloon-to-tissue, it may be more important to zotarolimus-coat balloons to sustain drug absorption than to paclitaxel-coat balloons. In addition, the use of nanoparticle excipients might be a promising method to reinforce the absorption of limus drugs.

In summary, the mechanism of DCB is attractive and the efficacy of DCB seems to be credible in patients with ISR and other coronary de novo lesions. Although there are a great number of experiments on DCB, when compared to the high-quality, randomized clinical trials published in the peer-reviewed literature, the total number is disappointing and the spectrum of clinical indications required further data. In order to better define the role of DCB devices in daily clinical practice, large-scale clinical trials with broad inclusion criteria are particularly needed.

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