

Drug-coated balloons in the treatment of acute myocardial infarction (Review)

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Abstract. Drug-eluting stents are the standard revascularization strategy for the treatment of symptomatic coronary artery disease. However, in-stent restenosis (ISR), stent thrombosis and reinfarction of target lesions following stent implantation present challenges. Drug-coated balloons (DCBs), which deliver antiproliferative drugs into the vessel wall without stent implantation, are a novel treatment option for percutaneous coronary intervention and have been proven to act as a promising strategy in the treatment of ISR and coronary small vessel disease. However, their role in acute myocardial infarction (AMI) remains unclear. The present review discusses current evidence for the treatment of AMI with DCBs.

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1. Introduction

Despite major advancements in primary and secondary prevention strategies, coronary artery disease (CAD) remains a major cause of morbidity and mortality worldwide (1-3). Percutaneous coronary intervention (PCI), which was introduced as an alternative means of coronary revascularization to coronary artery bypass grafting surgery in 1979 (4), is considered an effective and safe treatment modality for suitable patients with acute or stable CAD (1).

Patients with acute myocardial infarction (AMI) are among the highest-risk patients undergoing PCI. The introduction of stenting decreased the limitations of elastic recoil, restenosis and flow-limiting dissections associated with plain old balloon angioplasty (5). Due to their improved safety and efficacy compared with first-generation drug-eluting stents (DES) and bare-metal stents (BMS), new-generation DES are currently recommended for PCI in patients with AMI (1,3). However, in-stent restenosis (ISR), increased risk of bleeding due to prolonged dual antiplatelet therapy, as well as early and late stent thrombosis following implantation (6-10). Furthermore, late stent-related major adverse cardiovascular events (MACEs) occur between 1-5 years after PCI, which presents a challenge (11). For patients with AMI, routine stenting is associated with an increased rate of acute and subacute stent thrombosis compared with stable CAD, and the 1-year incidence of target lesion-related events remains high (12,13). In addition, permanent vascular implants impair coronary endothelial and vasomotor functions of the coronary artery (14).

These limitations resulted in the development of drug-coated balloons (DCBs). The rationale of DCB technology is that a combination of balloons and drugs is used for the treatment of coronary lesions to achieve lower rates of restenosis (Fig. 1) (15,16). DCBs have emerged as a novel application in PCI, and a DCB strategy has already exhibited successful therapeutic potential for ISR (17-20) and small vessel disease (21-23). DCBs are a class I indication to treat ISR, as described in the 2018 ESC/EACTS guidelines on myocardial revascularization (1); however, their role in AMI remains unclear. The present review discusses the current studies for the treatment of AMI with DCBs.

2. DCBs

The concept of DCBs has been extensively studied (15,24,25). DCBs are semi-compliant balloons covered with an antiproliferative drug, which is in direct contact with the vessel wall and inhibits the proliferation of smooth muscle cells (26). DCBs are a novel treatment strategy for CAD, based on the fast delivery of antiproliferative drugs into the vessel wall following single balloon inflation, which fulfills the concept of 'leaving nothing behind' (27,28). Although sirolimus and its analogues have been investigated in DCBs, limited data are available for their use in CAD (29-31). Paclitaxel-coated balloons, which contain a typical dose of 2.0-3.5 mg/mm² of paclitaxel on the balloon surface, remain a popular choice for coronary intervention (16).

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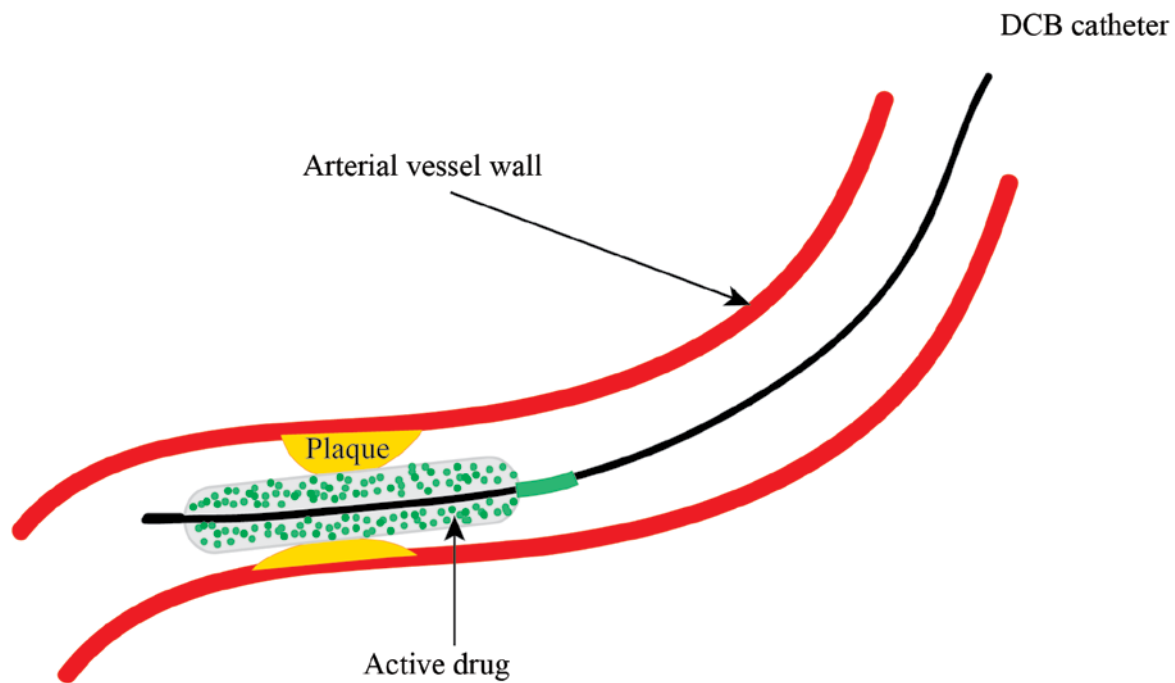


Figure 1. DCB Technique and Mechanism. DCB delivery of highly lipophilic drugs into the vessel wall by single balloon inflation. DCB, drug-coated balloon.

Paclitaxel is a highly lipophilic antiproliferative drug that can permeate through the vessel wall. In addition, it is relatively selective for smooth muscle cells, and its cytotoxicity persists for at least 14 days (26). Following inflation of the balloon for 30 sec, 16% of the drug is transferred into the vessel intima to exert a sufficient antiproliferative effect (32). Rapid tissue release makes paclitaxel-coated balloons attractive for use in DCBs. Table I lists currently available DCBs for coronary use, worldwide.

3. Clinical trials of DCBs for AMI

ST-segment elevation MI (STEMI). Primary percutaneous coronary intervention (PPCI) is the most effective reperfusion strategy for STEMI, and stenting has been demonstrated to decrease the incidence of repeat revascularization (33,34). However, intervention stent treatment is associated with an increased rate of thrombotic complications, as well as ISR in the long-term (10,13). Thus, avoiding permanent implants may be favorable to prevent stent-associated acute and long-term complications in patients with STEMI. A DCB strategy may be attractive because it provides a homogeneous delivery of the antiproliferative drug and also suppresses endothelial inflammation (35,36).

Currently, five studies have been performed to investigate the DCB strategy in patients with STEMI (Table II). Ho *et al* (37) investigated the feasibility of using DCBs in patients undergoing PPCI by treating 89 patients with STEMI with 89 coronary lesions with DCBs, among which 56% of patients underwent thrombus aspiration and 4% of patients received bailout stenting. At 30 days follow-up, four deaths were reported; however, no patients experienced abrupt closure of the infarct-related artery, target vessel revascularization (TVR), target-vessel-MI or target lesion thrombosis. In this study, the authors recommended thrombus aspiration for visible thrombus and sufficient predilatation prior to DCB

angioplasty to enable better contact, prolong balloon inflation and provide preliminary experiences with DCBs in PPCI. However, as the number of patients in the study was relatively small and it was a single-center registry, further studies with longer follow-up are required to confirm these preliminary findings.

The PAPP study (38) prospectively enrolled 100 patients with STEMI and evaluated the safety and feasibility of a DCB-only strategy in PPCI. In this study, 59 patients were treated with a DCB angioplasty, while bailout stenting was performed in 41 patients due to type C to F dissection or residual stenosis >50%. 1-year clinical follow-up was completed in 98% of patients, and five MACEs were reported. A total of two patients died from cardiac death, and three patients underwent target lesion revascularization (TLR). To the best of our knowledge, this was the first study that exhibited good 1-year clinical results of a DCB-only strategy in the setting of primary PCI; however, its major limitations include its observational nature, single-arm and single-center design, and the lack of long-term follow-up.

Gobic *et al* (39) also compared the clinical and angiographic outcomes in patients with STEMI treated with DCB-only strategy vs. DES implantation during PPCI. A total of 75 patients with STEMI were randomized into DCB or DES groups, and the study endpoints were MACEs and late lumen loss (LLL) after 6-months follow-up. After 1 month, two patients in each group experienced reinfarction. At 6 months, MACEs were only reported in 5.4% of patients in the DES group; LLL was 0.10 ± 0.19 mm in the DES group and -0.09 ± 0.09 mm in the DCB group ($P < 0.05$). This study demonstrated that the DCB-only strategy had good clinical and angiographic outcomes after a 6-months follow-up period. However, the limitations of this study included a small sample size, relatively short follow-up period and the lack of prior research on the topic.

Table I. Currently approved drug-coated balloons.

Device	Company	Drug	Dose, $\mu\text{g}/\text{mm}^2$
Agent	Boston Scientific	Paclitaxel	2.0
Elutax SV	Aachen Resonance	Paclitaxel	2.2
Danubio	Minvasys	Paclitaxel	2.5
Dior I and II	Eurocor	Paclitaxel	3.0
SeQuent Please Neo	Braun Melsungen	Paclitaxel	3.0
Pantera Lux	Biotronik	Paclitaxel	3.0
Restore	Cardionovum	Paclitaxel	3.0
Essential	iVascular	Paclitaxel	3.0
IN. PACT Falcon	Medtronic	Paclitaxel	3.5
Elutax	Aachen Resonance	Paclitaxel	2.2
Virtue	Caliber Therapeutics	Sirolimus	4.0
Selution	M.A. Med Alliance	Sirolimus	4.0
Magictouch	Concept Medical Research	Sirolimus	4.0

Table II. Clinical trials of DCBs for the treatment of ST-segment elevation myocardial infarction.

Trial	Year	DCB type	Control group	Sample size, n	Clinical follow-up, months	Angiographic follow-up, months	Primary endpoint	Secondary endpoint	(Refs.)
DEB-AMI	2012	DIOR II	DCB + BMS or DES	50/50/50	6	6	LLL	ISR, MACE (cardiac death, MI and TVR)	(40)
PAPPA	2014	Pantera Lux	None	100	12	None	Cardiac death, recurrent MI, TLR	The need for additional stenting, stent thrombosis and major bleeding	(38)
Ho <i>et al</i>	2015	SeQuent Please	None	89	1	None	Death, TVR, recurrent MI or ST	NR	(37)
Gobic <i>et al</i>	2017	SeQuent Please	DES	41/37	6	6	LLL, MACE (major bleeding, MI, TLR and cardiac death)	NR	(39)
REVELATION	2019	Pantera Lux	DES	60/60	9	9	FFR value	LLL, MACE (cardiac death, recurrent MI and TLR) and major bleeding.	(42)

DCB, drug-coated balloon; BMS, bare metal stent; DES, drug-eluting stent; LLL, late lumen loss; MACE, major adverse cardiovascular event; TLR, target lesion revascularization; MI, myocardial infarction; FFR, fractional flow reserve; TVR, target vessel revascularization; ISR, in-stent restenosis; NR, not reported.

The DEB-AMI trial (40), which compared intravascular imaging and clinical outcomes of patients with STEMI treated with BMS, DES or DCB plus BMS, demonstrated that the combination of DCB and BMS was not superior to BMS alone

and inferior to paclitaxel-eluting stents, in terms of LLL and binary restenosis at 6-months follow-up. In the non-randomized fourth arm of the DEB-AMI study, Nijhoff *et al* (41) reported that DCB-only treatment resulted in a similar LLL

Table III. Main outcomes of each study.

Study, year	DCB/competitor	Patients, n	Follow-up, months	Primary endpoint	Main results	(Refs.)
DEB-AMI, 2012	DIOR II/DIOR II + BMS/ Taxus Liberte	150	6	LLL	LLL, 0.51 ± 0.59 for DEB vs. 0.21 ± 0.32 mm for DES ($P < 0.01$); MACE, 17.5 for DEB vs. 4.1% for DES ($P = 0.68$)	(40)
PAPPA, 2014	Pantera Lux	100	12	Cardiac death, recurrent MI and TLR	MACE, 5%; TLR, 3%	(38)
Ho <i>et al.</i> , 2015	SeQuent Please	89	1	Death, TVR, recurrent MI or ST	Mortality, 4.5%; TVR, 0.0%	(37)
Gobic <i>et al.</i> , 2017	SeQuent Please/Biomime	78	6	LLL, MACE (major bleeding, MI, TLR and cardiac death)	LLL, -0.09 ± 0.09 vs. 0.10 ± 0.19 mm ($P < 0.05$); MACE, 0.0 vs. 5.4% ($P = 0.29$)	(39)
REVELATION, 2019	Pantera Lux/Orsiro or Xience	120	9	FFR value	FFR value, 0.92 ± 0.05 vs. 0.91 ± 0.06 mm ($P = 0.27$); LLL, 0.05 (-0.40 - 0.20) vs. 0.00 mm (-0.16 - 0.10) ($P = 0.51$)	(42)
PEPCAD NSTEMI, 2020	SeQuent Please/BMS or current generation DES	210	9	TLF	TLF, 3.8 vs. 6.6% ($p = 0.53$); MACE, 6.7 vs. 14.2% ($P = 0.11$)	(43)

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; MI, myocardial infarction; FFR, fractional flow reserve; TVR, target vessel revascularization; TLF, target lesion failure.

and binary restenosis rate compared with treatment with BMS alone or DCB plus BMS; however, significantly higher LLL and binary restenosis rate were achieved compared with the DES group, which may be due to the DCB compound used in the study (DIOR GmbH, Bonn, Germany). Notably, no statistically significant differences in MACEs, death, TLR, TVR, myocardial infarction and stent thrombosis rates were observed between DEB-only and DES treatments at 6-months follow-up. Thus, DEB-only treatment remains a potential alternative during PPCI in patients with contraindications to DES.

Recently, the REVELATION trial (42) was published, which was performed in patients with STEMI to assess the efficacy and safety of a DCB treatment strategy vs. DES treatment in PPCI. In this prospective randomized trial, 120 patients were treated with either DCB (Pantera Lux, Biotronik, Berlin, Germany) or DES (Orsiro, Biotronik, Bülach, Switzerland or Xience, Abbott) in a 1:1 ratio, and the primary endpoint was fractional flow reverse (FFR) at 9 months. At 9-months follow-up, the mean FFR value was 0.92 ± 0.05 in the DCB group vs. 0.91 ± 0.06 in the DES group ($P = 0.27$). Furthermore, no significant differences in LLL and clinical outcomes were observed between the DCB and DES groups. The DCB-only strategy was non-inferior to DES treatment, and exhibited improved safety and feasibility. However, this study had several limitations, including a small sample size, relatively short follow-up period and it was a single-center study.

Non-ST elevation MI (NSTEMI). Only one study (PEPCAD NSTEMI) has compared the clinical outcomes of patients with NSTEMI treated with DCBs or stent (43). In this study, 210 patients with NSTEMI were enrolled, the primary endpoint was target lesion failure (TLF), and second endpoints included MACEs and individual clinical endpoints. During a follow-up of 9.2 ± 0.7 months, DCB was determined to be superior to stents in terms of TLF, and no significant difference in the rates of death, MI and TLR was observed between DCB and stent treatments. DES are regarded as the standard of care in most settings of acute coronary syndrome (3,33), and the PEPCAD NSTEMI trial was the first to demonstrate the safety and efficacy of DCBs for patients with NSTEMI. However, DCBs in this setting require further investigation in the form of larger randomized trials.

4. Limitations and perspectives

DCBs appear to be a feasible and attractive treatment strategy for patients with AMI. However, DCB technology is not without limitations. DCBs are associated with increased risk of persistent residual stenosis and acute dissection, which may require bailout stenting (44,45). Furthermore, DCBs require optimal lesion preparation before the apposition of the drug-coating surface to the lesion endothelium, and in the presence of angiographic thrombus, DCBs may be unsuitable due to inhibition of drug delivery to the vessel wall (37,42,46). In addition, in patients who had DES-ISR, DCBs may be associated with higher TLR compared with DES (18).

Limited data are available for the use of DCBs in AMI (Table III) and current studies have several limitations. First,

the number of patients included in the studies have been relatively small. Secondly, the follow-up periods have been relatively short, whereby the longest follow-up period was only 12 months. Thus, the long-term safety and efficacy of DCBs in AMI remain unknown. Thirdly, despite half of the studies being randomized controlled trials (RCTs), only one study is a multi-center study. Finally, only paclitaxel-coated balloons were used in these studies, and no trials have investigated the safety and efficacy of other DCBs in AMI, such as sirolimus-coated.

Regarding the shortcomings of existing studies, larger multi-center RCTs with longer follow-up periods are required to evaluate the clinical use of paclitaxel or sirolimus-coated balloons in patients with AMI. Currently, sirolimus and its derivatives, such as everolimus, are successfully implemented in stent technology and are the main drugs used in DES in clinical practice (47-49). A recent study reported promising results of sirolimus-coated balloons ISR compared with paclitaxel-coated balloons (30). According to its success in stents and recent evidence in DCBs, sirolimus and its derivatives may be alternative drug coatings for AMI.

5. Conclusions

Stenting remains the standard reperfusion strategy in most settings of AMI; however, ISR, stent thrombosis and reinfarction present challenges. DCBs represent a safe and effective method for the treatment of ISR and coronary small vessel disease, and appear to be a promising strategy in the cases of AMI. However, further studies are required to determine the long-term benefits of DCBs compared with those of new-generation DES.

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Authors' contributions

HH drafted the initial manuscript and LS performed the literature review. HH and LS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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