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Drug-Coated Balloon in Acute Coronary Syndromes: Ready for the Prime Time?

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Abstract

Purpose of Review Acute coronary syndromes (ACS) are a major global health concern. Percutaneous coronary intervention (PCI) with new-generation drug-eluting stents (DES) has been endorsed as safe and effective in the management of culprit and non-culprit lesions of ACS. However, permanent metallic implants may have drawbacks, including the need for prolonged dual antiplatelet therapy (DAPT) and the risk of long-term stent-related complications. An alternative approach using drug-coated balloons (DCBs) is gaining growing interest, having the potential of delivering therapy directly to vulnerable plaques, avoiding the need for permanent metallic implants, and potentially allowing for better long-term medical treatment. Despite limited evidence, DCB is being explored in several patients' subgroups. This review aims to discuss the existing evidence regarding DCB in ACS management.

Recent Findings DCB appears to be a promising strategy in the management of ACS, showing comparable angiographic and clinical results as compared to new-generation DES in relatively small clinical trials or large prospective registries. The advantage of avoiding permanent implants is particularly appealing in this setting, where DCB has the potential of delivering anti-atherogenic local therapy directly to vulnerable plaques still amenable to atherogenic regression. This review seeks to underline the theoretical background of DCB use and reports the available evidence in its support in the specific setting of ACS.

Summary In the context of ACS, the use of DCB is highly attractive, offering a dedicated anti-atherogenic local therapy, capable of addressing a broad range of vulnerable plaques and patients.

Keywords Drug-coated balloons · Acute coronary syndrome · Percutaneous Coronary Intervention · Drug-eluting stents

Introduction

Acute coronary syndromes (ACS) represent a leading cause of mortality and morbidity worldwide [1]. The introduction of stents during PCI, firstly bare-metal (BMS) or drug-eluting stents (DES), aimed to overcome the occurrence of acute elastic recoil, to seal flow-limiting dissections, and to prevent long-term restenosis due to the acute barotrauma associated with plain old balloon angioplasty [2, 3]. Compared to BMS, new-generation DES have been proven to be both safe and effective reducing the incidence of device and vessel-oriented adverse events, earning endorsement from current guidelines [4, 5]. However, the use of permanent metallic implants comes with some potential

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drawbacks. On one hand, the requirement for prolonged DAPT can pose risks, particularly in elderly patients and those deemed at high bleeding risk (HBR) [6]. On the other hand, a constant risk of long-term stent-related complications (i.e., in-stent restenosis, stent thrombosis, and neoatherosclerosis) with an incidence rate of approximately 2–3% per stent per year has been described with current era devices [7].

The concept of an implant-free approach, facilitated by DCB, holds particular appeal in the context of ACS. Firstly, DCB offers anti-atherogenic local therapy that is delivered directly to vulnerable plaques still amenable to atherogenic regression [8]. Secondly, the absence of a metallic implant has the theoretical advantage of allowing for a deeper effect of long-term medical therapy (e.g., statins, PCSK-9 inhibitors) on vulnerable plaques. Nevertheless, the evidence in support of DCB in ACS is sparse and increasing interest and investigations are warranted. This is especially relevant given the wide spectrum of patients encountered, ranging from young individuals experiencing their initial cardiac event, where DES implants might hamper future surgical revascularizations, to patients with diabetes mellitus and/or diffuse and/or multivessel involvement, who face a heightened risk of stent-related complications. Additionally, the challenge of determining the appropriate duration of DAPT is particularly relevant for patients at high bleeding risk and elderly individuals.

Pathophysiology of AMI

The term "vulnerable plaque" refers to atherosclerotic lesions prone to progression and de-stabilization, leading to thrombosis and acute coronary syndromes or sudden cardiac death [9]. From a pathological perspective, three primary types of vulnerable plaques prone to thrombosis have been recognized in order of their occurrence: plaque rupture, plaque erosion, and calcified nodules. Plaque rupture is the most common cause of acute coronary thrombotic events (70%) [10]. Interestingly, plaque ruptures usually occur without clinically relevant events, and previously ruptured plaques that have healed ("healed plaques") are frequently detected in patients without clinical acute cardiac events, indicating a common mechanism of plaque progression [11]. Thin-cap fibroatheroma (TCFA) is a primary lesion within plaques that increases the risk of rupture. It is characterized by a large necrotic core containing cholesterol, dead macrophages, and tissue factor, often accompanied by neoangiogenesis and intraplaque hemorrhage [12].

Plaque erosions (25%) occur with endothelium denudation, which leads to direct blood contact with the arterial intima and subsequent thrombosis. In contrast with TCFA, plaques associated with thrombosis through surface erosion are more likely to be eccentric, fibrotic, with small or absent necrotic cores (although lipid pools can be present), and are rich in vascular smooth muscle cells and proteoglycans but tend to be less severe and lack significant inflammation, calcification, or hemorrhage.

Lastly, eruptive calcified nodules (5%) present with turbulent blood flow and plaque surface disruption [12, 13].

Several mechanisms contribute to the development of vulnerable plaques, including LDL-driven atherogenesis, lipoprotein (a)-driven inflammation, increased expression of adhesion molecules on endothelial cells, dysregulation of autophagy, and inflammation (i.e., IL-18, IL-6, and microRNAs, adipokines) [14]. The triggers leading to the rupture of TCFA and thrombosis in erosion-prone vulnerable plaques are not fully understood, but potential contributors include changes in plaque composition, blood supply alterations, and arterial intima integrity. Additionally, recent research has emphasized the role of matrix metalloproteinases in plaque vulnerability, as they can break down the arterial wall's extracellular matrix, a critical factor linked to a higher risk of acute arterial thrombotic events, particularly in areas with low endothelial shear stress [12, 13].

DCB Technology and Potential Advantages in ACS

DCB offers an alternative to DES for local drug delivery. These balloons, coated with medication, are used to deliver antiproliferative therapy during balloon inflation, once diseased blood vessels have been adequately prepared, leaving no residual implant in the vessel. In theory, DCB offers several advantages, including a broader surface area for more uniform drug distribution into surrounding tissue and a shorter period of arterial healing due to the absence of implanted stent struts [15, 16] (Fig. 1). Similarly, DCB serves as a drug delivery alternative in situations where DES is considered unfeasible, such as in small vessels, vessels with significant mechanical flexure, or in cases DES outcome has been shown impaired (Fig. 1).

However, DCB comes with a set of challenges, including drug delivery being restricted to the time of inflation, making it more challenging to control the amount of drug retained in the tissue and the duration of drug residence [16]. Additionally, a high initial drug loading is required, as the delivery is not primarily driven by diffusion or dissolution but is achieved by mechanically forcing the drug or drug-carrying coating into the vascular wall in the acute phase [17].

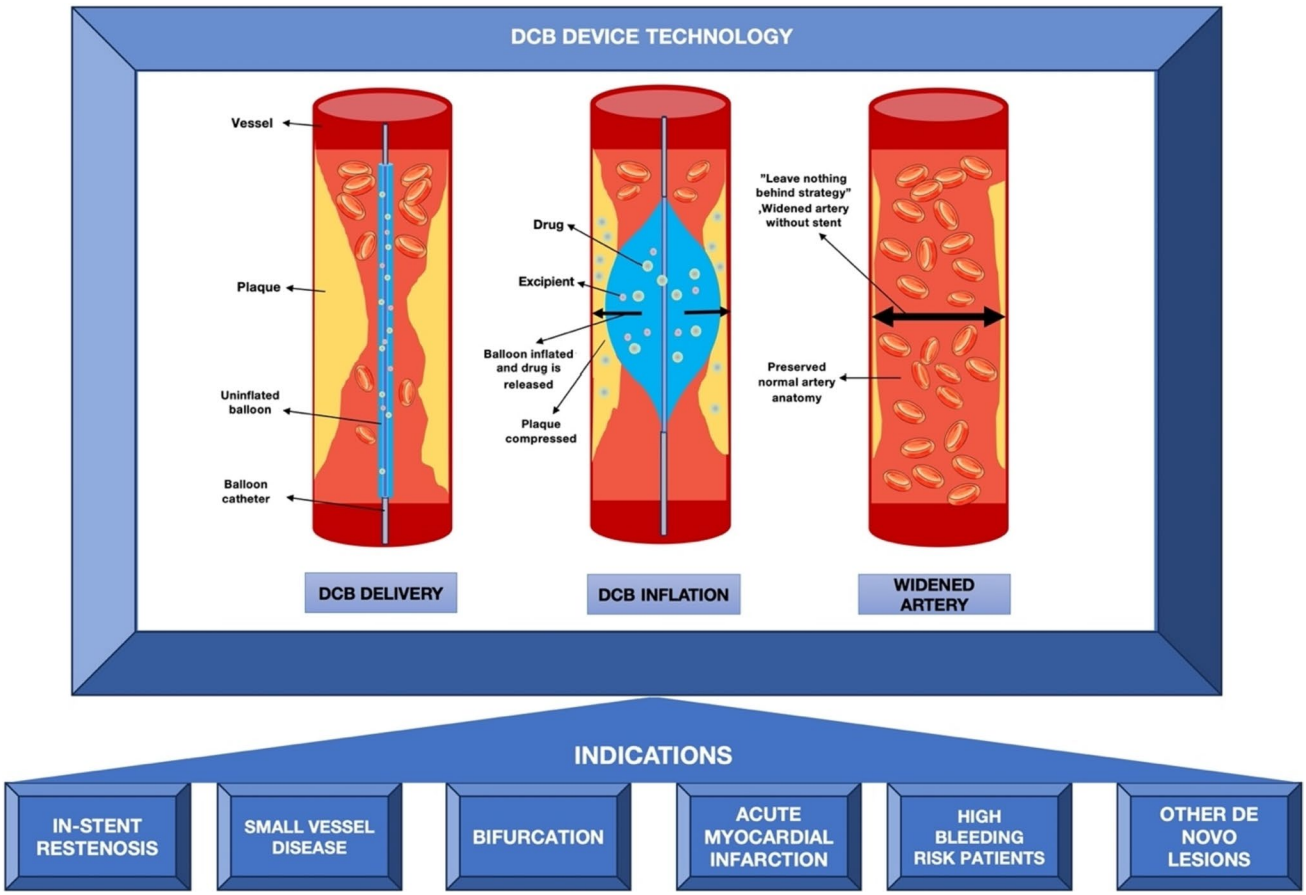

Fig. 1 DCB technology and indications

Various DCBs are available on the clinical market, with most using formulations of paclitaxel due to their lipophilic characteristics and favorable protein binding. Limus-based DCBs (especially sirolimus) also exist, where the drug is coated with a dedicated nanotechnology or a crystalline-bound form. However, decisive results demonstrating the superior efficacy and safety of limus-based DCBs over paclitaxel-based ones are yet to be reported.

Although the applicability of DCB in the setting of ACS is of potential interest especially when dealing with plaque erosions and ruptures, several studies have suggested that calcium and calcified nodules can hinder optimal DCB performance. Specifically, DCB relying on acute mechanical deposition may encounter difficulties with stiff superficial calcium [18, 19].

Additionally, concerns related to intraplaque thrombus have been raised, and the compression of tissue during balloon expansion might hinder optimal long-term delivery, as tightly packed vascular layers reduce diffusivity, possibly decreasing transluminal retention [20].

Clinical Studies Investigating the Role of DCB in ACS

STEMI

In patients experiencing ST-elevation myocardial infarction (STEMI), the prompt restoration of blood flow through primary percutaneous coronary intervention (pPCI) is of utmost importance for preserving heart muscle and reducing mortality. Despite the widespread adoption of second-generation DES as the standard of care, certain acute and long-term events related to stent implantation continue to pose challenges, despite significant advancements in stent technology.

In the acute setting, coronary spasm is common and hampers proper stent sizing, leading to stent undersizing, acute, and/or late malapposition, especially when post-dilatation is not performed to prevent distal thrombus embolization and no-reflow/slow flow phenomena. The use of DCB has the potential of allowing a uniform

delivery of the antiproliferative drug to the vessel wall, avoiding a permanent metallic implant, potentially maintaining endothelial function at long term [21]. Nevertheless, the presence of high thrombus burden has been linked with a suboptimal drug delivery [21].

The safety and feasibility of DCB during pPCI in the setting of STEMI was firstly investigated in the "first-in-human" PAPPA trial [22]. One hundred STEMI patients were included: 59 were treated with DCB angioplasty, while 41 underwent bail-out stenting due to type C to F dissections or residual degree of stenosis greater than 50%. At 1-year follow-up, five major adverse cardiac events (MACE) occurred, namely two cardiac deaths and three target lesion revascularization (TLR) (Fig. 2) (Table 1). Given several limitations (i.e., observational, single-center, non-randomized design), this pivotal experience suggested feasibility of DCB approach during pPCI but further data were required [22].

The DEB-AMI [23] randomized controlled trial (RCT) aimed at comparing three arms of treatment (1:1:1) during PPCI: paclitaxel DCB (Dior, Eurocor, Germany) followed by BMS implantation, BMS implantation, and DES implantation. The primary endpoint of the study was the mechanistic angiographic result at 6 months (late lumen loss, LLL). Overall, 150 STEMI patients were included, and 50 were assigned to the DCB-BMS arm. Pre-dilatation of the lesion was performed in 60% of the cases, and procedural success was achieved in 97.5%. At 6 months, LLL was lower in the DES group compared to BMS and DCB + BMS (0.21 ± 0.32 mm vs. 0.74 ± 0.57 mm, vs. 0.64 ± 0.56 mm, $p < 0.01$) (Table 1). Therefore, DCB followed by BMS implantation failed to show angiographic superiority to BMS or DES implantation. Moreover, based on an OCT substudy, DCB before implantation induced more uncovered and malapposed stent struts at follow-up as compared to BMS, but less than after DES. Clinically, a reduction in terms of MACE was observed in the DES arm (4.0% vs. 20.0% vs. 23.5%, $p = 0.02$) (Table 1) [23].

The PEBSI RCT [24] enrolled 223 pPCI patients treated with BMS followed by paclitaxel-DCB (Pantera Lux, Biotronik, Germany; $n = 111$) or with BMS ($n = 112$) treatment. At 9 months, LLL, the study primary endpoint, was higher in the BMS-alone group as compared to the DCB + BMS group (0.80 vs. 0.31 mm; $p < 0.0001$); solo-BMS patients also had a larger binary restenosis rate (29.8% vs. 2.2%, CI 3.2–54.2; $p < 0.0001$). Even clinically, the solo-BMS patients had a higher rate of MACE, compared to BMS + DCB (12.5% vs. 3.6%, $p = 0.016$) (Fig. 3) (Table 1) [24].

Gobic et al. [25] compared a DCB-only ($n = 38$, Sequent Please, BBraun, Germany) approach to DES ($n = 37$) implantation in a single-center RCT including a population of 75 pPCI patients. At the 6-month follow-up, MACE rate was higher in the DES group, although not reaching statistical significance (5.4% vs. 0%, $p = 0.29$). In addition, the DES group was associated with a larger LLL compared to the DCB group (0.10 ± 0.19 mm vs. -0.09 ± 0.09 mm; $p < 0.05$) (Table 1) [25].

The prospective REVELATION RCT [26•] also compared a DCB-only approach (Pantera Lux) to DES in a total of 120 STEMI patients. Interestingly, the primary endpoint of the study was the average fractional flow reserve (FFR) value at 9-month angiographic follow-up. Both groups achieved comparable epicardial FFR values (0.92 ± 0.05 in the DCB arm vs. 0.91 ± 0.06 in the DES arm; $p = 0.27$). In addition, no significant differences in terms of LLL or clinical outcomes between the two groups were detected (Fig. 4) (Table 1)[26•].

At 2 years, the MACE rate was also confirmed to be comparable between the two groups (5.4% in the DCB arm vs. 1.9% in the DES arm; $p = 0.34$). In addition, between 9 months and 2 years, only one additional TLR event occurred in the DCB treatment group [27].

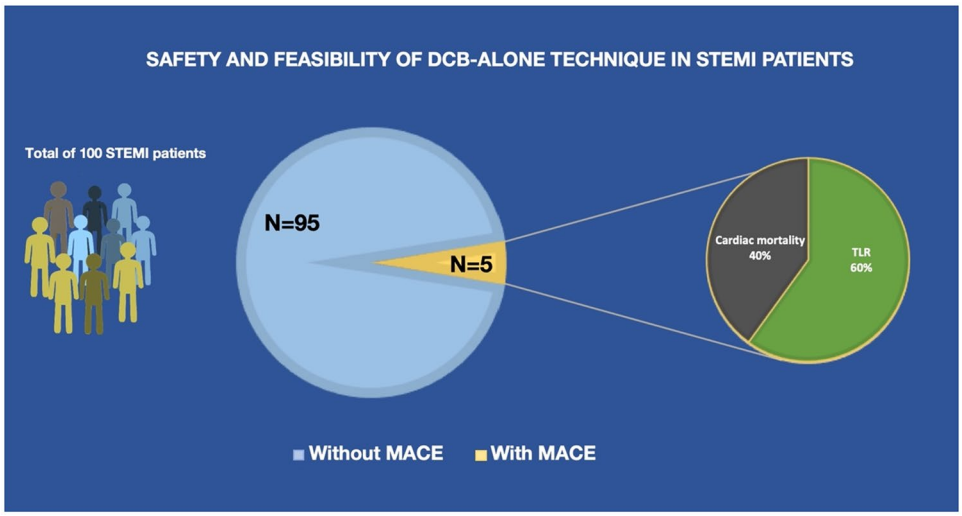

Fig. 2 A graphical demonstration of the first trial results that evaluated the safety and feasibility of DCB angioplasty without stenting in PPCI in 1-year follow-up (MOD:PAPPA trial [22]). MACE, major adverse cardiovascular events; TLR, target lesion revascularization

Table 1 Randomized clinical trials on DCB in acute coronary syndromes

Study name	Design	DCB	Comparator	n	Inclusion	Exclusion	Predilatation	Reference vessel	Primary endpoint	Secondary endpoints	Angiographic follow-up (p value)	MACE (p value)	TLR (p value)
REVELATION,2019 [26]	1:1 RCT Open-label non-inferiority Single-center Corelab CEC	Pantera Lux	Orsiro	120	STEMI referred to PCI Good predilatation result (DS<50 %)	Previous MI, recent stent implantation, contraindication to DAPT, cardiogenic shock	.	Any	9M FFR	9M LLL, 9M MACE, St, bleeding	9M FFR 0.92± 0.05 vs 0.91±0.06 (0.027)	9M 0 vs 0 (1)	9M 3 vs 2 (1)
DEB-AMI, 2012 [23]	1:1:1 RCT Open-label non-inferiority Two-center Corelab CEC	DIOR+ BMS	BMS vs DES	150	STEMI referred to PCI Good predilatation result (DS<50 %)	Controindication to DAPT, LE<12M,3 VD, LM, DM+typeC lesion	60	2.5-4 Length<25	6M LLL	6M ISR, MACE 6M OCT and endothelial function	6M LLL DCB+BMS 0.74±0.57 vs BMS 0.64±0.56 vs DES 0.21±0.32 (<0.01) ISR 26.2 vs 28.6 vs 4.7 (0.01)	6M 23.5 vs 20 vs 4 (0.02)	-
Gobic et al, 2017 [25]	Single center prospective 1:1 RCT Autonomous QCA	Sequent Please	DES	75	STEMI with de novo lesion	Allergies, stroke<6M, GFR<30, LE<12M, ISR, PCI/CABG <6M, tortuosity,	-	2.5-4	6M MACE	6M LLL	6M LLL- 0.09±0.09 vs 0.10±0.19 (0.05)	6M 0 vs 5.4 (0.29)	-
Hao et al, 2021 [28]	1:1 Randomized single center prospective trial Autonomous QCA	Biotech Bingo	DES	80	STEMI< 12H	Severe calcification, history of bleeding, intracranial disease, cardiogenic shock ISR, stent<6M, contraindication to DAPT	-	2.5-4	12M LLL	12M MACE	12M LLL - 0.11±0.45 vs 0.13±0.3 (<0.05)	12M 11 vs 12% (ns)	-
PEBSI, 2017 [24]	1:1 RCT Open-label non-inferiority Multi-center Corelab CEC	BMS + Pantera Lux	BMS	223	STEMI	Cardiogenic shock, LE<12M LM, bifurcation with SB>2.5, St, more than one stenosis in same artery, referred to CABG within 30D	18%	2.5-4mm Length<30mm	9M LLL	9M ISR and struts coverage (OCT), 9M MACE	9M LLL 0.31 vs 0.80 (0.001) ISR 2.2 vs 29.8 (0.001)	9M 3.6 vs 12.5 (0.016)	9M 1.8 vs 7.1 (0.06)
PAPPA 2014 [22]	Prospective, observational, single-centre,	paclitaxel-eluting balloon (Pantera	-	100	STEMI, De novo lesion in a native coronary artery	Active bleeding, intracranical disease, cardiogenic shock,	-	≥2.5 mm and ≤4 mm	1year, MACE, TLR	Need for additional stenting; stent thrombos	-	1year N:5(5%)	1year, N:3

Table 1 (continued)

	non-blinded	Lux™; Biotronik, Berlin, Germany; paclitaxel dose of 3.0 µg/mm^2)			without severe calcification	allergy to aspirin, clopidogrel, prasugrel, fondaparinux and/or bivalirudin, cardiac arrest requiring intubation, stent implantation<1month, planned major surgery within 6 weeks				is; major bleeding according to the non-CABG major bleeding score and TIMI major bleeding score			
PEPCAD NSTEMI, 2020 [31]	1:1:1 RCT Open-label non-inferiority Multi-center	Sequent Please and Sequent Please Neo	BMS (56%) and DES (44%)	210	NSTEMI and identifiable culprit lesion	Large thrombus	99.2% (bail out 15%)	Any	9M TLF	9M MACE	-	9M ITT 6.7 vs 14.2 (0.11) PP 5.9 vs 14.4 (0.056)	9M TLF ITT 3.8 vs 6.6 (0.11) PP 4.7 vs 6.3 (0.75)
Besic et al., 2015 [30]	Single center prospective 1:1 RCT Autonomous QCA	Elutax or Sequent Please + BMS	BMS	85	NSTEMI /UA	STEMI, cardiogenic shock, major bleeding<2 W, haemorrhagic diathesis, contraindication to DAPT ISR, LM	39%	Any	6M LLL and ISR	6M TLR, St, ACS	6M LLL 0.22 vs 0.68 (0.002) ISR 17 vs 22 (0.593)	6M 24 vs 29 (0.835)	6M 19.5 vs 22.7 (0.770)

Differentiation between randomized controlled trials (RCTs) and registries was accomplished by highlighting RCTs in bright blue and mentioning "RCT" below each study name

RCT randomized controlled trials, *DS* direct stenting, *BMS* bare metal stent, *DES* drug-eluting stents, *DCB* drug-coated balloon, *STEMI* ST-elevation myocardial infarction, *PCI* percutaneous coronary intervention, *DAPT* dual antiplatelet therapy, *MI* myocardial infarction, *FFR* fractional flow reserve, *MACE* major adverse cardiovascular events, *LLL* late lumen loss, *TLR* target lesion revascularization, *M* month, *OCT* optical coherence tomography, *ISR* in stent restenosis, *ST* stent thrombosis, *CABG* coronary artery bypass graft surgery, *GFR* glomerular filtration rate, *LE* life expectancy, *3VD* triple vessel disease, *LM* left main stenosis, *DM* diabetes mellitus, *TLF* target lesion failure, *ACS* acute coronary syndrome, *NSTEMI* non-ST-elevation myocardial infarction, *TIMI* thrombolysis in myocardial infarction, *UA* unstable angina

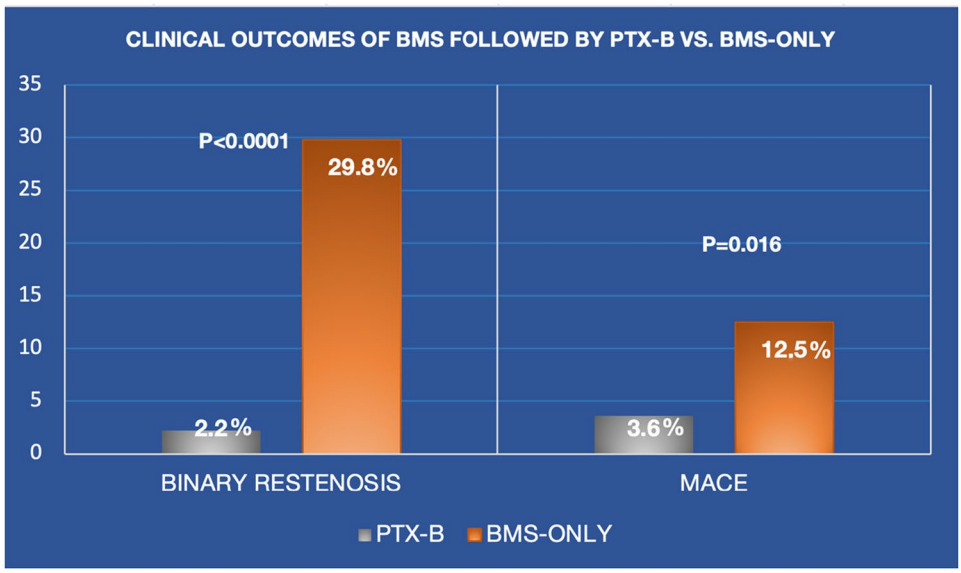

Fig. 3 A graphical demonstration of BMS followed by PTX-B vs. BMS-only clinical outcomes (MOD: PEBSI trial [24]). BMS, bare metal stent; PTX-B, paclitaxel-eluting balloon

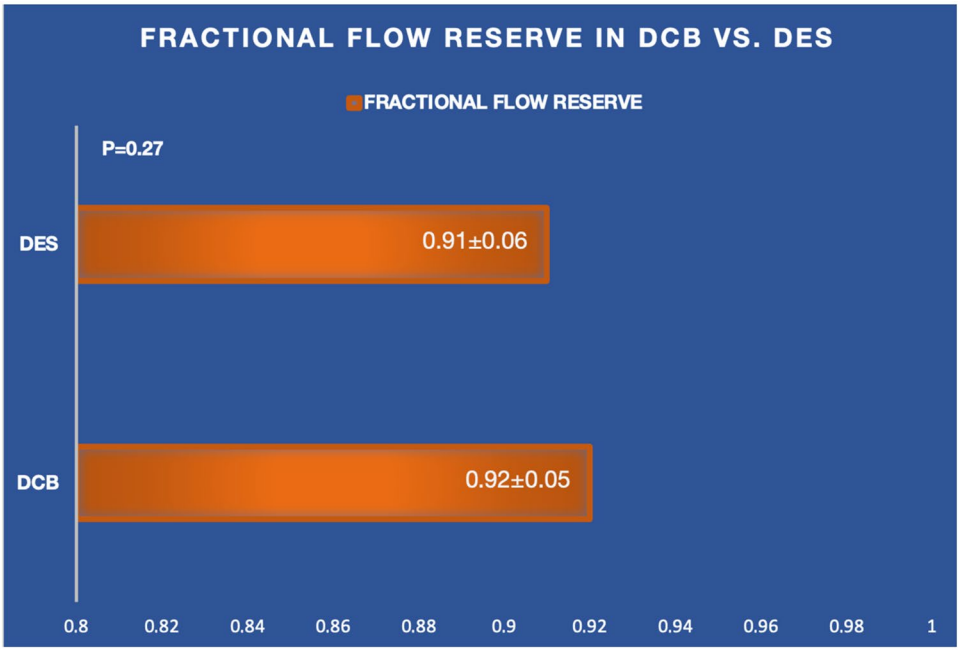

Fig. 4 A graphical demonstration of FFR results in DCB vs. DES at 9-month follow-up (MOD:REVELATION trial [26•])

Hao et al. [28] further evaluated the safety and efficacy of DCB in this setting, on a population of 80 patients randomly assigned to the paclitaxel Bingo (Yinyi Liaoning, Biotech Bingo, $n=38$) DCB and DES ($n=42$). At 1 year, angiographic LLL, the primary endpoint of the study, was significantly lower in the DCB group as compared to the DES one (-0.11 ± 0.45 mm vs. 0.13 ± 0.3 mm; $p<0.05$) (Fig. 5) (Table 1) [28].

More recently, Morinopoulos et al. [29] further supported the safety and efficacy of DCB use in the setting of STEMI. In a large retrospective propensity-matched analysis based on a real-world, single-center, STEMI cohort study, DCB was seen to yield comparable results to DES at long term follow-up. Among 1139 patients, 452 received DCB treatment, while 687 received DES treatment and over a median follow-up period exceeding 3 years, the mortality rate did not differ between the two arms (10.8% vs. 9.0%; $p=0.18$). At the multivariable Cox regression analysis, no significant difference was detected in terms of mortality between the DCB and DES groups, in both unadjusted and propensity-matched analyses. Even unplanned TLR did not differ between the two groups.

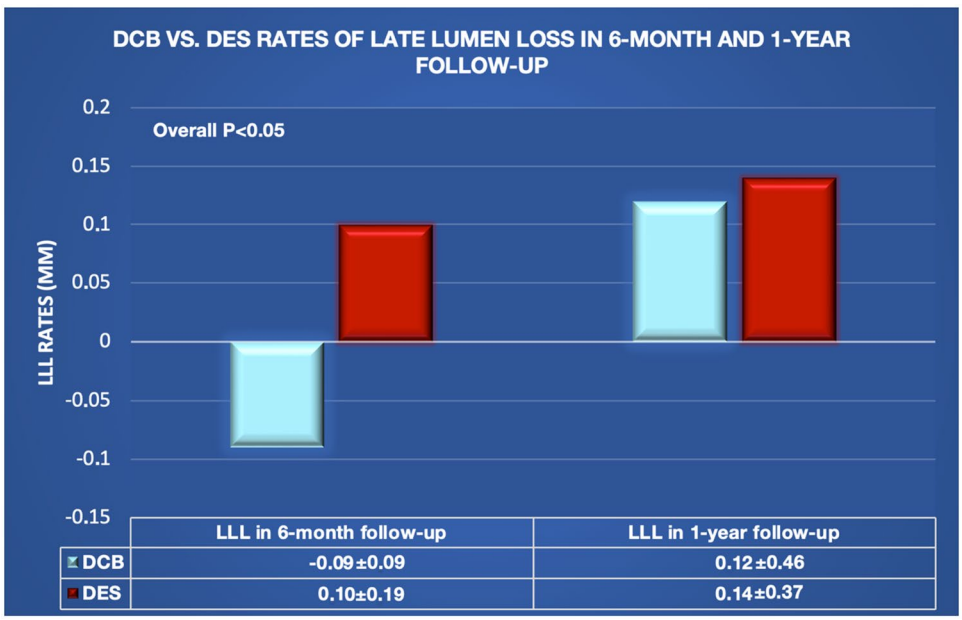

Fig. 5 A graphical demonstration of LLL rates in two different follow-up timelines (MOD: Gobic et al. [25] and Hao et al. [28]). LLL, late lumen loss

NSTEMI

Available clinical data assessing the use of DCB in the setting of non-ST-elevation MI (NSTEMI) are less robust so far. In a small randomized controlled trial Besic et al. [30] ($n=85$) compared the angiographic outcome of the combined use of BMS and DCB ($n=41$) with BMS-only treatment ($n=44$) in patients with NSTEMI. The trial showed no significant differences in binary restenosis, but significantly lower LLL in the BMS + DCB group (0.22 mm vs. 0.68 mm; $p=0.002$). The MACE rate did not differ between the groups (24.4% vs. 29.5%; $p=0.835$)[30] (Table 1).

The large multicenter PEPCAD NSTEMI [31] trial evaluated the clinical outcomes of Sequent Please (Bbraun B.Braun, Melsungen, Germany) DCB in comparison to BMS/DES in 210 NSTEMI patients. In the stent group, 56% of patients were treated with BMS and 44% with DES. In the DCB group, 85% of patients were treated with DCB alone, whereas 15% had an additional BMS implanted (Fig. 6). Over a follow-up period of 9.2 ± 0.7 months, the DCB approach was non-inferior in terms of target lesion failure (3.8% vs. 6.6%, $p=0.53$). In addition, the overall MACE rate was 6.7% in the DCB arm versus 14.2% in the stent arm ($p=0.11$) and 5.9% versus 14.4% in the per protocol analysis ($p=0.056$), respectively (Fig. 7) (Table 1) [31].

BASKET-SMALL 2 [32, 33] trial is the largest RCT investigating the role of DCB in native coronary artery disease, so far. Main findings of the study showed the clinical non-inferiority of Sequent Please DCB vs. DES in vessels with diameter ranging between 2.0 and 3.0 mm at 1 and 3 years. Among the 758 patients in the trial, 214 patients (28.2%) were diagnosed with ACS, including 15 patients (7%) with STEMI, 109 patients (50.9%) with NSTEMI, and 90 patients (42.1%) with unstable angina. One year after the procedure, there was no significant difference in the occurrence of the primary endpoint between patients with ACS (hazard ratio, 0.50 [95% CI, 0.19–1.26] for DCB compared to DES) and patients with chronic coronary syndrome (hazard ratio, 1.29 [95% CI, 0.67–2.47] for DCB compared to DES; *p* for interaction, 0.088).

For cardiac death (*p for interaction* = 0.049) and nonfatal myocardial infarction (*p for interaction* = 0.010), a significant interaction between clinical presentation and treatment effect was evident at one-year, with lower rates of these secondary endpoints in ACS patients treated with DCB. After 3 years, MACE rates were similar across all patient groups, with no significant interaction observed between clinical presentation and treatment (*p for interaction* = 0.301). Not surprisingly, all-cause mortality was higher in ACS patients when compared to those with chronic coronary syndrome; however, there was no difference in outcomes between DCB and DES, regardless of the clinical presentation.

In the last few years, some new DCB technologies eluting sirolimus (SCB) entered the market, with some initial important clinical data. The Magic Touch SCB (Concept Medical,

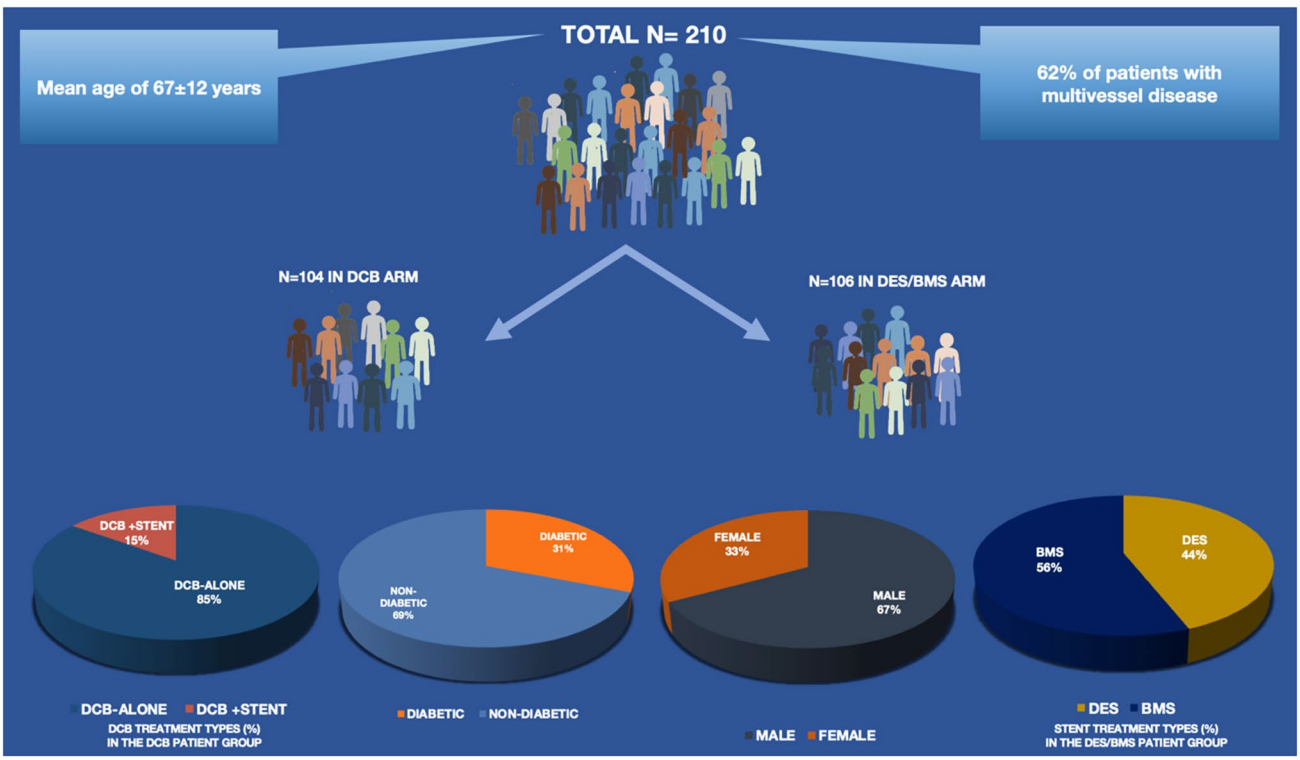

Fig. 6 A graphical demonstration of PEPCAD NSTEMI study population characteristics (MOD:PEPCAD NSTEMI [31])

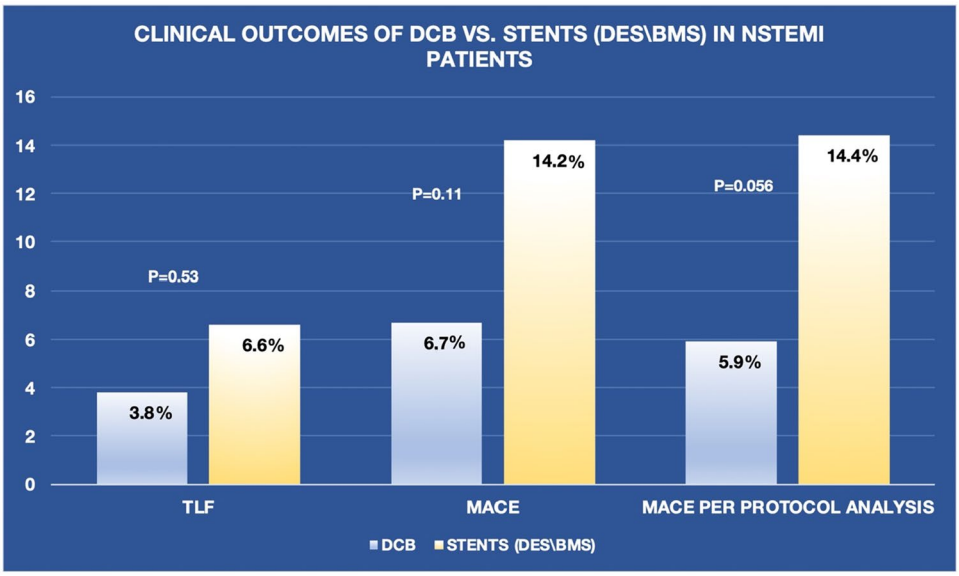

Fig. 7 A graphical demonstration of PEPCAD NSTEMI study results (MOD:PEPCAD NSTEMI [31]). TLF, target lesion failure

USA) was investigated in few small studies and in the large prospective multi-national investigator-driven EASTBOURNE study. Main results of this study were recently published [34••] and showed the safety and feasibility of this device in a broad spectrum of coronary artery disease ($n=2123$ patients, 2440 lesions) at 1 year. A recent *post hoc* analysis of all-comers EASTBOURNE registry, the PEACE study, analyzed the performance of SCB device (Magic Touch, Concept Medical, India) in ACS ($n=968$) vs. chronic coronary syndromes (CCS) ($n=1115$) patients. At 12 months, the cumulative incidence of TLR (ACS 6.6% vs CCS 5.2%, $p=0.258$) and MACE (ACS 10.4% vs CCS 8.3%, $p=0.009$) were comparable between these two categories of patients treated with SCB[35•].

Accordingly, several RCTs have already demonstrated promising and consistent results in this clinical setting. Meanwhile, new indications for the role of DCB in ACS management are being explored further in currently ongoing clinical trials (Table 2).

Pitfalls and Need for Bailout Stenting

The challenges of acute vessels recoil, acute vessel closure, and dissections, which initially favored stents over POBA, should be taken into account when performing a DCB-based strategy. Unlike DES, which can reduce vascular recoil through the radial force of the stent strut, DCB therapy is more influenced by vessel recoil [6].Therefore, appropriate lesion preparation is critical for obtaining favorable long-term outcomes with the DCB-only method. Lesion preparation promotes sufficient lumen gaining by decreasing vessel recoil and enhancing the contact area between the DCB and the vessel wall. The initial step in successful DCB treatment is to achieve lesion preparation using a pre-dilation balloon (scoring/cutting or non-compliant balloons, 0.9/1:1 ratio). In case of inappropriate expansion of the balloon or in case of severe calcification of the diseased segment based on angiography and/or intravascular imaging assessment, a non-balloon (i.e. rotational/orbital atherectomy) or balloon (intravascular lithotripsy) calcium debulking technology should be taken into account [36]. Appropriate lesion preparation may create an environment that allows for effective and homogenous drug distribution to the lesion, hence improving the efficacy and safety of DCB treatment.

The rate of acute vessel closure following DCB-only therapy is remarkably low, ranging between 0 and 0.2% [37, 38]. A recent meta-analysis of eleven studies involving 2349 CAD patients found no significant difference in terms of acute vessel closure between the DCB group and all stent groups (2.6% vs. 1.0%, OR: 2.13 (0.74–6.44), $p=0.16$) [39].

Consistently, a low rate of silent vessel occlusion has been reported following DCB PCI (1%) [32, 33]. This is due to acute recoil and/or dissection not related to vessel thrombosis. Dissection in the era of balloon angioplasty was a double-edged sword, leading to complications such as myocardial infarction and emergency coronary artery bypass graft surgery [40]. Nevertheless, the impact of residual dissections following DCB PCI on long-term clinical outcomes is still a matter of debate. According to the international DCB consensus group, type C-F dissections should be treated with bail-out DES implantation. Hue et al. [41] aimed to assess the angiographic and clinical impact of non-flow limiting coronary dissections after DCB, comparing 95 individuals with dissection and 132 patients without dissections. No difference in terms of 6 months LLL at the elective angiographic follow-up was detected (0.05 ± 0.19 mm in non-dissection group vs. 0.05 ± 0.30 mm in dissection group,

Table 2 Ongoing randomized clinical trials

Identifier	Status	Study Title	Study Design	Inclusion	Exclusion	Outcomes	Reference Vessel	DCB	DES	Target Sample Size	Follow-Up
NCT04937803	Active, not recruiting	**Safety and Efficacy of Drug-Coated Balloon for De-novo Lesions in Patients With Acute Coronary Syndromes (DCB-ACS) (DCB-ACS)**	Prospective multicenter randomized (DCB vs ZES) in ACS	ACS undergoing PCI Single culprit or one lesion in each of two vessels Successful preparation (residual <30%, TIMI 3, dissection <C) RVD 2.25-4.0mm Lesion length ≤28mm	CCS or asymptomatic ischemia cardiogenic shock or requiring mechanical support Unstable tachyarrhythmia or bradyarrhythmia Surgery within 24M Stroke<6M, severe renal disease CTO, LM, 2-stents bifurcations, distortion (moderate-to severe), angulation or severe calcification, grafts, ISR, myocardial bridge	9M FFR 1-6-9-12-24M TLF, CD, TV MI, TLR, BARC3-5, Procedure success, POCE, DS%, LLL, restenosis, ST, stroke, rehospitalization for angina	RVD 2.25-4.0mm and lesion length≤ 28mm	Any	Zotarolimus eluting	216	24M
NCT04971356	**Not yet recruiting**	**1-month DAPT Plus 5-month Ticagrelor Monotherapy Versus 12-month DAPT in Patients With Drug-coated Balloon (CAGE FREEII)**	Randomized (ASA +Ticagrelor 1M, Ticagrelor 5M, ASA 6M vs ASA+ Ticagrelor 12M), prospective, non inferiority	ACS	Previous intracranial hemorrhage, NOAC, cardiogenic shock, stent<6M, IS thrombosis, graft	12M NACE 1-12M BARC 3-5, 1M NACE, 1-12 DOCE, CD, TVMI, TLR, POCE, Death, stroke, MI, TVF, ST	Any	Any	No DES	1908	12M
NCT01489449	**Active, not recruiting**	**Bare Metal Stent Versus Drug Coated Balloon With Provisional Stenting in Non-ST-Elevation Myocardial Infarction**	Prospective, single-blinded, randomized (Sequent DCB vs BMS)	NSTEMI <72H, identifiable culprit lesion	Cardiogenic shock, STEMI, <12M life expectancy	1 MACE 9M 3Y 5Y ST, mortality, reinfarction, TLR, TVR	Any	Sequent R DCB	BMS	210	36M

Table 2 (continued)

NCT04475978	**Recruiting**	**Intravascular Ultrasound Versus Angiography Guided Drug-coated Balloon Treatment for STEMI Patients：a Prospective, Multicenter, Randomized Controlled Trial**	Prospective, randomized (IVUS vs Angio), triple blinded	STEMI<12H De novo lesion, RVD 2.5-4mm, DS>50% after thrombus aspiration and pre-dilatation	Previous MI, Non target vessel needing treatment Lesion length >30mm LM, ostial, severe calcification, tortuosity, angulation, cardiogenic shock, intracranial disease Bleeding, planned surgery<6M, stent implantation<1W before, life expectancy<12M	1 LLL 12M TLF	2.5-4.0mm RVD and length <30mm	Any	No DES	208	12M
NCT04072081	**UNKNOWN**	**Drug-coated Balloon Versus Drug-eluting Stent in the Treatment of Coronary Artery Lesions in STEMI Patients in De Novo Coronary Lesions**	Prospective, multicenter, randomized clinical trial (DCB vs. DES)	STEMI De novo RVD 2.5-3.5 length<28mm, DS>80%	LVEF<30%, Killip3, bleeding diathesis Intracranial disease, elective surgery planned, Life expectancy<12M LM; dissection >=C, bridge, ISR, Non TV requiring treatment	1 LLL 12-24M RR, TLF, MACE, target lesion thrombosis	2.5–3.5 mm and <28 mm in length	Any	Any	4000	12–24M
NCT04565561	**Recruiting**	**Bioabsorbable Scaffold vs Drug-coated Balloon for Coronary de Novo Lesions in STEMI: Prospective Observational Trial**	Observational registry, prospective, cohort	STEMI<12H, SVD suitable for PPCI,	Calcification, residual stenosis after pre-dilatation/thrombus aspiration >30%, LM, previous PCI, cardiogenic shock Intracranial diseases, vasculitis, thrombotic diseases, Life expectancy<1Y	M LLL 12M TLR, CD	2.5-4.0 mm RVD and length <20mm	Any	Neovas BRS*	40	12M

Differentiation between randomized controlled trials (RCTs) and registries was accomplished by highlighting RCTs in bright blue and mentioning "RCT" below each study name

DCB drug-coated balloon, *ACS* acute coronary syndrome, *TIMI* thrombolysis in myocardial infarction, *RVD* reference vessel diameter, *PCI* percutaneous coronary intervention, *LM* left main stenosis, *CCS* chronic coronary syndromes, *CD* cardiac death, *CTO* chronic total occlusion, *FFR* fractional flow reserve, *TLF* target lesion failure, *M* month, *TVMI* target vessel myocardial infarction, *BARC* bleeding academic research consortium, *TLR* target lesion revascularization, *POCE* patient-oriented composite endpoint, *ST* stent thrombosis, *LLL* late lumen loss, *NACE* net adverse clinical event, *NOAC* non-vitamin K antagonist oral anticoagulants, *DOCE* device oriented composite endpoint, *pPCI* primary percutaneous coronary intervention, *SVD* small vessel disease. %DS percentage diameter stenosis, *IVUS* intravascular ultrasound

$p = 0.886$), while 93.9% of the dissections were seen to be completely healed. Consistently, at 3-year follow-up, TLF rate was also similar in both groups regardless of whether a dissection was present or not (6.8% in non-dissection and 8.4% in dissection group, $p = 0.799$).

The incidence of bail-out stenting after DCB has been reported to be generally low (< 10%) [32, 33], while showing to be influenced significantly by a learning curve. For instance, the rate of bail-out stenting was reported to be higher in pivotal trials, such as PICCOLETO I (36%) and BELLO (20%), while decreasing over time, as shown in larger RCTs (5% in BASKET SMALL 2 [32, 33], PICCOLETO II [42], and RESTORE SVD CHINA [43]).

The safety and efficacy of employing third generation limus eluting bailout stenting after paclitaxel DCB were supported by several studies [44].

More recently, Khattak et al. [45] evaluated the safety and outcomes of bail-out stenting following DCB PCI with Magic Touch Sirolimus DCB (Concept Medical Limited, India). In a cohort of 406 patients, 39 lesions (8%) required bailout stenting, of which 22 were caused by dissections and 17 were the result of recoil greater than 50% after DCB application. At a median follow-up time of 302 days, a low rate of adverse events was reported in the bail-out group, with one case of target vessel MI (2.6%), three cases of TLR (7%), and no cases of cardiac death or stent thrombosis, suggesting no toxic effect from the double dose of limus drug when performing DCB + DE.

DAPT Duration Following DCB Use in ACS

While contemporary DES permits a short 1-month DAPT regimen [46], the ideal composition and duration of antiplatelet therapy after DCB-only PCI remain uncertain. The current consensus for DAPT duration after DCB-only PCI in stable coronary artery disease patients is one month, initially established for treating in-stent restenosis and subsequently adopted for *de novo* lesions. No dedicated trials have investigated specific DAPT regimens with DCB in the setting of ACS, both in terms of DAPT duration (i.e., short vs. long DAPT) and intensity (i.e., ASA monotherapy, ASA-free strategy, potent P2Y12 inhibitors vs. clopidogrel). According to the current guidelines, DAPT should be continued for 12 months after an ACS, whenever no HBR is present[47]. In case bleeding risk supersedes ischemic risk, DAPT discontinuation at 1 or 3–6 months and/or P2Y12 de-escalation (from prasugrel/ticagrelor to clopidogrel) should be considered.

The DEBUT RCT [48] found that in 220 HBR patients (46% ACS), DCB-only PCI outperformed BMS implantation, with a lower occurrence of MACE (1.9% vs. 12.4%; $p = 0.003$ for superiority) at 9 months. However, this trial did not investigate the optimal duration of DAPT. In a subgroup analysis of the BASKET-SMALL 2 trial focusing on HBR patients, there was a trend towards fewer severe bleeding events when using DCB-only PCI combined with shorter DAPT compared to DES with standard DAPT [49].

DCB lack of metallic components could potentially offer advantages in HBR patients, allowing for DAPT shorter than one month or, in cases of life-threatening bleeding, the option to discontinue antiplatelet therapy at any time. Recent registry studies suggest that DCB-only PCI can be safely performed with single antiplatelet therapy. Räsänen et al. [50], in a real-world population of 172 patients undergoing PCI (58% ACS), suggested that single antiplatelet therapy (SAPT) at discharge in DCB-only strategy is feasible and safe, having an acceptable rate of MACE (1.4% in stable CAD, 7.1% in ACS), target lesion revascularization (0.0% in stable CAD, 3.0% in ACS) and significant bleedings (bleeding academic research consortium 2–5; 10.5%) at 12 months.

Cortese et al. further supported the safety of a SAPT strategy following DCB. In a retrospective analysis, patients undergoing PCI with DCB and discharged on SAPT ($n = 107$) had comparable 12 months outcomes to patients managed with DAPT ($n = 1100$), in terms of MACE (10% vs. 9%, $p = 0.78$), but with a reduction in the cumulative rate of BARC 2–5 bleedings (6% vs. 9%, $p = 0.04$) [51••].

Conclusions

Implant-free "leave nothing behind" strategies, fulfilled by DCB use, offer a promising alternative to DES in the management of ACS. DCB provide targeted treatment for vulnerable plaques, potentially preventing long-term complications related with permanent implants. To date, clinical trials in ACS are limited by relatively small sample sizes, by the comparison of DCB against BMS and/or old generation DES and by the short duration of follow-up. However, several clinical trials and real-world experiences have provided pivotal and promising evidence in support of DCB as safe and effective in restoring vessel patency, reducing late lumen loss, and potentially impacting on long-term MACE in ACS patients. Further evidence is warranted, aiming at (i) confirming the role of DCB in ACS at long term, (ii) characterizing patients and lesions that would benefit most from DCB use, and (iii) clarifying the choice of P2Y12 inhibitor and/or the need and duration of DAPT.

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Data Availability No datasets were generated or analyzed during the current study.

Compliance with Ethical Standards

Conflict of Interest Dr. Cortese serves as advisor and consultant for several companies working in interventional cardiology. The other authors have no disclosures to report.

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