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Review

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Diffuse coronary artery disease management with drug-coated balloons

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Abstract

Drug-coated balloons (DCB) have emerged as a valid alternative for drug-eluting stents in the treatment of in-stent restenosis and de-novo lesions in small vessels. In the past years, a significant effort has been made to investigate the role of this strategy in larger vessel disease, with promising preliminary results being reported for several clinical scenarios, including complex lesions, such as bifurcations, chronic total occlusions and diffuse, long lesions. A DCB strategy appears to be of significant interest in diffuse coronary disease, as the total stent length represents an independent predictor for target-vessel failure and a surgical approach does not seem to improve mid- and long-term results compared to optimal medical treatment. Several studies have investigated the safety and efficacy of a non-stent-based approach in this complex setting, and as promising results have been reported, it is fair to assume that reducing the amount of implanted metal in diffusely affected vessels could become the standard of care for these patients if a full or blended therapy with DCB is adopted. However, long-term results from large-scale studies are awaited to confirm these preliminary and intriguing results.

Keywords: Drug-coated balloon, diffuse coronary artery disease, long coronary lesions

INTRODUCTION

Percutaneous coronary interventions (PCI) have continuously been refined in the past decade, mainly by

adopting advanced modifying/debulking strategies, such as atherectomy, intravascular lithotripsy, cutting and scoring balloons; the increase in the usage of routine intravascular imaging and physiological assessment in the complex lesion setting has led to terrific clinical improvements for our patients. Despite the current armamentarium, long-term outcomes in complex lesions, such as calcified or diffuse stenoses, are still under expectations.

Historically, the incidence of diffuse coronary artery disease (CAD) was reported to be approximately 20%[1], but daily practice has shown that even a larger number of patients require long lengths of drug-eluting stents (DES), which currently represent the gold standard in treating CAD[2]. However, Costopoulos *et al.* had shown that total stent length represents an independent predictor for target-vessel failure (TVF), reporting target-lesion revascularization (TLR) rates of up to 24% when more than 60 mm DES were overlapped[3].

A surgical approach for diffuse CAD is frequently impossible, and even when it is performed, it does not seem to improve mid- and long-term results, as recent studies showed no difference between optimal medical therapy and coronary artery bypass grafting (CABG) in terms of mortality, myocardial infarction (MI), revascularization and symptom reduction after 2 years of follow-up[4].

Taking all these into consideration, drug-coated balloons (DCB) alone or in combination with DES have emerged as a valid alternative for long or multiple metal devices[5], as cardiac death, target-vessel MI and TLR at 1-year follow-up are not influenced by the use of a single ultra-long 48 mm DES in comparison to multiple stenting[6], thus suggesting that a reduction in the total stent length could be associated with improved outcomes.

PREDICTORS OF STENT FAILURE

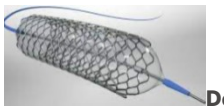
Current second-generation DES have led to high angiographic and clinical performance and remain the standard of care in most countries.

Although on extended long-term follow-up, this technology offers reduced rates of patient- and device-oriented composite endpoints compared to traditional bare-metal stents (BMS) (32.4% *vs.* 38.0%, HR 0.81; 95%CI: 0.68 - 0.96; $P = 0.013$ and 13.6% *vs.* 18.4%, HR 0.72; 95%CI: 0.55 - 0.93; $P = 0.012$), there are no advantages in terms of TLR and stent thrombosis (ST) between years 1 - 10 (1.4% *vs.* 1.3%, $P = 0.96$; 0.6% *vs.* 0.4%, $P = 0.70$)[7].

What is more, due to various mechanical, technical or biological factors, stent failure remains a pressing matter [Table 1], as data from the ISAR-TEST-5 trial shows 10-year device-oriented composite endpoint rates of up to 43%[8].

Although DES implantation reduces intima proliferation compared to BMS, hypersensitivity to the polymer and drug or local inflammation can occur, which can trigger in-stent restenosis (ISR), the most frequent mechanism of stent failure[9]. Neoatherosclerosis is usually responsible for late-occurring ISR[10]. Konigstein *et al.* analyzed over 10,000 patients and found total stent length to be the only short-term predictor of target-lesion failure (TLF), while small vessel diameter was the only lesion-related predictor at 5 years[11]. Complex lesion morphology, particularly when accompanied by a high calcium burden, is a strong predictor for ISR, which is associated with elevated rates of stent underexpansion and malapposition[12].

Table 1. Risk factors for stent failure

 **Device and procedure-related**	**Clinical-related** 
Long stents/stent overlap	Premature DAPT discontinuation
Small vessel/stent diameter	Diabetes mellitus
Complex lesion morphology (calcium++/bifurcations)	Chronic kidney disease
Final TIMI flow < 3	History of PCI/bypass surgery/polyvascular disease
Stent undersizing/malapposition/underexpansion	Hypersensitivity to polymer/drug
Stent fracture	Active smoking
Thick struts	HF with reduced EF
Stent gap	Malignancy
Geographical miss	
Edge dissection (especially if distal)	
Uncovered struts	
Neoatherosclerosis	

DAPT: Dual antiplatelet therapy; EF: ejection fraction; HF: heart failure; PCI: percutaneous coronary interventions; TIMI: thrombolysis in myocardial infarction.

Other factors independently associated with ISR include stent fracture, high stent strut thickness, stent gaps or geographical miss[13], as well as clinical conditions such as diabetes mellitus (DM), chronic kidney disease, and a history of CABG[11].

ST represents the other less frequent but more severe manifestation of stent failure, especially in the context of an increasing number of complex PCI. While premature dual antiplatelet therapy (DAPT) discontinuation is the strongest predictor of ST[14], other factors exist with different implications in early *vs.* late ST. Obtaining good stent expansion is critical, as minimal stent area < 5.5 mm^2 on optical coherence tomography correlates with ST[15]. Stent undersizing or malapposition, significant edge dissection (> 60°, > 2 mm), and geographical miss are also associated with increased risks of ST. The persistence of uncovered struts and neoatherosclerosis play a role in late ST[16].

LONG-TERM RESULTS OF STENTS IN DIFFUSE CORONARY ARTERY DISEASE

Although long and diffuse lesions represent a non-negligible entity in modern-day PCI, particularly with the rising number of diabetic patients, large-scale studies on the clinical impact of newer DES are currently lacking.

Very long-term follow-up (8 - 10 years) studies on first-generation DES reveal that stent length was already identified as a predictor of treatment failure[17,18]. Data on newer-generation DES in the setting of diffuse disease relies mainly on two large-scale registries. In the GRAND-DES registry, over 9,200 patients were included and classified into two groups based on the length of stented segment. At long-term follow-up (2 years), the primary endpoint of the study, TLF (a composite of cardiac death, target-vessel MI, and TLR), occurred more often in the long-stent (≥ 40 mm) group (8.1% *vs.* 4.5%; $P < 0.001$). Additionally, cardiac death (4.3% *vs.* 2.5%; $P < 0.001$), TLR (4.1% *vs.* 2.1%; $P < 0.001$) and early ($P = 0.001$) but not late ST rates were also higher[19]. Furthermore, Lee *et al.* identified specific cutoff points of stent length and diameter for different stent types in predicting future poorer 3-year events [Figure 1]. A cutoff > 38 - 40 mm applied for

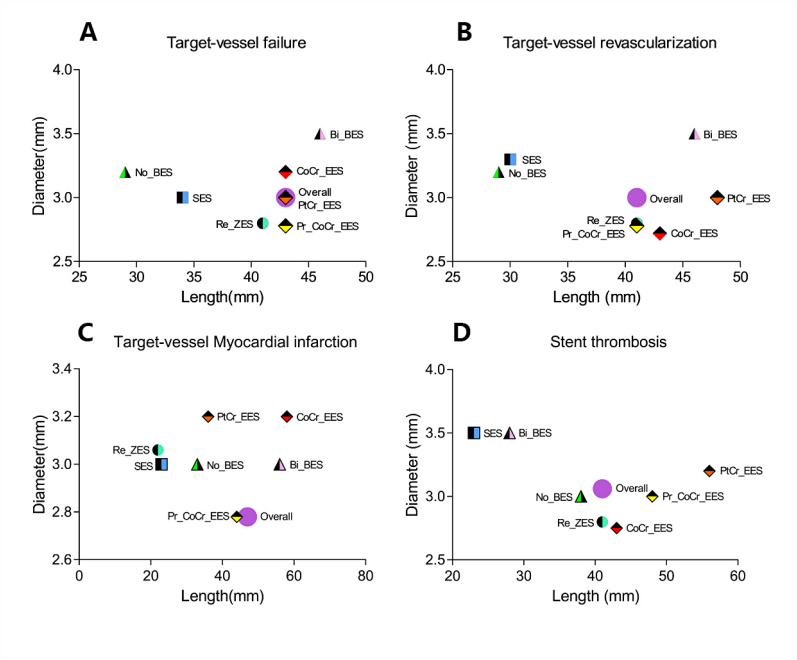


Figure 1. Cutoff values of stent length for different DES to predict future adverse events[20]. Bi-BES: Biomatrix biodegradable-polymer biolimus-eluting stents; CoCr-EES: cobalt-chromium everolimus-eluting stents; DES: drug-eluting stents; No-BES: Nobori biodegradable-polymer biolimus-eluting stents; Pr-CoCr-EES: Xience Prime cobalt-chromium everolimus-eluting stents; PtCr-EES: platinum chromium everolimus-eluting stents; Re-ZES: resolute zotarolimus-eluting stents; SES: sirolimus-eluting stents.

most everolimus- and zotarolimus-DES, while biodegradable-polymer biolimus-DES performance was subpar. Of note, the combination of long and small diameter stents had the worse outcome, irrespective of the technology used[20].

Extended long-term follow-up on available DES shows an increased frequency of adverse events when using overlap stenting[21]. A recent meta-analysis including mainly observational studies indicates that using single very-long stents when tackling diffuse lesions can be associated with higher rates of cardiac death and TLR (RR: 1.51, CI: 1.03 - 2.21; RR: 1.64, CI: 1.02 - 2.65)[22].

DRUG-COATED BALLOON USE IN NATIVE VESSELS

Small coronary native vessels disease

Three pivotal studies that investigated the use of DCB in de-novo small coronary vessels have recently reported long-term follow-up results.

The RESTORE SVD trial enrolled 230 patients with reference vessel diameter (RVD) ranging between 2.25 and 2.75 mm, which were randomized to the Restore paclitaxel-DCB (Eurocor, Germany) or the RESOLUTE Integrity DES in a 1:1 ratio. During TCT 2022, Shao-Liang Chen reported the 5-year follow-up results and the TLF rates between the groups were similar (8.0% *vs.* 7.3%; P = 0.85), while no device thrombosis was described.

BASKET-SMALL 2 trial compared SeQuent Please DCB (B. Braun, Germany) *vs.* DES (75% EES, 25% paclitaxel-DES) in terms of MACE and all-cause death in patients with RVD ranging between 2 and 3 mm. At the 3-year follow-up, no significant differences between the groups were found (MACE was 15% in both

the DCB and DES groups, HR 0.99; 95%CI: 0.68 - 1.45; $P = 0.95$), once more highlighting the safety and efficacy profile of DCB in the treatment of native small vessels disease. What is more, DCB was shown to significantly reduce the rates of major bleeding in patients with chronic kidney disease (12 *vs.* 3, HR 0.26; 95%CI: 0.07 - 0.92; $P = 0.037$)[23,24].

Another important randomized trial, PICCOLETO II, compared the efficacy of DCB (Elutax SV, AR Baltic, Germany) with EES (Abbott Vascular, USA) in de-novo vessels < 2.75 mm, reporting significantly higher late lumen loss (LLL) in the DES arm (0.17 ± 0.39 mm *vs.* 0.04 ± 0.28 mm; $P = 0.03$ for superiority) at the 6-month follow-up[25]. The final follow-up of this study was recently published[26]. After 3 years, the authors reported a significant reduction in abrupt vessel closure and MACE in the DCB arm (10.8% *vs.* 20.8%; $P = 0.046$).

Large native vessels disease

Based on the encouraging results reported for the use of DCB in small-vessel disease, continuous efforts have been made to investigate the role of this promising technology in large native vessels. In consequence, an important number of studies have recently reported data for this scenario as well.

Yu *et al.* enrolled 288 consecutive patients with RVD between 2.25 and 4.0 mm in a randomized clinical trial which compared the performance of DCB (Sequent Please) with DES (Resolute Integrity, Medtronic; EES; SYNERGY; Firehawk, MicroPort, China) in terms of LLL at 9-month angiographic follow-up and 12-month MACE[27]. The angiographic follow-up reported the excellent performance of the DCB, as minimal lumen diameter (MLD) was significantly increased compared with post-intervention level (2.02 ± 0.62 mm *vs.* 1.83 ± 0.44 mm; $P < 0.001$) only in the DCB group and LLL was -0.19 ± 0.49 with the DCB *vs.* 0.03 ± 0.64 mm with the DES. Moreover, 12-month MACE was similar in the two groups (2.44% *vs.* 6.33%; $P = 0.226$).

In another study, Uskela *et al.* enrolled 463 patients with 562 lesions, most of them located in large coronary vessels (79% > 2.75 mm) which were treated using paclitaxel-DCB. MACE rate at 12 months was 7.1% for stable CAD and 12% for acute coronary syndromes (ACS); TLR occurred in 1.4% of stable CAD and in 2.8% of ACS patients, with only one acute vessel closure occurring after this strategy[28].

Rosenberg *et al.* conducted a large-scale trial including 1,025 patients (more than 65% with de-novo CAD) treated with a stentless strategy and, after 9 months of follow-up, reported lower TLR rates in the de-novo group (2.3%) compared to DES-ISR (5.8%) ($P = 0.049$)[29]. Moreover, when comparing small with large vessels disease, no significant differences between the two groups regarding TLR (3.8% *vs.* 1%; $P = 0.20$) or MACE (5.7% *vs.* 6.11%; $P = 0.903$) were observed, thus suggesting that the outcomes after a DCB-only strategy for de-novo lesions may be independent of the vessel diameter[30].

With these encouraging results in mind, many experienced centers started using this strategy for large native vessels disease, in order to limit the amount of implanted metal, especially in complex lesions occurring in frail patients. Figures 2 and 3 illustrate the excellent immediate- and mid-term results of a "leave nothing behind" strategy used for the treatment of diffuse large vessel disease. What is more, Figure 3 shows the important late lumen enlargement (LLE) obtained after the use of DCB at 5 months of follow-up. This LLE phenomenon is related to paclitaxel-DCB, probably due to an effect of this drug at the level of tunica adventitia and seems to be more pronounced in cases of types A and B dissections after DCB angioplasty. The role of LLE with some DCB seems particularly appealing in cases of DCB usage for the management of long lesions and diffuse disease[31].

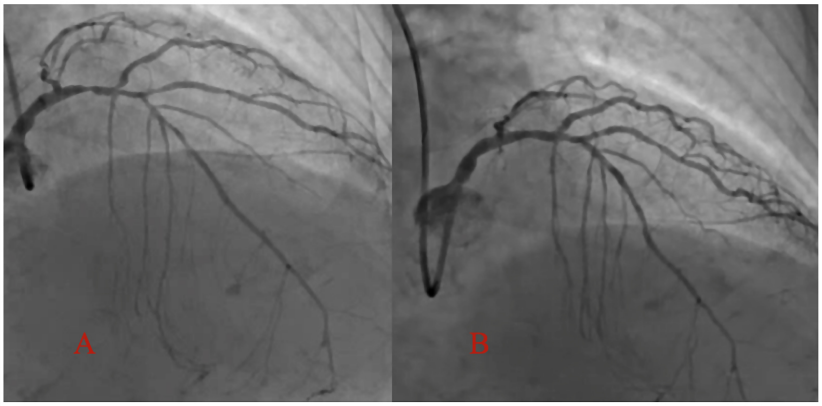


Figure 2. A "leave nothing behind" strategy using sirolimus-DCB and paclitaxel-DCB for treating a complex diffuse LAD lesion involving 2 bifurcations. (A) Basal angiography showing diffuse proximal LAD disease, involving 2 bifurcations with important diagonal branches; (B) Final optimal angiographic result after angioplasty using a sirolimus-coated balloon for the D1-LAD lesion and a paclitaxel-coated balloon for the D2-LAD lesion. D: Diagonal branch. DCB: drug-coated balloon. LAD: left anterior descending artery.

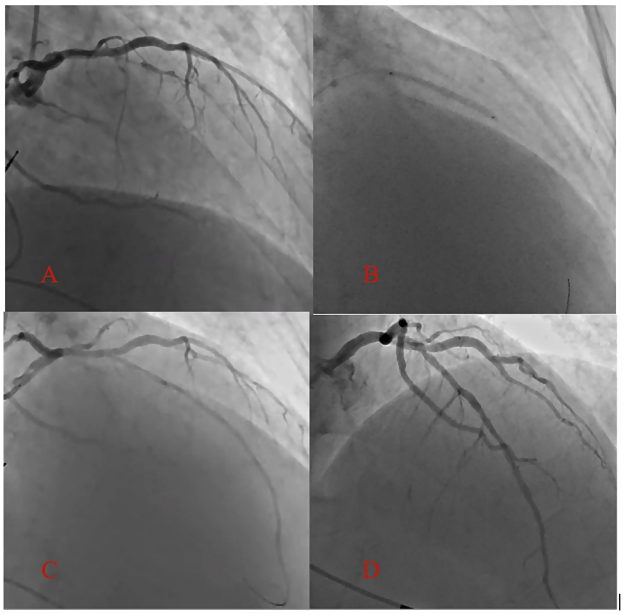


Figure 3. Immediate- and mid-term results after the use of DCB for treating diffuse large vessel disease. (A) Basal angiography showing critical diffuse LAD stenosis; (B) Paclitaxel-coated balloon inflation after optimal lesion preparation using semi- and non-compliant balloons; (C) Final angiographic result showing no important dissections, with optimal distal flow; (D) Five-month follow-up angiography showing vessel healing, with important lumen gain. DCB: Drug-coated balloon. LAD: left anterior descending artery.

LONG-TERM RESULTS OF DRUG-COATED BALLOONS ALONE OR IN COMBINATION WITH STENTS IN DIFFUSE CORONARY ARTERY DISEASE

Even with the development of very-long stents which reduce the amount of overlapping metal, stent failure remains an issue, and thus a blended DCB/ DES or even a full-DCB strategy emerges as an interesting alternative option.

A single-center retrospective study evaluated the role of a DCB (IN.Pact Falcon paclitaxel-DCB, Medtronic Inc., USA) in 275 lesions from 184 patients, 38% of which had de-novo diffuse CAD. The overall mean DCB

length was 34.4 mm, while 70% of the de-novo lesions were located in vessels ≤ 2.5 mm in diameter. At a median follow-up of 14.6 months, there were no cardiac deaths in the de-novo cohort, with an acceptable frequency of the other clinical parameters- target vessel MI (1.3%), TLR (17.7%), target-vessel revascularization (TVR) (16.5%) and MACE (16.5%)[32]. The Magic Touch sirolimus-DCB (Concept Medical, India) was also assessed in a cohort of 373 primarily de-novo (68%), small and diffuse (60%) lesions with even more promising results at 1 year. There was no documented acute vessel closure, and while hard clinical endpoints showed low rates (cardiac death- 1.7%, MI- 3.4%), TLR and MACE were also adequate (12 and 10%, respectively)[33].

Costopoulos *et al.* included patients with long coronary lesions (cutoff of 25 mm, 45.2% with DM) and compared a DCB *vs.* a DES strategy in this context. What is more, in the DCB group, 36.6% of lesions were treated with a blended DCB/DES approach in cases of very-long lesions (mean length = 67.7 mm). Paclitaxel-DCB used were IN.Pact Falcon in the majority of cases and Pantera Lux (Biotronik SE, Germany). The end of the 26-month follow-up shows a similar frequency of MACE (a composite of all-cause death, MI and TVR) (20.8% *vs.* 22.7%; $P = 0.74$) and TVR (14.8% *vs.* 11.5%; $P = 0.44$) between the DCB ± DES and DES-only groups. Similar results were reported in cases of TLR rates (9.6% *vs.* 9.3%; $P = 0.84$), with more events arising in the DCB/ DES compared to the DCB-only subgroup[3].

A hybrid strategy using a bioresorbable vascular scaffold (BRS) and a DCB was attempted by Ielasi *et al.* on a relatively small number of patients, 88% of them with diffuse lesions. DCB were used exclusively to treat small vessels (< 2.75 mm). One year follow-up showed an excellent safety profile with no cardiac death and target-vessel MI, as well as no BRS/DCB thrombosis being reported. Although angiographic follow-up is available only in half of the patients, ischemia-driven TLR occurred in 4.7% of cases, related to the BRS-treated segment[34].

SPARTAN DCB was a prospective cohort study offering a head-to-head comparison between paclitaxel-DCB-only and second-generation DES in native stable CAD. The mean lesion length in the DCB arm was 26 mm. Over 1,500 patients were included and follow-up was available for up to 5 years. There was a signal towards better survival in the DCB group sustained after propensity score-matching (no. at risk 30 *vs.* 468, $P = 0.083$; no. at risk 30 *vs.* 162, $P = 0.018$)[35]. DCB show encouraging results even in a population of young (< 45 years) patients with ACS. At a mean follow-up period of 3.1 years as opposed to the DES group, patients treated with DCB (mean device length = 26 mm) had a trend towards a lower incidence of the composite endpoint (cardiac death, MI and TLR) driven mainly by TLR (3.0% *vs.* 11.0%, $P = 0.12$; 3.0% *vs.* 9.1%, $P = 0.19$). There was no difference between the groups with respect to the incidence of heart failure or major bleeding (0.0% *vs.* 1.9%, $P = 0.39$; 1.5% *vs.* 4.8%, $P = 0.30$)[36].

DCB have been used as a single tool in treating chronic total occlusions (CTO) associated with diffuse disease[37-39]. Jun *et al.* retrospectively included 93 CTO lesions with a mean length of 42.4 mm revascularized with a DCB-only strategy (SeQuent Please). Two-year follow-up shows a low incidence of hard clinical endpoints: cardiac death- 2.4%, MI- 3.6%, no vessel thrombosis and a negligible LLL of 0.03 ± 0.53 mm. The MACE rate was 16.7%, mainly driven by TVR (13.1%)[39].

With DM being a known risk factor for stent failure, Pan *et al.* conducted a propensity score analysis comparing the outcomes of 1,156 patients with and without DM treated with DCB (SeQuent Please). The mean DCB length was 25 mm, while over 80% of lesions were de-novo. At 1 year of follow-up, DCB show similar results in both the DM and non-DM groups in terms of MACE (OR: 1.580, 95%CI: 0.912 - 2.735), cardiac death (OR: 1.608, 95%CI: 0.523 - 4.946) or any revascularization (OR: 1.534, 95%CI: 0.983 - 2.393;

P = 0.058), but the rates of TLF and TLR were higher in patients with DM (5.36% *vs.* 2.77%; OR, 1.991, 95%CI: 1.077 - 3.681, *P* = 0.025; 4.15% *vs.* 1.90%; OR, 2.233, 95%CI: 1.083 - 4.602, *P* = 0.026)[40].

More recently, the prospective multicentre HYPER study evaluated the safety and efficacy of a novel paclitaxel-DCB (Restore DCB, Cardionovum GmbH, Germany) in conjunction with a current-era DES on lesions ≥ 28 mm in 100 patients. DCB was used on the distal lesion or the side branch. Dr Ielasi presented the results during EuroPCR 2022. The primary endpoint of the study was a device-oriented composite endpoint of cardiac death, target-vessel MI and ischemia-driven TLR in the DES- or DCB-treated segments. At 1 year, a low event rate of 3.7% was reported, mostly linked to TLR at the DCB level, while there were no recorded thrombotic events[41]. The HYPER II study is awaited to confirm these optimistic results.

Yang *et al.* conducted a recent large-scale multicentre prospective study comparing DCB alone or as part of a hybrid strategy with DES in treating long and diffuse coronary lesions (in the DCB arm, mean lesion length = 43.5 mm and mean vessel diameter = 2.47 mm). SeQuent Please DCB was used in a hybrid manner in 60% of cases. Both MLD immediately after PCI and LLL were significantly lower in the DCB group (1.79 ± 0.46 mm *vs.* 2.38 ± 0.54 mm, *P* < 0.001; 0.06 ± 0.61 mm *vs.* 0.41 ± 0.64 mm, *P* < 0.001). Interestingly, in 46.3% of cases, the lesions displayed LLE. At the 3-year follow-up [Figure 4], DCB-angioplasty was similar to DES regarding the primary endpoint of the study (TLR: 7.3% *vs.* 8.3%; log-rank *P* = 0.636). Moreover, similar results were observed in cases of MACE (11.3% *vs.* 13.7%; log-rank *P* = 0.324) and cardiac death (1.7% *vs.* 2.1%; log-rank *P* = 0.82), while no thrombotic events were registered among the DCB-treated patients (0 *vs.* 4; log-rank *P* = 0.193). In addition, when comparing DCB-only with the blended strategy, TLR and MACE rates were again similar (6.4% *vs.* 8.0%, log-rank *P* = 0.651; 11.4% *vs.* 11.2%, log-rank *P* = 0.884)[42].

A recent retrospective study on the value and relevance of DCB in 254 patients with multivessel CAD was published. Patients were assigned to either a DCB ± DES or a DES-only strategy. The primary endpoint was MACE (a composite of cardiac death, MI, stroke, ST, TVR and major bleeding). After 2 years of follow-up, DCB were associated with a lower frequency of MACE compared to the DES group (3.9% *vs.* 11.0%; *P* = 0.002). The data remained consistent for cardiac death, TVR and major bleeding rates as well (0.4% *vs.* 2.4%; 3.1% *vs.* 6.3%; 0.4% *vs.* 2.8%)[43].

Noteworthy, a meta-analysis conducted by Giacoppo *et al.* has shown that with respect to ISR treatment, although DCB are superior to DES in cases of focal lesions, the primary endpoint of all-cause death, MI, or target-lesion thrombosis was comparable between groups in case of diffuse-ISR[44]. Thus, the benefit of DCB-PCI seems to be influenced by lesion length not only in de-novo CAD, but also in cases of ISR. Moreover, for the overall ISR population, at 3 years of follow-up, the rate of the primary endpoint was again similar between groups (HR 0.80, 95%CI: 0.58 - 1.09; *P* = 0.152), while TLR was higher following DCB treatment, compared with DES (HR 1.32, 95%CI: 1.02 - 1.70; *P* = 0.035; number-needed-to-harm 28.5).

LIMITATIONS

A special mention should be given to the need for randomization in clinical studies comparing DCB and DES, especially in complex lesion subsets, as in daily practice, DES are more likely to be used in those settings. Also, certain high-risk scenarios, such as large thrombus burden, residual stenosis or significant dissection after lesion preparation, could also determine a selection bias, and are usually excluded from DCB treatment. Current information on the outcomes of DCB (small mechanistic RCT, propensity-matched studies, and large registries) are useful, but some ongoing and future RCT will need to have clinical primary and secondary endpoints before we can allow for a diffusive use of DCB instead of stents in many

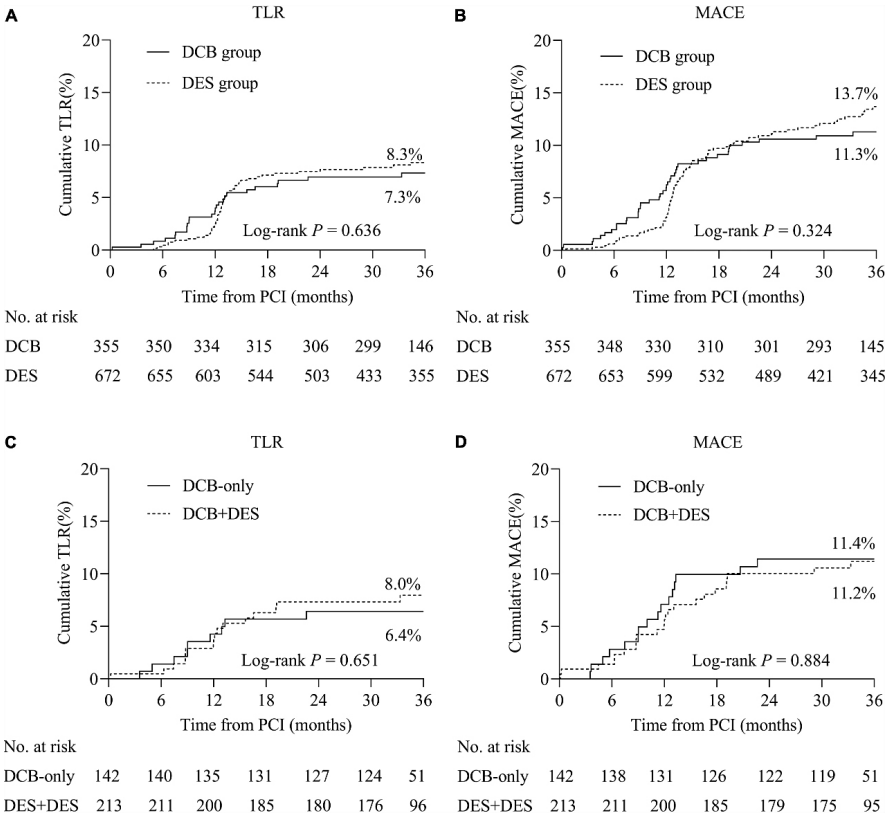


Figure 4. Rate of the primary and secondary endpoints at the 3-year follow-up[42]. (A) TLR between the DCB and DES groups; (B) MACE between the DCB and DES groups; (C) TLR between the DCB-only and DCB/ DES strategies; (D) MACE between the DCB-only and DCB/ DES strategies. DCB: Drug-coated balloon; DES: drug-eluting stent; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention; TLR: target lesion revascularization.

clinical and lesion settings. Unfortunately, stents are being used in many clinical and lesion scenarios not previously tested in ad hoc trials.

Comparing DCB *vs.* DES in terms of LLL may not be an appropriate endpoint and is a limitation of current trials because acute luminal gain is higher following DES implantation. However, other angiographic markers such as percent diameter stenosis or MLD are also far from being perfect, as in a given segment, distal flow is dependent on all the existing stenoses, and not just the narrowest one. Ultimately, hard clinical outcomes are the most relevant in daily practice, and all the angiographic endpoints are to be regarded as surrogates[45].

Bail-out stenting is sometimes required following DCB-PCI, but it still happens at a low rate (between 3% and 7%) in both small vessels[25] and diffuse lesion subsets[42].

FUTURE PERSPECTIVES

Several promising studies are currently underway and will provide more robust data on the use of DCB in the treatment of de-novo coronary disease. However, most of the investigators excluded patients with diffuse lesions.

The aforementioned HYPER II study (ClinicalTrials.gov Identifier: NCT05650450) aims at assessing the feasibility and outcome of a blended DCB (Restore DCB)/ DES approach in treating diffuse CAD, defined as lesion length > 38 mm in 500 patients. The primary endpoint of the study, TLF, as well as its individual components (cardiac death, any target-vessel MI excluding peri-procedural MI, TLR), will be available at 12 up to 24 months.

Following the same direction, another study will randomize patients to either a hybrid DCB (SeQuent Please)/DES or DES strategy. A longer follow-up period of up to 3 years is expected, taking into account both device- and patient-related cardiovascular clinical endpoints (ClinicalTrials.gov Identifier: NCT03589157).

On the other hand, D-Lesion Long (ClinicalTrials.gov Identifier: NCT03155971) and GINGER (ClinicalTrials.gov Identifier: NCT05471245) studies will evaluate the performance of a DCB-only strategy using SeQuent Please or Magic Touch by means of 9-month angiographic LLL.

RENOVATE study will randomize over 1,600 patients with complex coronary features, including long lesions (cutoff ≥ 38 mm). Intravascular imaging guidance will be compared to angiography-guided PCI using current-generation DES or DCB while TVF (a composite of cardiac death, MI, and clinically-driven TVR) will be assessed at 1 year (ClinicalTrials.gov Identifier: NCT03381872).

PICCOLETO III is another randomized clinical trial evaluating the efficacy of either a paclitaxel- or a sirolimus-DCB in comparison to DES, foreseeing a long follow-up of up to 5 years. Various complex settings will be addressed, including very-long lesions.

TRANSFORM II trial will compare the Magic Touch DCB with EES in the setting of CAD with lesions up to 50 mm, in vessels between 2 - 3 mm. Co-primary endpoints are TLF and net adverse clinical events at 12 months.

CONCLUSION

With increasingly higher rates of diffuse coronary lesions to be treated by means of PCI, and still suboptimal long-term results using the current DES, the need for a new modern approach to these lesions represents an important research activity. In this context, the use of DCB, which has demonstrated its safety and efficacy in a wide spectrum of complex scenarios, including native vessel disease, could become a valid alternative to long stenting, which has been demonstrated to be associated with poorer outcomes. Even though data is still scarce, this approach has become of great interest in daily practice, but large randomized clinical trials are needed to confirm the results reported in current studies.

DECLARATIONS

Authors' contributions

Conceived and designed the analysis, collected the data, and wrote the paper: Onea HL, Lazar FL
Conceived and designed the analysis, collected the data, and revised the paper: Olinic DM
Conceived and designed the analysis, collected the data, wrote the paper, and revised the paper: Cortese B
All authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

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None.

Conflicts of interest
Bernardo Cortese is a consultant for several DCB producers: B. Braun, Medtronic, Concept Medical, and MedAlliance.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

REFERENCES

1. Morice M, Serruys P, Sousa E. A randomized comparison of a sirolimus eluting stent with a standard stent for coronary revascularization. *ACC Current Journal Review* 2002;11:61. DOI
2. Neumann FJ, Sousa-Uva M. 'Ten commandments' for the 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:79-80. DOI PubMed
3. Costopoulos C, Latib A, Naganuma T, et al. The role of drug-eluting balloons alone or in combination with drug-eluting stents in the treatment of de novo diffuse coronary disease. *JACC Cardiovasc Interv* 2013;6:1153-9. DOI PubMed
4. van Beek KAJ, van Steenbergen GJ, Vervaat FE, et al. Single center experience in the treatment of hemodynamically significant diffuse coronary artery disease of the left anterior descending. *Int J Cardiol* 2022;352:40-4. DOI PubMed
5. Cortese B, Sanchez-Jimenez E. Back to the future: DCB use instead of DES for the treatment of complex, native coronary artery disease. *Eur Heart J Suppl* 2021;23:E63-7. DOI PubMed PMC
6. Youn YJ, Jeon HS, Kim YI, et al. Impact of the ultra-long 48 mm drug-eluting stent on procedural and clinical outcomes in patients with diffuse long coronary artery disease. *Clin Cardiol* 2023;46:416-24. DOI PubMed PMC
7. Brugaletta S, Gomez-Lara J, Ortega-Paz L, et al. 10-year follow-up of patients with everolimus-eluting versus bare-metal stents after ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2021;77:1165-78. DOI PubMed
8. Kufner S, Ernst M, Cassese S, et al; ISAR-TEST-5 Investigators. 10-year outcomes from a randomized trial of polymer-free versus durable polymer drug-eluting coronary stents. *J Am Coll Cardiol* 2020;76:146-58. DOI PubMed
9. Shlofmitz E, Iantorno M, Waksman R. Restenosis of drug-eluting stents: a new classification system based on disease mechanism to guide treatment and state-of-the-art review. *Circ Cardiovasc Interv* 2019;12:e007023. DOI PubMed
10. Chen Z, Matsumura M, Mintz GS, et al. Prevalence and impact of neoatherosclerosis on clinical outcomes after percutaneous treatment of second-generation drug-eluting stent restenosis. *Circ Cardiovasc Interv* 2022;15:e011693. DOI PubMed
11. Konigstein M, Madhavan MV, Ben-Yehuda O, et al. Incidence and predictors of target lesion failure in patients undergoing contemporary DES implantation-individual patient data pooled analysis from 6 randomized controlled trials. *Am Heart J* 2019;213:105-11. DOI PubMed PMC
12. Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart* 2014;100:153-9. DOI PubMed
13. Alfonso F, Coughlan JJ, Giacoppo D, Kastrati A, Byrne RA. Management of in-stent restenosis. *EuroIntervention* 2022;18:e103-23. DOI PubMed PMC
14. Généreux P, Rutledge DR, Palmerini T, et al. Stent thrombosis and dual antiplatelet therapy interruption with everolimus-eluting stents: insights from the xience V coronary stent system trials. *Circ Cardiovasc Interv* 2015;8:e001362. DOI PubMed
15. Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation* 2016;133:650-60. DOI PubMed
16. Condello F, Spaccarotella C, Sorrentino S, Indolfi C, Stefanini GG, Polimeni A. Stent thrombosis and restenosis with contemporary drug-eluting stents: predictors and current evidence. *J Clin Med* 2023;12:1238. DOI PubMed PMC
17. Lee CW, Ahn JM, Lee JY, et al; OPERA Steering Committee and Investigators. Long-term (8 year) outcomes and predictors of major adverse cardiac events after full metal jacket drug-eluting stent implantation. *Catheter Cardiovasc Interv* 2014;84:361-5. DOI PubMed
18. Kjøller-Hansen L, Kelbæk H, Christiansen EH, et al. Predictors of 10-year stent-related adverse outcomes after coronary drug-eluting stent implantation: the importance of stent size. *Cardiology* 2021;146:705-12. DOI

19. Kong MG, Han JK, Kang JH, et al; Collaborators. Clinical outcomes of long stenting in the drug-eluting stent era: patient-level pooled analysis from the GRAND-DES registry. *EuroIntervention* 2021;16:1318-25. DOI PubMed PMC
20. Lee CH, Kang DY, Han M, et al; IRIS-DES Registry Investigators. Differential cutoff points and clinical impact of stent parameters of various drug-eluting stents for predicting major adverse clinical events: an individual patient data pooled analysis of seven stent-specific registries and 17,068 patients. *Int J Cardiol* 2019;282:17-23. DOI
21. Coughlan JJ, Aytekin A, Koch T, et al. Long-term clinical outcomes after drug eluting stent implantation with and without stent overlap. *Catheter Cardiovasc Interv* 2022;99:541-51. DOI PubMed
22. Şaylık F, Çınar T, Selçuk M, Çiçek V, Hayıroğlu MI, Orhan AL. Comparison of outcomes between single long stent and overlapping stents: a meta-analysis of the literature. *Herz* 2023. DOI PubMed
23. Mangner N, Farah A, Ohlow MA, et al; BASKET-SMALL 2 Investigators. Safety and efficacy of drug-coated balloons versus drug-eluting stents in acute coronary syndromes: a prespecified analysis of BASKET-SMALL 2. *Circ Cardiovasc Interv* 2022;15:e011325. DOI PubMed
24. Mahfoud F, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease in patients with chronic kidney disease: a pre-specified analysis of the BASKET-SMALL 2 trial. *Clin Res Cardiol* 2022;111:806-15. DOI PubMed PMC
25. Cortese B, Di Palma G, Guimaraes MG, et al. Drug-coated balloon versus drug-eluting stent for small coronary vessel disease: PICCOLETO II randomized clinical trial. *JACC Cardiovasc Interv* 2020;13:2840-9. DOI
26. El-Mokdad R, di Palma G, Cortese B. Long-term follow-up after sirolimus-coated balloon use for coronary artery disease. Final results of the Nanolutè study. *Catheter Cardiovasc Interv* 2020;96:E496-500. DOI PubMed
27. Yu X, Wang X, Ji F, et al. A non-inferiority, randomized clinical trial comparing paclitaxel-coated balloon versus new-generation drug-eluting stents on angiographic outcomes for coronary de novo lesions. *Cardiovasc Drugs Ther* 2022;36:655-64. DOI PubMed PMC
28. Uskela S, Kärkkäinen JM, Eränen J, et al. Percutaneous coronary intervention with drug-coated balloon-only strategy in stable coronary artery disease and in acute coronary syndromes: an all-comers registry study. *Catheter Cardiovasc Interv* 2019;93:893-900. DOI PubMed
29. Rosenberg M, Waliszewski M, Chin K, et al. Prospective, large-scale multicenter trial for the use of drug-coated balloons in coronary lesions: the DCB-only All-Comers registry. *Catheter Cardiovasc Interv* 2019;93:181-8. DOI PubMed
30. Rosenberg M, Waliszewski M, Krackhardt F, et al. Drug coated balloon-only strategy in de novo lesions of large coronary vessels. *J Interv Cardiol* 2019;2019:6548696. DOI PubMed PMC
31. Yamamoto T, Sawada T, Uzu K, Takaya T, Kawai H, Yasaka Y. Possible mechanism of late lumen enlargement after treatment for de novo coronary lesions with drug-coated balloon. *Int J Cardiol* 2020;321:30-7. DOI
32. Basavarajaiah S, Latib A, Shannon J, et al. Drug-eluting balloon in the treatment of in-stent restenosis and diffuse coronary artery disease: real-world experience from our registry. *J Interv Cardiol* 2014;27:348-55. DOI
33. Basavarajaiah S, Athukorala S, Kalogeras K, et al. Mid-term clinical outcomes from use of Sirolimus coated balloon in coronary intervention; data from real world population. *Catheter Cardiovasc Interv* 2021;98:57-65. DOI PubMed
34. Ielasi A, Miyazaki T, Geraci S, et al. Hybrid strategy with a bioresorbable scaffold and a drug-coated balloon for diffuse coronary artery disease: the "no more metallic cages" multicentre pilot experience. *EuroIntervention* 2016;11:e1589-95. DOI PubMed
35. Merinopoulos I, Gunawardena T, Wickramarachchi U, et al. Long-term safety of paclitaxel drug-coated balloon-only angioplasty for de novo coronary artery disease: the SPARTAN DCB study. *Clin Res Cardiol* 2021;110:220-7. DOI PubMed PMC
36. Yang YX, He KZ, Li JY, et al. Comparisons of drug-eluting balloon versus drug-eluting stent in the treatment of young patients with acute myocardial infarction. *J Cardiovasc Dev Dis* 2023;10:29. DOI PubMed PMC
37. Wickramarachchi U, Corballis NH, Maart CA, Gilbert TJ, Eccleshall SC, et al. 24 drug coated balloon-only angioplasty in chronic total occlusions, a UK single centre experience. *Heart* 2017;103:A11. Available from: https://heart.bmj.com/content/103/Suppl_7/A11.1. [Last accessed on 10 Jul 2023]
38. Köln PJ, Scheller B, Liew HB, et al. Treatment of chronic total occlusions in native coronary arteries by drug-coated balloons without stenting - a feasibility and safety study. *Int J Cardiol* 2016;225:262-7. DOI
39. Jun EJ, Shin ES, Teoh EV, et al. Clinical outcomes of drug-coated balloon treatment after successful revascularization of de novo chronic total occlusions. *Front Cardiovasc Med* 2022;9:821380. DOI PubMed PMC
40. Pan L, Lu W, Han Z, et al. Clinical outcomes of drug-coated balloon in coronary patients with and without diabetes mellitus: a multicenter, propensity score study. *J Diabetes Res* 2021;2021:5495219. DOI PubMed PMC
41. Ielasi A, Buono A, Pellicano M, et al. A hybrid approach evaluating a drug-coated balloon in combination with a new-generation drug-eluting stent in the treatment of de novo diffuse coronary artery disease: the HYPER pilot study. *Cardiovasc Revasc Med* 2021;28:14-9. DOI PubMed
42. Yang X, Lu W, Pan L, et al. Long-term outcomes of drug-coated balloons in patients with diffuse coronary lesions. *Front Cardiovasc Med* 2022;9:935263. DOI PubMed PMC
43. Shin ES, Jun EJ, Kim S, et al. Clinical impact of drug-coated balloon-based percutaneous coronary intervention in patients with multivessel coronary artery disease. *JACC Cardiovasc Interv* 2023;16:292-9. DOI PubMed
44. Corrigendum to: paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J* 2020;41:3728. DOI PubMed PMC
45. Cortese B, Erriquez A, Alfonso F. Reply: seeking an appropriate primary endpoint for trials comparing DCB and DES. *JACC Cardiovasc Interv* 2021;14:710-1. DOI PubMed