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REVIEW

Long-term benefits of drug-coated balloons for coronary artery revascularization

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ABSTRACT

Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) represents the treatment of choice for the majority of patients with coronary artery disease. While currently available DES, in addition to physiological support, has failed to show the non-inferiority to coronary artery bypass grafting (CABG) in terms of cumulative incidence of clinical events over the short-term follow-up. Studies have also shown that DES is associated with an increased risk of target vessel revascularization compared to CABG after long-term follow-up. Drug-coated balloons (DCB) have been shown to provide clinically significant benefits in the management of in-stent restenosis and diffuse coronary artery disease, as well as small coronary artery lesions. The aim of this review was to describe the inherent technical limitations of DES and highlight the potential advantages of PCI with DCB for long-term outcomes and potentially demonstrate its non-inferiority to CABG. Currently, ongoing studies will provide more information and help to understand if a blended therapy of DCB+DES can match the performance of CABG in the need for revascularization in more complex patients.

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KEY WORDS: Percutaneous coronary intervention; Drug-eluting stents; Coronary restenosis.

Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is the treatment of choice for the majority of coronary artery disease patients. In addition, DES significantly reduces restenosis compared with bare metal stents and balloon angioplasty.[1] However, regardless of having DES as a therapy option, in up to 10% of patients in-stent restenosis (ISR) requiring revascularization may occur. Importantly, in patients undergoing PCI for diffuse coronary artery lesions, as well as in diabetic patients, the rate of stent failure including stent thrombosis (ST) and target lesion revascularization (TLR) may reach 20%[2, 3].

Drug-coated balloons (DCB) represent a promising alternative to stent implantation, with the potential of overcoming some of these drawbacks. Multiple studies have shown the safety and efficacy of DCB for the treatment of ISR[4, 5] and small native vessel diseases.[6] With increasing evidence, DCB have further gathered an important role for the treatment of bifurcation lesions,[7] larger vessels,[8] and high bleeding risk patients.[6] However, most of the current studies have exclusively analyzed short-term outcomes. This paper aims to provide a summary of the currently available data on the very long-term performance of DCB-based coronary revascularizations as compared to other treatment strategies.

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Methods

This review summarizes the evidence on the long-term outcome of DCB coronary interventions and provides suggestions for further investigation. The results of recent large-scale studies that describe the inherent technical limitations of DES and highlight the potential advantages of PCI with DCB, which may show noninferiority to CABG in patients with various lesion types over the long-term follow-up, were primarily summarized. The nature of the research findings and duration of follow-up were among the most important criteria in selecting studies for this review. In contrast, articles for which full texts were not available, were not written in English or had only short-term follow-up, met the exclusion criteria. The sources for this review were found using various electronic databases, such as MEDLINE, PubMed, EMBASE, and Google Scholar, for articles published between 2000 and 2023. Specifically, the search strategy included three concepts: 1) types of coronary interventions (such as DCB, DES, and CABG); 2) kind of lesion and patient population (*e.g.*, left main coronary artery disease, multivessel disease, de novo coronary disease, complex lesions, and high-risk patients); and 3) desired outcomes consistent with the objectives of our review (*e.g.*, long-term outcomes of DCB performed alone or in combination with another intervention). Terms were adjusted for each database to ensure that no studies were missed in the search. Using this research technique, we found 31 articles published between 2002 and 2023.

Results

Long-term outcomes of DES *vs.* CABG in patients with multivessel disease

Multivessel coronary artery disease is associated with poorer outcomes, regardless of the revascularization strategy. However, some important studies have reported inferior long-term results for PCI with DES when compared to CABG.[9-12]

A randomized controlled trial (Park *et al.*) assigned 1776 individuals with multi-vessel coronary arteries to compare PCI and CABG treatments. The authors reported that the risk of significant adverse cardiovascular events (death, MI, and TVR) was greater in patients treated with PCI compared to CABG, both at two-year follow-up (11% *vs.* 7.9%, P=0.32) and at 4.6-year follow-up (15.3% *vs.* 10.6%, P=0.04) (Figure 1).[9]

Another study, the SYNTAX Trial,[10] compared PCI *vs.* CABG at 5-year follow-up in patients with 3-vessel disease (N.=1095). In this trial, the rate of MACCE was significantly higher in patients with PCI compared to CABG (37.5 *vs.* 24.2%; P<0.001). PCI, in contrast to CABG, resulted in significantly higher rates of combined death/stroke/MI (22.0 *vs.* 14.0%, respectively; P<0.001), and all-cause death (14.6 *vs.*

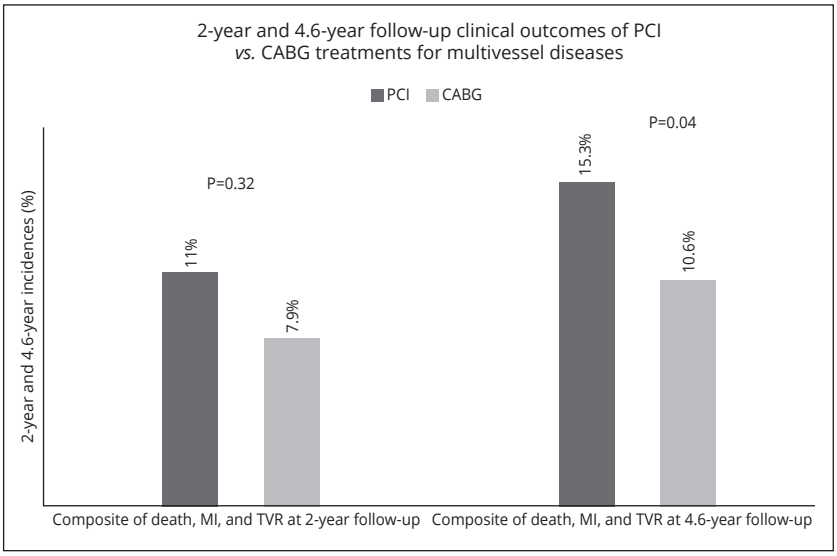

Figure 1.—A graphic demonstration to compare the clinical events between PCI and CABG treatment groups in the 2-year and 4.6-year follow-up. [From Park *et al.*].[9] MI: myocardial infarction; TVR: target vessel revascularization.

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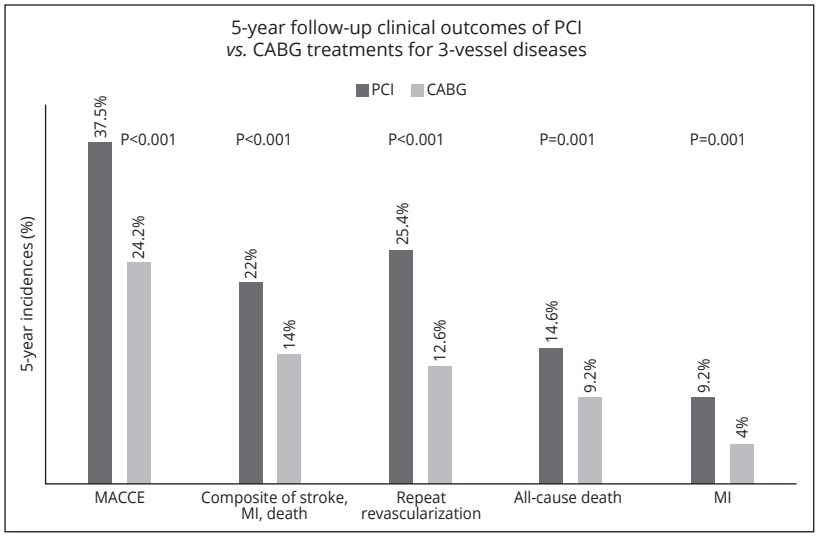

Figure 2.—A graphic demonstration the SYNTAX Trial results (the SYNTAX Trial[10]). MACCE: major adverse cardiac or cerebrovascular event(s).

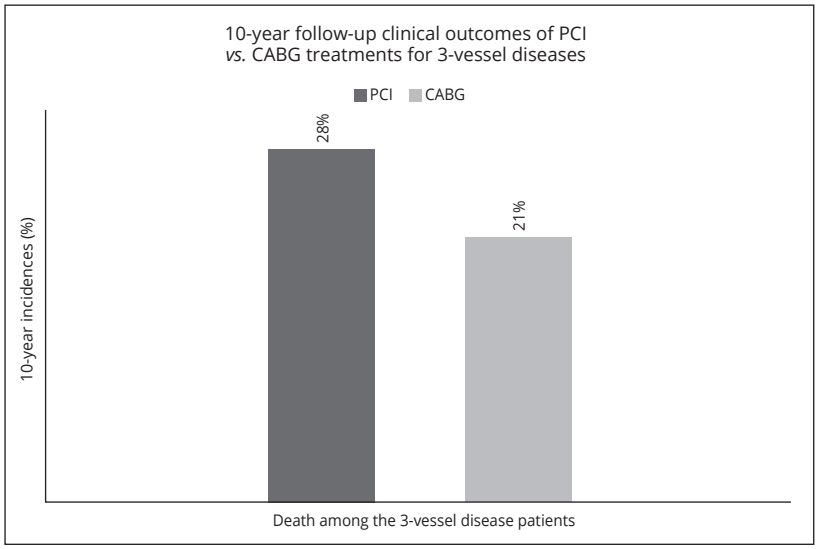

Figure 3.—A graphic demonstration of significant survival benefit in patients with three-vessel disease treated with CABG *vs.* PCI in the 10-year follow-up (The SYNTAX Trial[11]).

9.2%). respectively; P=0.006), MI (9.2 *vs.* 4.0%; P=0.001), and repeat revascularization (25.4 *vs.* 12.6%, respectively; P<0.001) (Figure 2).[10]

Recently the pivotal SYNTAX Trial also reported the 10-year clinical results, which were in favor of CABG as well. This study was an investigator-driven extension of the follow-up of a multicenter, randomized controlled trial done in 85 hospitals across 18 North American and European countries with the primary endpoint of 10-year all-cause death. From March 2005, to April 2007, 1800 patients with de-novo three-vessel and left main coronary artery disease were randomly assigned (1:1) to the PCI (N.=903) group or CABG (N.=897) group. At 10 years, among the three-vessel disease group of patients, 153 (28%) of 546 had died after PCI *vs.* 114 (21%) of 549 after CABG (HR 1.42 [95% CI 1.11-1.81]). Therefore, this study concluded that CABG showed a significant survival benefit in patients with three-vessel disease (Figure 3).[11]

A recent study based on real-world data analysis has evaluated the 10-year clinical outcomes of CABG *vs.* PCI. The authors reported higher incidences of the necessity TVR in the PCI group as compared to CABG (25.1% *vs.* 3.5% respective-

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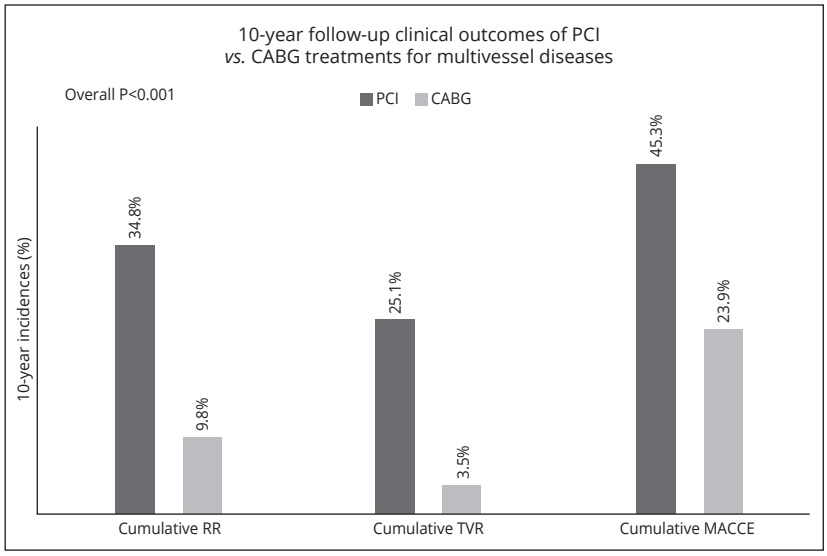

Figure 4.—A graphic demonstration of a recent study results to compare the clinical events between PCI and CABG treatments for multivessel diseases in the 10-year follow-up. [From Ding T *et al.* research[13]].
RR: repeat revascularization.

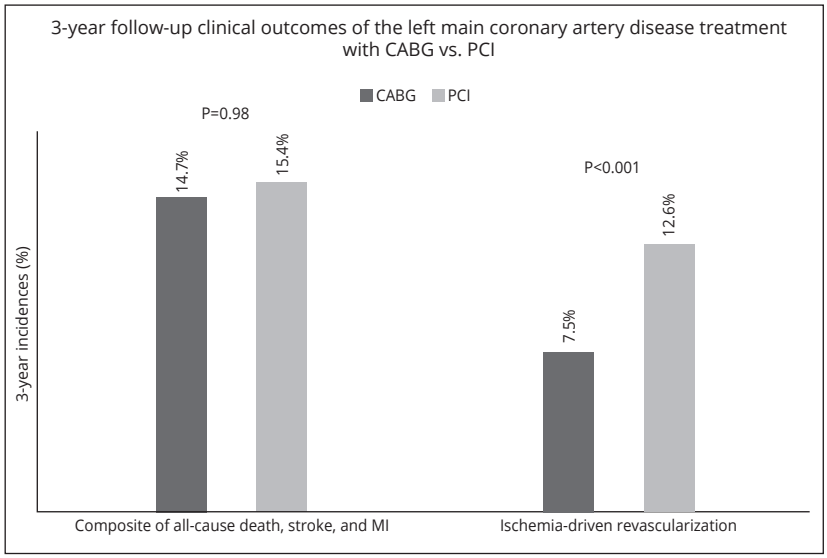

Figure 5.—A graphic demonstration of EXCEL Trial results (EXCEL Trial[14]).

ly, P<0.001), as well as higher rates of MACE (45.3% *vs.* 23.9%, P<0.001) and repeat revascularization (34.8 *vs.* 9.8%, P<0.001) (Figure 4).[13]

Long-term outcomes of DES *vs.* CABG in patients with left main coronary artery disease

Regarding left main coronary artery revascularization, despite continuous technical improvements, there are remaining concerns in terms of long-term outcomes when PCI is compared to CABG. In this context, the recently published final clinical results of the NOBLE and EXCEL trials were discordant, mainly because EXCEL is not taking into account of the need of repeat revascularization in the definition of MACCE, while NOBLE included this endpoint.

At three years follow-up, the rate of a composite of death from any cause, stroke, or MI was similar in the CABG and PCI group in the EXCEL trial (14.7 *vs.* 15.4%; HR 1.00, 95% CI 0.79-1.26, P=0.98) (Figure 5).[14] While the events rate was lower in the PCI vs CABG group in the first 30 days (4.9% *vs.* 7.9%), fewer primary end point events occurred in the CABG group than

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in the PCI group between 30 days and 3 years. Regarding the secondary end-points, early MI and major periprocedural adverse events within 30 days were significantly lower with PCI than with CABG (3.9% *vs.* 6.2% and 8.1% *vs.* 23.0%, respectively), but ischemia-driven revascularization during follow-up was more frequent after PCI than after CABG (12.6% *vs.* 7.5%, P<0.001) (Figure 5).[14]

On the other hand, the NOBLE randomized clinical trial assigned 1201 patients with significant LM disease to either CABG or PCI. At a median follow-up of 5 years, the primary endpoint of death, non-procedural MI, stroke, and repeat revascularization occurred more frequently in the PCI than the CABG group (28 *vs.* 19%; HR 1·58 [95% CI 1.24-2.01], P=0.0002). Therefore, in the NOBLE Trial repeat revascularizations were significantly higher at 17% after PCI *vs.* 10% after CABG (HR 1.73; 95% CI [1.25-2.40], P=0.0009) (Figure 6).[15] As a notable mention, even if a SYNTAX Score was not a prespecified inclusion criteria, this trial excluded patients with >3 additional noncomplex lesions or any complex additional coronary lesions.

In conclusion, for patients with multivessel coronary diseases, the CABG treatment option seems to provide superior long-term outcomes compared with the PCI technique in terms of MACCE and TVR. Regarding left main coronary artery revascularization, despite the only two available trials with long-term follow-up being discordant, a higher TLR rate was observed in both of them. Notably, all of these studies have used a common strategy for the management of coronary lesions in the PCI arm, consisting of long stenting (approximately 80 mm per patient) or the adoption of complex techniques.

Long-term outcomes of DES *vs.* CABG in patients with complex lesions

Unfortunately, several studies have shown how in the very long term, a DES approach, especially in complex lesions, is associated with a continuous increase in adverse events, at a rate ranging between 2-3.3%/year. ISAR-TEST randomized clinical trial showed a cumulative rate of target lesion failure (TLF) of 43.8% at 10 years.[16] In another study, the rate of 10-year adverse events was significantly higher in specific clinical and lesion settings: the presence of diabetes, small coronary vessels, or longer stented segments.[17]

Long-term outcomes of drug-coated balloons in patients with small and mid-sized coronary artery diseases

In the last 10 years, several DCB studies with long-term follow-up were published. In the BELLO study DCB angioplasty with the In.Pact Falcon paclitaxel-DCB (Medtronic-Invatec, Frauenfeld, Switzerland) was associated with less

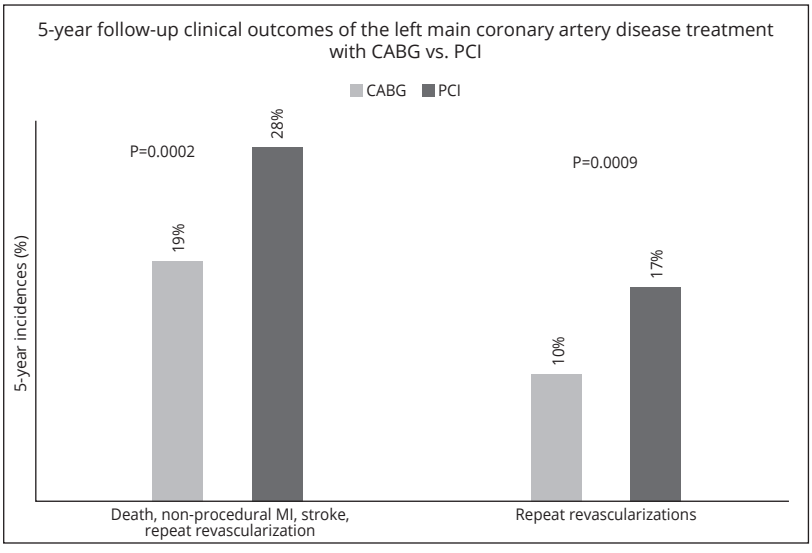

Figure 6.—A graphic demonstration of NOBLE Trial results (NOBLE Trial[15]).

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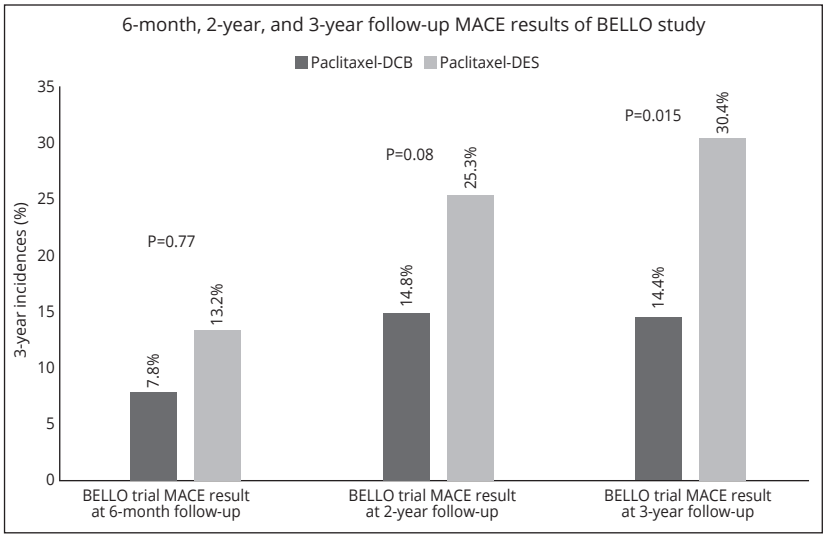

Figure 7.—A graphical comparison between 3 different follow-up timelines of BELLO study. (BELLO Study[18-20]). MACE: major adverse cardiac event(s).

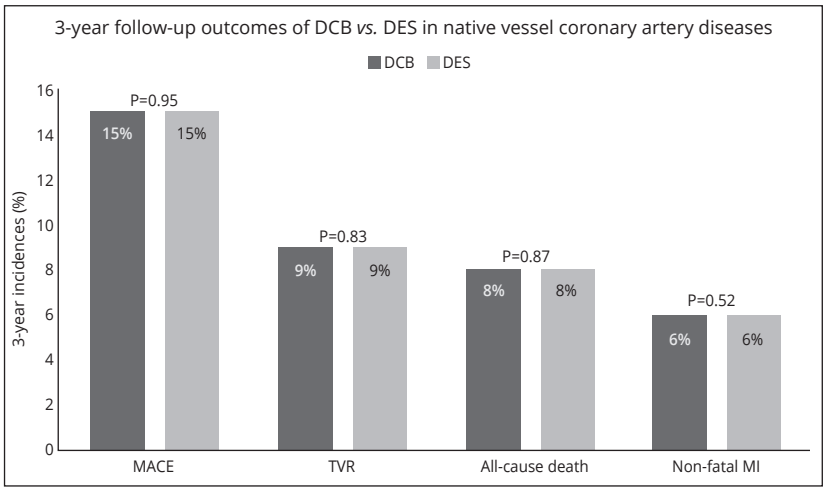

Figure 8.—A graphic demonstration of the BASKET-SMALL II Study results (BASKET-SMALL II[21]).

angiographic LLL and similar rates of restenosis and revascularization in comparison with the paclitaxel-DES at six months.[18] While the two-year follow-up showed a trend toward lower clinical events in patients in the DCB group;[19] the three-year follow-up[20]demonstrated a MACE rate significantly lower in the DCB arm as compared to the DES one (14.4% *vs.* 30.4%, P=0.015) (Figure 7).[18-20] Importantly, patients treated with a pure "leave nothing behind" strategy did not have any thrombotic events or peri-procedural myocardial infarction.

The three-year follow-up of the BASKET-SMALL II Study, the largest to date to investigate the efficacy of paclitaxel-DCB use in native vessel coronary artery disease, showed similar rates of MACE between DES and DCB (15% in both arms, HR 0.00, 95% CI 0.68-1.45)[21] (Figure 8).[21]

RESTORE SVD Investigators recently reported the five-year final follow-up of this SVD study, which compared a paclitaxel-DCB to a current-generation DES. The data presented at TCT 2022 showed similar outcomes in terms of TLF (DCB 8% *vs.* DES 7.3%, HR 1.12, 95% CO 0.43-2.89).[22]

Recently, also the final outcome of the PICCOLETO II trial has been published. The primary outcome published in 2020 showed the

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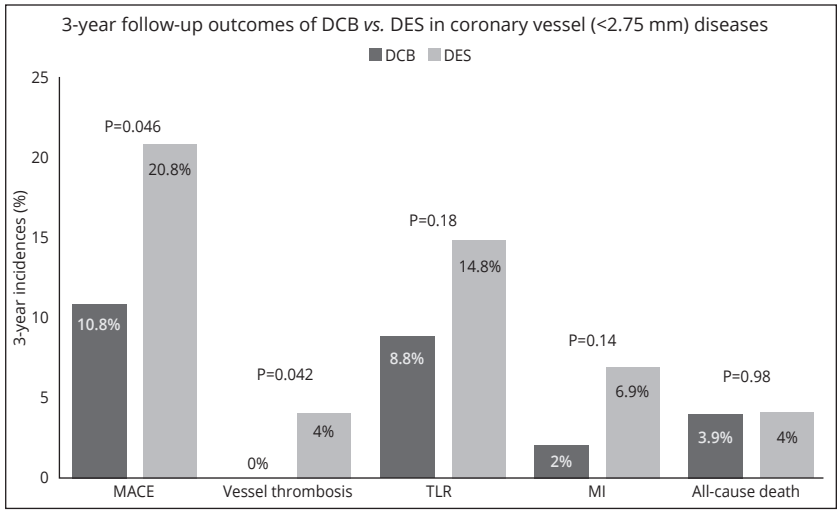

Figure 9.—A graphic demonstration of the PICCOLETO II Study results (PICCOLETO II[23]).
TLR: target lesion revascularization.

angiographic superiority of a paclitaxel-DCB *vs.* current-generation DES in terms of LLL (DCB 0.04±0.28 mm *vs.* DES 0.17±0.39 mm, P=0.03).[23] The just published final three-year outcome showed for the first time a significant reduction in MACE in patients treated with the DCB (10.8% *vs.* 20.8%, P=0.046), along with a significantly lower rate of abrupt vessel occlusion in the DCB arm, during the follow-up (Figure 9).[23, 24]

The trials mentioned were all conducted on small or mid-sized coronary vessels (less than 3 mm or smaller). Currently, scientific data on the performance of DCB in larger coronary vessels are scarce and mostly derive from few registries, thus do not fulfill the requirements of this review.

Combination therapy of DCB and DES in multivessel, diffuse vessel disease, or high-risk patients

Several studies have evaluated the blended approach of combining DCB and DES in patients with multivessel, diffuse vessel disease, or high-risk conditions. This approach has the major advantage of reducing the length of the stent, which is beneficial to the very long-term outcome of the patients. In general, the most commonly adopted strategy involves preparing the lesion according to the vessel size and characteristics of the lesion, which should be determined by intravascular imaging.

Initial clinical evidence for this approach derives from observational studies. Costopoulos *et al.* showed how a DES+DCB strategy was associated with an acceptable initial result, with MACE and TLR rates comparable to a full-DES approach (MACE 20.8% *vs.* 22.7%, P=0.74; TLR 9.6% *vs.* 9.3%, P=0.84) after 24 months (Figure 10).[25]

A blended (hybrid) approach of DCB+DES was also recently evaluated and compared to a full DES one in a study by Shin and coauthors. A total of 508 multivessel disease patients from two different studies were evaluated using propensity matching after two years. Total number of devices used and device length and diameter were similar. The final follow-up showed a reduced incidence of MACE (3.9 *vs.* 11%, P=0.002), cardiac death (0.4 *vs.* 2.4%, P=0.047), and major bleedings (0.4 *vs.* 2.8%, P=0.027) and target vessel revascularization (3.1 *vs.* 6.3%, P=0.095) in the blended-therapy arm (Figure 11).[26]

Will technological improvements of new-generation DCB reflect on long-term results?

Recently, also sirolimus-coated balloons entered the market as an alternative to paclitaxel. Limus-based drugs are cytostatic, with a wider therapeutic window as compared to paclitaxel. However, the main problem with using sirolimus in

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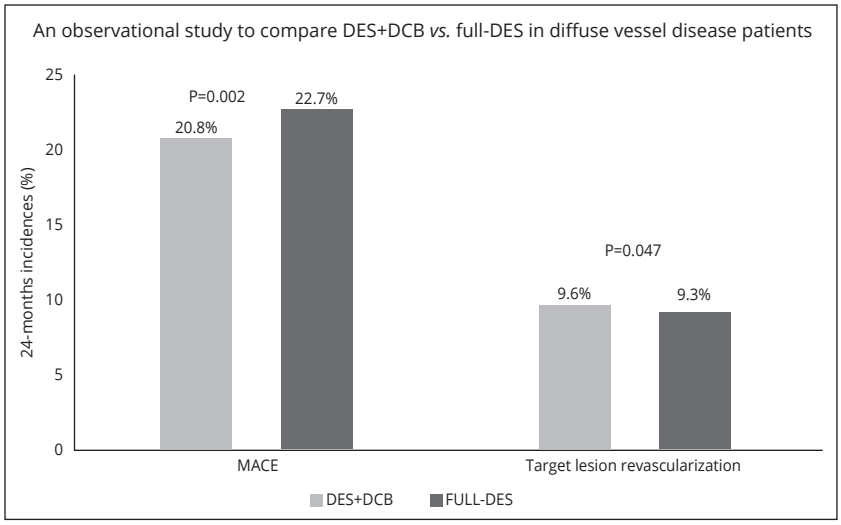

Figure 10.—A graphic demonstration of observational study clinical results [From Costopoulos *et al.*[25]].

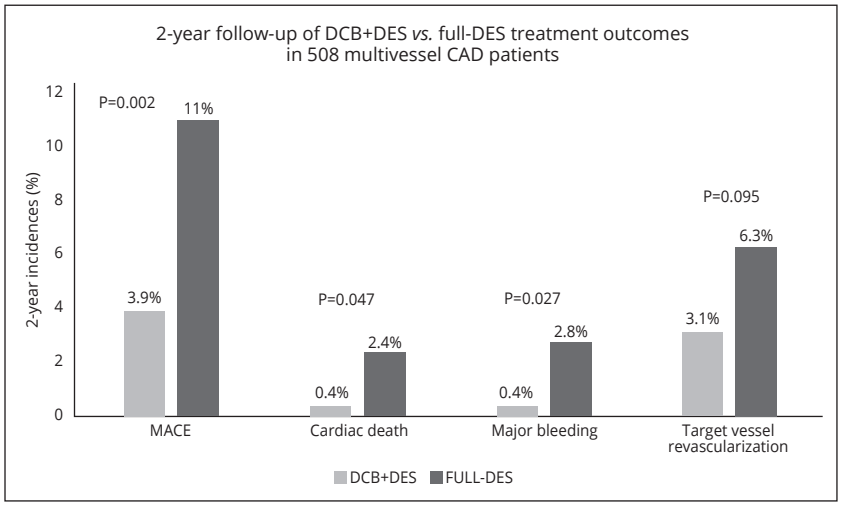

Figure 11.—A graphic demonstration of DCB+DES *vs.* full DES clinical outcomes [From Shin *et al.*[26]].

DCB is that its lower lipophilic profile makes tissue absorption and subsequent elution more difficult. Therefore, this new generation DCB was developed using different delivery technologies to address this issue. The Magic Touch (Concept Medicals, India) sirolimus-coated balloon catheter uses the Nanoluté technology, a nano-carrier-based drug-delivery technology in which nano-sized encapsulated particles carry the drug protected by a phospholipid bilayer (sirolimus 1.27 micrograms/mm2 of balloon surface). So far, this is the only new technology with clinical data in several settings and a clinical program.[27, 28]

The Selution sirolimus DCB (MedAlliance, Switzerland) uses microspheres derived from a biodegradable polymer intermixed with sirolimus (1 microgram/mm^2 of balloon surface), which ensures a controlled, sustained release with the maintenance of the therapeutic effect in tissue over long periods. The Selution DCB also has a novel cell-adherent technology (CAT), which protects micro reservoirs during balloon insertion, lesion crossing, and expansion. The CAT membrane, with embedded micro-reservoirs, adheres to the vessel wall during inflation and releases the drug from the balloon delivery system. This device does not have published data so far.

Also, a crystalline formulation of sirolimus

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DCB entered the market (BBraun, Germany), with a higher dosage of sirolimus eluted (4 micrograms/mm2 of balloon surface) and initial clinical data of comparison with paclitaxel-DCB.[29]

The beneficial effect of some paclitaxel-DCB in terms of positive vascular remodeling has not yet been demonstrated by this new wave of technology, and it has not been demonstrated whether sirolimus-DCB could have a long-term beneficial effect on coronary revascularization until now. The only available data with long-term follow-up with this technology derives from the Nanoluté registry, which showed a good clinical outcome after two years in an Indian population with simple coronary artery disease (MACE rate 4.2%, TLR 3.2%) (Table I).[18-26, 30] Currently ongoing, adequately powered trials will shed light on the properties of this new class of devices in the upcoming years (Supplementary Digital Material 1: Supplementary Figure 1).[31]

Conclusions

Currently used stents have a high safety and efficacy profile; however, metallic prostheses share

TABLE I.—*Summary of the real-world evidence on the long-term performance of DCB.*[18-26, 30]

Study	Aim	Key findings
BELLO Trial 6-month, 2-year and 3-year follow-up[18-20]	Compared DCB angioplasty of In.Pact Falcon paclitaxel-DCB with paclitaxel-DES in 3 different timeline follow-ups	• Less angiographic LLL and similar rates of restenosis and revascularization in DCB *vs.* paclitaxel-DES at 6 months • Lower clinical events in patients in the DCB group at 2 years • Significantly lower MACE rate in DCB *vs.* DES (14 *vs.* 30%) at 3 years • No thrombotic events or peri-procedural myocardial infarction in the DCB group
BASKET-SMALL II[21]	Evaluated efficacy of paclitaxel-DCB use in native vessel coronary artery disease in the 3-year follow-up	• Similar rates of MACE between DES and DCB (both 15%) • Similar rates of TVR (both 9%), All-cause death (both 8%), and Non-fatal MI (both 6%)
RESTORE SVD Trial[22]	Reported the 5-year final follow-up of this SVD study, which compared a paclitaxel-DCB to a current-generation DES	• Similar outcome in terms of TLF (DCB 8% *vs.* DES 7.3%)
PICCOLETO II Trial [23]	Evaluated clinical outcomes of new generation DCB *vs.* EES in patients with de novo SVD lesions (<2.75 mm)	• Angiographic superiority of a paclitaxel-DCB *vs.* current-generation DES in terms of LLL (DCB 0.04±-0.28 mm *vs.* DES 0.17±0.39 mm, P=0.03)
PICCOLETO II Trial [24]	Evaluated the 3-year follow-up clinical outcomes of new generation DCB *vs.* EES in patients with de novo SVD lesions (<2.75 mm)	• Significant reduction in MACE in patients treated with the DCB (10.8 *vs.* 20.8%) • Significantly lower rate of abrupt vessel occlusion in the DCB arm (0 *vs.* 4%) • Lower TLR (8.8 *vs.* 14.8), MI (2 *vs.* 6.9%), and All-cause death (3.9 *vs.* 4%) in the DCB arm
Costopoulos *et al.* Trial [25]	Compared DES+DCB with Full-DES in 24-month follow-up	• Acceptable initial result of MACE and TLR rates in hybrid approach comparable to a full-DES (MACE 20.8 *vs.* 22.7%; TLR 9.6 *vs.* 9.3%)
Shin *et al.*[26]	Compare the hybrid approach of DCB+DES with full DES in 508 multivessel disease patients from two different studies in the 2-year follow-up	• Reduced incidence of MACE (3.9 *vs.* 11%), cardiac death (0.4 *vs.* 2.4%), and major bleedings (0.4 *vs.* 2.8%) in the hybrid-therapy arm
El-Mokdad *et al.* Trial[30]	Evaluated long-term follow-up (3 year) of Sirolimus-coated balloons for CAD	• MACE rate 4.2%, TLR 3.2% • Showed safety and feasibility of SCB in both ISR and de novo lesions

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a continuous risk of lesion-related adverse events which does not seem to interrupt a not negligible number of patients, in the long term. This event rate negatively reflects on comparisons with CABG.

Drug-coated balloons demonstrate an optimal safety and efficacy profile in terms of lesion-related events, due to the absence of prosthesis, a homogeneous drug distribution, and, in the case of paclitaxel, a positive remodeling effect on the vessel. Initial data seem to show how these properties have an impact on long-term outcomes. Currently ongoing trials will provide more information and will help to understand if a blended therapy of DCB+DES can match the performance of CABG in terms of the need for revascularization.

Key messages

• CABG treatment option appears to provide superior long-term outcomes when compared with PCI in terms of MACCE and TVR for patients with multivessel coronary artery disease. Regarding left main coronary artery revascularization, despite the only 2 available trials with long-term follow-up being discordant, a higher TLR rate has been observed in both.

• In long-term follow-up, PCI is associated with a continuous increase in adverse events at the rate of 2-3.3%/year after year 1, especially when lesions are complex (presence of diabetes, small coronary vessels, or long stented segments), with a cumulative rate of 43.8% of target lesion failure (TLF) after 10 years.

• When comparing the DCB *vs.* DES in *de novo* small coronary lesion (<3 mm), many studies have shown similar results in the two arms. Notably, the PICCOLETO II 3-year outcome showed, for the first time, a significant reduction in MACE rates in patients treated with the DCB approach.

• A blended therapy of DCB and DES in patients with multivessel disease, diffuse vessel disease, or high-risk conditions was associated with reduced MACE, cardiac death, major bleeding, and TVR compared to DES alone.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Bernardo Cortese: study conception and design, data collection, manuscript preparation, writing, and revision; Sara Malakouti: data collection, manuscript preparation and writing, creating figures, creating graphical abstract; Waqas Mazhar: data collection, manuscript preparation and writing; Florin Leontin Lazar: revising the manuscript; Amit Munjal and Yolanda Ketchanji Mougang: finding the resources. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Figure 1.—Graphical abstract. (Park S *et al.*,[9] Ding T *et al.* research [13], EXCEL Trial [14], NOBLE Trial [15], PICCOLETO II [23], BASKET-SMALL II [21], Shin ES *et al.* [26]).