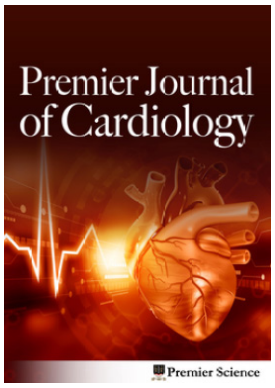

Evidence on Treating Coronary Artery Disease with Drug-Coated Balloons

Vedran Radonić

ABSTRACT

Percutaneous transluminal coronary angioplasty with drug-coated balloons (DCBs) is the modality of coronary artery revascularization with local application of antiproliferative agents, paclitaxel or sirolimus. It has become an appealing alternative to drug-eluting stents (DESs) due to intervention simplification, absence of permanent metallic mesh implantation, preserved vasomotion, and shorter duration of dual antiplatelet therapy because of reduced risk of acute thrombosis. Numerous studies have assessed DCB safety and efficacy for various aspects of coronary artery disease (CAD) for in-stent restenosis (ISR) and de novo CAD, while interventional cardiologists worldwide report good results with DCB in everyday practice. However, data is not robust enough to recommend DCB according to the European Society of Cardiology guidelines, except for the ISR of bare-metal stents (BMSs). At the same time, the United States Food and Drug Administration approved the DCB usage for ISR of both BMS and DES in March 2024. Further studies are underway to increase the body of evidence, and new technologies, including DCB with combined paclitaxel and sirolimus, are developing.

Keywords: Drug-coated balloons, Coronary artery revascularization, Paclitaxel and sirolimus, In-stent restenosis, Chronic total occlusion

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Additional material is published online only. To view please visit the journal online.

Cite this as: Radonić V. Evidence on Treating Coronary Artery Disease with Drug-Coated Balloons. Premier Journal of Cardiology 2025;2:100007

DOI: https://doi.org/10.70389/PJC.100007

Received: 2 March 2025
Revised: 17 March 2025
Accepted: 19 March 2025
Published: 27 March 2025

Ethical approval: N/a
Consent: N/a
Funding: No industry funding
Conflicts of interest: N/a
Author contribution: Vedran Radonić – Conceptualization, Writing – original draft, review and editing
Guarantor: Vedran Radonićе
Provenance and peer-review: Commissioned and externally peer-reviewed
Data availability statement: N/a

Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide.[1] It is a prevalent cardiovascular condition caused by atherosclerotic plaque buildup within the coronary arteries. Risk factors include hyperlipidemia, arterial hypertension, diabetes, obesity, and smoking. Controlling risk factors with regular physical activity, appropriate lifestyle, nutrition, and medications is crucial for CAD prevention or limiting disease progression. Progressive narrowing of the arterial lumen limits blood flow to the heart muscle, causing chronic coronary syndrome (CCS) symptoms, including chronic chest pain or shortness of breath in exertion due to myocardial ischemia. Long-term myocardial ischemia may compromise systolic heart function, leading to heart failure.[2] Atherosclerotic plaque rupture or erosion causes acute coronary syndrome (ACS) with rapid partial or total vessel occlusion with thrombus.[3] Invasive coronary angiography is performed in most cases of both ACS and CCS. Revascularization is needed in case of a significant coronary artery obstruction, but revascularization modality depends on the patient's characteristics. Surgical coronary artery bypass grafting (CABG) is preferred in patients with extensive CAD (triple vessel disease and/or left main artery disease).[2,4,5] Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is a faster and less invasive option. Hence, it is recommended for less extensive CAD (usually single or double vessels), including ACS with acute vessel closure.[2,3,6,7]

Since the implantation of a stent implies a permanent metal mesh implant, modalities of revascularization without a foreign body were considered. One idea was the installation of a bioresorbable scaffold (BRS), but due to increased procedural complexity, reduced efficiency, and increased risk of acute thrombosis, BRS is currently not part of routine clinical practice, and technology is still developing.[8] On the other hand, the drug-coated balloon (DCB) revascularization model has shown promising results for coronary artery revascularization.

Historical Perspective on Coronary Revascularization

While the first coronary angiography was performed in 1958, the first revascularization occurred in 1967, and it was CABG. The first percutaneous transluminal coronary angioplasty (PTCA) was done in 1977, but it was just plain balloon angioplasty (PBA) without stenting.[9] Though PBA can achieve transient luminal width gain by plaque extrusion, procedural and clinical success was only around 60% in the first 9 months due to early and late vascular recoil.[10] The next advance was introducing stents to provide mechanical support of the vessel wall with metallic mesh, reducing elastic recoil. The first bare-metal stent (BMS) was implanted in 1986. The problem of prevalent stent thrombosis (ST) was reduced by adopting dual antiplatelet therapy (DAPT) with acetylsalicylic acid and P2Y12 inhibitors. Thus, BMS was proven superior to PBA.[10–12] The obstacle that persisted was neointimal hyperplasia due to stretching and injury of vascular smooth muscle cells, which induces an inflammatory response with cell growth and fibrosis. The consequence was in-stent restenosis (ISR) in 15–30% of treated lesions at mid- and long-term follow-up.[10,13] In preclinical studies, local administration of antiproliferative drugs like paclitaxel showed promising results in reducing arterial endothelial cell proliferation.[14] An antiproliferative agent is added to the stent to form a DES, first implanted in 1999. Though DES introduction reduced ISR incidence compared to BMS, delayed endothelialization due to antiproliferative agents with an inflammatory response to the polymer coating increased the late ST rate in the first DES generation.[10,15] Subsequent DES generation technology improvements resulted in increased flexibility, thinner struts, and faster drug elution, leading to early stent endothelization with lower ST incidence.[10,16] After clinical studies confirmed DES's superiority over BMS, DES became the clinical standard of care, and BMS became obsolete.[2,10] On the other hand, stent implantation still

poses obstacles like compromising natural vasomotion and vessel flexibility. Furthermore, although DES usage reduced ISR and ST rates, these are still present at 5–8% and 0.7–1.3%, respectively, and prolonged DAPT is often indicated.[10,16,17]

Nevertheless, the successful introduction of DES demonstrated the importance of antiproliferative drugs and yielded the hypothesis that the medication may be locally administered without the need for metallic stents, respecting the idea of leaving nothing behind.

DCBs Concept

In a way, the DCB introduction represents returning to the roots. The first PTCA procedures were performed with plain semi-compliant balloons, but this time, a locally applied antiproliferative drug would prevent vessel recoil instead of a stent. Adding an antiproliferative agent layer on a semi-compliant balloon forms DCB. Drugs that are currently in use are paclitaxel and sirolimus. Paclitaxel was the first DCB with clinical studies starting in the early 2000s, while sirolimus studies began in the late 2010s. Data about paclitaxel DCBs are much more robust than sirolimus.[19]

Paclitaxel (Figure 1), a tetracyclic diterpenoid, is a chemotherapy cytotoxic drug used to treat various cancers, including ovarian, breast, and lung cancers. When locally applied by DCB, it effectively inhibits smooth muscle cell proliferation in the vessel wall via stabilizing microtubules by binding the β-tubulin subunit inside the microtubule lumen. By inhibiting the shortening and lengthening of microtubules, paclitaxel blocks mitotic spindle function, arrests cells in the G2/M phase of the cell cycle, and induces apoptosis. Since paclitaxel is a lipophilic substance, it is coated on balloons using solvents like ethyl acetate or acetone, resulting in a homogeneous drug layer. Its high lipophilicity allows rapid uptake, with more than 80% of the drug transferred to the vascular cells within the first 24 hours. Still, prolonged retention in the vessel wall makes it detectable even after 90 days.[14,20,21]

Sirolimus (Figure 2), also known as rapamycin, is an immunosuppressant with anti-inflammatory and antiproliferative properties. It is widely used to prevent organ transplant rejection and treat various autoimmune and malignant conditions. Chemically, it is a macrocyclic lactone produced by the bacterium *Streptomyces hygroscopicus*. It is a cytostatic drug that blocks smooth muscle cell proliferation in the vascular wall by inhibiting the mammalian target of rapamycin, a key regulatory protein kinase involved in cell growth, proliferation, and survival, halting the cell cycle at the G1 phase. Since it is not a cytotoxic drug, it provides less endothelial damage than paclitaxel. Due to its low lipophilicity, sirolimus is applied either as a crystalline coating to the balloon surface combined with excipients like butylated hydroxytoluene or encapsulated in liposomal nanocarriers. In the case of crystalline coating, the complex is delivered to the vessel wall, which

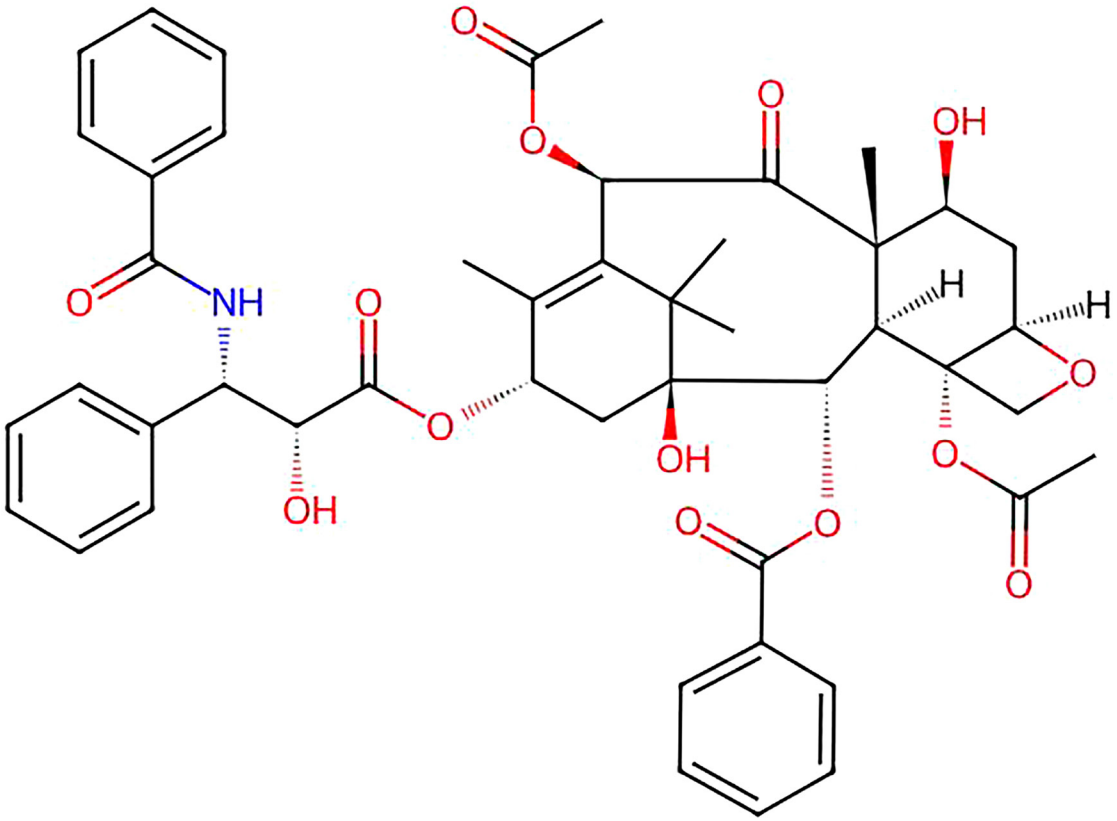

Fig 1 | Paclitaxel structure[18]

DOI: https://doi.org/10.70389/PJC.100007 | Premier Journal of Cardiology 2025;2:100007

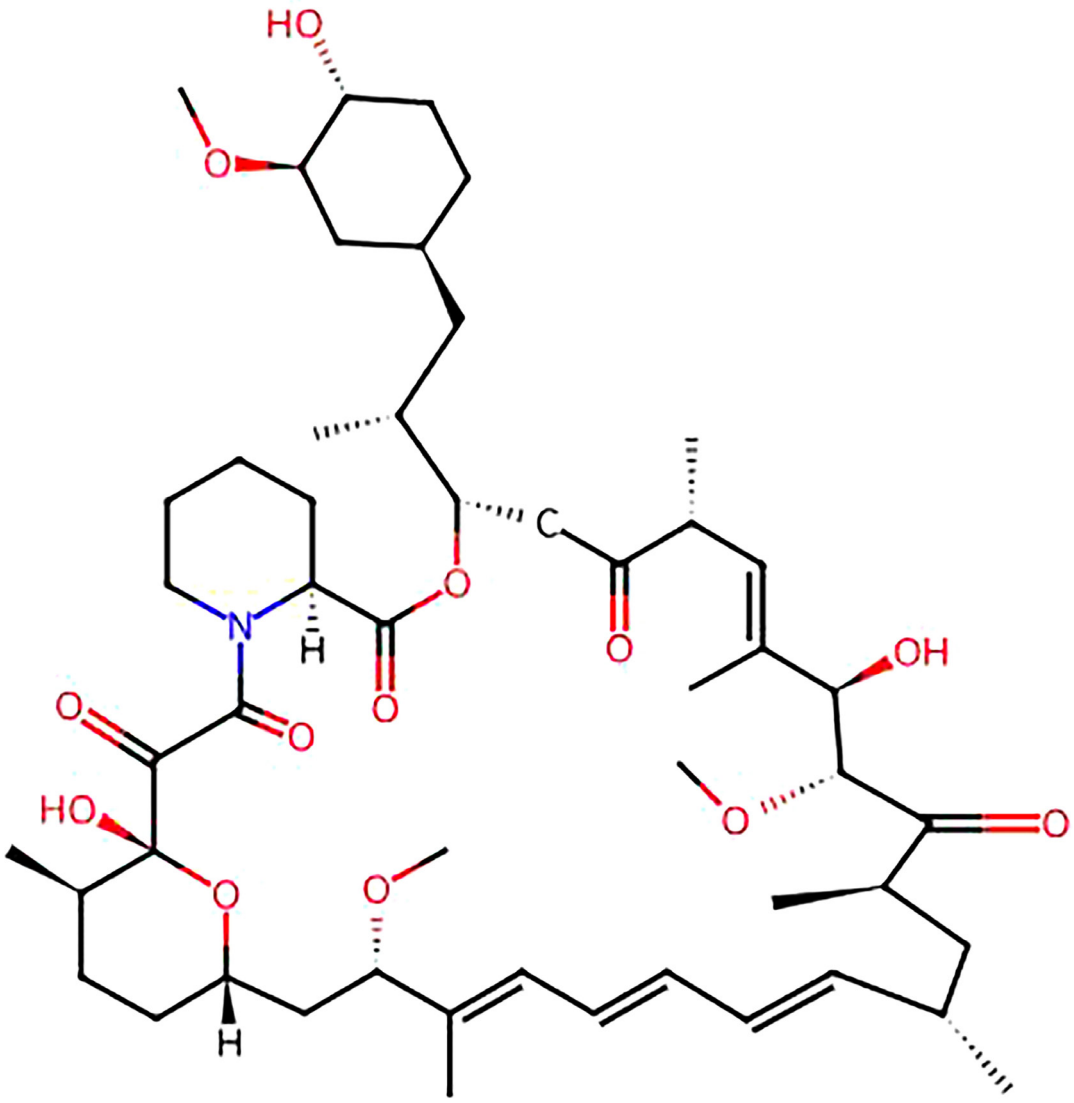

Fig 2 | Sirolimus structure[34]

acts like a drug depot, and the drug is gradually transferred into the cells over 30 days. It is worth noting that new-generation paclitaxel DCBs have included crystalline paclitaxel to gain gradual drug release. Liposomal carriers mimic cell membranes, facilitating cellular uptake via endocytosis and protecting sirolimus from washout during balloon transit. Pharmacokinetics is slightly closer to basic paclitaxel-coated balloons, but nanocarrier technology still provides a more gradual sirolimus transfer over 60–90 days to the locus of action.[20,22] New DCB generations use the lipophilic analogue of sirolimus called biolimus.[23] Despite favorable sirolimus characteristics, including a safer therapeutic range, paclitaxel DCBs usually achieve better late angiographic results. On the other hand, clinical outcomes are similar. Hence, sirolimus DCBs are also considered safe and effective.[24,25] It is important to note that production technology differences between DCB brands with the same antiproliferative agent may affect procedural success. Thus, the results of the studies with more than one DCB brand used in the same patient groups might be challenging to interpret.

Unlike other PTCA balloons, the primary purpose of DCB is delivering the drug, not lesion dilatation or preparation. In order to administer the drug successfully, the lesion had to be adequately prepared. Besides lesion dilatation with semi-compliant and/or non-compliant (NC) balloons, preparation with a scoring balloon is advised to create controlled vessel incisions for securing deeper drug penetration once DCB is applied. Several clinical studies, including ISAR DESIRE 4, showed scoring balloons superior over NC balloons in lesion preparation optimization.[26] After lesion preparation, the DCB should be inflated with lower pressures, usually around six atmospheres. Inflation duration varies from 30 seconds to more than 180 seconds. It is influenced by procedure characteristics, operator preference, and DCB type (crystalline sirolimus-coated balloons require more extended inflation due to decreased drug lipophilicity). The DCB to vessel size ratio should be 1:1. If the vessel diameter

is measured between two sizes, a bigger size is recommended because undersized balloons may not adequately deliver the drug due to insufficient contact surface with the vessel wall. During the periprocedural maneuvering with the DCB, it is important not to touch the balloon to avoid damaging the drug coating.[27]

Acceptable angiographic results before and after DCB application imply TIMI III flow, less than 30% residual stenosis, and absence of significant dissection of grade C or higher. However, there were reported cases of successful DCB procedures with dissection grade C.[28] Fractional flow reserve (FFR) assessment is not mandatory but should be greater or equal to 80% if performed. Intravascular lesion visualizations with optical coherence tomography (OCT) or intravascular ultrasound (IVUS) are helpful to assess whether the lesion preparation and final result are proper.[29] In the case of an unsatisfactory result, bailout stenting is the most common strategy. Target lumen enlargement (TLE) is expected around 6 months after the procedure, though a significant proportion of patients who did not have TLE at that point had late TLE even after a year.[27,28] Mechanisms of TLE include plaque regression and vessel wall enlargement.[30–32] Due to the proven safety from postprocedural lesion thrombosis, DAPT can be administered for just 1 month, which makes DCB an attractive choice for high-bleeding-risk patients.[33] Further text will review evidence for DCB in specific indications.

ISR

The DCB PTCA has been investigated for ISR with more evidence than any other indication. The first randomized clinical trial (RCT) was PACCOCATH ISR, which showed paclitaxel-coated balloon superiority over PBA in BMS ISR with better clinical and angiographic results.[35] The next important RCT was the PEPCAD II trial, which found DCB non-inferior to DES in both clinical and angiographic endpoints in BMS ISR.[36] ISAR DESIRE III trial found DCB superiority over PBA and non-inferiority compared to DES in DES ISR on angiographic endpoints and significantly longer clinical follow-up (initially 3 years with the update at 10 years) compared to previous trials.[37] Other trials that compared DCB and DES in DES ISR yielded conflicting results. RIBS IV trial found DCB inferior to DES, while PEPCAD China ISR, DARE, RESTORE, and BIOLUX-RCT trials showed DCB non-inferiority compared to second-generation DES in BMS and DES ISR.[23,38–40] Still, when the DAEDALUS pooled analysis of the above trials was performed, it showed DCB inferior to DES, while the non-inferiority in BMS ISR remained. The same study found DCB non-inferior to DES in BMS ISR in pooled analysis.[41] The European Society of Cardiology (ESC) guidelines on myocardial revascularization have recommended DCB for either BMS or DES ISR with IA recommendations in 2014 and 2018 editions.[42,43] However, the latest 2024 ESC guidelines on CCS treatment cited the DEADALUS study and stated while DCB PTCA is safe and effective for BMS ISR, PCI with DES is recommended over DCB in DES ISR with IA recommendation. In contrast, the guidelines highlighted the possibility of DCB safety and effectiveness comparable to DES in DES ISR, referring to the ISAR DESIRE III trial results at a 10-year follow-up. The superiority of both methods over uncoated balloons was stated.[2]

DCB for coronary artery revascularization was unavailable in the USA until March 2024, when the Food and Drug Administration (FDA) approved paclitaxel DCB for BMS and DES ISR based on the results of the AGENT IDE trial. This pivotal trial showed paclitaxel DCB superiority over uncoated balloons in treating BMS and DES ISR.[44] DCB was tested against PBA instead of DES because no stents in the USA have been labeled to treat ISR. Hence, PBA was the official standard of care before DCB.

All the studies mentioned in this paragraph have investigated paclitaxel DCB. The first-in-human clinical study for sirolimus DCB was the SABRE study, conducted on patients with ISR in 2017. It showed promising angiographic results at a 1-year follow-up.[45] Malaysian and German-Swiss randomized trials were published in 2022 and found non-inferiority of sirolimus DCB compared to paclitaxel for ISR.[46] A meta-analysis found insignificant differences between angiographic and clinical outcomes of paclitaxel and sirolimus/biolimus DCB in ISR.[47] However, additional research is necessary to bridge the evidentiary gap between sirolimus and paclitaxel DCBs.

De Novo Lesions: Small and Large Vessels

Revascularization of de novo CAD with DCB has been researched less extensively than ISR. Among de novo lesions, small vessel lesions (SVLs) have been the most studied. Vessels with a diameter of less than 2.75 mm are considered small. Though small vessels usually do not supply a large portion of the heart muscle, significant stenosis may cause CCS or ACS symptoms. The DCB use in SVLs is particularly attractive because of the increased acute thrombosis risk for PCI on small vessels. Trials BASKET-SMALL 2, BELLO, PICCOLETO, RESTORE SVD, and PICCOLETO II compared clinical and angiographic outcomes of paclitaxel DCB versus DES in SVLs. Non-inferiority of DCB was shown in all of the trials, including the pooled analysis of all the trials combined. An interesting finding was the absence of acute thrombosis in the DCB arm, while several cases were observed in the DES group.[40,48–52]

While the aforementioned studies researched paclitaxel, sirolimus was also studied. Although a meta-analysis found better late angiographic results for paclitaxel compared to the sirolimus DCB, there was no significant difference in clinical outcomes.[53] Regarding large vessel lesions (LVLs) with 3 mm or greater diameter, few retrospective studies examined DCB use both exclusively or combined with DES. A study from South Korea showed good safety and efficacy results for paclitaxel DCB, while a study from Italy used sirolimus DCB in 77% of cases yielding similar results.[54,55] Another study from South Korea assessed DCB in multivessel CAD and found a lower rate of

DOI: https://doi.org/10.70389/PJC.100007 | Premier Journal of Cardiology 2025;2:100007

major adverse cardiovascular events (MACE) in the DCB-based arm compared to the DES-only strategy. In the DCB-based group, 34.3% of patients were treated with the DCB-only approach, and the rest with DCB and DES combined.[56] The SCBDNMAL trial met angiographic non-inferiority for sirolimus versus paclitaxel DCB in de novo CAD with LVL majority at a 6-month follow-up, though lumen enlargement was more common in paclitaxel DCB.

Patients with CAD and diabetes form a specific population characterized by increased periprocedural and long-term clinical risk. Meta-analysis of studies that assessed the DCB application in diabetic patients found promising results for DCB.[57] As mentioned before, intravascular imaging is a helpful tool to optimize lesion preparation and proper balloon sizing. In the ULTIMATE III trial, IVUS-guided DCB angioplasty for de novo coronary lesions resulted in lower late lumen loss and better lumen diameter than angiography guidance. However, clinical outcomes showed limited differences in the short term.[29]

Not all studies found favorable results for DCB. REC-CAGEFREE I is a recently published RCT that failed to show the non-inferiority of paclitaxel DCB to DES for uncomplicated de novo CAD lesions, irrespective of vessel size.[58] Several RCTs for de novo CAD are currently underway.

Bifurcations

Approximately every fifth PCI targets bifurcation lesions. These are challenging due to technical complexity and increased risk for adverse cardiovascular events. DCB usage is appealing because reducing the number of stents simplifies these procedures significantly. Thus, several studies examined that option. The DEBSIDE trial conducted in France showed favorable clinical and angiographic results for a hybrid approach with implanting DES in the main branch and DCB in the side branch.[59] In the DCB-BIF trial, the side branch compromised after provisional main branch stenting was treated either with NC balloon PBA or DCB. The DCB group had significantly fewer unwanted cardiovascular events.[60] Several publications have shown the efficacy and safety of a pure DCB strategy for bifurcation interventions.[61,62] PEPCAD-BIF trial found the DCB-only approach safe and superior to PBA in treating the distal main branch or side branch.[63] Furthermore, an observational study found lumen enlargement on a side-branch ostium 9 months after paclitaxel DCB was applied exclusively to the main branch lesions. The findings were evaluated with OCT.[64]

However, high-powered RCTs are lacking, especially regarding the DCB-only approach. Nonetheless, the International DCB Consensus Group recommends that both the DCB-only approach and the hybrid DCB with DES approach may be attempted in treating bifurcation lesions.[27]

Calcified Lesions

Coronary artery calcification (CAC) represents an advanced stage of atherosclerosis secondary to smooth muscle cell apoptosis. Metabolic syndrome, diabetes, chronic kidney disease, smoking, and advanced age increase the calcific burden in coronary arteries due to increased inflammatory levels. Coronary calcification affects approximately 30% of all coronary lesions, making them challenging for revascularization and increasing the risk of ISR and ST. Due to calcium hardness, lesion preparation is complex. There is often a need for cutting balloons, intravascular lithotripsy, rotational atherectomy, or high-pressure balloons.[65] Despite the fact that DCBs are attractive options for procedure simplification and the possibility of reducing the complication rate, the data on DCB use in calcified lesions is limited. A retrospective study evaluated DCB use in calcified and noncalcified de novo lesions. Although late lumen loss was numerically higher among patients with calcified lesions mostly prepared with rotational atherectomy, the difference was not statistically significant, while clinical outcomes were similar. Few studies have compared paclitaxel DCB versus DES in calcified lesions and found similar clinical outcomes in both groups.[66,67] Another study included patients with CAC and found promising procedural and clinical outcomes for sirolimus DCB.[68] Though these results are encouraging, high-powered trials for DCB in CAC are needed.

ACS

Implantation of DES has been the golden standard in primary PCI of STEMI patients for the last two to three decades. A PAPPA study published in 2014 tested paclitaxel DCB in STEMI patients and found favorable clinical outcomes at a 1-year follow-up.[69] In 2019, the REVELATION trial showed FFR non-inferiority of paclitaxel DCB compared to DES in STEMI patients at a 9-month follow-up. Patients were randomized to either DCB or DES after balloon dilatation.[70] PEPCAD NSTEMI trial found paclitaxel DCB non-inferior to stents in angiographic and clinical outcomes.[71] Further large-scale trials are needed to learn more about DCB in ACS indications.

Chronic Total Occlusions (CTOs)

A complete or nearly complete blockage of one or more coronary arteries for at least 3 months constitutes CTO. Alternative blood supply flows through interarterial collaterals, which open primarily due to the pressure gradient that develops when a coronary artery becomes blocked. When CTO causes CCS symptoms, revascularization is a treatment option.

CTO interventions pose a risk for undersized stent implantation because postprocedural vessel enlargement extent may be hard to predict, especially for thin distal segments of presumably large vessels. DCB may be an appropriate solution to that problem. Furthermore, CTO interventions often imply intraplaque wiring, resulting in periprocedural coronary dissection, which is beneficial for DCB application. However, evidence about DCB in CTO is limited. Data from prospective registries found non-inferior results for the hybrid approach of DCB and DES compared to the DES-only strategy, with the stent being an independent MACE predictor.[72] A retrospective study from South Korea

tested the DCB-only strategy with good angiographic and clinical results.[73] However, the body of evidence is still insufficient, and further research is needed.

Current Status and Future Perspectives

The year 2024 was turbulent in the field of DCB. As of August 2024, ESC guidelines recommend DES instead of DCB for DES ISR, referring to the DEADALUS study. For that indication, ESC recommended DCB from 2014 until 2024. The only DCB indication endorsed by ESC guidelines remained the ISR of today's obsolete BMS.[2,42,43] On the other hand, the American FDA approved paclitaxel DCB for DES and BMS ISR based on the AGENT IDE trial.[44] MAGICAL-ISR is an ongoing trial with the goal of establishing sirolimus DCB as an approved treatment option for ISR in the USA.[74]

Regarding indications other than ISR, despite a significant number of studies showing the efficacy and safety of DCB, data is not robust enough to recommend DCB in the guidelines. Although the guidelines are cautious, DCB use in both ISR and de novo lesions is considered safe and effective by expert associations, including the International DCB Consensus Group and Asia-Pacific Consensus Group.[27,75] Furthermore, many interventional cardiologists have good experience with DCB. Real-world data of the DCB to DES PCI usage ratio ranging from 1:20 in Europe to 1:10 in the Asia-Pacific region, with up to 1:4 in Japan, shows that DCBs are endorsed in everyday practice worldwide.[19] As mentioned above, the USA has recently been added to the DCB map.

The success rate of future DCB procedures should be improved with the use of proper tools and appropriate lesion selection. Results of the ULTIMATE III trial showed that broader use of intracoronary imaging may contribute to better lesion preparation and balloon sizing.[29] It is worth noting that DCBs are not meant to replace DES completely. REC-CAGEFREE I results showed that stents are still superior in non-complex large vessel interventions.[58] On the other hand, DCBs may simplify complex procedures involving bifurcations, calcified lesions, SVLs, and CTOs.

The body of DCB evidence will grow with new trials on the way. Several trials are planned to compare sirolimus or paclitaxel DCB with DES in treating de novo SVLs or LVLs with or without intravascular imaging.[76–80] CTO DENOVO is an ongoing multinational registry that will assess the DCB-only strategy with the use of intravascular imaging in CTO procedures.[81] The DEBATE trial will include a comparison of ACS patients with high bleeding risk in DCB versus DES.[82] EBC DCB is a trial supported by the European Bifurcation Club that will compare DCB- and DES-based strategies in non-left main coronary bifurcations.[83] DCB technology is expected to advance. Balloons coated with both agents, sirolimus and paclitaxel, as well as those coated with another antiproliferative agent, everolimus, are showing promising results in preclinical studies. Clinical trials have yet to be conducted.[84,85]

Conclusion

DCBs are already a valuable revascularization tool that operators use worldwide across the entire CAD spectrum. The main advantages of DCBs include procedure simplification, preserved natural vasomotion, and shorter DAPT due to reduced risk of acute thrombosis. Intravascular imaging may help achieve adequate lesion preparation, which is crucial for a successful outcome. Although the DCB has been assessed in many studies, further research is ongoing to add more data on its safety and efficacy.

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