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JACC STATE-OF-THE-ART REVIEW

Drug-Coated Balloon for De Novo Coronary Artery Disease

JACC State-of-the-Art Review

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ABSTRACT

Percutaneous coronary intervention with a drug-eluting stent is the most common mode of revascularization for coronary artery disease. However, restenosis rates remain high. Non-stent-based local drug delivery by a drug-coated balloon (DCB) has been investigated, as it leaves no metallic mesh. A DCB consists of a semicompliant balloon coated with antiproliferative agents encapsulated in a polymer matrix, which is released into the wall after inflation and contact with the intima. DCB have demonstrated effectiveness in treating in-stent restenosis. Clinical studies using DCB in de novo coronary artery disease have shown mixed results, with a major benefit in small-vessel disease. Differences in study results are not only due to variations in DCB technology but also to disparity in procedural approach, "leave nothing behind" or "combination therapy," and vessel size. This review focuses on the available evidence from randomized trials and proposes a design for future clinical trials. (J Am Coll Cardiol 2020;75:1061–73)

Percutaneous coronary intervention, whether through plain old balloon angioplasty (POBA) or stent implantation, has continued to benefit from improvements in technology. The introduction of stenting alleviated the limitations of POBA related to elastic recoil and flow-limiting dissections. Higher restenosis rates due to exaggerated neointimal growth in bare-metal stents (BMS) led to the development of drug-eluting stents (DES), which elute an antiproliferative drug (e.g., paclitaxel, sirolimus) to the vessel wall and reduce the restenosis rate. However, late stent thrombosis and restenosis, with a hazard of nearly 2% per year after implantation, remained a concern (1) and motivated the development of drug-coated balloons (DCB). The rationale of DCB technology was a combination therapy of balloon and drug to treat coronary lesions, eliminating stent thrombosis, and achieving lower rates of restenosis by leaving no metal behind.

Clinical studies using DCB have shown promising results for the treatment of in-stent restenosis (ISR), and DCB are a Class I indication to treat ISR, as per European Society of Cardiology guidelines (2). Following the success of the treatment of ISR, the use of DCB was proposed as an alternative for DES for de novo coronary lesions. Unlike the success with treating ISR, the use of DCB in de novo coronary artery disease has shown mixed results. In the United States, DCB are currently approved for use only in peripheral arterial disease and not for coronary artery disease. The purpose of this review is to outline different approaches and trial results with the use of

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

DCB = drug-coated balloon(s)

DES = drug-eluting stent(s)

ISR = in-stent restenosis

LLL = late lumen loss

MACE = major adverse cardiovascular event(s)

POBA = plain old balloon angioplasty

STEMI = ST-segment elevation myocardial infarction

TLR = target lesion revascularization

DCB for de novo lesions, review new drugs for DCB, and propose a novel design for future trials with new-generation DCB for the de novo indication.

DCB DESIGN

The concept of DCB technology has been described elsewhere (3). In short, DCB were developed with the premise that direct contact of the antiproliferative drug with the vessel wall via a semicompliant balloon would be sufficient to inhibit the proliferation of smooth muscle cells (4). An excipient on the DCB facilitates drug retention on the balloon during transit, provides adhesion of the drug to the vessel wall, and promotes drug deposition in the tissue (3). The lipophilic property of paclitaxel ensures rapid cellular uptake with a homogeneous distribution, allowing for a lasting effect on smooth muscle cells. These properties of rapid tissue penetration and sustainability made it attractive for use in DCB. **Table 1** lists all commercially available DCB worldwide.

DCB IN DE NOVO CORONARY ARTERY DISEASE

The efficacy and safety of DCB in the treatment of native-vessel coronary artery disease have been extensively studied, yet results are conflicting. **Table 2** outlines all the randomized clinical trials comparing DCB with BMS or DES, or both. **Figures 1 and 2** and the **Central Illustration** display major adverse cardiovascular events (MACE) and target lesion revascularization (TLR) rates in the studies within 12 months and >12 months, respectively. **Table 3** outlines late lumen loss (LLL) and binary restenosis in all the studies.

Two main approaches were used in all the studies. In combination therapy, DCB angioplasty was performed initially, and then a BMS or DES was implanted, while in the "leave nothing behind strategy," DCB angioplasty was performed, and a stent was implanted only as a bailout for the treatment of suboptimal result after the DCB. A combination of DCB and DES was advocated in patients at high risk for restenosis, such as those with diabetes, but clinical data are limited for this group.

"LEAVE NOTHING BEHIND STRATEGY" ("DCB WITH A BAILOUT STENTING STRATEGY")

With this strategy, there is a theoretical advantage of leaving no metal in the blood vessel and respecting the vessel anatomy. Notable studies that used this strategy were the PICCOLETO (Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small Coronary Artery Diseases) (5), BASKET-SMALL 2 (Basel Stent Kosten-Effektivitäts Trial: Drug-Coated Balloons vs. Drug-Eluting Stents in Small Vessel Interventions) (6), BELLO (Balloon Elution and Late Loss Optimization Study) (7), RESTORE SVD (Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease) (8), and REVELATION (REVascularization With PaclitaxEL-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial InfarcTION) (9) trials and a study by Gobic et al. (10). The majority of these studies were in small-vessel disease, except the REVELATION trial and study done by Nishiyama et al. (11).

HIGHLIGHTS

- DCB shows mixed results in treating de novo coronary artery disease.
- Procedural approach and technology variations account for differences in results.
- "Leave nothing behind" strategy has shown better outcomes than combined therapy.
- Future well-designed clinical trials with strict inclusion criteria are needed.

Small-vessel disease has been noted to have higher rates of restenosis irrespective of the type of intervention (12). The advantages of DCB in this subgroup are that there is no further reduction of lumen by metallic struts and the drug's sustained ability to reduce neointimal proliferation. BASKET-SMALL 2 (6) is the largest study to date on small-vessel coronary artery disease. It compared SeQuent Please DCB (Braun Melsungen AG, Berlin, Germany) with everolimus or Taxus DES (Boston Scientific, Marlborough, Massachusetts). This study concluded that at 12-month follow-up, DCB was noninferior to DES (MACE 8% vs. 9%). RESTORE SVD (8) compared the Restore DCB (Cardionovum, Bonn, Germany) with zotarolimus DES. It showed that DCB was noninferior to new-generation DES for the primary endpoint for percentage stenosis (11% vs. 7.5%, p value for noninferiority <0.001) and showed no significant clinical or angiographic differences in comparison with DES (MACE 9.6% vs. 9.6%; LLL 0.25 ± 0.42 vs. 0.27 ± 0.36; p = 0.41) at 12-month follow-up.

In BELLO (7), DCB angioplasty with the IN.PACT Falcon DCB (Medtronic-Invatec, Frauenfeld,

TABLE 1 Currently Approved Drug-Coated Balloon

Device	Company	Drug	Excipient
Paccocath	Bayer, Leverkusen, Germany	Paclitaxel	Iopromide
SeQuent Please Neo	Braun Melsungen, Berlin, Germany	Paclitaxel	Iopromide
Dior I and II	Eurocor, Bonn, Germany	Paclitaxel	Shellac/dimethyl sulfate
Biostream	Biosensors International Group, Switzerland	Paclitaxel	Shellac
Agent	Boston Scientific, Marlborough, Massachusetts	Paclitaxel	Citrate ester
Essential	iVascular, Sant Vicenç dels Horts, Spain	Paclitaxel	Organic ester
IN.PACT Falcon	Medtronic, Dublin, Ireland	Paclitaxel	Urea
Pantera Lux	Biotronik, Bülach, Switzerland	Paclitaxel	Butyryl-tri-hexyl citrate
Elutax	Aachen Resonance, Aachen, Germany	Paclitaxel	Dextrane
Danubio	Minvasys, Gennevilliers, France	Paclitaxel	Butyryl-tri-hexyl citrate
Restore	Cardionovum, Bonn, Germany	Paclitaxel	Shellac
Protégé	Blue Medical, Helmond, the Netherlands	Paclitaxel	Butyryl-tri-hexyl citrate
Virtue	Caliber Therapeutics, New Hope, Pennsylvania	Sirolimus nanoparticles	Porous balloon
Selution	M.A. Med Alliance, Mont-sur-Rolle, Switzerland	Sirolimus nanoparticles	Cell-adherence technology
Magictouch	Concept Medical Research, Gujarat, India	Sirolimus nanoparticles	Phospholipid excipient

Switzerland) was associated with less angiographic LLL and similar rates of restenosis and revascularization in comparison with the Taxus DES at 6 months. At 2-year follow-up of the BELLO study (13), there was trend toward lower clinical events in patients in the DCB group, and at 3-year follow-up (14), MACE rates were significantly lower with DCB than with DES (14% vs. 30%, $p = 0.015$). The positive results of the BELLO study are encouraging. The findings are due to longer follow-up and the comparator being a paclitaxel-eluting stent. Other notable features of this study are a higher percentage of participants with diabetes (40%), one-half of the lesions being <2.25 mm, predilation rates of 97%, and lower bailout stenting rate (20%). Importantly, patients treated with a pure "leave nothing behind" strategy did not have any thrombotic events or peri-procedural myocardial infarction. Optimal results were also shown in retrospective studies (15,16) in the treatment of small-vessel disease, as DCB respects the vessel anatomy. The recently presented PICCOLETO II study with a current-generation Elutax SV DCB (Aachen Resonance, Aachen, Germany) (17) showed significantly better LLL (DCB 0.04 ± 0.28 mm vs. DES 0.17 ± 0.39 mm) and acceptable clinical outcomes when compared with DES at 6 months.

All the studies involving small-vessel disease showed the benefit of DCB, except the PICCOLETO study (5). This study was prematurely stopped because of high MACE rates in the DCB group, which was likely due to the first-generation Dior DCB (Eurocor Tech, Bonn, Germany), which elutes a lower concentration of paclitaxel (18). This study shows the importance of the excipient in DCB, the fact that not all DCB are equal, and that they cannot be treated as a "class effect." Furthermore, inadequate lesion preparation (only 25% were predilated); higher rate of bailout stenting for type B dissections, which is against the recommendations from the DCB consensus group (19); and the possibility of higher rates of geographic mismatch may also be reasons for the negative results. Whereas studies with a "leave nothing behind" strategy, except the BELLO (7) study, have shown noninferior results, the lessons learned should be applied to all future studies. Well-designed randomized clinical trials with strict inclusion and procedural criteria are needed for future DCB trials, as the benchmark (DES) is already widely used because of its simplicity and safety.

DCB show another potential advantage during high thrombus burden and inflammatory state. Local drug delivery by DCB at the time of peak inflammatory state, as in an ST-segment elevation myocardial infarction (STEMI), has many potential advantages in endothelial function preservation, such as lower risk of thrombosis due to less malapposition and homogeneous administration of the drug. The REVELATION trial (9) was conducted in STEMI patients with large coronary artery disease. DCB angioplasty with the Pantera Lux balloon (Biotronik AG, Buelach, Switzerland) was compared with sirolimus or everolimus DES. The DCB showed no significant difference in LLL (0.05 ± 0.13 mm vs. 0.00 ± 0.05 mm, $p = 0.51$) and clinical outcomes (MACE 3% vs. 2%, $p = 1.00$) at 9-month follow-up. Another study performed in STEMI patients, by Gobic et al. (10), also showed similar results at 6-month follow-up. Although in the DEB-AMI (Drug Eluting Balloon in Acute ST-Segment Elevation Myocardial Infarction) (20) trial DCB in STEMI was prematurely stopped for safety reasons, REVELATION (9) and Gobic et al. (10)

TABLE 2 Randomized Trials of DCB in De Novo Coronary Artery Disease

First Author/Study (Ref. #)	Year	Study	Reference Vessel Diameter	N (Study)	n (DCB)	n (DES)	n (BMS)	DCB	DES
Cortese et al./PICCOLETO (5)	2010	DCB vs. DES	<2.75 mm	57	28	29	N/A	Dior	P-DES
Jeger et al./BASKET-SMALL 2 (6)	2018	DCB vs. DES	<3 mm	758	382	376	N/A	SeQuent Please	E-DES or P- DES
Tang et al./RESTORE SVD (8)	2018	DCB vs. DES	>2.25 mm and <2.75 mm	230	116	114	N/A	Restore	Z-DES
Vos et al./REVELATION (9)	2019	DCB vs. DES	3.24 mm ± 0.5 mm	120	60	60	N/A	Pantera Lux	S-DES or E-DES
Gobic et al. (10)	2017	DCB vs. DES	2.8 mm ± 0.47 mm	75	38	37	N/A	SeQuent Please	S-DES
Nishiyama et al. (11)	2016	DCB vs. DES	>3 mm	60	30	30	N/A	SeQuent Please	N/A
Naganuma et al./BELLO (13)	2015	DCB vs. DES.	<2.8 mm	182	90	92	N/A	IN.PACT Falcon	P-DES
Belkacemi et al./DEB AMI (20)	2012	DCB + BMS vs. BMS vs DES	>2.5 mm	150	50	49	51	Dior	P-DES
Poss et al./PEPCAD III (22)	2009	DCB + BMS vs. DES	N/A	637	312	325	N/A	Coroflex DeBlue	S-DES
Ali et al./PEPCAD IV DM (23)	2011	DCB + BMS vs. DES	>2.5 mm and <3.5 mm	84	45	39	N/A	SeQuent Please	P-DES
Liistro et al. (25)	2013	DCB + BMS vs. DES	>2.5 mm	125	59	66	N/A	Elutax	E-DES
Chae et al. (26)	2017	DCB + BMS vs. DES	>2.9 mm	180	90	90	N/A	SeQuent Please	Z-DES
Zurakowski et al. (27)	2015	DCB + BMS vs. DES	2.5–2.6 mm	202	102	100	N/A	SeQuent Please	P-DES
Clever et al. (28)	2014	DCB + BMS vs. BMS vs. DES.	>2.5 mm and <3.5 mm	77	27	25	25	Experimental by B. Braun (DCB + BMS)	S-DES
Poerner et al. (29)	2014	DCB + BMS vs. DES	>2.5 mm	105	54	51	N/A	SeQuent Please	E-DES
Stella et al./DEBIUT (31)	2012	DCB + BMS vs. BMS vs. DES	>2.5 mm in MB, >2 mm in SB	117	40	40	37	Dior	P-DES
Lopez Minguez et al./BABILON (32)	2014	DCB + BMS vs. DES	>3 mm MB and SB >2 mm	108	52	56	N/A	SeQuent Please	E-DES
Burzotta et al./IN-PACT CORO (34)	2015	DCB + BMS vs. BMS.	>2.8 mm	30	20	N/A	10	IN.PACT Falcon	N/A
Garcia-Touchard et al./PEBSI (35)	2017	DCB + BMS vs. BMS	2.9–3.1 mm	222	110	N/A	112	Pantera Lux	N/A
Seeger et al./PERFECT (36)	2015	DCB + BMS vs. BMS	2.5–4.00 mm	120	62	N/A	58	SeQuent Please	N/A
Rissanen et al. (37)	2019	DCB vs. BMS	2.5–4 mm	208	102	N/A	106	SeQuent Please	N/A
Besic et al. (38)	2015	DCB + BMS vs. BMS	>3 mm	85	41	N/A	44	SeQuent Please	N/A
Shin et al. (39)	2019	DCB vs. BMS	>2.8 mm	40	20	N/A	20	SeQuent Please	N/A

BABILON = Study of the Paclitaxel-Coated Balloon Catheter in Bifurcated Coronary Lesions; BASKET-SMALL 2 = Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions; BMS = bare-metal stent(s); DCB = drug-coated balloon(s); DEBIUT = Drug-Eluting Balloon in Bifurcations Trial; DES = drug-eluting stent(s); E-DES = everolimus drug-eluting stent(s); IN-PACT CORO = Intimal Hyperplasia Evaluated by Optical Coherence Tomography in de Novo Coronary Lesions Treated by Drug-Eluting Balloon and Bare-Metal Stent; MB = main branch; N/A = not available; P-DES = paclitaxel drug-eluting stent(s); PEBSI = Paclitaxel Eluting Balloon in ST Elevation Myocardial Infarction; PEPCAD = Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease; PICCOLETO = Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small Coronary Artery Diseases; RESTORE SVD = Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease; SB = side branch; S-DES = sirolimus drug-eluting stent(s); Z-DES = zotarolimus drug-eluting stent(s).

showed no difference in clinical and angiographic outcomes. In STEMI, an immediate and stable result is of paramount importance. The current body of evidence does not support use of DCB in these high-risk situations.

Overall, DCB angioplasty with bailout stenting strategy studies demonstrated safety and efficacy for small-vessel disease.

COMBINATION THERAPY

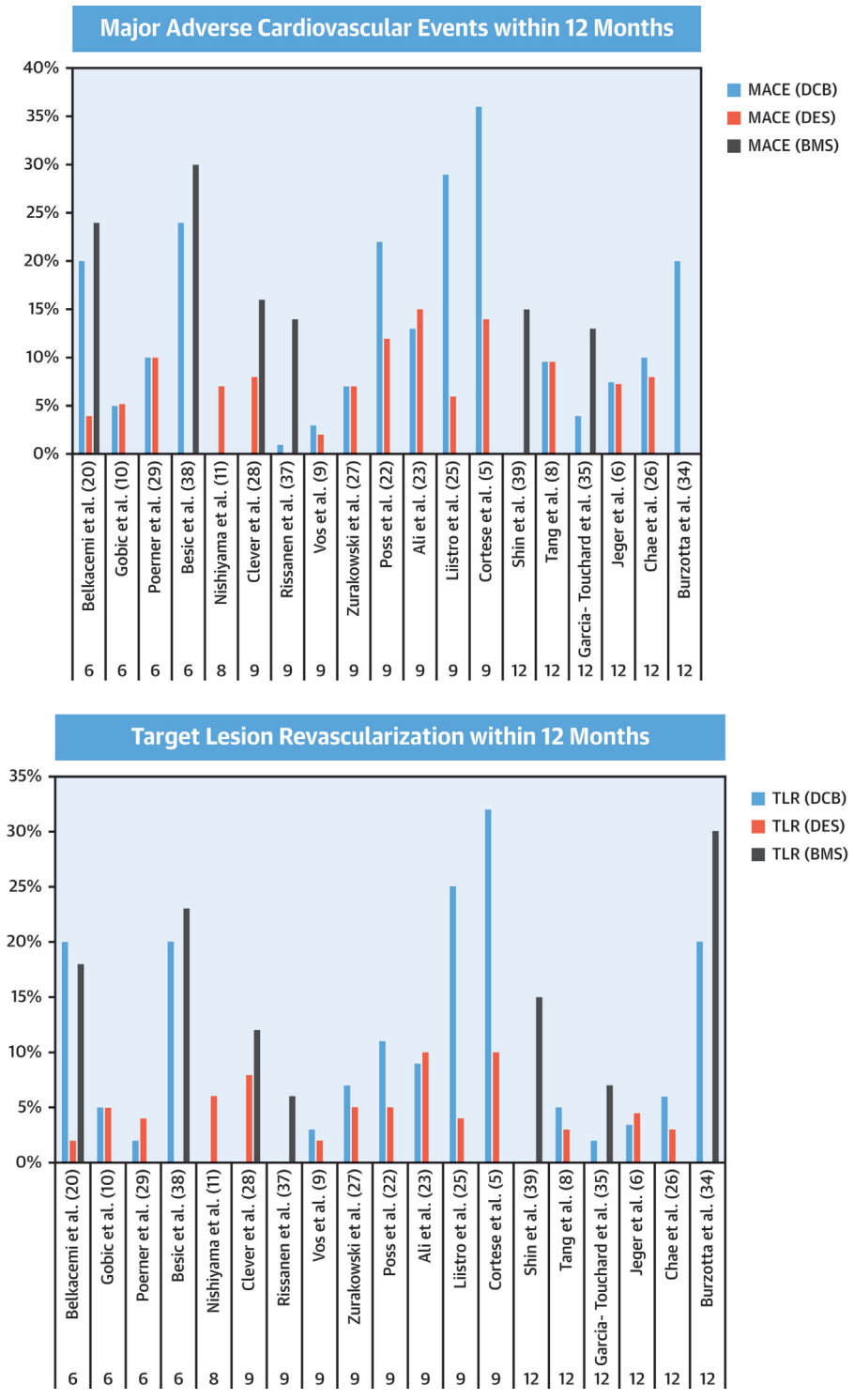
Combination therapy has the advantage of delivering the antiproliferative drug by DCB and overcoming mechanical complications of POBA.

COMBINATION THERAPY OF DCB AND BMS VS. DES.

Notable studies testing this approach are DEB-AMI (20), LOCAL TAX (Local Intracoronary Delivery of Paclitaxel After Stent Implantation for Prevention of Restenosis in Comparison With Implantation of a Bare-Metal Stent Alone or With Implantation of a Paclitaxel-Coated Stent) (21), PEPCAD (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) III (22), and PEPCAD IV DM (23).

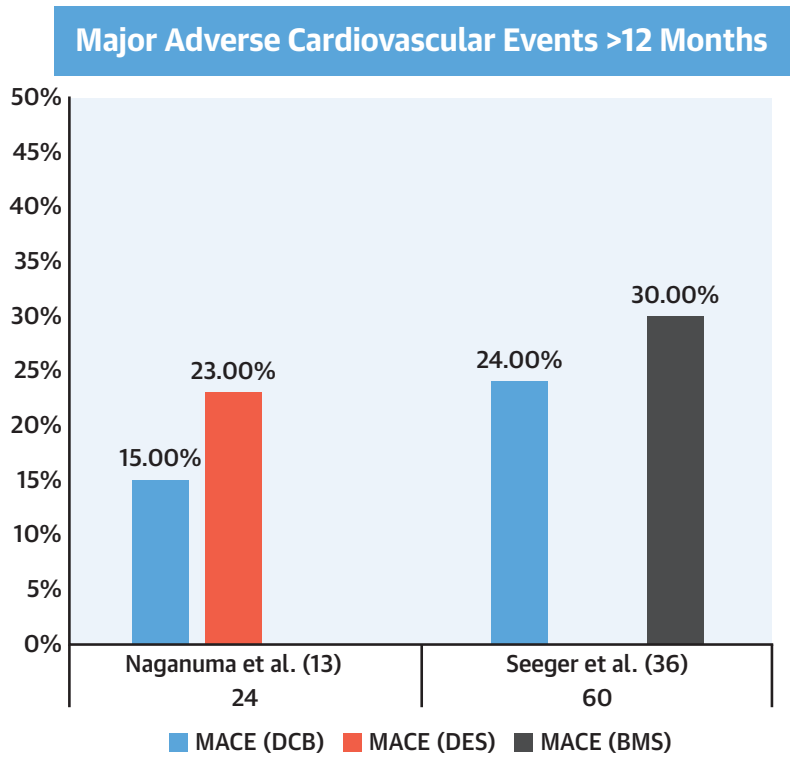
In the LOCAL TAX (21) study, Herdeg et al. (21) used an intravascular paclitaxel delivery catheter (Genie, Acrostak Corp., Geneva, Switzerland). This study showed that this strategy was superior to BMS and inferior to DES, both clinically and angiographically. PEPCAD III (22) was a major randomized trial that evaluated DCB technology pre-mounted on BMS for de novo lesions versus first-generation sirolimus DES. At 9-month follow-up, there was significantly higher LLL (0.41 ± 0.51 mm vs. 0.16 ± 0.39 mm, $p < 0.001$) and MACE (22% vs. 12%, $p < 0.001$) in the DCB arm. Although there was no evidence of geographic mismatch (deployment of the stent outside of the area treated with DCB) on an intravascular ultrasound substudy (24), there was

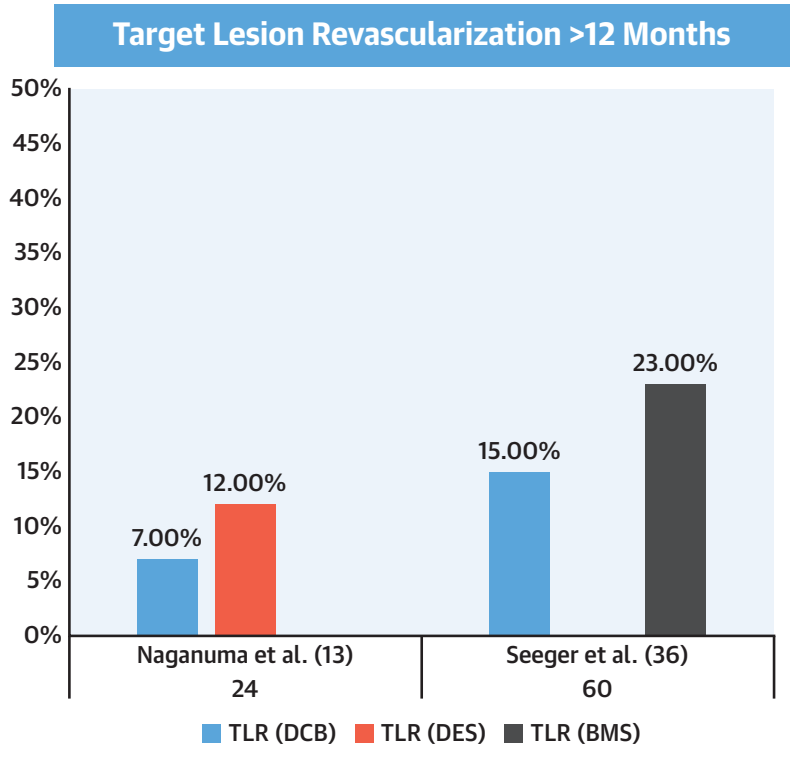
FIGURE 1 **MACE and TLR Within 12 Months**



Major adverse cardiovascular events (MACE) and target lesion revascularization (TLR) rates in all studies with <12 months follow-up are shown. The number of months of follow-up are listed at the bottom of the x-axis. BMS = bare-metal stent(s); DCB = drug-coated balloon(s); DES = drug-eluting stent(s).

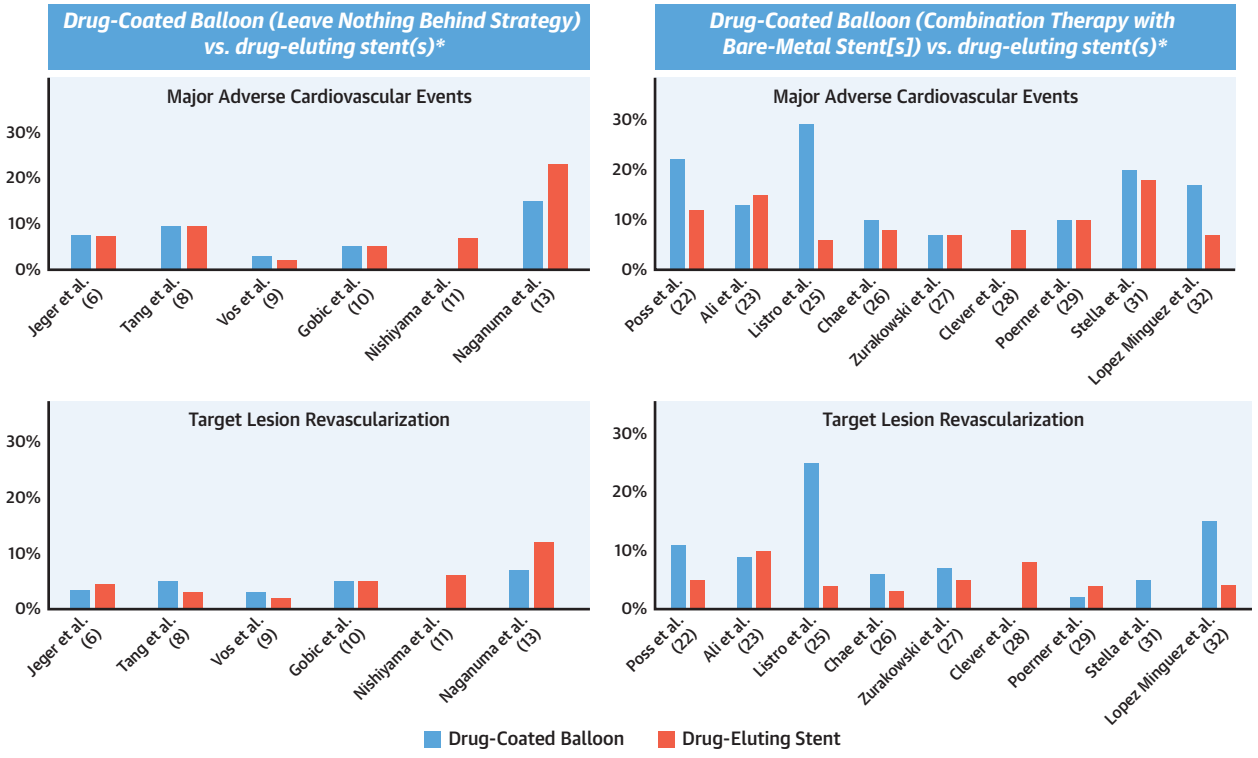
FIGURE 2 **MACE and TLR >12 Months**





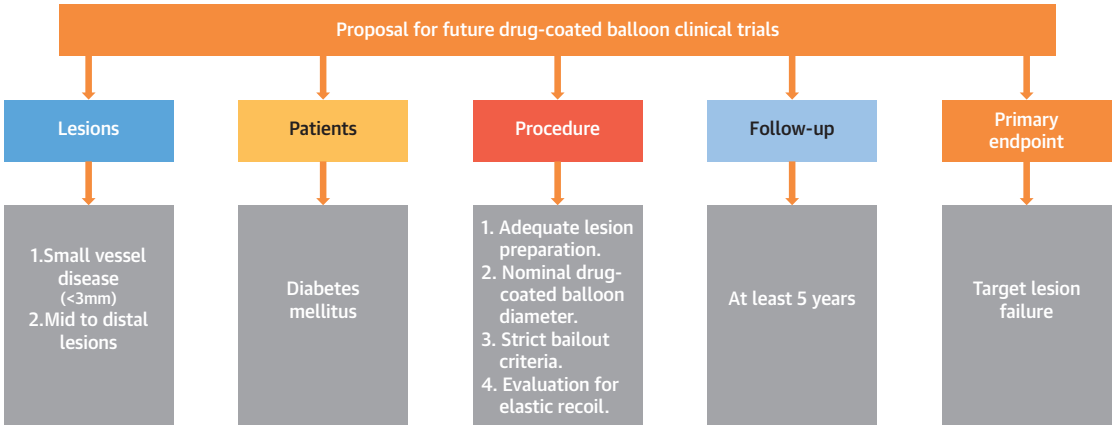
MACE and TLR rates in all studies with >12 months of follow-up are shown. The number of months of follow-up are listed at the bottom of the x-axis. Abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Major Adverse Cardiovascular Events and Target Lesion Revascularization Rates in Trials Evaluating 2 Approaches for Drug-Coated Balloon in De Novo Coronary Artery Disease and Proposal for Future Drug-Coated Balloon Trials**



Factors Supporting Drug-Coated Balloon Performance
-Small vessel disease
-Decreased bailout stenting
-Adequate pre-dilation

Factors Opposing Drug-Coated Balloon Performance
-Geographic mismatch
-Variations in pre-dilation
-Variation in inflation time
-Excipient type



Yerasi, C. et al. J Am Coll Cardiol. 2020;75(9):1061–73.

Major adverse cardiovascular events (MACE) and target lesion revascularization (TLR) rates in drug-coated balloon (DCB) studies with 2 approaches are shown. A proposal for future randomized clinical trial is also displayed. *Excluded 2 studies that used first-generation Dior I DCB (Eurocor, Germany). BMS = bare-metal stent; DCB = drug-coated balloon; DES = drug-eluting stent.

TABLE 3 LLLL and Binary Restenosis

First Author (Ref. #)	LLL (DCB)	LLL (DES)	LLL (BMS)	BR/DCB	BR/DES	BR/BMS
Cortese et al. (5)	1.43 ± 0.88	0.64 ± 0.6	N/A	9/28 (32)	3/29 (10)	N/A
Tang et al. (8)	0.25 ± 0.42	0.27 ± 0.36	N/A	11/100 (11)	7/93 (7.5)	N/A
Vos et al. (9)	0.05 ± 0.13	0.00 ± 0.05	N/A	N/A	N/A	N/A
Gobic et al. (10)	0.09 ± 0.09	0.10 ± 0.09	N/A	N/A	N/A	N/A
Nishiyama et al. (11)	0.25 ± 0.25	0.37 ± 0.40	N/A	N/A	N/A	N/A
Naganuma et al. (13)	0.08 ± 0.38	0.29 ± 0.44	N/A	8/81 (10)	10/82 (12)	N/A
Belkacemi et al. (20)	0.64 ± 0.56	0.21 ± 0.32	0.74 ± 0.57	12/50 (24)	2/49 (4)	10/51 (20)
Ali et al. (23)	0.37 ± 0.59	0.35 ± 0.63	N/A	5/39 (22)	5/36 (14)	N/A
Liistro et al. (25)	1.14 ± 1.0	0.34 ± 0.70	N/A	10/59 (17)	2/66 (3)	N/A
Chae et al. (26)	0.54 ± 0.48	0.28 ± 0.43	N/A	8/74 (11)	2/72 (3)	N/A
Zurakowski et al. (27)	0.63 ± 0.5	0.54 ± 0.5	N/A	N/A	N/A	N/A
Clever et al. (28)	0.36 ± 0.46	0.25 ± 0.34	0.85 ± 0.73	N/A	N/A	N/A
Poerner et al. (29)	0.24 ± 0.21	0.16 ± 0.15	N/A	0/42 (0)	0/48 (0)	N/A
Burzotta et al. (34)	0.59 ± 0.42	N/A	0.85 ± 0.28	N/A	N/A	N/A
Garcia-Touchard et al. (35)	0.32 ± 0.49	N/A	0.85 ± 0.67	2/88 (2)	N/A	25/83 (30)
Besic et al. (38)	0.69 ± 0.72	N/A	0.87 ± 0.65	7/41 (17)	N/A	10/44 (23)
Shin et al. (39)	0.2 ± 0.3	N/A	1.2 ± 0.8	N/A	N/A	N/A

Values are mean ± SD or n/N (%). BR is a diameter stenosis >50%. LLL is the difference of minimum lumen diameter between baseline and follow-up.
BR = binary restenosis; LLL = late lumen loss; other abbreviations as in Table 2.

significantly higher neoatherosclerosis in the DCB + BMS group.

The DEB-AMI trial (20) and the studies done by Liistro et al. (25), Chae et al. (26), and Zurakowski et al. (27) all showed inferior results with a combined approach of DCB + BMS when compared with DES. Other studies, such as PEPCAD IV DM (23), Clever et al. (28), and Poerner et al. (29), did not show any significant benefit with a combined approach because of their small sample sizes. Also, treatment of bifurcation lesions remains suboptimal, primarily because of higher adverse event rates in side branches (30). A hybrid combination approach was tested in bifurcation disease in 2 randomized trials—DEBIUT (31) and BABILON (Study of the Paclitaxel-Coated Balloon Catheter in Bifurcated Coronary Lesions) (32). DEBIUT used first-generation Dior DCB, and BABILON used SeQuent Please DCB, in the side branch with a stent in the main branch. As with other combination approach trials, DCB use in bifurcation disease did not translate to improved clinical outcomes.

The inferior performance of DCB in these studies had several explanations:

1. Geographic mismatch of the stent placement in an area not covered by the DCB. Some studies have suggested that implantation of BMS can result in accelerated rates of atherosclerosis in these areas (33).
2. Variation in vessel preparation in terms of predilation. Pre-dilation is an important procedural step, as it creates microdissections, which are required for optimal uptake of the drug. DCB are intended only to deliver the drug but not to prepare the lesion. Whereas it is still unclear whether a scoring balloon or a regular balloon should be used for pre-dilation, an ongoing clinical trial (HYPER [Drug-Coated Balloon in Combination With New Generation Drug-Eluting Stent for de Novo Diffuse Disease Treatment]; NCT03939468) might provide more information.
3. Variation in inflation time of DCB to transfer the drug to the wall. Shortened inflation times may not be enough to deliver an adequate amount of drug.
4. Excipient type can differ in efficacy to transfer the drug and release it to the vessel wall, as shown in different pharmacokinetics studies (18).

COMBINATION THERAPY OF DCB AND BMS VS. BMS. Notable studies that evaluated this approach were DEB-AMI (20), IN-PACT CORO (Intimal Hyperplasia Evaluated by Optical Coherence Tomography in de Novo Coronary Lesions Treated by Drug-Eluting Balloon and Bare-Metal Stent) (34), PEBSI (Paclitaxel Eluting Balloon After Bare Metal Stent Implantation vs. Drug-Eluting Stent in ST Elevation Myocardial Infarction) (35), PERFECT (Paced Electrocardiogram Requiring Fast Emergent Coronary Therapy Study) (36), and DEBUT (Drug-Eluting Balloon in Stable and Unstable Angina) (37). PEBSI was the largest randomized study that used this approach in STEMI patients. It showed that post-dilatation with the Pantera Lux balloon after BMS implantation significantly reduced LLL at 1 year. In IN-PACT CORO (34), optical

coherence tomography performed at 12-month follow-up showed reduction of neoatherosclerosis with DCB use after BMS implantation. In small studies done by Clever et al. (28) and Besic et al. (38), the combined strategy was associated with a lower LLL than BMS. In PERFECT, the combined intervention strategy was superior to the BMS-alone approach with lower MACE from 6 months to 5 years. Rissanen et al. (37) and Shin et al. (39) also showed that DCB with a BMS was superior to BMS alone, both angiographically and clinically, in high-bleeding-risk patients.

The combined intervention strategy consistently has shown superiority over BMS alone except in DEB-AMI (20). This strategy could be a potential alternative in high-bleeding-risk patients, as they only need a short course of antiplatelet therapy. However, the use of DCB in the era of new ultrathin-stent struts, which also require shorter dual antiplatelet therapy (40), needs to be further tested.

COMBINATION THERAPY OF DCB AND DES IN HIGH-RESTENOSIS-RISK PATIENTS. The hybrid approach of combining DCB with DES has been evaluated in long de novo lesions and diffuse coronary artery disease. In this approach, a DES was implanted in the proximal lesion, and DCB angioplasty was performed in the distal lesion. The advantage of this approach is an overall reduction in stent length, which in turn is beneficial for lower restenosis rates. However, it is important to note that these devices are not intended to treat the same diseased vessel segment. In the combination therapy approach for diffuse disease, the sequential lesions should be treated separately, and there should be no overlap between the treated segments because of a higher risk of restenosis. Small observational studies done by Costopoulos et al. (41) show that this approach was acceptable, with comparable MACE and TLR rates (MACE 20.8% vs. 22.7%, $p = 0.74$; TLR 9.6% vs. 9.3%, $p = 0.84$) in the treatment of diffuse coronary artery disease. Ielasi et al. (42) tested this strategy using bioresorbable scaffolds and showed good clinical outcomes. A large nonrandomized, prospective, multicenter trial, HYPER, is being planned to evaluate the feasibility and clinical effectiveness of this approach using Restore DCB (Cardionovum).

NEW-GENERATION SIROLIMUS DCB

Limus-based drugs are cytostatic, with a higher margin of safety than paclitaxel, which is cytotoxic. A patient-level meta-analysis done by Dangas et al. (43) showed that everolimus DES was associated with lower mortality and superior clinical outcomes when compared with Taxus DES. However, the problem of using sirolimus in DCB is that the lower lipophilic property of the drug makes tissue absorption and elution more difficult. Newer-generation DCB have been developed using different delivery technologies to address this issue. The Magictouch (Concept Medicals, Surat, India) sirolimus-coated balloon catheter used the Nanolute technology (Concept Medicals), which is a nano-carrier-based drug-delivery technology in which nano-sized encapsulated particles carry the drug. The Selution sirolimus DCB (MedAlliance, Sankt Gallen, Switzerland) uses microspheres made from a biodegradable polymer intermixed with sirolimus, which ensures a controlled, sustained release with maintenance of the therapeutic effect in tissue over long periods of time. The Selution DCB also has a novel cell-adherent technology (CAT), which protects microreservoirs during balloon insertion, lesion crossing, and expansion. The CAT membrane, with embedded microreservoirs, adheres to the vessel wall during inflation and releases the drug from the balloon delivery system. The Virtue sirolimus DCB (Caliber Therapeutics, New Hope, Pennsylvania) has a microporous angioplasty system with numerous 4-μm laser-drilled pores, which delivers sirolimus nanoparticles and allows enhanced tissue penetration with controlled and sustained drug delivery. Registry studies using these DCB have shown promising results, with lower MACE and TLR rates (44–46).

FUTURE RANDOMIZED CLINICAL TRIAL DESIGN

DCB technology continues to evolve with improvements in excipient technology and introduction of sirolimus to replace paclitaxel. **Table 4** provides an overview of ongoing clinical trials of DCB for de novo coronary artery disease (PREPARE-NSE [Comparison of Scoring Balloon and Conventional Balloon Predilation Before Drug Coated Balloon for de Novo Lesion in Patients With High Bleeding Risk], NCT03817801; FADDY [Fractional Flow Reserve Guided Drug Coated Balloon Only Strategy in De Novo Coronary Lesions], NCT03452904; Drug-Coated Balloon Versus Drug-eluting Stent in the Treatment of Coronary Artery Lesions in STEMI Patients in De Novo Coronary Lesions, NCT04072081; Comparison of Safety and Efficacy of Coronary Drug-Coated Balloon Combined With Spot Stenting of Drug-Eluting Stent Versus Second-Generation Drug-Eluting Stent for Treating Diffuse Coronary Artery Lesions: a Prospective, Randomized, Controlled Clinical Trial, NCT03589157; AGENT Japan SV [Safety

TABLE 4 Ongoing Clinical Trials of DCB in De Novo CAD

ClinicalTrials.gov Identifier	Status	Study Title	Study Design
NCT03939468	Not yet recruiting	Drug-Coated Balloon in Combination with New Generation Drug-Eluting Stent for de Novo Diffuse Disease Treatment (HYPER)	Prospective, nonrandomized, single-arm, multicenter study (DCB + DES)
NCT03817801	Recruiting	Comparison of Scoring Balloon and Conventional Balloon Predilation Before Drug Coated Balloon for de Novo Lesion in Patients with High Bleeding Risk (PREPARE-NSE)	Prospective, randomized clinical trial (DCB with scoring balloon dilation vs. DCB with standard balloon dilation)
NCT03452904	Recruiting	Fractional Flow Reserve Guided Drug Coated Balloon Only Strategy in De Novo coronary Lesions (FADDY)	Prospective, randomized clinical trial (DCB vs. DES)
NCT04072081	Not yet recruiting	Drug-coated Balloon Versus Drug-eluting Stent in the Treatment of Coronary Artery Lesions in STEMI Patients in De Novo Coronary Lesions	Prospective, multicenter, randomized clinical trial (DCB vs. DES)
NCT03589157	Not yet recruiting	Comparison of Safety and Efficacy of Coronary Drug-coated Balloon (DCB) Combined with Spot Stenting of Drug-eluting Stent (DES) Versus Second-generation DES for Treating Diffuse Coronary Artery Lesion	Prospective, randomized clinical trial (DCB + DES vs. DES)
NCT04058990	Not yet recruiting	Safety and Effectiveness of Agent Paclitaxel-Coated PTCA Balloon Catheter (AGENT Japan SV)	Prospective, randomized clinical trial (New experimental DCB with lower paclitaxel dose vs. standard DCB)
NCT04104854	Not yet recruiting	Safety and Efficacy of Drug Coated Balloon Therapy for de Novo Lesions in Patients with Coronary Heart Disease Under the Guidance of QFR (UNIQUE-DCB study)	Prospective, multicenter, randomized clinical trial (DCB vs. DES)
NCT03223974	Recruiting	Clinical Trial on Safety and Efficacy of Drug-coated Balloon in Treatment of Coronary Bifurcation Lesions (BJDCB-BIF)	Prospective, randomized clinical trial (DCB vs. DES)
NCT02760732	Recruiting	Drug Eluting Balloon for Treatment of Unstable Angina	Prospective, randomized clinical trial (DCB vs. DES)
NCT03376646	Recruiting	A Safety and Efficacy Study of Dissolve (DK Medical Technology Co., Ltd., Suzhou, China) in Treatment of Coronary Small Vessel Disease	Prospective, multicenter, randomized clinical trial (DCB vs. DES)

CAD = coronary artery disease; FFR = fractional flow reserve; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; RR = restenosis rates; TLF = target lesion failure; TLR = target lesion revascularization; other abbreviations as in Tables 1 to 3.

Continued on the next page

and Effectiveness of Agent Paclitaxel-Coated PTCA Balloon Catheter], NCT04058990; Safety and Efficacy of DCB Therapy for de Novo Lesions Under the Guidance of QFR in CHD Patients, NCT04104854; BJDCB-BIF [Clinical Trial on Safety and Efficacy of Drug-Coated Balloon in Treatment of Coronary Bifurcation Lesions], NCT03223974; Drug Eluting Balloon for Treatment of Unstable Angina, NCT02760732; A Safety and Efficacy Study of Dissolve in Treatment of Coronary Small Vessel Disease, NCT03376646). The recent reports on late all-cause mortality with paclitaxel DCB technology when compared with POBA in peripheral artery disease (47) raised concerns in the coronary application, although this phenomenon so far has not been demonstrated in coronary artery disease. The recently performed DAEDALUS (Difference in Antirestenotic Effectiveness of Drug-Eluting Stent and Drug-Coated Balloon Angioplasty for the Occurrence of Coronary In-Stent Restenosis) patient-level meta-analysis study (48) did not show any evidence of increased mortality with DCB in coronary in-stent restenosis. Further randomized trials are needed to address whether limus-based DCB will be able to demonstrate safety when compared with limus-based DES.

Negative remodeling effects of balloon angioplasty (vessel shrinkage) and intravascular stent (neointimal proliferation) can be overcome by DCB-only angioplasty. Because of the drug's hydrophilic nature, paclitaxel stays in the arterial vascular wall for prolonged periods and inhibits smooth muscle cell proliferation, and with the absence of a metallic implant, DCB leads to positive remodeling of the arterial wall. Whereas the effects of positive remodeling were not shown in DCB clinical trials, prospective intravascular ultrasound and optical coherence tomography studies (49,50) have shown a trend toward positive remodeling without any aneurysm formation with the use of DCB. Long-term follow-up studies clearly are needed to identify this possible benefit of DCB-positive remodeling.

We propose that use of DCB be examined in small vessels (<3 mm), or in mid and distal vessels, where distal stents may be a disadvantage for future coronary artery bypass grafting. These studies should be randomized 1:1 to best-in-class DES with the primary

TABLE 4 Continued

Outcomes	Reference Vessel	DCB	DES	Target Sample Size	Follow-Up
Device-oriented composite endpoint, procedural success, peri-procedural myocardial infarction, vessel thrombosis, flow limiting dissection	>2.75 mm for DES and 2–2.75 mm for DCB	Restore DCB (Cardionovum, Bonn, Germany)	Any	100	12 months
Changes in lumen area, bailout stenting, FFR, LLL, TLR, MACE	De novo CAD in patients with high bleeding risk	Any	No DES used	60	6 months
FFR, LLL, TLF, MACE, success rates	2.5–3.5 mm and <28 mm in length	Any	Any	80	9 months
LLL, RR, TLF, MACE, target lesion thrombosis	2.5–3.5 mm and <28 mm in length	Any	Any	4000	12–24 months
LLL, RR, TLR, MACE	2.5–4.0 mm and length <25 mm	SeQuent Please (Braun, Melsungen, Berlin, Germany)	Any	140	36 months
TLF	2–3 mm and length <28 mm	New experimental DCB with lower paclitaxel dose and SeQuent Please (Braun Melsungen)	No DES used	150	6 months
LLL, MACE, TLR	Small vessel disease	Any	Any	110	12 months
LLL, MACE, MI, and ischemia-driven revascularization	Bifurcation lesions	Any	Any	80	24 months
Changes in target lumen and MACE	2.5–3.5 mm and <25 mm in length	SeQuent Please (Braun Melsungen)	YINYI DES (Liaoning Biomedical Materials, Dalian, China)	60	12 months
Percentage of stenosis, success rate, LLL, TLR, MACE	2.25–2.75 and <26 mm in length	Dissolve TM (China)	Resolute DES (Medtronic, USA)	278	60 months

endpoint of target lesion failure. Another subset of patients could be those with diabetes, who often present with higher TLR even with best-in-class DES. Patients enrolled into these studies must be followed up for at least 5 years and treated with optimal medical therapy during follow-up. Before these studies are conducted, detailed instructions for use should be developed and should include the following: all the lesions must be pre-dilated as per the consensus group's updated recommendations (19), adequate lesion preparation with use of atherectomy devices or scoring balloons if needed for calcified lesions; DCB diameter should be 0.8× to 1× nominal vessel size to avoid the mechanical complications from POBA; bailout stenting should be applied only in cases of residual stenosis >50% or type C coronary dissections; and a thorough evaluation of elastic recoil should be done by performing another angiogram 10 to 15 min after initial angioplasty. If there is any significant reduction in lumen diameter, a stent should be implanted. Experience from prior studies has shown that the combination strategy with a BMS was associated with worse outcomes and should be avoided. In these bailout stenting situations, a current-generation DES should always be preferred; however, more studies should investigate the safety of combination therapy with a DES. Finally, intravascular imaging guidance should be recommended before and after angioplasty.

CONCLUSIONS

The motivation not to leave the metal behind remains, and with the decline in use of bioresorbable vascular scaffold technology, DCBs remain an attractive alternative to meet this goal. DCB have many advantages in comparison with DES, as DCB leave no metallic mesh and ensure homogeneous distribution of the drug and promote positive remodeling of the vessel and potentially shorter course of dual antiplatelet therapy. However, to date, the available data do not support broad usage of DCB for de novo lesions. Although the safety signal with paclitaxel DCB in the peripheries was not demonstrated in the coronaries, the number of studies to evaluate the use of DCB in the coronaries was small, with short follow-up time. Large randomized studies are needed in coronary artery disease, in which DES have shown suboptimal results,

as in small-vessel disease, the distal coronary bed, in diabetic patients, and in long, diffuse lesions that require long DES. The next wave of limus-based DCB should take an academic approach to the trial design as definitive noninferiority studies comparing them to best-in-class DES with at least 5 years of follow-up. With the emergence of the newer sirolimus DCB (i.e., Magictouch, Virtue, Selution), a new opportunity and era would arise to establish the role of limus-based DCB for the treatment of de novo lesions, which would hopefully alleviate some of the concerns raised by paclitaxel DCB.

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