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EXPERT CONSENSUS

Definitions and standardized endpoints for the use of drug-coated balloon in coronary artery disease: consensus document of the Drug Coated Balloon Academic Research Consortium

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ABSTRACT

The Drug Coated Balloon Academic Research Consortium project originated from the lack of standardization and comparability between studies using drug-coated balloons in the treatment of obstructive coronary artery disease. This document is a collaborative effort between academic research organizations and percutaneous coronary intervention societies in Europe, the USA, and Asia. This consensus sought to standardize study designs and endpoints for clinical trials involving drug-coated balloons, including defining angiographic, intravascular, and non-invasive imaging methods for lesion assessment, alongside considerations for post-revascularization pharmaco-therapy. The concept of 'blended therapy', which advocates for combining device strategies, is also discussed. This paper delineates study types, endpoint definitions, follow-up protocols, and analytical approaches, aiming to provide consistency and guidance for interventional cardiologists and trialists.

KEYWORDS: drug-coated balloon; randomized clinical trial; Academic Research Consortium; coronary artery disease

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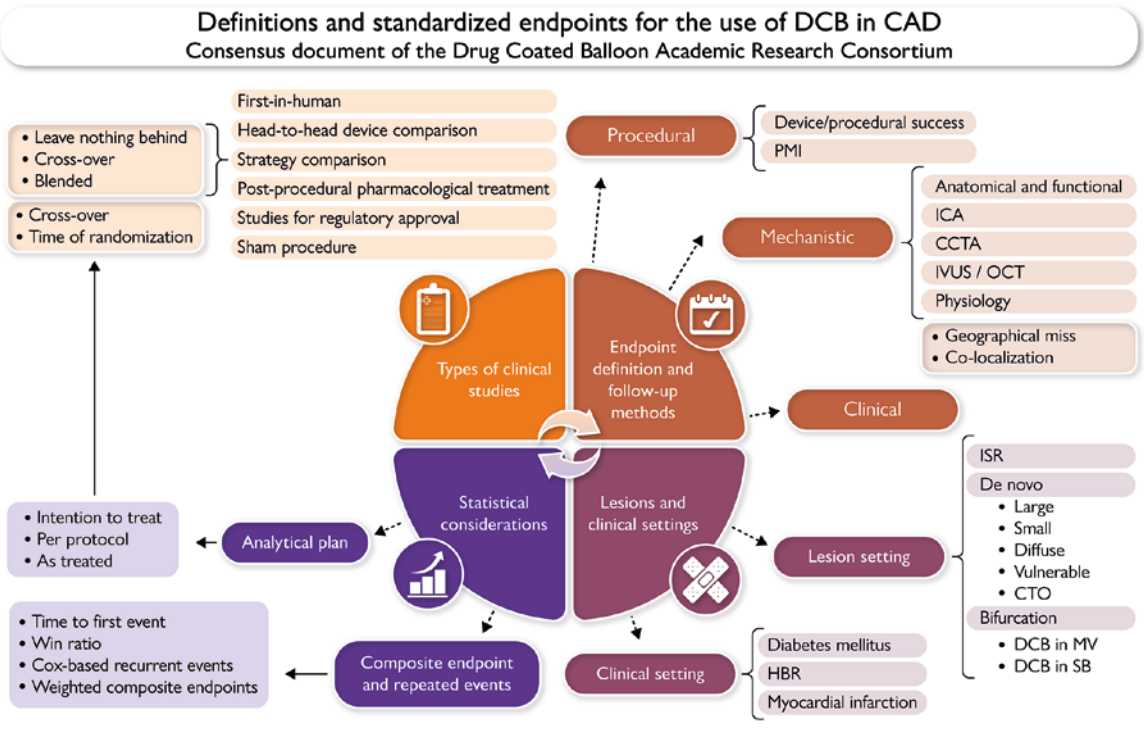
Objectives

Drug-coated balloons (DCBs) are part of the armamentarium for the treatment of obstructive coronary artery disease (CAD). They have inherently different characteristics to drug-eluting stents (DES), relying on a fast and homogeneous transfer of antiproliferative drug into the vessel wall during balloon inflation, thereby removing the requirement for permanent vessel scaffolding and caging[1,2]. Their use offers several distinct advantages over DES: (1) they ensure lesions remain amenable to regression with antiatherogenic drugs; (2) they can be used in diffuse/small vessels/distal lesions where percutaneous coronary intervention (PCI) with stents yields suboptimal results[3]; and (3) they 'leave nothing behind' preventing long-term permanent implant-related cardiovascular events[4-6]. Nevertheless, the absence of metallic caging or radio-opaque markers that identify treated segments creates challenges (i.e. geographic miss) with analysing and colocalizing treated lesions at different time points and during final clinical event adjudication (i.e. restenosis, occlusion).

As part of the Academic Research Consortium (ARC), this document aims to standardize study designs for trials involving DCBs and define the recommended parameters for lesion assessment and trial endpoints, so that consistent, practical, and reproducible terminology is made available to interventional cardiologists and trialists in the field These comprehensive definitions incorporate, among others, methods of angiographic assessment, as well as the role of intravascular imaging, non-invasive coronary imaging, new image-based methods of functional lesion evaluation, and dedicated post-revascularization anti-platelet therapy (type, duration, intensity) **(Graphical Abstract)**.

Secondly, this document seeks to offer a high-level interpretation of the existing data in the field, which has been limited by the small sample sizes of clinical trials and poor or inconsistent-quality metrics. These challenges have contributed to the delay in producing large-scale, randomized clinical trials capable of impacting clinical practice guidelines.

Lastly, this document aims to define the emerging concept of 'blended therapy', namely the combination of various devices and technologies as a treatment strategy that can supersede the classical antagonism between various *'devices'* of intervention.



Graphical Abstract. *Definitions and standardized endpoints for the use of drug-coated balloon in coronary artery disease: consensus document of the Drug Coated Balloon Academic Research Consortium (DCB ARC). The DCB ARC initiative addresses the need for standardizing approaches in drug-coated balloon (DCB) research to enhance comparability between studies. This consensus aims to establish uniform study designs and endpoints for DCB clinical trials. Key components include standardized assessment parameters covering various imaging methods and post-revascularization therapy considerations. The paper outlines types of clinical studies, endpoint definitions and follow-up methods, lesions and clinical settings for the use of DCB, and statistical considerations, offering guidance and consistency to interventional cardiologists and trialists. CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CTO: chronic total occlusion; DCB: drug-coated balloon; HBR: high bleeding risk; ICA: invasive coronary angiography; ISR: in-stent restenosis; IVUS: intravascular ultrasound; MV: main vessel; OCT: optical coherence tomography; PMI: peri-procedural myocardial infarction; SB: side branch*

Specifically, this position paper aims to describe:
(1) Types of clinical studies performed with DCBs;
(2) Endpoint definitions including composite clinical endpoints; procedural, mechanistic (anatomical and functional), and cost-effectiveness endpoints; patient-, site-, and central adjudication-reported endpoints;
(3) Follow-up methods;
(4) Analytical plans related to intention-to-treat, per-protocol, and as-treated analyses (with the option of sham treatment); the statistical approach for composite endpoints and interpretation of repeated events using various types of assessment;
(5) Definitions of lesion and clinical settings for the use of DCB.

Types of clinical studies in drug-coated balloon

The nomenclature commonly used in clinical trials investigating DCBs are described in **Table 1**, with the types of clinical studies using DCBs shown in **Table 2**. First-in-human, sham procedure and studies for regulatory approval are described in the **Supplementary data**[7-13].

HEAD-TO-HEAD DEVICE-COMPARING STUDIES

These studies aim at comparing the performance of new devices using standard of care as reference or another promising innovative device. These comparisons can be inter-device (e.g. DCB vs. DES), such as the Balloon Elution and Late Loss Optimization trial (BELLO)[14] or intradevice (e.g. DCB vs. DCB), which includes comparing DCBs delivering

Table 1. Drug-coated balloon clinical trials' nomenclature.

	Nomenclature	Description
1	Drug-coated balloon (DCB)	Percutaneous coronary angioplasty balloon covered by antiproliferative drug, transferred homogenously into the vessel wall during a single balloon inflation by means of a carrier or a coating matrix
2	Drug-eluting balloon (DEB)[a]	Percutaneous coronary angioplasty balloon provided with delivery technologies (i.e. micro-pore) ensuring intraparietal drug release
3	Bail-out stenting/ scaffolding	Implantation of a DES/BRS due to deterioration of flow (TIMI ≤2), flow-limiting dissections, or excessive recoil following pre-dilatation and/or DCB treatment, despite intracoronary medication (e.g. nitroglycerine, nitroprusside, calcium antagonist, nicorandil) are given and ~5 min is waited
4	Cross-over	Change of intended pre-specified procedural strategy to another
5	Dissection • Angiography	Mechanical disruption of the subintima, media, and/or adventitia layer of a coronary artery followed by extravasation of blood in the three above-mentioned layers, following lesion preparation and/or DCB treatment NHLBI classification (based on the depth and breadth of dissection and the presence of intimal flap or spiral appearance) (A) Minor radiolucency within the lumen during contrast injection with no persistence after dye clearance (B) Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance (C) Extraluminal cap with persistence of contrast after dye clearance from the lumen (D) Spiral luminal filling defects (E) New persistent filling defect within the coronary lumen (F) Non–A-E types that lead to impaired flow or total occlusion
	• Intracoronary imaging	Tissue laceration categorized into intimal dissections, medial dissections, or adventitial dissections according to the depth the dissection reaches Morphometric measurements are: • Cross-sectional: thickness, area, depth, aperture, and width (arc) of the dissected flap • Longitudinal: length of the dissection • Dissection volume: computation of the dissection area with the dissection length
6	Target lesion • In-balloon	Lesion treated with DCB during the index procedure. Angiographic co-localization with DCB's markers or during DCB inflation is needed (i.e. co-registration, two different projections during DCB inflation, matched segment analysis using fiducial points).
	• In-segment	1 mm proximal and distal to the balloon
7	Geographic miss	Angiographic mismatch between the lesion preparation (i.e. pre-dilatation with semi/non-compliant, cutting/ scoring balloons, rotational or orbital atherectomy, IVL) and DCB application
8	Late lumen loss or gain	Difference between post-procedural and follow-up MLD
9	Acute recoil	Difference between balloon diameter and post-procedural MLD
10	Late recoil	Difference between balloon diameter and follow-up MLD
11	Acute gain	Difference between post- and pre-procedural MLD
12	Net gain	Difference between follow-up and pre-procedural MLD
13	Late functional loss/ gain	Paired difference of physiological epicardial values between post-procedure and follow-up. Fiducial co-localization is needed (PW sensor or distal marker of angiography-derived computation)
	• ΔFFR/QFR/iFR/ FFR-CT	Physiological drop across the targeted lesion (trans-DCB gradient, by analogy with trans-stent gradient), defined as the difference between instantaneous values assessed at the proximal and distal edges
14	Net functional gain	Paired difference of physiological epicardial values between pre-procedure and follow-up. Fiducial co-localization is needed (PW sensor or distal marker of angiography-derived computation)
15	Acute functional gain	Paired difference of physiological epicardial values between pre-procedure and post-procedure. Fiducial co-localization is needed (PW sensor or distal marker of angiography-derived computation)

BRS: bioresorbable scaffold; CT: computed tomography; DES: drug-eluting stent; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVL: intravascular lithotripsy; min: minutes; MLD: minimal lumen diameter; NHLBI: national heart: lung and blood institute; PW: pressure wire; QFR: quantitative flow ratio; TIMI: Thrombolysis In Myocardial Infarction. [a]No RCT data are available yet for DEB. Clinical trials are still at phase I.

Table 2. Types of drug-coated balloon clinical trials.

Type of study	Description	Procedural endpoints	Mechanistic (imaging and functional) endpoints	Clinical endpoints
First-in-human studies	Assessment of a new device's use feasibility and safety, with strict data safety monitoring and stopping rules	(1) Procedural success: • Device success • Free from event during index hospitalization (CV death, TLF, PMI, any stroke)	(1) Acute endpoints: • Residual stenosis (QCA, IVUS, OCT) • Acute gain • Dissection (type, extension, classification) • Perforation • Post-procedural invasive functional assessment and/or image-based FFR • IVUS/OCT: expansion index, dissection (volume, extension, length, depth) • Shear stress (2) Late endpoints: • Late lumen loss (using the same method and projection as per post-procedural assessment) comparison with performance index derived from historical data • Acute and net gain • Binary restenosis (using the same method and projection as per post-procedural assessment) • Invasive (e.g. PW-, IVUS-, OCT-based) or image-based FFR assessment using classical criteria of flow-limiting lesions (FFR ≤ 0.80)	Objective performance criteria: (1) Safety endpoint: • All-cause death • CV death • Stroke • Any MI • Definite lesion thrombosis (2) Efficacy endpoint: • Any coronary revascularization • TVR • TLR (3) Composite efficacy and safety: • CV death, TV-MI, and TLR (DOCE) • All-cause death, any MI, and any • revascularization (POCE) • TV-MI, TLR, definite lesion • thrombosis (LOCE)
Studies for regulatory approval	Assessment of device safety to obtain a CE Mark or Investigational device exemption (IDE/FDA/ PMDA/CFDA). Non-inferiority comparison with available approved standard of care	(1) Procedural success: • Device success • Free from event during index hospitalization (CV death, TLF, PMI, any stroke) (2) Health–economic endpoints: • Procedural time (min) • Procedural cost • Fluoroscopy time (min) • Contrast medium amount (mL)	(1) Acute endpoints: • Residual stenosis (QCA, IVUS, OCT) • Acute gain • Dissection (type, extension, classification) • Perforation (2) Late endpoints: • Late lumen loss or gain (using the same method and projection as per post-procedural assessment) • Binary restenosis (using the same method and projection as per post-procedural assessment)	Short term (30 days) (1) LOCE: • Definite lesion thrombosis • TLR (clinically driven) • Device failure-related MI (not clearly attributable to a non-target vessel) (2) Efficacy endpoint: • TVR • Target lesion-related ischaemia • TLR (3) Safety endpoint: • BARC 3–5 • Definite lesion thrombosis • Any stroke • Any MI • CV death • All-cause death
Device-comparing studies	Comparison of different devices: • DCB vs. DES • DCB vs. DCB 'molecules eluted' (e.g. paclitaxel vs. sirolimus/biolimus); 'coating' (e.g. hydrophilic matrix vs. phospholipid based vs. sub-micrometre nanoparticles) • DCB vs. DEB	(1) Procedural success: • Device success • Free from event during index hospitalization (CV death, TLF, PMI, any stroke) (2) Myocardial injury (delta in troponin pre- vs. post-) (3) Health–economic endpoints: • Procedural time (min) • Procedural cost • Fluoroscopy time (min) • Contrast medium amount (mL)	(1) Acute endpoints: • Residual stenosis (QCA, IVUS, OCT) • Acute gain • Dissection (type, extension, classification) • Perforation • Post-procedural invasive functional assessment and/or image-based FFR • IVUS/OCT: expansion index, dissection (volume, extension, length, depth) • IMR pre- and post-DCB • Shear stress (1) Late endpoints: • Late lumen loss or gain (using the same method and projection as per post-procedural assessment) • Binary restenosis (using the same method and projection as per post-procedural assessment) • Invasive (e.g. PW-, IVUS-, OCT-based) or image-based FFR assessment using classical criteria of flow-limiting lesions (FFR ≤ 0.80)	(1) DOCE: • CV death • Device failure-related MI • Device failure-related ischaemia • TLR (2) Efficacy endpoint: • TVR • Target lesion-related ischaemia • TLR (3) Safety endpoint: • BARC 3–5 • Definite lesion thrombosis • Any stroke • Any MI • CV death • All-cause death

Strategy-comparing studies	(1) Leave-nothing-behind strategy (cross-over to stent implantation either after pre-dilatation or DCB's inflation is a strategy failure) (2) Cross-over strategy (cross-over stent implantation is according to the intended strategy based on operator's decision) (3) Blended strategy and use of the complete PCI armamentarium (pre-specified combination of different technologies; i.e. DCB, DES, DEB, atherectomy, IVL, cutting/scoring balloons)	(1) Intended primary strategy success (e.g. cross-over rate: the placement of a stent, as part of a declared leave-nothing-behind strategy in the pre-procedural planning, is considered a strategy failure) (2) Procedural success: • Device success • Free from event during the index hospitalization (CV death, TLR, PMI, any stroke, BARC 3–5 bleeding) (3) Health–economic endpoints: • Procedural time (min) • Procedural cost • Fluoroscopy time (min) • Contrast medium amount (mL)	(1) Acute endpoints: • Residual stenosis (QCA, IVUS, OCT) • Acute gain • Dissection (type, extension, classification) • Perforation • Post-procedural invasive functional assessment and/or image-based FFR • IVUS/OCT: expansion index, dissection (volume, extension, length, depth) • IMR pre- and post-DCB (2) Late endpoints: • Late lumen loss or gain (using the same method and projection as per post-procedural assessment) • Binary restenosis (using the same method and projection as per post-procedural assessment) • Invasive (e.g. PW-, IVUS-, OCT-based) or image-based FFR assessment using classical criteria of flow-limiting lesions (FFR ≤ 0.80)	(1) DOCE: • CV death • Device failure-related MI • Device failure-related ischaemia • TLR (2) Efficacy endpoint: • TVR • Target lesion-related ischaemia • TLR (3) Safety endpoint: • BARC 3–5 • Definite lesion thrombosis • Any stroke • Any MI • CV death • All-cause death
Post-procedural pharmacological comparison	Comparison between different anti-platelet strategies after PCI (1) DAPT vs. aspirin-free monotherapy (2) DAPT vs. SAPT (3) Short DAPT vs. long DAPT	(1) Final strategy adopted (i.e. leave-nothing-behind vs. cross-over strategy) (2) Procedural success: • Device success • Free from event during the index hospitalizations (CV death, TLR, PMI, any stroke, BARC 3–5 bleeding)	(1) Acute endpoints: • Residual stenosis (QCA, IVUS, OCT) • Acute gain • Dissection (type, extension, classification) • Perforation • Post-procedural invasive functional assessment and/or image-based FFR • IVUS/OCT: expansion index, dissection (volume, extension, length, depth) • IMR pre- and post-DCB (2) Late endpoints: • Late lumen loss or gain (using the same method and projection as per post-procedural assessment) • Binary restenosis (using the same method and projection as per post-procedural assessment) • Invasive (e.g. PW-, IVUS-, OCT-based) or image-based FFR assessment using classical criteria of flow-limiting lesions (FFR ≤ 0.80)	(1) Bleeding endpoint: • BARC 3–5 bleeding (2) POCE: • All-cause death • Any stroke • Any MI • Any revascularization (3) NACE • Bleeding endpoint • POCE (4) Nonadherence classifications according to NARC (5) PROMs (i.e. SAQ)
Sham procedure studies	Sham procedure should be similar in every respect to the treatment being investigated with the exception that the active ingredient or component is lacking	(1) Procedural success: • Free from event during the index hospitalization (CV death, TLR, PMI, any stroke, BARC 3–5 bleeding)	(1) Acute endpoints: • Residual stenosis (QCA, IVUS, OCT) • Acute gain • Dissection (type, extension, classification) • Perforation • Post-procedural invasive functional assessment and/or image-based FFR • IVUS/OCT: expansion index, dissection (volume, extension, length, depth) • IMR pre- and post-DCB (2) Late endpoints: • Late lumen loss or gain (using the same method and projection as per post-procedural assessment) • Binary restenosis (using the same method and projection as per post-procedural assessment) • Invasive (e.g. PW-, IVUS-, OCT-based) or image-based FFR assessment using classical criteria of flow-limiting lesions (FFR ≤ 0.80)	(1) POCE: • All-cause death • Any stroke • Any MI • Any revascularization (2) NACE • Bleeding endpoint • POCE (3) Nonadherence classifications according to NARC (4) PROMs (i.e. SAQ)

BARC: Bleeding Academic Research Consortium; CE: Conformité Européenne; CFDA: China food and drug administration; CV: cardiovascular; DAPT: dual anti-platelet therapy; DCB: drug-coated balloon; DEB: drug-eluting balloon; DES: drug-eluting stent; DOCE: device-oriented composite endpoint; FDA: food and drug administration; FFR: fractional flow reserve; IDE: investigational device exemption; IMR: index of microvascular resistance; IVL: intravascular lithotripsy; IVUS: intravascular ultrasound; LOCE: lesion-oriented composite endpoint; MI: myocardial infarction; min: minutes; mL: milliliters; NACE: net clinical benefit composite endpoint; NARC: non-adherence academic research consortium; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; PMDA: pharmaceuticals and medical devices agency; PMI: peri-procedural myocardial infarction; POCE: patient-oriented composite endpoint; PROMs: patient-reported outcome measures; PW: pressure wire; QCA: quantitative coronary angiography; SAPT: single-anti-platelet therapy; SAQ: Seattle Angina Questionnaire; TLF: target lesion failure; TLR: target lesion revascularization; TV-MI: target vessel myocardial infarction; TVR: target vessel revascularization

different antiproliferative drugs, e.g. the TRANSFORM I study[15]. The focus of these studies is primarily procedural success and efficacy, which is best fulfilled using procedural, imaging and functional endpoints.

STRATEGY-COMPARING STUDIES

This category includes studies comparing different strategies and philosophies of using DCBs in the management of CAD. Pre-procedure it should be clear whether the study is a strict comparison between treatments or whether a 'blended treatment approach' is permitted. In the former, failure of the DCB strategy and cross-over to the comparator group is considered a strategy failure inducing a penalty for the composite endpoint, while in the latter, a mixture of the two technologies is allowed by protocol to a pre-defined limit, and the blending of devices is not considered a failed treatment strategy.

In both types of study, the intended strategy must be declared and characterized pre-procedure, with the study protocol clearly describing the procedural and clinical scenarios allowed within each. Typically, the randomization should indicate the first steps of the strategy, with the subsequent stages documented according to the previous responses (e.g. cross-over to stent after initial pre-dilatation). If the strategy allows multiple procedural scenarios, details of the procedure should be recorded.

For example, according to the 'leave nothing behind' strategy, the intended primary success is achieved when a DCB treatment is carried out without cross-over interventions, which would be considered a strategy failure. In contrast, when the primary comparison is between a DCB and DES, and the DCB strategy allows cross-over to implantation of a DES (the 'cross-over' strategy), this is not considered a strategy failure. This second option examines the real clinical value of the technology in different clinical or anatomic settings. The SELUTION DeNovo trial compares in terms of target vessel failure a strategy of PCI with provisional DCB and rescue DES vs. intended DES implantation. Non-inferiority is tested at 1 and 5 years, and if met at 5 years, superiority will be tested[16].

The REC-CAGEFREE I trial demonstrated that in patients with *de novo*, non-complex lesions, a strategy of provisional DCB angioplasty with rescue stenting did not achieve non-inferiority compared with intended DES implantation in terms of the occurrence of the device-oriented composite endpoint at 2 years. However, a predefined and powered analysis of vessel sizes, particularly those smaller than 3 mm (which represent 48% of the studied population), demonstrated that DCB was non-inferior to DES in vessels smaller than 3 mm[17].

Lastly, according to the 'blended' strategy, the pre-specified use of the complete available armamentarium (i.e. DCB, DES, bioresorbable scaffolds [BRS], intravascular lithotripsy [IVL], scoring/cutting balloons) is allowed. The Drug Coated Balloon Academic Research Consortium (DCB ARC) highlights the potential of using such strategies in several settings, such as treatment of diffuse disease or multivessel disease. In this subgroup, the mixture of available technologies is part of the strategy (e.g. calcium debulking technologies comparison) which finishes with using a DCB, while the comparator could be the use of a DES or even surgical revascularization.

The time of randomization is a crucial factor that is influenced by the type of study and must be pre-defined according to the study protocol: upfront randomization occurring before lesion preparation and DCB treatment is preferable in studies comparing strategies. Conversely, in studies comparing devices, the investigated treatment should not be influenced by the result of lesion preparation, and therefore randomization should occur once treatment with a DCB strategy is felt to be suitable, with this approach allowing alignment between the two cohorts.

POST-PROCEDURAL PHARMACOLOGICAL COMPARISON

The international DCB consensus recommendation for 4 weeks of dual anti-platelet therapy (DAPT) following DCB treatment in *de novo* chronic coronary syndrome is based on expert opinion and the promising results from recent clinical trials[18,19]. DCBs however have the potential to facilitate early $P2Y_{12}$ de-escalation or discontinuation of DAPT ($P2Y_{12}$ or aspirin discontinuation), which is particularly attractive in the high bleeding risk (HBR) population[20]. In a recent all-comers real-world registry, which included HBR patients (65% on oral anticoagulation), DCB treatment followed by a single anti-platelet regimen was shown to be safe[21]. To date, however, no outcomes studies are available testing the use of $P2Y_{12}$ inhibitor monotherapy (aspirin-free strategy)[22,23] or different anti-platelet regimens after DCB treatment. The latter encompasses numerous permutations such as comparing different $P2Y_{12}$ inhibitors (clopidogrel vs. prasugrel vs. ticagrelor), DAPT vs. single-anti-platelet therapy (SAPT; aspirin or aspirin-free), reduced DAPT duration, or early de-escalation from a more potent agent to clopidogrel. Ultimately, evaluating these scenarios in dedicated trials will help establish the optimal DAPT strategy after DCB/DES procedures.

Endpoint definitions

According to DCB ARC, endpoints for clinical studies can be categorized as *procedural, mechanistic* (anatomical and functional), and *clinical*.

Procedural endpoints encompass procedure-related outcomes and are relevant for all types of clinical study. The definition of procedural success includes the concept of device success, freedom from adverse events during the index hospitalization [cardiovascular death, target lesion failure, peri-procedural myocardial infarction (PMI), and stroke] and peri-procedural myocardial injury, which might be of greatest interest in studies comparing devices. In studies comparing strategies, procedural endpoints should include the 'intended primary strategy success' that nevertheless permits cross-over from the planned strategy.

Mechanistic endpoints include imaging and functional efficacy endpoints derived from invasive (angiography, intracoronary imaging, invasive coronary physiology) and non-invasive [coronary computed tomography angiography (CCTA), fractional flow reserve derived from computed tomography (FFR_{CT})] assessments. They are intended to report the mechanical result of the procedure being investigated and generally include a pre-procedure, post-procedure, and follow-up assessment and should be assessed by an independent and blinded core lab using standardized methodology.

Clinical endpoints include the occurrence of individual and composite safety and efficacy endpoints. The choice of composite endpoints, which can include device-, lesion-, patient-, and net adverse clinical event-related endpoints, is based on the type of clinical study being performed.

The DCB ARC proposes specific individual and composite endpoints according to the type of clinical study being considered. Potential endpoints should be blindly adjudicated by an independent Clinical Events Committee (CEC) based on redacted source documents and supported by core lab evaluation.

TRIALS AIMED AT DEVICE/PROCEDURAL SUCCESS

The primary aim of first-in-human studies is to test the feasibility (device success) and safety (early safety) of the device, and since these studies usually have limited statistical power, pre-specified performance goals are often used as criteria for success or failure [e.g. ASET (Acetyl Salicylic Elimination Trial) pilot study[24]]. An independent data safety monitoring board is mandatory, with their role advising continuation or discontinuation of the trial with respect to safety concerns (pre-defined stopping rules). Subsequently, clinical registries and small randomized controlled trials (RCTs) can be undertaken aimed at investigating the clinical efficacy of the technology, taking advantage of the comparison with pre-existing objective performance criteria[7], and using performance indexes stemming from well-established historical data.

In trials comparing devices and/or strategies, procedural and mechanistic (imaging and functional) endpoints are of particular importance: imaging and functional endpoints are based on post-procedural and mid-term follow-up assessment (cf. Follow-up methods). Preferentially, such analyses should be performed by an independent and blinded core laboratory having standardized operational methodology and pre-defined analytical plans. The DCB ARC recommendation for angiography, physiology, and intravascular imaging analysis included herein should be strictly followed. If a core lab analysis is planned, a test run should be performed to assess the adequacy of data acquisition prior to starting the trial. In this specific subgroup of trials, clinical endpoints play a secondary role and should be set as secondary endpoints.

TRIALS INVESTIGATING CLINICAL BENEFIT

The primary outcome measures in studies for regulatory approval should be clinical endpoints of safety and performance (efficacy), with surrogate endpoints ancillary. Adequately powered device- and strategy-comparing trials should aim at comparing clinical benefit of the investigated device/strategy. The primary outcomes in trials comparing post-procedural pharmacological and in sham procedure studies should be clinical composite endpoints with safety (e.g. bleeding events), ischaemic, and patient-oriented composites of greatest relevance. Net adverse clinical events that incorporate safety-related and patient-reported outcomes should also be reported. In sham procedure studies, on top of patient-oriented endpoints, patient-reported outcome measures (PROMs) play a key role, with the comparison between the two study arms potentially having a significant impact on the patient's perceived health status.

INDIVIDUAL ENDPOINTS

PROCEDURAL ENDPOINT

The international DCB consensus[1] proposes that, in clinical practice, an optimal balloon angioplasty comprises (i) a fully inflated balloon of the correct size for the vessel; (ii) ≤30% residual stenosis by visual estimation; (iii) Thrombolysis In Myocardial Infarction (TIMI) flow grade 3; and (iv) the absence of flow-limiting dissections. However, visual estimation in the assessment of post-angioplasty residual stenosis is flawed by significant investigator-dependent variations of ≥10%[25]; therefore, in clinical trials, the use of quantitative coronary analysis (QCA) is recommended. Notably, QCA evaluation after DCB PCI can be hampered by dissections and cannot detect and depict accurately complex intraluminal dissections, not visible on the luminal contours. The need for the development of dedicated QCA protocols might emerge in future. In clinical trials, device success is defined as the composite of successful delivery within a reasonable transfer time to the target lesion (e.g. <2 min) and inflation for 30-60 s of the allocated DCB device at the intended target lesion during an attempt with a DCB not previously used (first use), with successful withdrawal of the device system, while attaining a final in-segment or in-lesion residual per cent diameter stenosis (%DS) of <40% by off-line core lab adjudicated QCA[26].

According to the CAGEFREE (NCT04561739) real-world registry of 2473 patients treated for *de novo* and in-stent restenosis (ISR) lesions, the median %DS after DCB treatment was 30%, with a %DS <20% and <50% achieved in 20% and >90%, respectively[27]. Therefore, DCB ARC recommends that device success after DCB treatment should be considered when the %DS < 40% is achieved using off-line QCA; however, a post-procedural stratification into optimal (%DS < 30%) and suboptimal (30% < %DS < 40%) is also supported. When DCBs are being directly compared to DES, DCB ARC recommends using specific thresholds for each device (<40% for DCB, <20% for DES).

Stent implantation may be performed for sub-optimal results after lesion preparation (i.e. a dissection or unacceptable recoil) or, if necessary, as bail-out after DCB application.

In contrast to PCI using coronary stents, no validated cut-offs for procedural success using intravascular imaging have yet been validated for DCBs. Depending on the study design, the use of bail-out devices (as allocated by randomization) due to severe dissections (type C-F) or impaired coronary flow (TIMI <3) may or may not be judged as device failure.

Procedural success herein is ascertained at discharge as the composite of device success plus the absence of adverse procedural clinical outcomes including cardiovascular death, target lesion revascularization, PMI, any stroke, and Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding, regardless of whether the protocol-assigned device is used. In the 'leave-nothing-behind' strategy trials, a penalty for cross-over is included in the composite assessment of procedural success.

CLINICAL ENDPOINTS

Individual endpoint definitions are reported in **Table 3**, composite endpoints in **Table 4**, and surrogate endpoints in **Table 5**.

MYOCARDIAL INFARCTION

PERI-PROCEDURAL MYOCARDIAL INFARCTION

Myocardial infarctions (MIs) may occur in the peri-procedural phase, as well as during follow-up, either due

Table 3. Individual endpoints' definition.

	Nomenclature	Description
1	Device success	All of: • Successful delivery in time and inflation within 30–60 s of the allocated DCB device at the intended target lesion during an attempt with a DCB not previously used (first use) • Successful withdrawal of the device system • Attainment of a final in-segment or in-lesion residual stenosis of <40% with final data reported by core laboratory QCA (preferred methodology)
2	Procedure success	All of: • Device success • Freedom from in-hospital cardiovascular death, target lesion revascularization, peri-procedural myocardial infarction, any stroke, and BARC 3–5 bleeding • Freedom from bail-out stenting (for 'leave-nothing-behind' strategy)
3	Cardiovascular death	• Death caused by acute MI • Sudden cardiac, including unwitnessed, death • Death resulting from heart failure • Death caused by stroke • Death caused by cardiovascular procedures • Death resulting from cardiovascular haemorrhage (haemorrhage deriving from cardiac and/or vascular disease/injuries)
4	Peri-procedural MI	Evaluation 24–48 h: • hs-cTn T rise ≥35xURL AND ≥1 of the following criteria: • 'Flow-limiting' angiographic complications in a major epicardial vessel at the end of the procedure • New significant Q-waves (or equivalent) in two contiguous leads, after the procedure • A new wall motion abnormality on echocardiography, after the procedure OR • hs-cTn T rise ≥70xURL (all events should be adjudicated, ideally after core lab analysis, by an independent CEC)
5	Cardiac biomarker rise	Any CK-MB and/or hs-cTn T rise >6 h after the procedure Type 1: due to other angiographic complications (a) Intraprocedural occlusion of the target vessel (b) Intraprocedural distal embolization (c) Intraprocedural coronary perforation (d) Intraprocedural dissection (after pre-dilatation, after DCB) (e) Residual flow-limiting dissection at the end of the procedure (f) Intraprocedural lesion thrombus (g) Residual thrombus at the end of the procedure (h) Increased IMR or angio-IMR (≥25) at the end of the procedure Type 2: no angiographic identifiable causes
6	Stroke	Neuro-ARC definitions (according to ARC-2 criteria)
7	Bleeding	BARC definitions (according to ARC-2 criteria)
8	Target lesion ischaemia	The target lesion ischaemia is defined in presence of ischaemic myocardium supplied by the coronary segments treated during the initial procedure. Identification and localization of ischaemia requires the use of the same ischaemic test, utilized during the inclusion in the study
9	Target lesion revascularization	The target lesion is considered as the treated coronary segment during the index procedure plus 1 mm distance from the balloon edges Target lesion revascularization is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion
10	Target vessel revascularization	The target vessel is defined as the entire major treated coronary vessel, including side branches Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel
11	Target lesion-related MI	Any MI associated with angiographic confirmation that the culprit lesion corresponds to the DCB-treated segment (1 mm proximal and distal to the balloon)
12	Target vessel non-target Lesion MI	Any MI attributed to the target vessel, but not involving the target lesion's segment
13	Definite lesion thrombosis	Angiographic confirmation: the presence of a thrombus that originates the segment 1 mm proximal or distal to the treated lesion and the presence of at least one of the following criteria: (1) Acute onset of ischaemic symptoms at rest (2) New electrocardiographic changes suggestive of acute ischaemia (3) Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction) OR Pathological confirmation: (1) Evidence of recent thrombus within the target lesion determined at autopsy (2) Examination of tissue retrieved following thrombectomy (visual/histology) Early acute: 0–24 h; early subacute: 1–30 days; late: 30 days–1 year; very late: >1 year

Table 3. Individual endpoints' definition (cont'd).

	Nomenclature	Description
14	Probable lesion thrombosis	Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischaemia in the territory of the treated lesion without angiographic confirmation of thrombosis and in the absence of any other obvious cause Early acute: 0–24 h; early subacute: 1–30 days; late: 30 days–1 year; very late: >1 year
15	Silent target segment occlusion	The incidental angiographic documentation of DCB-treated segment occlusion in the absence of clinical signs or symptoms. Silent target segment occlusion is not adjudicated as lesion thrombosis.
16	Major dissection	Dissection in the target lesion ≥ type C the from National Heart, Lung, and Blood Institute classification
17	Perforation	Type 1) extraluminal crater without jet extravasation Type 2) pericardial or myocardial blushing without jet extravasation Type 3) active jet extravasation exit jet >1 mm Type 4) leaking into another cardiovascular cavity Type 5) distal perforation
18	Binary stenosis	>50%DS in the target segment at follow-up

ARC: Academic Research Consortium; BARC: Bleeding ARC; CEC: Clinical Events Committee; CK-MB: creatine kinase MB; d: day; DCB: drug-coated balloon; DS: degree of stenosis; hs- cTnT: high-sensitivity troponin T; IMR: index of microvascular resistance; MI: myocardial infarction; mm: millimiter; QCA: quantitative coronary analysis; URL: upper reference limit; y: years

Table 4. Composite endpoints' definition.

	Nomenclature	Description
1	DOCE	Hierarchical occurrence of: (1) Cardiovascular mortality (2) Device failure-related MI (not clearly attributable to a non-target vessel) (3) Device failure-related ischaemia (4) TLR (clinically driven)
2	VOCE	Hierarchical occurrence of: (1) Vessel-related cardiac death (2) Target vessel MI (not clearly attributable to a non-target vessel) (3) TVR
3	POCE	Hierarchical occurrence of: (1) All-cause mortality (2) Any stroke (3) Any MI (includes non-target vessel territory) (4) Any revascularization
4	LOCE	Hierarchical occurrence of: (1) Definite lesion thrombosis (2) TLR (clinically driven) (3) Device failure-related MI (not clearly attributable to a non-target vessel)
5	Functional LOCE	Hierarchical occurrence of: (1) Definite lesion thrombosis (2) TLR (clinically driven) (3) Device failure-related MI (not clearly attributable to a non-target vessel) (4) Trans-DCB functional gradient ≥0.06
6	MACE	Hierarchical occurrence of: (1) All-cause mortality (2) Any MI (3) Any stroke (4) Hospitalization for heart failure (5) Any revascularization
7	NACE	(1) POCE (2) Bleeding type 3 or 5 according to the Bleeding ARC
8	TVF	(1) Cardiovascular death (2) Target vessel MI (3) TVR
9	TLF	(1) Cardiovascular death (2) Target vessel MI (3) TLR (clinically driven)

Table 4. Composite endpoints' definition (cont'd).

	Nomenclature	Description
10	Safety endpoints	(1) Bleeding type 3 or 5 according to the Bleeding ARC (2) Definite lesion thrombosis (3) Any stroke (4) Any MI (5) Cardiovascular mortality (6) All-cause mortality
11	Efficacy endpoints	(1) Target vessel revascularization (2) Device failure-related ischaemia (3) TLR

ARC: academic research consortium; DCB: drug coated balloon; DOCE: device-oriented composite endpoint; LOCE: lesion-oriented composite endpoint; MACE: major adverse cardiac event; MI: myocardial infarction; NACE: net adverse clinical events; POCE: patient-oriented composite endpoint; TLF: target lesion failure; TLR: target lesion revascularization; TVF: target vessel failure; TVR: target vessel revascularization; VOCE: vessel-oriented composite endpoint

to a spontaneous event or late complications related to the investigated device/strategy. Several definitions of MI, and in particular PMI, have been proposed by different cardiac societies and adopted in different clinical trials[28,29]. Specific criteria should be adopted to define the occurrence and the clinical relevance of MIs, according to study type and design, in order to properly weigh the sensitivity of cardiac biomarkers of subtle myocardial injury (e.g. troponin I, troponin T) and balance them against clinically relevant adverse events[28]. Notably, while contemporary definitions of PMI largely rely on high-sensitivity cardiac troponin (hs-cTn), no correlation between the different types of available hs-cTn assays has been clearly established, hampering the comparisons between different studies.

The DCB ARC supports the Society for Cardiovascular Angiography and Interventions (SCAI) PMI definition, by using hs-cTn T, measured with a single assay within 24–48 h of the PCI. In DCB studies, a PMI is defined as an absolute increase in hs-cTnT ≥35 × upper limit of normal (ULN) combined with clinical evidence of MI, or as an absolute increase of hs-cTnT ≥70 × ULN[30].

Table 5. Surrogate endpoints for drug-coated balloon clinical trials.

Endpoints		Advantages	Disadvantages
Coronary computed tomography angiography			
Minimal lumen area (MLA)	Minimal lumen area along the length of the target lesion	• Non-invasive assessment • No drawbacks in case of calcified or tortuous vessel • Definition of the amount of plaque, remodelling, functional assessment • PcD eliminate blooming artefacts associated with calcium or metallic struts while improving the delineation of low-attenuation areas	• Complexity of assessing the geographical miss on CCTA • No metal present (fiducial co-localization with side branches) • Small vessels (1.5 mm) beyond the temporal resolution of CCTA • Blooming artefact due to severe calcification (not for PcD)
Plaque burden (PB)	Plaque area divided by the cross-sectional area of the EEM		
Remodelling	Outer vessel diameter of the lesion divided by the outer vessel diameter of the reference normal segment in the same vessel		
Vessel patency			
FFR-CT	Distal vessel FFR-CT, ΔFFR-CT across the treated segment		
Coronary angiography			
Acute gain	Difference between post- and pre-procedural MLD	• Gold standard • No need for dedicated PW or imaging catheters • Costs • Possibility of co-localization with the DCB-treated segment • Possibility of angiography-derived physiology computation	• Low spatial resolution • Limited assessment of dissections • Limited assessment of thrombus • No assessment of plaque composition and morphology
Net gain	Difference between follow-up and pre-procedural MLD		
Late lumen loss or gain	Difference between post-procedural and follow-up MLD		
Degree of stenosis change	Difference between post-procedural and follow-up %DS		
Intracoronary imaging (IVUS, OCT)			
Minimal lumen area (MLA)	Minimal lumen area along the length of the target lesion	• Evaluation of dissections (dissection classification/ quantitative assessment) • Plaque composition and morphology • Thrombus presence exclusion • Pre-dilatation result and DCB sizing • Angio-imaging co-registration and accurate longitudinal measurement • Functional assessment with OFR or UFR	• Lower resolution with IVUS (difficult to assess and classify dissections) • Need for high pressure contrast injection with OCT (potential worsening of dissections) • Cost of the device • Attrition • Potential bias for the event case adjudication
Plaque burden (PB)	Plaque area divided by the cross-sectional area of the EEM		
Neointimal area (mean/ max) and volume	Difference between stent and minimal lumen area and computation of the neointimal area with the lesion length		
Remodelling	CSA of the lesion EEM divided by the CSA of the reference EEM		
Dissection volume/ extension	Computation of the dissection area with the longitudinal dissection length		
Expansion index	MLA divided by the average reference lumen area		
Coronary physiology (FFR, iFR, QFR)			
Vessel FFR/QFR	Functional pressure drop along the entire vessel	• Assessment of the physiological relevance of a given stenosis • Assessment of physiological pattern of coronary disease • Assessment of microcirculation • Angiographic co-registration and co-localization with the treated segment (QFR and iFR Syncvision)	• Need for dedicated PW and for hyperaemic agents (in case of FFR and PPGi)
Trans-DCB gradient (TDCBG)	Trans-segment pressure gradient measured by iFR PW pullback co-registration (Syncvision) or by the instantaneous QFR value on the virtual pullback		
PPGi–QVPi	Magnitude of pressure drop over 20 mm and the extent of functional disease in order to assess the functional pattern of disease (focal vs. diffuse)		
dFFR/dT–dQFR/dS	Local functional disease severity		
IMR–angio-IMR	Microvascular resistance and coronary microvascular function		

CCTA: coronary computed tomography angiography; CSA: cross-sectional area; CT: computed tomography; DCB: drug-coated balloon; DS: degree of stenosis; EEM: external elastic membrane; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IMR: index of microvascular resistance; IVUS: intravascular ultrasound; MLA: minimal lumen area; MLD: minimal lumen diameter; OCT: optical coherence tomography; OFR: optical flow ratio; PcD: photon-counting detector CT; PPGi: pullback pressure gradient index; PW: pressure wire; QFR: quantitative flow ratio; QVPi: QFR virtual pullback index; dT: unit time; dS: unit space; UFR: ultrasonic flow ratio

Due to the complexity and uniqueness of the definition and adjudication of PMI, and since a sensitive and inclusive definition of PMI could potentially drive most of the composite clinical endpoints and, even if equally affecting the two arms, may drastically affect the study results, ARC is simultaneously working on a document dedicated to the definition of PMI. DCB ARC will be updated accordingly.

Post-procedural cardiac biomarkers rise, and spontaneous MI definitions are reported in the **Supplementary data**[31-33].

BLEEDING

Bleeding events should be classified and reported according to the BARC criteria[34]. Type, intensity, and duration of anti-platelet medication at the time of bleeding should be captured. Significant bleeding is categorized as BARC 3–5 bleeding[35]. BARC 2 bleeding may also be included to enhance the power calculation for composite endpoints. It is important to note that these are nuisance events with limited clinical relevance, and their inclusion might reduce the sensitivity and specificity of bleeding assessment.

REPEAT REVASCULARIZATIONS

Repeat revascularizations are defined according to the vessel/lesion treated and are identified as target or non-target, based on the initial site of the DCB treatment. The target lesion is considered as the treated coronary segment during the index procedure plus 1 mm from the proximal and distal edge of the DCB; accurate angiographic segment co-localization is needed (see Follow-up methods).

Target lesion revascularization (TLR) is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. Reintervention should be guided by clinically significant renarrowing and thus includes two fundamental factors: a clinical and a functional component [i.e. fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), quantitative flow ratio (QFR)]. In case of recurrent symptoms (angina pectoris) and chronic coronary syndrome, image-based non-invasive functional tests are recommended. In acute coronary syndrome, cardiac biomarkers must be assessed before revascularization. A comprehensive algorithm for the interpretation of unplanned or inter-current catheterization is provided in **Figure 1**.

The DCB ARC endorses ARC-2 support for functional assessment with invasive pressure wire (i.e. FFR, iFR), but includes angiographyderived technologies [i.e. QFR, vessel FFR, Murray law-based QFR (μQFR)] as reliable alternatives to establish the functional indication for revascularization, using the conventional cut-offs for ischaemia (i.e. FFR ≤0.80; iFR ≤0.89; QFR ≤0.80)[36]. In case of discordance between invasive physiological assessment and non-invasive testing or results on QCA, the former should take precedence in the decisionmaking hierarchy. When invasive functional assessment is not performed prior to revascularization, CEC adjudication, with the aid of independent QCA and QFR assessment of baseline and reintervention angiograms, is mandatory in trials in which TLR or target vessel revascularization (TVR) is an endpoint[37]. When the epicardial physiological assessment is negative despite the presence of angina pectoris, DCB ARC suggests assessing the presence of microvascular dysfunction [i.e. index of microvascular resistance (IMR)][38]. These measurements, in conjunction with symptoms and the results of non-invasive testing, will form the basis for event adjudication. In DCB vs. coronary artery bypass graft (CABG) trials, the ascertainment of TLR can be challenging in the CABG arm and should be based on angiography pre-bypass surgery. The ARC recommends that only TVR is considered in such trials, since surgery bypasses the target lesion.

According to the DCB ARC, planned staged procedures are not considered repeat revascularization events. However, study protocols must define the recommended time interval within which such procedures should be completed, and if this time interval is not respected (the staged procedure is performed earlier or later), the repeat revascularization should be adjudicated by the CEC. If a staged intervention is planned for a non-culprit vessel and this is performed before the scheduled time due to a readmission with symptoms, the procedure should be classified as an unplanned PCI. The ARC strongly recommends that staged procedures should not be allowed in vessels treated during the index procedure to avoid reinterventions on the index treated lesion/s.

THROMBOSIS

The DCB ARC endorses the ARC-2 definition of thrombosis, with modifications to make it more specific for DCBs. Definite thrombosis needs angiographic or pathologic confirmation. Angiographic confirmation requires the presence of intracoronary thrombus that originates in the target segment (1 mm proximal or distal to the DCB applied segment) and at least one of the following criteria within a 48-h time window: (i) acute onset of ischaemic symptoms at rest; (ii) new ischaemic ECG changes that suggest acute ischaemia; and (iii) typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI). Intracoronary thrombus refers to a non-calcified spherical, ovoid, or irregular contrast-filling defect or lucency surrounded by contrast material seen in multiple views, persistence of contrast material within the lumen after washout, or visible downstream embolization of intra-luminal material[30]. Intravascular imaging by means of optical coherence tomography (OCT, first choice) or intravascular ultrasound (IVUS) should be performed to confirm the presence of thrombus in the treated segment. Angiographic thrombosis can be defined as non-occlusive or occlusive in cases of impaired flow in the target lesion (TIMI 0-1). Small thrombi detected by OCT immediately after DCB treatment, without flow and lumen limitation, should not be considered clinically relevant, as this could be pre-existing (e.g. acute coronary syndrome), and may not lead to vessel closure and will disappear with anti-platelet therapy. Moreover, no information about their predictive value in terms of total vessel occlusion and/or MI is available.

At follow-up, thrombus detected by OCT in the appropriate clinical context (ischaemic complains, ECG alterations, and troponin release) should be considered as vessel thrombosis. Conversely, the incidental angiographic detection of an occluded target segment in the absence of the above-mentioned ancillary criteria is not considered a thrombosis, but instead is a silent target segment occlusion, which may be the chronic sequelae of a late restenotic occlusion.

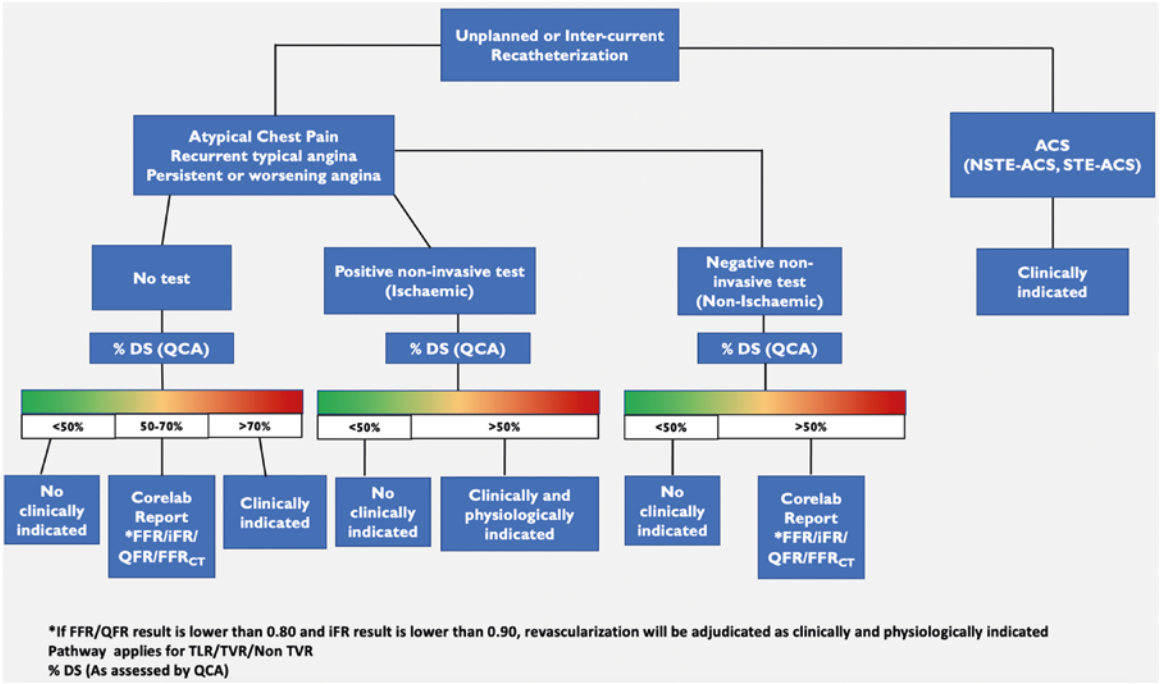


Figure 1. *Process for inter-current core lab event adjudication during unplanned or follow-up catheterizations. On the right side of the panel, in cases of acute coronary syndromes, coronary angiography and intervention are considered clinically indicated and adjudicated as an event. For stable situations, such as atypical chest pain or typical recurrent/persistent/worsening angina, the evaluation of ischaemia through non-invasive tests is crucial. If non-invasive tests indicate ischaemia, and quantitative coronary analysis shows >50% stenosis in the target lesion, revascularization is deemed clinically and physiologically appropriate and adjudicated as an event. If quantitative coronary analysis shows 50%–70% stenosis, physiological assessment using pressure-derived (fractional flow reserve/instantaneous wave-free ratio) or angiography-derived methods (quantitative flow ratio/fractional flow reserve derived from computed tomography) is necessary to justify revascularization from a physiological and clinical perspective and to adjudicate it as an event. In cases of angiographic assessment which have not been preceded by non-invasive ischaemic diagnostic tests, which is not the preferred clinical approach, but required in some mechanistic studies with specified angiographic follow-ups, revascularization is considered clinically indicated if the stenosis exceeds 70% by quantitative coronary analysis or 90% by visual estimation and adjudicated as an event. For stenoses between 50% and 70% by quantitative coronary analysis, physiological assessment through pressure-derived (fractional flow reserve/instantaneous wave-free ratio) or angiography-derived methods (quantitative flow ratio/fractional flow reserve derived from computed tomography) is mandatory to support revascularization as physiologically and clinically justified and to be adjudicated as an adverse cardiac event. ACS: acute coronary syndrome; CAG: coronary angiography; CT: computed tomography; DS: degree of stenosis; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; NSTE: non-ST-segment elevation; QCA: quantitative coronary angiography; QFR: quantitative flow ratio; STE: ST-segment elevation; TLR: target lesion revascularization; TVR: target vessel revascularization*

Pathological confirmation requires evidence of recent thrombus within the target segment at autopsy or by the analysis of tissue retrieved following thrombectomy.

Thrombosis can be classified according to the onset time as early acute (0–24 h), early subacute (1–30 days), late (30 days–1 year), and very late (>1 year).

Probable thrombosis is defined as follows: (i) any unexplained death within the first 30 days of the DCB procedure provided the index procedure was not performed for an ST-elevation MI and (ii) irrespective of the time after the index procedure, any MI that is related to documented acute ischaemia in the territory of the DCB-treated segment, without angiographic/OCT confirmation of thrombosis, and in the absence of any other obvious cause[30]. Similar to TLR, the adjudication of segment thrombosis is challenging due to the difficulty in identifying the DCB-treated segment at follow-up. Hence, accurate segment matching and co-localization using fiducial landmarks (i.e. side branches, bifurcations, calcifications) is warranted. For this purpose, the use of the same fluoroscopic angles and projections is recommended during the angiographic assessment of lesion thrombosis.

Follow-up methods

The DCB ARC outlines two separate methods of follow-up:

(1) Clinical and patient-level (e.g. clinical and patient-reported endpoints)

(2) Procedural mechanistic (e.g. anatomical and functional)

CLINICAL AND PATIENT-LEVEL FOLLOW-UP

COMPOSITE ENDPOINTS

The adoption of composite clinical endpoints, as the combination of different individual endpoint measurements, can increase the statistical power for identifying potentially significant differences between treatments. Each individual component is conceived to reflect clinically significant events and should be reported individually. Hierarchical classification of clinical events is based on the interpretation of each individual component according to a pre-defined clinical relevance (e.g. death comes first and covers the others), while the frequency of the events describes the recurrence of each event.

Net clinical benefit composite endpoints are conceived to include different types of clinical endpoints (e.g. bleeding and ischaemic events); however, caution is necessary in their interpretation, since it may include opposite effects for safety and effectiveness.

A statistical analytical plan other than time to first event may use different hierarchical composite endpoint analyses, such as Finkelstein–Schoenfeld or win ratio. The time-to-first-event analysis only considers the first event irrespective of its severity, whereas other methods are designed to weigh both event repetition and severity, as exemplified in the GLOBAL LEADERS study[39].

The minimum recommended clinical follow-up time when angiographic follow-up is not planned is 12 months. When angiographic follow-up is required, clinical endpoints should be collected in advance of the invasive procedure (e.g. 30 days/12 months clinical–13 months angiographic) to capture a purely clinical course not contaminated by the classical oculostenotic reflex (e.g. restenosis leading to clinically non-indicated revascularization) triggered by angiography or other objective assessment (e.g. CCTA, positron emission tomography, single-photon emission computed tomography).

In general, DCB ARC recommends clinical follow-up is extended for 5 years. When a surgical comparison is included in the study design, a longer follow-up time extended up to 10 years is recommended.

PROCEDURAL MECHANISTIC (ANATOMICAL AND FUNCTIONAL)

INVASIVE FOLLOW-UP

Coronary angiography

Endpoints definition. Although in the setting of DES RCTs and registries late lumen loss (LLL) has been shown to best discriminate the effectiveness of treatment, with DCBs, LLL may not reflect the balance between neointimal hyperplasia (late loss), constrictive remodelling (late loss), and late expansive enlargement (late gain). Indeed, due to a vessel's elastic retraction, balloon angioplasty has a smaller acute gain compared with permanent stenting and thus a smaller LLL at follow-up. In addition, late vessel enlargement and remodelling are achievable in a non-caged vessel following DCB treatment (see Supplementary data online, **Supplementary Figure 1**)[40,41]. Therefore, for DCB trials, an appropriate surrogate for parametric assessment depends on the control strategy adopted: LLL is expected to be reliable when comparing DCB vs. plain old balloon angioplasty or when comparing different types of DCBs, while net gain seems to be more informative in comparisons between DCB vs. DES (or vs. BRS). This difference appears to be more pronounced and relevant when targeting *de novo* vessels, as compared to ISR lesions[42]. In a recent pooled analysis including ISR and *de novo* DCB trials, the use of LLL or net gain led to significant discrepancies in the interpretation of the angiographic endpoint[42].

In-lesion QCA assessment encompasses the analysis of the treated lesion, easily recognized by means of the presence of metallic struts when a stent has been implanted. 'In-segment QCA' includes the treated lesion and 1 mm proximal and distal. In the DES era (ENDEAVOR III trial)[43], 'in-segment LLL' showed the advantage of incorporating the edge effect (e.g. radioactive stent, actinomycin DES). Although 'in-segment minimal lumen diameter' is the flow-limiting anatomic parameter relevant for the patient, 'in-segment LLL' may not adequately reflect the neointimal inhibition of the investigated DES. 'In-segment LLL' incorporates the tapering effect of the vessel, artificially masking 'in-stent LLL', which truly reflects intrastent neointimal inhibition of the DES.

In the setting of DCB trials, 'in-segment analysis' provides the advantage of mitigating the risk of 'geographic miss' by adding a proximal and distal 'buffer' zone and erroneous co-localization in different time points. The DCB ARC recommends the use of 'in-segment net gain' in place of 'in-segment LLL' for clinical trials of DCB **(Figure 2)**. A representative illustration of different QCA analysis protocols is provided in **Figure 3**.

Angiographic co-localization of the treated segment. The absence of visible radio-opaque markers and of stent struts poses challenges in the identification of the treated segment at follow-up. Matching and colocalization of the segment that has been subject to barotrauma during pre-dilatation with the area or segment covered with the DCB is mandatory. The DCB length technically has to be longer than the length of the pre-dilatation balloon. In addition to the appropriate length, we must also ensure that the DCB is deployed within the area dilated by the predilatation balloon. A comprehensive classification of geographic miss phenomenon with DCBs is provided in **Figure 4**[44]. To assess potential geographic miss and ensure co-localization, DCB ARC recommends the acquisition of two angiographic projections at baseline (pre-procedure), with the use of one of the two throughout the procedure (during predilatation and DCB inflation) as a working projection. Moreover, it recommends acquiring one angiographic projection (in the working angles) immediately before and/or after deflation of the DCB, with the balloon in the same position. Two final angiographic projections are required (post-procedure) using the same angles as pre-procedure, and these same fluoroscopic angles and projections should be used at follow-up. This process facilitates matching and co-localization of the treated segment at different time points by means of angiographic superimposition, which needs to be done at the same point in the cardiac cycle (preferentially end-diastole). A representative workflow is provided in **Figure 5**, while the concept of angiographic superimposition to match segments at different time points in order to achieve precise co-localization of the treated segment is exemplified in **Figure 6**.

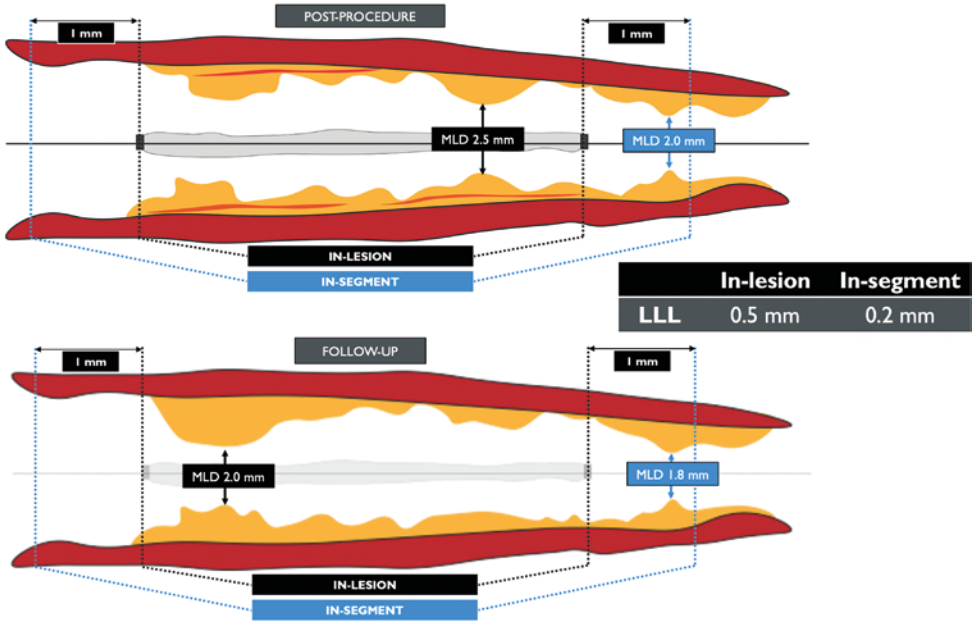


Figure 2. *'In-segment' vs. 'in-lesion' late lumen loss in drug-coated balloon's trials. In the drug-eluting stent setting, although 'in-segment minimal lumen diameter' is the flow-limiting anatomic parameter relevant for the patient, 'in-segment late lumen loss' may not adequately reflect the neointimal inhibition of the investigated device. 'In-segment late lumen loss' incorporates the tapering effect of the vessel, artificially masking 'in-stent late lumen loss' which truly reflects intrastent neointimal inhibition of the drug-eluting stent. In the drug-coated balloon setting, 'in-segment analysis' provides the advantage of mitigating the risk of 'geographical miss' by adding a proximal and distal 'buffer' zone and erroneous co-localization in different time points.*
LLL: late lumen loss; MLD: minimal lumen diameter; mm: millimetre

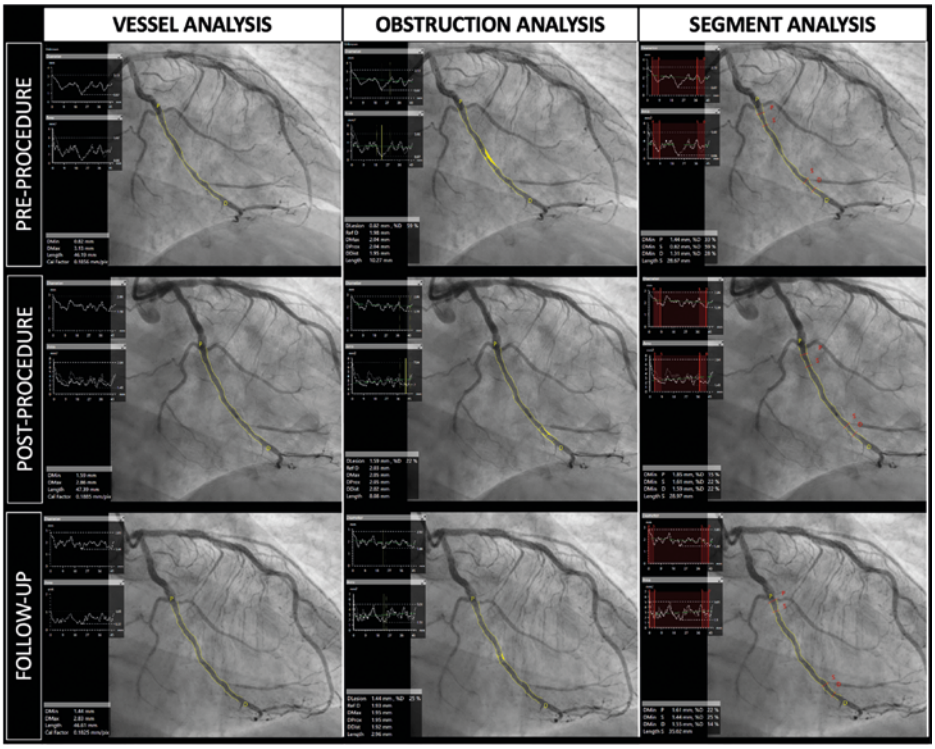


Figure 3. *Quantitative coronary analysis in drug-coated balloon's trials. Three different quantitative coronary analysis algorithms applied to drugcoated balloon percutaneous coronary intervention: vessel analysis (left column), obstruction analysis (middle), and segment analysis (right column)*

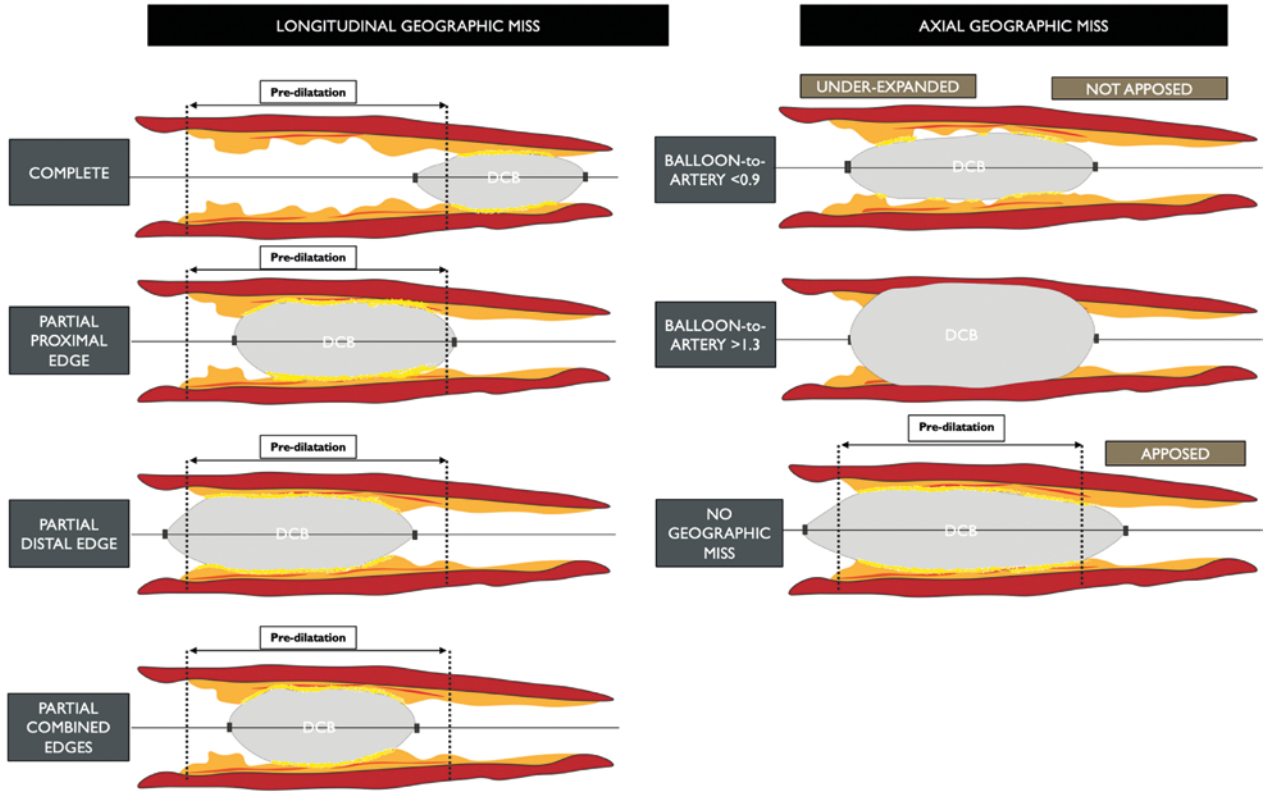


Figure 4. *Geographic miss phenomenon with drug-coated balloons. In drug-coated balloon percutaneous coronary intervention, geographic miss can be both longitudinal (left) and axial (right). Longitudinal miss occurs due to the inflation of the drug-coated balloon not completely (complete) or only partially (partial/combined proximal and/or distal edges) covering the pre-dilated segment of the vessel. Axial geographic miss describes the use of an undersized/under expanded balloon (balloon to artery ratio < 0.9) or an oversized/overexpanded balloon (balloon to artery ratio >1.3). DCB: drug-coated balloon*

Moreover, the use of angiography-derived FFR technologies allows assessment of the physiological drop along the vessel (vessel QFR) and, by applying fiducial landmarks (i.e. side branches, bifurcations, calcifications), precise co-localization of the treated segment. More sophisticated techniques, such as pullback pressure gradient index (PPGi) and derivative of QFR, may be used to characterize the physiological pattern of restenosis (focal vs. diffuse)[45,46] **(Figure 7)**. In device comparison studies, the assessment of microvascular resistance and function could be beneficial, allowing detection of sub-clinical microvascular damage potentially related to the procedure. In this respect, novel angiography-derived technologies and computations could provide a valid, reproducible, widely available, and fast computational assessment, with no need for dedicated guidewires or hyperaemia[47,48].

Optical coherence tomography/intravascular ultrasound co-localization of the treated segment. Automatic co-registration of OCT/IVUS and coronary angiography allows precise co-localization of the anatomical and imaging data[49], and can be performed online (Syncvision, Philips Corporation; OPTIS Integrated System, Abbott) or retrospectively offline (AngioPlus Core and OctPlus, Pulse Medical Imaging Technology)[50]. This is of potential relevance in the DCB field by matching the segment that underwent lesion preparation and subsequent DCB treatment with the same segment visualized at follow-up to detect any possible geographic miss. The role of co-registration in assessing lesion and dissection healing, and vessel remodelling is still under investigation. Intravascular ultrasound, which does not require contrast injection for visualization, theoretically appears to be safer than OCT, which necessitates clearing the vessel from blood through contrast injections. Currently, there is no evidence indicating an increase in dissections with the use of OCT.

Non-invasive follow-up and CCTA are described in the **Supplementary data**[51-59].

Statistical consideration

Statistical considerations related to the analytical plan (intention-totreat, per-protocol, and as-treated analyses) and to composite endpoint and repeated events interpretation (Finkelstein, win ratio analysis) are reported in the **Supplementary data** and **Supplementary Figure 2**[60-65].

Lesions and clinical settings for drug-coated balloon treatment

An overview of the evidence and indications of the use of DCBs in different lesions and clinical settings are summarized in the **Supplementary data**, **Supplementary Table 1**-Supplemenntary **Table 6** and **Supplementary Figure 3**[1,4,15,18,19,21,35,45,56,66-92]. Relevant definitions are summarized in **Table 6**.

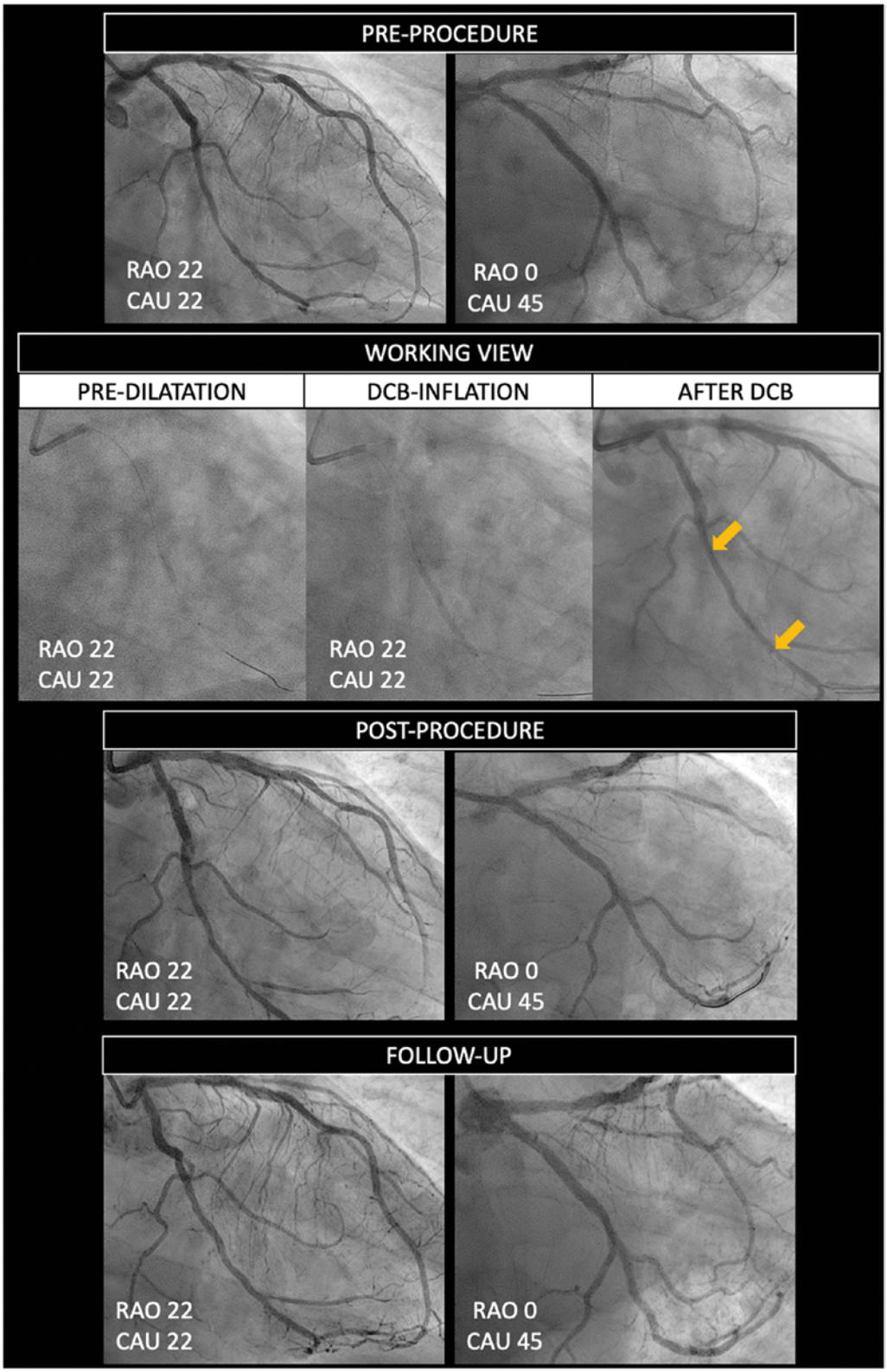


Figure 5. *Drug-coated balloon percutaneous coronary intervention workflow in clinical trials. Two angiographic projections are acquired at baseline (pre-procedure). A working view is used during pre-dilatation and drug-coated balloon inflation. One angiographic projection (in the working angles) should be acquired immediately before and/or after deflation of the DCB, with the balloon in the same position, in order to allow precise co-localization of the device. Two final angiographic projections are required (post-procedure) using the same angles as pre-procedure. The same fluoroscopic angles and projections should also be used at follow-up. DCB: drug-coated balloon; RAO: right anterior oblique; CAU: caudal*

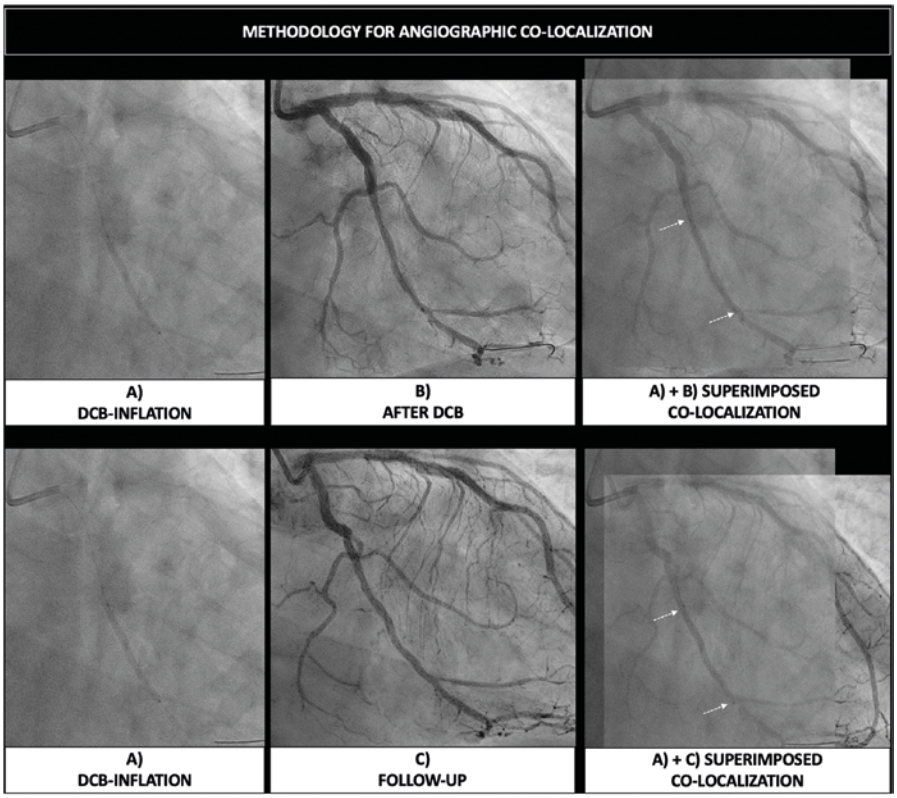


Figure 6. *Angiographic co-localization of drug-coated balloon's treated segment in different time points. The same fluoroscopic projections allow matching and co-localization of the treated segment during drug-coated balloon inflation (A), after drug-coated balloon inflation (B), and at follow-up (C), by means of angiographic superimposition, which needs to be done at the same point in the cardiac cycle (preferentially end-diastole). DCB: drug-coated balloon*

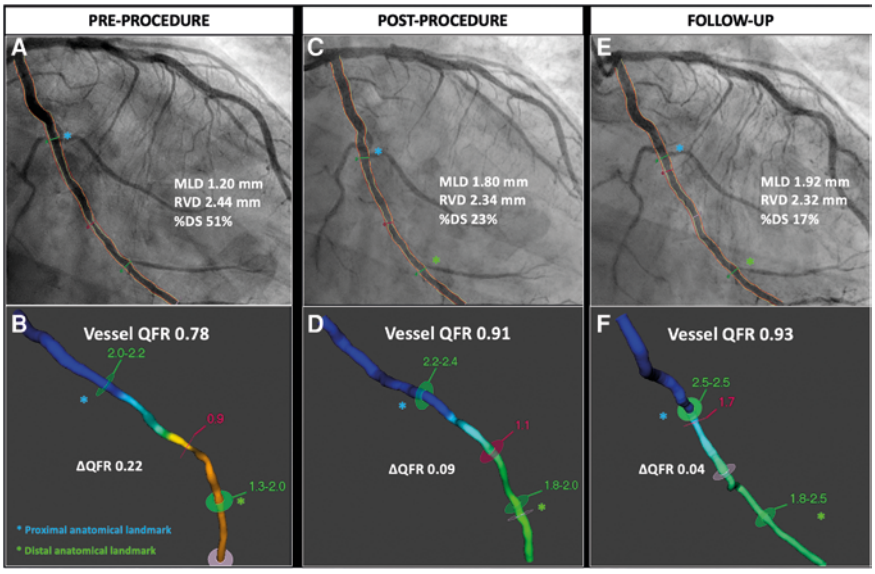


Figure 7. *Angiography-derived quantitative flow ratio in drug-coated balloon. The use of angiography-derived fractional flow reserve technologies allows assessment of the physiological drop along the entire vessel while reaching precise co-localization of the treated segment by applying fiducial landmarks (i.e. side branches, bifurcations). Pre-procedure quantitative flow ratio depicts a flow-limiting disease (quantitative flow ratio 0.78) that improves to 0.91 after drug-coated balloon treatment. At follow-up, a non-flow-limiting quantitative flow ratio value is measured (0.93). DS: degree of stenosis; MLD: minimal lumen diameter; ΔQFR: delta QFR; QFR: quantitative flow ratio; RVD: reference vessel diameter*

Table 6. Definitions of lesions and clinical settings for drug-coated balloon treatment.

	Nomenclature	Description
1	In-stent restenosis (ISR)	A diameter stenosis >50% in the stented segment or within a 5 mm proximal or distal margin • Avoid the inclusion of patients with acute MI (<72 h) and very early (<1 month) ISR
2	Small vessels Very small vessels	Reference vessel diameter (RVD) <2.75 mm Lesion length <25 mm Reference vessel diameter (RVD) <2.25 mm
3	Late lumen enlargement Positive vessel remodelling	Negative lumen loss CCTA: outer vessel diameter >10% of the reference normal segment in the same vessel (remodelling index >1.1) IVUS: >5% difference in the external elastic membrane cross-sectional area at the site of plaque compared to a non-diseased reference segment
4	Diffuse disease	Coronary segment ≥25 mm in length, with vessel wall irregularities and no clear focal lesion
5	Large vessels	Reference vessel diameter (RVD) ≥2.75 mm Lesion length <25 mm
6	Calcified lesions	Angiographic appearance of radiopacities without cardiac motion before contrast injection affecting both sides of the arterial wall (tramway-track appearance)
7	Chronic total occlusion	Occlusion with the absence of antegrade flow with a documented (definite CTO) or presumed (probable CTO) duration of ≥3 months
8	Bifurcations	Coronary artery narrowing occurring adjacent to, and/or involving, the origin of a significant side branch (SB), anatomically represented by complex vessel/function structure composed of three different vessel segments (proximal main vessel, distal main vessel and SB)
9	High bleeding risk	1-year risk of BARC 3 or 5 bleeding ≥4% or of an intracranial haemorrhage ≥1% ARC-HBR proposed 20 clinical criteria and patients are at HBR if at least one major or two minor criteria are met

ARC: Academic Research Consortium; BARC: Bleeding Academic Research Consortium; CCTA: coronary computer tomography angiography; CTO: chronic total occlusion; HBR: high bleeding risk; ISR: in-stent restenosis; IVUS: intravascular ultrasound; MI: myocardial infarction; RVD: reference vessel diameter; SB: side branch

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Data availability

No data were generated or analysed for this manuscript.

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Supplementary data

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Definitions and standardized endpoints for the use of drug coated balloon in coronary artery disease: consensus document of the Drug Coated Balloon Academic Research Consortium

<<Supplementary material>>

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1. Types of clinical studies in DCB

a. First-in-human studies

Studies in the DCB field investigating for the first time a new balloon, drug, or coating to improve transfer capabilities, vessel wall penetration or extend local drug retention in human applications are referred to as a "First-in-Human" (FIH) or "First-in-Man" (FIM), and are aimed at providing preliminary information on device feasibility (proof of principle) in humans whilst identifying any major safety concerns. Consequently, their design should primarily be single-arm with outcomes reported through descriptive statistics, and as their intent is to expose only a minimal number of subjects to the new device as they are typically not powered for specific endpoints and include sample sizes of <100 patients. They are expected to provide clear pre-specified "stopping" rules to prevent the exposure of further patients to futile or dangerous treatments. These studies are appropriate early in device development when initial clinical experience is necessary because non-clinical testing methods are neither available nor adequate to provide the information needed to advance product development. As with all clinical studies, initiation of an early feasibility study must be justified by an appropriate benefit-risk analysis and adequate human subject protection measures[1]. Following FIH studies, the efficacy of the technology should be investigated in clinical registries or small randomized clinical trials, usually designed to have mechanistic endpoints and to compare performance with predefined "Objective Performance Criteria" (OPC)[1].

In the case of DCBs, several technologies have been tested for in-stent restenosis (ISR) or de-novo lesions in coronary arteries. For the latter, the limited available evidence has mainly been accrued in small-vessel disease. Future dedicated studies should target the application of different DCB technologies in distinct lesion types (i.e., de-novo, large vessels, bifurcations, complex lesions including chronic total occlusions and left-main) and/or specific clinical patient conditions (i.e., high bleeding risk, diabetes mellitus, acute coronary syndromes).

b. Studies for regulatory approval

FIH studies, conducted as the first step in generating evidence, are not sufficient for regulatory approval, and must be supplemented by larger pivotal studies preferably powered for clinical endpoints of safety and performance (efficacy). Surrogate endpoints can be embedded as ancillary and/or in support of clinical endpoints.

Currently, in the European Union, to obtain a CE-mark (CE = Conformité Européene) for a new device under the Medical Device Regulation (MDR), an EU-pivotal study is needed that typically characterizes the new device through mechanistic safety and efficacy endpoints, or composites. These studies can be randomized or single arm in design and seek to compare the outcomes of the experimental arm with the contemporary standard of care (control group) through superiority or non-inferiority comparisons. For single-arm designs, comparison with historical trial data or an OPC can be used, once medically and statistically justified[1]. CE-mark certificates for a short period (e.g., 2 years) can be granted once safety is confirmed, in the presence of limited additional clinical evidence from surrogate endpoints with short follow-up (e.g., 6 months), limited samples size and/or non-randomized designs. Granting certificates with longer durations (e.g., 5 years) requires pivotal studies with clinical primary endpoints, evaluated at appropriately long follow-up (12 months), with adequate sample sizes delivering more substantial evidence. The ultimate goal of these more comprehensive clinical outcome trials is to more reliably detect potential safety signals not identified in the initial surrogate endpoint study. In non-inferiority trials, sample sizes are driven by the need for a smaller non-inferiority margin, that still should be clinically acceptable.

Alternatively, in the United States, the manufacturer needs an investigational device exemption (IDE) to conduct significant risk, pre-approval device trials[2], which are typically clinical-outcomes trials, with large sample sizes. Another major difference to other regions is that in the United States the trial design may be discussed and developed jointly with the Food and Drug Administration (FDA), which may subsequently facilitate final approval once the trial has been completed and published.

The specific principles and requirements for approval by the Chinese Food and Drug Administration (CFDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) are beyond the

scope of this document[3,4]. The DCB ARC endorses the “Harmonization by Doing" (HBD) approach for medical device regulation, which is employed by the FDA and the PMDA. This aims to achieve regulatory harmonization and streamline the evaluation and approval processes for medical devices, supporting a practical collaboration and ongoing communication between regulatory authorities, industry stakeholders, and other relevant parties, to reduce duplicative efforts, minimize regulatory barriers, and enhance the efficiency of the regulatory review and approval processes.

The DCB ARC recommends that trials comparing the performance of DCBs to plain old balloon angioplasty (POBA) should be designed to show superiority of the DCB, whereas when comparing DCBs to DES or alternatively approved DCB, the study design should aim to show, at the very least, non-inferiority of the DCB.

c. *Sham procedure studies*

Clinical endpoints with a subjective component, quality-of-life assessments, or patient-reported outcomes, have recently gained increasing attention and importance in the cardiovascular field. However, phenomena like the Hawthorne Effect (patients behave differently once they feel observed) or the Pygmalion Effect (high expectations led to better outcomes and vice versa) have the potential to hamper such assessments, and therefore, if feasible, trial designs utilising placebo assignments and “blinding” would be preferrable[5]. “Sham procedures” can be used as the placebo arm of randomised control trials (RCT) of medical devices[6], whilst a double-blind trial design is critical in trials aiming to test subjective outcome metrics.

Although DCB ARC acknowledges the relevance of sham-controlled trials in the setting of CCS, by comparison of DCB treatment with optimal medical therapy (OMT)[7], it does not recognize a clear need for sham procedure studies in the DCB field. Performance of sham-controlled trials is challenging and may be also controversial from an ethical stand point. Careful study design, in terms of sample size, primary endpoint and duration of follow-up is paramount.

b. Clinical endpoints

Myocardial infarction

Postprocedural cardiac biomarkers rise

DCB ARC suggests reporting any rise in cardiac biomarkers occurring after a minimum of 6 hours following the end of the procedure, even if they do not meet the criteria for a PMI. In trials comparing devices, the detection of differences in the rise of cardiac biomarkers, even if not clinically significant, may be of relevance in the adjudication of their safety profile[8].

Post-procedural cardiac biomarkers rise should be classified according to the angiographic findings as related to angiographic complications (type 1) or not (type 2). Angiographic complications should be recorded as transient (intraprocedural) or persisting at the end of the procedure, as shown in **Table 3**. For this purpose, the accurate report of intraprocedural complications, including transient ones, is relevant and has been linked to adverse short-term outcomes in patients undergoing PCI[9].

Spontaneous myocardial infarction

Spontaneous MI is defined according to the 4th universal definition of MI (UDMI; Type 1, 2, 3, 4b or 4c)[10]. ARC-2 already reported the difficulty in differentiating between Type 1 and Type 2 MI or non-ischemic myocardial injury from necrosis, as additional investigations that might allow clarification, are usually judged inappropriate from a clinical perspective.

Prior or silent/unrecognized MI is defined as abnormal Q waves with or without symptoms in the absence of non-ischaemic causes, imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic etiology, or pathoanatomical findings of a prior MI. DCB ARC suggests that “prior or silent/ unrecognized MI” should not be included in the primary endpoint adjudication, as no proof of cardiac biomarker elevation is available.

Target-lesion MI is defined as any MI associated with angiographic confirmation that the culprit lesion corresponds to the DCB treated segment (1 mm proximal and distal to the balloon). Any MI

attributed to the target vessel, but not involving the target lesion should be defined as “target-vessel non-target lesion MI”.

3. Follow-up methods

a. Clinical and patient-level follow-up

Patient-, site-, central adjudication–reported and cost-effectiveness endpoints

The role of coronary revascularization in preventing hard adverse cardiac events (MI, death), especially in the setting of CCS, has been recently questioned[11]. However, in CCS revascularization plays an important role in reducing symptoms, and improving functional status, and quality of life (QoL). Traditional clinical outcome measures (laboratory tests, mechanistic outcomes), may not fully capture from a patient's perspective their experience of the treatment[12,13]. PROMs are becoming increasingly relevant as they provide valuable insights into a patient's QoL, symptoms, and treatment satisfaction. Several methods to assess PROMs are available, such as questionnaires [Seattle Angina Questionary (SAQ) 19 and 5, EuroQol 5D, SF-36, SF-12], interviews, and electronic health records. PROMs are especially valuable in chronic conditions, where the impact of treatment on a patient's daily life is significant. For this purpose, the measurement of quality-adjusted life-years (QALY) in cases of long, or very-long term follow-up, is preferred combining hard clinical events and QoL improvement. The QALY metric is also used in cost-effectiveness analyses to compare the costs and benefits of different interventions, helping to prioritize healthcare resources (e.g., EXCEL trial)[14].

Adjudication of PROMs, however, can pose several challenges, as patients may not have the ability or willingness to accurately self-report their experiences. Additionally, the validity and reliability of PROMs may be impacted by bias (recall bias, social desirability bias, self-report bias). To overcome these challenges the assessment of PROMs must be designed and executed to ensure the accuracy and validity of the collected data, providing psychometric properties (validity, reliability, responsiveness, and interpretability) proven to measure the intended domain[12]. Therefore, the

utilization of digital health technologies, such as the incorporation of cartoon or graphic representations, holds the potential to enhance the willingness and ability of patients to provide accurate self-reported PROMs. Double blinded assessment with or without the ancillary use of a sham procedure, is particularly valuable in ensuring PROMs accuracy and validity.

EuroQol-5D (EQ-5D) and SF-36 are commonly used PROMs in clinical trials. The EQ-5D is a standardized instrument used to measure health-related QoL based on five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), while the SF-36, with a shortened version (SF-12), is a broader tool that measures both physical and mental health-related QoL[15].

PROMs play a key role in studies investigating the clinical benefit derived from different pharmacological regimens and sham-controlled studies, when the two competing comparators might lead to significant differences in patient's perceived health status, and not in those comparing strategies or devices.

b. Procedural mechanistic (anatomical and functional)

Noninvasive follow-up

CCTA

CCTA provides high diagnostic accuracy for detecting obstructive stenoses in patients with suspected CAD[16]. It enables a comprehensive assessment of the epicardial conductance vessels by analyzing the lumen, plaque composition and the functional characteristics of lesions and vessels. In the follow-up of vessels that underwent PCI, it provides a net advantage by avoiding an invasive procedure and the related risks to the patient. Nevertheless, metallic stents hamper its diagnostic accuracy due to the occurrence of a blooming artifact generated by the metal[17]. Conversely, CCTA was seen to yield good diagnostic accuracy compared to IVUS during the follow-up of patients treated with bioresorbable technologies[18,19]. Notably, CCTA seems to be of potential use during follow-up after DCB treatment, overcoming potential drawbacks related to the invasive assessment of severely calcified or tortuous

vessels and allowing the definition of the amount of plaque, vessel remodeling and functional evaluation. On top of anatomic surrogate endpoints, such as minimum lumen area (MLA), plaque burden (PB) and vessel remodeling, CCTA potentially allows assessment of plaque composition and vulnerability (i.e., low-attenuation plaque, positive remodeling, spotty calcifications, napkin-ring sign). Moreover, the distribution of physiological values along the studied vessel can be analyzed. In particular a distal FFR-CT value can be measured, as well as the physiological drop across the treated segment (ΔFFR-CT). The adoption of these methodologies is growing and could be of potential application in future DCB trials, pending greater availability in different participating centers.

However, CCTA analysis is particularly susceptible to "geographical miss", with co-localization of the treated segment challenging (with coronary angiography). The use of fiducial co-localization (e.g., side branches) can overcome such limitations, especially when functional assessment along the vessel is performed. CCTA analysis may also be limited in very small vessels (<2.0 mm)[16].

4. Statistical consideration

Analytical plan (intention-to-treat, per-protocol, and as-treated analyses)

DCB ARC recommends specifying up-front the analytical plan to be used in DCB trials, which is largely dependent on the study design. As a class effect is not anticipated for DCBs, an appropriate sample size and non-inferiority margin, is recommended.

In this regard, the interpretation of cross-over and adjudication is crucial. According to the intention-to-treat (ITT) principle, statistical analyses are conducted according to the group to which patients are randomized, regardless of whether they actually received the intervention or adhered to the protocol. ITT is always accompanied by a per-protocol analysis, which aims to ensure the intrinsic comparability of the two arms (comparators) to detect true differences. In the specific setting of DCB trials, especially in "device-comparing" or in the "leave nothing behind" strategy-comparing studies, an ITT analysis may result in inaccurate conclusions, and a different analytical plan may better reflect

the comparison between the two arms (i.e., Per-protocol, As-treated). Hence, ITT is reliable whenever a "cross-over" or "blended" strategy therapy is allowed.

According to the per-protocol analysis plan only those participants who received the assigned intervention (per randomization) and strictly followed the specific protocol for the device are included in the statistical analysis, better estimating the true treatment effect. According to the as treated plan, participants are analyzed based on the treatment they actually received, rather than the treatment to which they were allocated by randomization[20].

Novel trials designs should be also considered. The adaptative trial design, often incorporating Bayesian analyses of the data, represents a dynamic approach that allows for flexibility and responsiveness during a study. Pre-defined interim analyses with pre-defined statistical penalties, enable informed decisions to be made about the trial's course as data accumulates.

Bayesian analysis is particularly useful when dealing with small sample sizes, complex models, and situations where prior knowledge or expert opinions are relevant, by providing a coherent framework for incorporating both existing knowledge and new data to make probabilistic inferences.

Event-driven clinical trials, exemplified by the PROSPECT trial design[21], introduce an additional layer of adaptability. In these trials, enrollment continues until a predefined event rate or outcome is reached. Once this threshold is achieved, the trial is halted, ensuring that the study's conclusions are drawn from a sufficient number of events, potentially providing valuable clinical data.

Statistical approach related to composite endpoint and repeated events interpretation (Finkelstein, Win-ratio analysis)

Composite endpoint interpretation is influenced by the statistical approach that is used, and the choice relies on the study design, the nature of the composite endpoint, and the objectives of the analysis. Time-to-first-event analysis treats all the components of the composite endpoint as having equal relevance and considers the first event occurring during follow-up as the most important. This statistical approach is considered the standard method for the analysis of composite endpoints, being

simple to perform and easy to understand, providing a straightforward interpretation of the result. However, non-fatal events that occur early have more impact than more serious events (i.e., stroke or death) occurring later. Alternative methods, such as win ratio analysis, Cox-based models for recurrent events, or weighted cumulative events (WCE) analysis, are designed to weigh the number (repeated events) and the severity of each event, which may provide a more complete and accurate assessment of the treatment effect. The win ratio analysis and Cox-based models for recurrent events consider all the events occurring during follow-up and incorporates the severity of the clinical events by assigning different weights to different types of events. The WCE analysis is a more complex method that considers the total burden of events and assigns different weights to different types of events based on their clinical significance. This method considers the timing, type, and frequency of all events occurring during follow-up and provides a more comprehensive assessment of the treatment effect[22].

The application of these statistical plans may empower clinical trial interpretation, especially when individual components of the composite endpoints seem to vary substantially in severity and timing. Such methods should be used as pre-specified secondary analyses, according to patient type, and the devices and strategies used. The ranking and severity of each event should be pre-defined in the study design[23]. A decision tree for statistical models is illustrated in **Supplementary Figure 2**.

The sample size calculation should be based on the primary analysis, having time-to-first-event analysis as reference. When recurrent events and/or event severity are used, simulation techniques and dedicated codes are required for sample size calculations[24,25].

5. Lesions and clinical settings for DCB treatment

a. In-stent restenosis

The main evidence-based indication for using a DCB is to treat ISR, and according to many RCTs and meta-analyses DCBs are superior to conventional POBA, BMS, and first-generation DES, and comparable to new generation DES in the management of ISR[26]. Although acute and late

angiographic findings tend to be superior with DES over DCB, clinical safety and efficacy are largely comparable[27,28]. A comprehensive description of the study design, angiographic and clinical endpoints of clinical trials evaluating the performance of DCB in the setting of ISR is provided in **Supplementary Table 1**.

ISR is defined as a diameter stenosis (DS%) >50% in the stented segment or within a 5 mm proximal or distal margin[29], and when associated with angina and/or documented ischaemia, repeat revascularization is indicated.

The American College of Cardiology/American Heart Association lesion classification and the widely used Mehran's angiographic ISR classification provide useful tools to determine acute procedural results and the long-term angiographic outcome of patients with ISR (**Supplementary Table 2**)[30-32].

Intracoronary imaging plays a pivotal role in tackling ISR by helping determine the mechanistic causes of the restenosis other than intimal hyperplasia, such as chronic under-expansion (18–40%), stent fracture (<5%), and neoatherosclerosis.

Intravascular ultrasound (IVUS) ISR classification and optical coherence tomography (OCT) based ISR mechanisms classification are presented in **Supplementary Table 2**.

DCB ARC recommends determining the angiographic and intracoronary imaging-defined pattern of ISR, as these are the major predictors of recurrent restenosis and subsequent reintervention[33].

To avoid the inclusion of patients presenting with stent thrombosis, DCB ARC recommends excluding patients with acute MI (<72H) and very early (<1 month) ISR.

b. De novo lesions

The rationale of using DCBs for the treatment of *de novo* CAD is to prevent restenosis by releasing anti-proliferative drug into the arterial wall, without permanent vessel caging. Although this strategy has yielded non-inferior results in selected lesions compared to DES in several RCTs, it is yet to be endorsed by international guidelines[34,35].

◊ ***Small vessels***

Coronary arteries with a reference vessel diameter (RVD) <2.75 mm, as assessed by coronary angiography are defined as "small vessels" and this criterion is used by most RCTs of DCBs in small vessels; although notably the BASKET-SMALL 2 study used a <3 mm cut-off criteria[35,36]. Very small vessels are usually defined as those with an RVD <2.25 mm[37], whilst universally, the minimum RVD required for treatment is ≥2 mm. In order to differentiate between trials of small vessel and diffuse disease, DCB ARC suggests a lesion length <25 mm as the cut-off for eligibility.

Assessment of vessel size should be performed after administering intracoronary nitroglycerin to maximize RVD, regardless of which imaging modality is used. Intravascular OCT enables the most precise assessment of target vessel size, with angiography associated with several degrees of under-estimation, and IVUS overestimation[38]. PCI in small vessels disease is hampered by an inverse relationship between vessel diameter and the future risk of restenosis[39].

A comprehensive description of study design, angiographic and clinical endpoints of clinical trials evaluating the performance of DCB in the setting of de novo small vessels is provided in **Supplementary Table 3.**

Late lumen enlargement

DCB ARC defines angiographic late lumen enlargement as negative late lumen loss. Positive remodeling is defined on CCTA as an outer vessel diameter > 10% of the reference normal segment in the same vessel (remodeling index >1.1), or on IVUS by a >5% difference in the external elastic membrane cross-sectional area at the site of plaque compared to a non-diseased reference segment[16].

◊ ***Diffuse disease***

Diffuse disease is defined as a coronary segment ≥25 mm in length, with vessel wall irregularities and no clear focal lesion[40]. DCB ARC suggests a lesion length ≥25 mm, either determined by

quantitative coronary angiography or by intravascular imaging, as the cut-off for eligibility in clinical trials of diffuse disease. Adequate views should be use to prevent angiographic foreshortening of lesion length.

◊ ***Large vessels and left main***

Large coronary vessels are defined by an RVD ≥2.75 mm, as assessed by coronary angiography. DCB ARC suggests a lesion length <25 mm as cut-off to differentiate trials of large vessels from diffuse disease (≥25mm). To date, there has been no dedicated RCTs of DCBs in large vessels.

Clinical trials assessing the performance of DCB in the setting of de novo large vessels are summarized in **Supplementary Table 4.**

◊ ***Calcified lesions (calcium debulking devices)***

Severe coronary calcification is defined as the angiographic appearance of radiopacities without cardiac motion before contrast injection affecting both sides of the arterial wall (tram-track appearance)[41]. Besides being associated with larger plaque burden, a greater degree of lesion complexity (i.e., involvement of coronary bifurcation or chronic total occlusion [CTO]) and vulnerability (i.e., microcalcifications, calcified nodules), calcified lesions increase PCI complexity and worsen long term results[42,43].

Lesion preparation may also be hampered by challenges in crossing and dilating lesions using standard devices (i.e., semi-compliant, non-compliant balloon). Of note, inadequate lesion preparation increases the risk of stent loss, stent under-expansion, stent-malapposition and asymmetric and eccentric lumen enlargement, with higher rates of intraprocedural complication (i.e., no reflow, coronary dissection, or perforation) and long-term adverse events[44]. Adequate lesion preparation is key for good outcomes following PCI, including those performed with DCBs, as poor lesion preparation can lead to less efficient drug transfer to the vessel wall.

Intravascular imaging is pivotal, providing a higher sensitivity for detecting calcium, enabling additional assessment of the calcium's properties (depth, thickness, length) and morphology (concentric, eccentric, nodular), which are crucial for procedural optimization, and for providing evidence of effective calcium debulking by showing fractures not detectable with angiography[45].

Considering the circumferential calcium arc, calcified lesions can be divided into eccentric (arc < 180°), concentric (arc > 180°) and nodular (eruptive protrusion into the lumen). Calcium can also be divided into superficial (located at < 50% of the depth of the plaque) or deep (located at > 50%)[46].

The morphological characteristics of calcium which are associated with sub-optimal results with DES-based PCI include a superficial calcium angle >270°, calcium length> 5 mm, 360° of superficial calcium or a calcified nodule according to IVUS analysis[47], or an angle >180°, calcium thickness >0.5 mm, and calcium length >5 mm, as per OCT[48]. To date, there are no RCTs assessing the performance of DCBs in calcified lesions, and moreover angiography-defined severely calcified lesions have traditionally been excluded from DCB RCTs. As obtaining good angiographic results with balloon angioplasty in heavily calcified lesion is challenging and as the drug may be less active in a calcific lesion, data and experience on DCB results in these lesions remains scarce. In the DEBUT RCT, which evaluated a DCB-only approach in HBR patients, 10% of randomized lesions were judged to be calcified and rotational atherectomy was used in 5%[49]. Further registries have suggested the feasibility of a DCB-only approach after rotational atherectomy, while no data are available on this approach after orbital atherectomy or intra-vascular lithotripsy in de novo coronary artery lesions[50,51].

DCB ARC supports the use of intravascular imaging as an adjunctive technique in dedicated DCB RCTs, with the aim optimal lesion preparation before DCB treatment. DCB ARC will have to document in its electronic case report form (eCRF) which adjunctive devices, such as scoring/cutting balloons, intravascular lithotripsy, and laser have been used for optimal lesion preparation in order to investigate the favorable or unfavorable interaction of DCBs with these adjunctive devices.

◊ ***High risk lesions (flow limiting/non flow limiting)***

Vulnerable atherosclerotic plaques are at increased risk of destabilization leading to adverse events [52]. The three main underlying lesion types prone to thrombosis are plaque rupture, plaque erosion and calcified nodules, with the former the commonest cause of coronary thrombotic events and cardiovascular death.

To date, only the DEBuT-LRP study (NCT04765956) has investigated the role of DCB in the treatment of vulnerable plaques. DCB ARC suggests using intravascular imaging as an adjunctive technique in DCB trials focused on the detection and treatment of vulnerable coronary plaques (**Supplementary Table 5**).

◊ ***Chronic total occlusion***

DCB ARC endorses the definitions and classifications proposed in the CTO ARC[53]. Briefly, a CTO is considered as an occlusion with the absence of antegrade flow with a documented (definite CTO) or presumed (probable CTO) duration of ≥3 months.

In CTO-dedicated DCB studies two different approaches could be tested: a DCB-only approach that appears to be feasible when wiring (anterograde or retrograde) is intraplaque, and not feasible for dissection re-entry techniques; a blended DCB and DES approach to reduce overall stent length, especially distally where estimation of true vessel size could be challenging.

c. Bifurcations

DCB ARC endorses the definitions and classifications provided in the Bif ARC[54,55].

Two different types of studies with DCBs in coronary bifurcations can be conceived: the first is a DCB-only strategy, with DCB use in the main vessel across the SB with or without DCB use in the SB (leave nothing behind strategy). Alternatively, DCBs can be used to treat the SB in the setting of a provisional bifurcation technique, either before (if planned) or after (as a bailout if required after main vessel stent) a DES is used in the main branch across the SB (blended strategy).

Some concerns have emerged with the use of DCBs during kissing-balloon inflations, due to the time required and the proximal interaction of the two balloons, which might impact on the delivery of the antiproliferative drug to the vessel wall. A similar concern relates to the use of DCBs to treat the SB after DES implantation in the main branch across the SB, as the interaction between the balloon and stent's struts, potentially compromises drug delivery.

An approach to a DCB-only bifurcation PCI is comprehensively laid out in the recent international consensus document[36]. However, evidence of the value of a systematic use of DCB in the side-branch in patients with bifurcation lesions treated with provisional stenting strategy is lacking. The ostium of a side-branch may experience acute elastic recoil which is not prevented by DCB. Clinical trials evaluating the performance of DCB in bifurcation lesions are summarized in **Supplementary Table 6**, while the technical use of DCB in bifurcation lesions is presented in **Supplementary Figure 3**.

d. High bleeding risk

DCB ARC recommends assessing patients deemed at HBR according to the ARC-HBR definitions[56]. Briefly, HBR is defined as a 1-year risk of Bleeding ARC (BARC) 3 or 5 bleeding ≥4% or of an intracranial hemorrhage ≥1%. ARC-HBR proposed twenty clinical criteria, with patients at HBR if at least 1 major or 2 minor criteria are met. DCB ARC highlights the need for investigating whether DCBs allow de-escalation of P2Y12 inhibitors or early discontinuation of DAPT (P2Y12 inhibitor or aspirin discontinuation) in HBR patients.

According to the DEBUT RCT, DCB-only PCI was found to be superior to BMS implantation in patients deemed at HBR in terms of major adverse cardiac events (1.9% vs. 12.4%; p=0.003 for superiority) at 9 months[49]. However, the optimal duration of dual anti-platelet therapy (DAPT) was not investigated in this trial. In a prespecified subgroup analysis of the BASKET-SMALL 2 trial addressing the HBR cohort, a trend towards reduced severe bleedings was seen after DCB-only PCI and a shorter duration of DAPT as compared to DES and standard DAPT[57].

Whilst the use of current generation DES allows a short 1-month DAPT[58], the optimal composition and duration of antiplatelet therapy after DCB-only PCI is not yet known. The current consensus on DAPT duration after DCB-only PCI in CCS patients is 1-month, stemming from the first RCT of DCBs for the treatment of ISR[59], with this duration then adopted for the treatment of all *de novo* lesions[36,60]. Due to the lack of metallic foreign body, use of DCBs could offer advantages for patients at HBR including the shortening of DAPT to less than 1-month or, in case of life-threating bleeding, the possibility of stopping antiplatelet therapy during the first month. Recent registry studies suggest that DCB-only PCI can be safely done using a single anti-platelet in selected populations[61].

Given the lack of dedicated powered RCTs in HBR patients, comparing DCBs to current generation DES, DCB ARC recognizes the need for further powered and high quality RCTs.

Clinical trials evaluating the performance of DCBs in HBR populations are summarized in **Supplementary Table 4**.

DCB and international guidelines

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. United States and European guidelines weigh the class of recommendation according to the strength of the available evidence. DCB ARC supports a Class I recommendation to be used in the presence of evidence from superiority RCT that a given treatment is beneficial, useful and effective, preferentially. When evidence comes from non-inferiority RCTs, the same class of recommendation could be used in certain clinical settings, in which the avoidance of permanent implants is particularly advantageous (i.e., ISR). The international community should be aware that in the specific field of DCB, their expected benefits in terms of improved clinical outcomes may not be evident short term, and might require long- and very-long term follow-up time. Therefore, the adoption and advancement of DCB technology is expected to progress further as long-term follow-up data accumulate.

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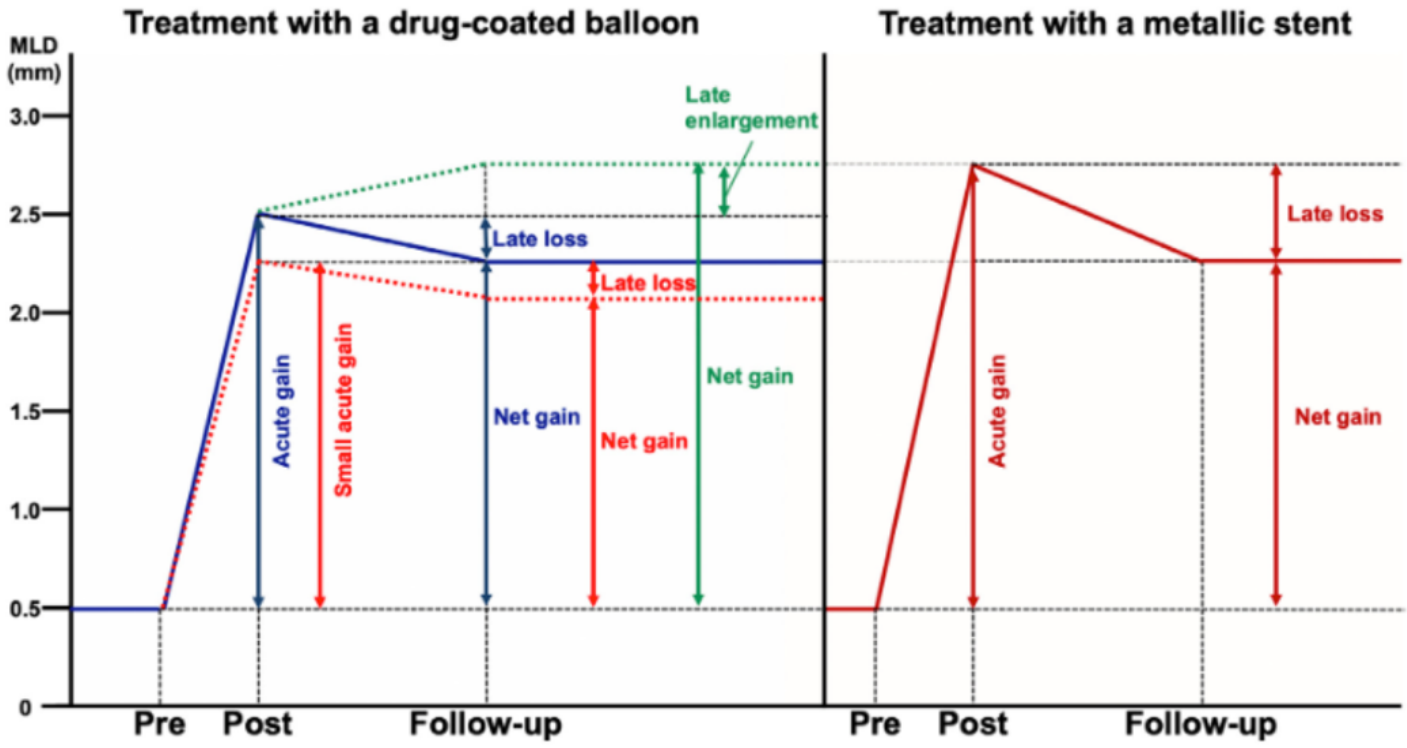
Supplementary Figure 1. Angiography changes after treatments with DCB or DES (From Ono M et al. Rationale and Design of the TRANSFORM I Trial. Cardiovasc Revascularization Med. 2021; 25:29–35. https://doi.org/10.1016/j.carrev.2020.10.004)

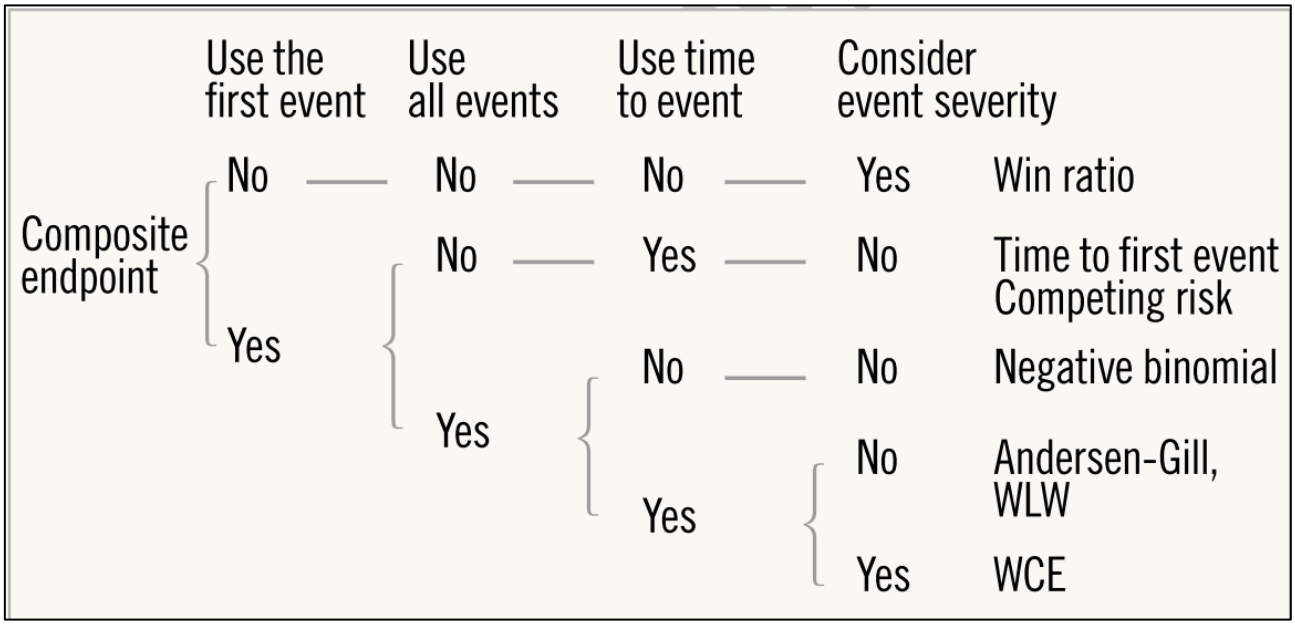


	Drug-coated balloon			Metallic stent
	Reference	Small acute gain	Late enlargement	
Pre MLD	0.50 mm	0.50 mm	0.50 mm	0.50 mm
Post MLD	2.50 mm	2.25 mm	2.50 mm	2.75 mm
Follow-up MLD	2.25 mm	2.10 mm	2.25 mm	2.25 mm
Acute gain	2.00 mm	1.75 mm	2.00 mm	2.25 mm
Late lumen loss	**0.25 mm**	**0.15 mm**	**-0.25 mm**	**0.50 mm**
Net gain	**1.75 mm**	**1.60 mm**	**2.25 mm**	**1.75 mm**

MLD, minimal lumen diameter; mm, millimeter

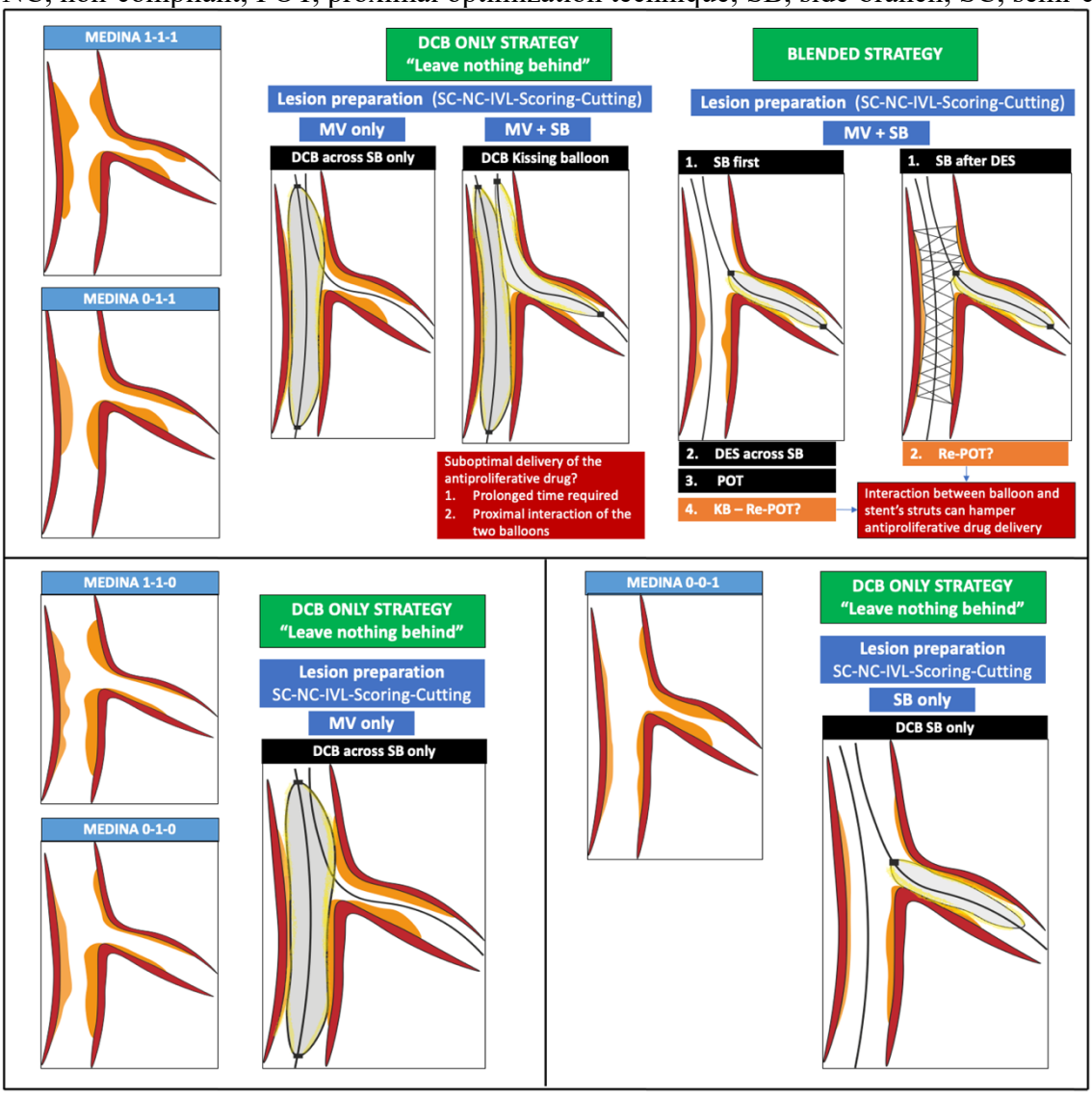
Supplementary Figure 2. Decision tree for statistical models (from Hara H et al. Statistical methods for composite endpoints. *EuroIntervention*. 2021;16:E1484–E1495)

WCE: weighted composite endpoint; WLW: Wei-Lin-Weissfeld



Supplementary Figure 3. DCB use in bifurcation lesions

In cases where disease involves both the MV and the SB (MEDINA 1-1-1 or 0-1-1; top panels), the use of DCB can follow either a "leave nothing behind" strategy, such as DCB treatment across the SB only or DCBs kissing balloon inflation, or a "blended" strategy with DES, with DCB treatment performed either before or after provisional DES implantation.
In cases where the side branch is not diseased (MEDINA x-x-0; bottom panel left), DCB treatment can follow a "leave nothing behind" strategy, such as DCB treatment across the SB only.
In case of side-branch only disease (MEDINA 0-0-1; bottom panel right), DCB treatment can follow a "leave nothing behind" strategy, such as DCB inflation to the SB only.
DCB, drug coated balloon; DES, drug eluting stent; IVL, intravascular Lithotripsy; MV, main-vessel; NC, non-compliant; POT, proximal optimization technique; SB, side-branch; SC, semi-compliant.



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Supplementary Table 1. Clinical trials evaluating the performance of DCBs in in-stent restenosis

Study name	Design	DCB	Comparator	n	ISR	Inclusion	Exclusion	Reference vessel	Primary endpoint	Secondary endpoints	Angiographic follow-up (p value)	MACE (p value)	TLR (p value)
BMS ISR													
PACCOCATH ISR I -II	1:1 RCT Open-label Corelab CEC	PCB	POBA	108	BMS (96) DES (4)	CCS or UA or ischaemia	MI<72H, CKD (crea>2), allergies Thrombus, severe calcification, stenosis<70%	RVD>2.5, length<30mm	6M LLL	6M ISR 12-24-60M ST, TLR, MI, stroke, death	6M LLL 0.14 ± 0.46 mm vs 0.81 ±0.79 (0.001)	12M 9 vs 44 (0.001) 60M 27.8 vs 59.3 (0.009)	12M 4 vs 37 (0.001) 60M 9.3 vs 38.9 (0.004)
PEPCAD II	1:1 RCT Open-label Corelab CEC	PCB Paccocath	PES	131	BMS	CCS or UA or ischaemia	MI<48H, GFR<30, Allergies, life expectancy <2Y DS<70%, LM, stents covering a major side branch >2mm	RVD 2.5-3.5, length ≤22mm	6M LLL	6M ISR 12-36M MACE (ST, TLR, MI, death)	6M LLL 0.17 ± 0.42 mm vs 0.38 ±0.61 (0.03)	12M 9 vs 22 (0.08) 36M 34.8 vs 41.5 (?)	12M 6 vs 15 (0.015) 36M -
RIBS V	1:1 RCT Open-label Corelab CEC	PCB Sequent please	EES	189	BMS	CCS or ischaemia DS>50%	Small vessels (<2mm), diffuse lesions (>30mm) Early (<1m) ISR, MI, thrombus	RVD>2mm, length<30mm	9M in-segment MLD	12-36M MACE, ISR	6M LLL 0.14 ± 0.5 mm vs 0.04 ±0.5 (0.14) ISR (9.5 vs 4.7) (0.22)	12M 8 vs 6 (0.60) 36M 12 vs 10 (0.64)	12M 6 vs 1 (0.09) 36M 8 vs 2 (0.04)
SEDUCE	1:1 RCT Open-label Corelab CEC	PCB Sequent please	EES	50	BMS	Any ISR	LVEF <30, crea>2, LM, bifurcations, LE<1Y	RVD 2-4mm, length<24mm	9M uncovered struts (OCT)	9M LLL 12M MACE, TLR	6M 1.4 vs 3.1% (0.025) LLL 0.28 vs 0.07 (0.1)	12M -	12M 4.2 vs 8 (0.576)
TIS	1:1 RCT Open-label Corelab CEC	PCB Sequent please	EES	136	BMS	Any ISR (DS>50)	LE<1Y, contraindication to DAPT	Any	12M LLL	12-36M MACE TVR	6M LLL 0.02 vs 0.19 (0.0004) ISR 8.7 vs 19.12% (P=0.078)	12M 10.3 vs 19.1 (0.213) 36M 19.1 vs 29.4 (0.230)	12M 7.6 vs 16.2 (0.110) 36M 12.9 vs 22.2 (0.205)
DES ISR													
PEPCAD DES, 2012	1:1 RCT Open-label Corelab CEC	PCB Sequent please	POBA	110	DES	Any ISR	Thrombus, bifurcation, grafts, CTO, ostial, LM, planned surgery	RVD 2.5-3.5; length <22mm	6M LLL	6-36M MACE or TLR	6M LLL 0.43 ± 0.61 vs 1.03 ± 0.77 mm ISR 17.2 vs 58.1% (0.001)	6M 16.7 vs 50 (0.001) 36M 20.8 vs 52.6 (0.001)	6M 15.3 vs 36.8 (0.005) 36M 19.4 vs 36.8 (0.046)
PEPCAD CHINA ISR, 2014	1:1 RCT Open-label Corelab CEC	PCB Sequent please	PES	220	DES	ISR DS>70 or 50 with ischemia	MI<7D, bifurcation Sb >2.5, thrombus, NYHA IV, severe VHD, stroke<6M, GFR<30	RVD 2.5-4 Length <30mm	9M LLL (non-inferiority)	9M ISR 12-24M TLF, TLR	9M LLL 0.46 ± 0.51 vs 0.55 ± 0.61 mm (0.0005) ISR 13 vs 10 (0.16)	12M TLF 16.5 vs 16 (0.92) 24M TLF 16.8 vs 18.6 (0.73)	12M 15.6 vs 12.3 (0.48) 24M 15.9 vs 13.7 (0.66)

ISAR DESIRE III, 2013	1:1 RCT Open-label Corelab CEC	PCB Sequent please	PES vs POBA	402	DES	ISR>50%	STEMI<48H, grafts, LM, bifurcation, GFR<30, shock, LE<12M, allergy	Any	6-8M DS (non-inferiority)	12-36M TLR, DEATH+MI, St	6-8M DS 38 vs 37.4% (0.007)	12M 23.5 vs 19.3 (0.5) vs 46 (0.001) 36M 38 vs 38 (0.91) vs 56 (0.001)	12M 22 vs 13 (0.09) vs 43 (0.001) 36M 33 vs 24 (0.11) vs 51 (0.001)
ISAR DESIRE IV, 2017	1:1 RCT Open-label Corelab CEC	PCB Panteria lux	Scoring vs POBA	252	DES	ISR>50%	LM, MI<48H, LE<12M, GFR<30	Any	6-8M DS (non-inferiority)	6-8M ISR 12M death MI TLR ST	6-8M DS 35 ±17 vs 40 ± 21 (0.047) LLL 0.31 ± 0.59 vs 0.41 ± 0.74 mm (0.27) ISR 19 vs 32 (0.026)	12M 18.4 vs 23.3 (0.35)	12M 16.2 vs 21.8 (0.26)
RIBS IV, 2015	1:1 RCT Open-label Corelab CEC	PCB	EES	309	DES	ISR	CTO, early<1M ISR, acyte MI, thrombus, multiple TLR, LE<1Y	RVD>2.0 mm length<30nn	6-9M In-segment MLD (superiority of EES)	12-36M MACE, TLR	6-9M MLD 1.80±0.6 vs 2.03±0.7 (0.004) ISR 19 vs 11% (0.06)	12M 18 vs 10 (0.04) 36M 20.1 vs 12.3 (0.04)	12M 16 vs 8 (0.035) 36M 15.6 vs 7 (0.015)
RESTORE, 2018	1:1 RCT Open-label Corelab CEC	PCB SeQuent Please	EES Xience	172	DES	DES ISR DS>50%	LE<1Y, contraindication to paclitaxel/everolimus, DAPT	Any	9M LLL (superiority of DCB)	9M MLD and DS 12M MACE, TLR	9M LLL 0.15 ± 0.49 vs 0.19 ± 0.41 (0.54)	12M 7.0 vs 4.7 (0.51)	12M 5.8 vs 1.2 (0.10)
FILM LIMUS, 2019	1:1 RCT Open-label Corelab CEC	SCB SeQuent Neo	PCB SeQuent Please Neo 3	50	ISR	CCS or UA DES ISR up to 2 lesions	MI<72H, crea>2, contraindications to DAPT, paclitaxel, sirolimus	Length<35mm RVD <2.5mm	6M LLL	Procedural success (<30% final stenosis, TMI 3, no flow limiting dissections) 6-12M MACE, CD, St, TLR, ISR	6M LLL 0.21 ± 0.54 vs 0.17 ± 0.55 (0.794)	12M 16 vs 12 (0.99)	12M 16 vs 12 (0.99)
PREVAIL	Open label Single arm ISR, De novo, small vessels	Prevail	-	50	?	Any De novo small or ISR	PCI of target vessel<9M, stroke TIA <&M, MI<72H	Length<25mm, RVD 2-4mm, DS 50-100	6M LLL	6M DS, MLD, ISR 1M, 6M, 12M death, MI, MACE, TLR, TVF, TLF	LLL 0.05±0.44 ISR 10%	6%	6%
AGENT ISR, 2021	1:1 RCT Open-label non-inferiority Corelab CEC	Agent PCB	Sequent please PCB	125	Any	Any	LM, recent or planned PCI, CTO, recent MI	Length<28mm RVD 2-3.5	6M LLL	1-6-12M MI, death, TLR, TVR	6M LLL 0.397±0.43 vs 0.393±0.536 mm (p non inferiority 0.046)	-	12M 7.7 vs 10 (0.89)

RESTORE ISR China, 2018	1:1RCT Open-label non-inferiority Corelab CEC	Restore PCB (SAFEPAX shellac-ammonium salt excipient)	Sequent please PCB	240	Any	Any ISR (Mehran I-III) DS>70% or 50% with ischemia	MI<7D, >2lesions requiring PCI, bifurcation with SB ≥2.5, thrombus NYHA IV, stroke<6M, GFR<30, SVHD	RVD 2.5-4	9M LLL	Acute success (device, procedure, lesion) 9M ISR 12M TLF, POCE	9M LLL 0.38 ±0.50 vs 0.35± 0.47 (p non inferiority 0.02) ISR 24.6 vs 18.8 (0.29)	12M TLF 13.3 vs 12.6 (0.87)	12M 13.3 vs 11.8 (0.71)
PEPPER trial	First in man, observational, single arm	Panter a lux PCB	-	81	Any	Any	MI<72H, LVEF<30%, allergies	Any	6M LLL	6,12M MACE	6M LLL 0.07±0.31 mm	12M 11.8%	12M 9.2%
GENOSS, 2022	1:1RCT Open-label non-inferiority Corelab CEC	Genoss PCB (Shellac + vit E)	Sequent Please	82	Any	Mehran I-III DS>50%, More than 90D after stent placement	Acute MI, thrombosis, grafts, Mehran IV, allergies	Any	6M LLL	6M MACE, TLR Device, Lesion, Procedure Success	6M LLL 0.15± 0.43 vs 0.24± 0.39 (p non inferiority 0.001)	6M 7.7 vs 10.3 (0.692)	6M 5.1 vs 5.1
BIOLUX, 2018	2:1RCT Open-label non-inferiority Corelab CEC	Panter a Lux PCB	SES	229	BMS (37) DES (63)	CCS or ischaemia with ISR >50% In case or two lesions, both need to be treated with DCB	STEMI<72H, LVEF<30, LM, thrombus Allergies, crea>2.5, LE<18M	RVD<2 />4mm Length <6 >28mm	6M LLL	6M DS, MLD 12M TLF, St Device success	6M LLL 0.03 ± 0.40 vs 0.20±0.70 (0.40)	12M TLF 16.9 vs 14.2 (0.65)	12M 12.5 vs 10.1 (0.82)
DARE, 2018	1:1RCT Open-label non-inferiority Corelab CEC	Sequent Please PCB (if crossover BMS in PCB arm)	EES (Xience)	278	BMS (44) vs DES (56)	All ISR (>50%) even CTO, ostial, LM, bifurcation, grafts	STEMI, BRS	RVD 2 -4	6M MLD	6M ISR, persisting dissection MI, TLR; St	6M MLD 1.71 ± 0.51 vs 1.74± 0.61 (non inferiority <0.0001)	12M 10.9 vs 9.2 (0.66)	12M TVR 7.1 vs 8.8 (0.65)

BMS, bare metal stent; BRS, bioresorbable scaffold; CEC, central clinical events committee; CCS, chronic coronary syndrome; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; DCB, drug coated balloon; DES, drug eluting stent; DS, degree of stenosis; EES, everolimus eluting stent; GFR, glomerular filtrate rate; ISR, in-stent restenosis; LLL, late lumen loss; LM, left main; LVEF, left ventricle ejection fraction; M, months; MACE, major adverse cardiac death; MI, myocardial infarction; MLD, minimal lumen diameter; NYHA, New York Heart Association; PCB,

paclitaxel coated balloon; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; POCE, patient oriented composite endpoint; RCT, randomized clinical trial; RVD, reference vessel diameter; SES, sirolimus eluting stent; St, stent thrombosis; STEMI, ST-segment elevation MI; TIA, transient ischemic attack; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization; UA, unstable angina; VHD, valvular heart disease.

Supplementary Table 2. ISR lesions classification based on angiography, intravascular ultrasound and optical coherence tomography

Angiography Mehran's classification		
Class I	**Focal ISR**	Lesions ≤10 mm in length - IA: At the un-scaffolded segment (i.e., articulation or gap) - IB: at the proximal or distal margin (but not both) - IC: at the body of the stent - ID: combination of these sites (multifocal ISR)
Class II	**Diffuse intrastent**	Lesions >10 mm in length and extended beyond the margin(s) of the stent(s)
Class III	**Diffuse proliferative**	Lesions >10 mm in length and extended beyond the margin(s) of the stent(s)
Class IV	**Total occlusion**	Lesions have a TIMI flow grade of 0.
Intravascular ultrasound ISR pattern classification		
Class I	**Focal ISR**	Lumen area <4 mm^2 and ≤10 mm in length - Focal body type: confined to the body of stent - Focal marginal type: extending to the margins of stent
Class II	**Multifocal ISR**	- Multifocal body type: multiple focal ISR lesions confined to the body of the stent without involvement of the stent margins - Multifocal marginal type: multiple focal ISR lesions that included marginal involvement
Class III	**Diffuse ISR**	Lumen area <4 mm^2 and >10 mm in length - Diffuse body type: confined to the body of stent - Diffuse marginal type: extending to the margins of the stent
Optical coherence tomography Waksman's ISR classification		

Type I	**Mechanical**	- IA: DES under-expansion - IB: DES fracture
Type II	**Biologic**	- IIA: intimal hyperplasia - IIB: non-calcified neoatherosclerosis - IIC: calcified atherosclerosis
Type III	**Mixed**	Combination of mechanical and biological mechanisms
Type IV	**Chronic total occlusion**	
Type V	**Multiple stent layers**	More than two metallic layers of stents are present

DES, drug eluting stent; ISR, in-stent restenosis; TIMI, Thrombolysis in Myocardial Infarction

Supplementary Table 3. Clinical trials evaluating the performance of DCBs in de-novo small vessels

Study name	Design	DCB	Comparator	n	Inclusion	Exclusion	Predilatation/Bail-out stenting	Reference vessel	Primary endpoint	Secondary endpoints	Angiographic follow-up (p value)	MACE (p value)	TLR (p value)
PICCOLETO, 2010	Single center prospective 1:1 RCT Autonomous QCA	DIOR PCB	TAXUS Libertè PES	57	Predilatation mandatory only in DES group	MI<48H, unstable, crea>2, allergies, LE<2Y	25 vs 86% 36%	<2.75	ITT 6M DS in-segment	6M MLD, ISR 9M MACE, TLR Procedural/device success	6M DS%43.6±27.4 vs 24.3±25.1 (0.029) MLD 1.11±0.65 vs 1.94±0.72 (0.0002)	9M 35.7 vs 13.8 (0.054)	9M 32.1 vs 10.3 (0.15)
BELLO, 2012	1:1 RCT Open-label non-inferiority Corelab CEC	INPACT FALCON PCB	TAXUS Libertè PES	182	CCS or UA	MI<48H, previous PCI<3M, LVEF<30%, crea>2, allergies, stroke<6M 3VD, ostial, restenosis, grafts, CTO, thrombus, bifurcation (2Stent, SB≥2.5)	97 vs 83% 20%	<2.8	6M LLL in-segment	6M ISR 12-36M MACE, TLR	6M LLL 0.08 ± 0.38 vs 0.29±0.44 (0.001) ISR 9 vs 14 (0.25)	12M 10 vs 16 (0.21) 36M 14 vs 30 (0.015)	12M 4.4 vs 7.6 (0.37) 36M 6 vs 13 (0.14)
RESTORE SVD, 2018, 2020	1:1 RCT Open-label non-inferiority Corelab CEC	Restore PCB	Resolute Integrity ZES	230 (32 in very small)	DS>70% or >50% with ischemia	MI<7D, LVEF<35%, CTO, bifurcation, LM, >=2lesions	100 vs 100 5.2%	2.25-2.75 Very small 2-2.25 Length<26	9M DS (ITT) In-segment	9M DS 9M LLL 12-24M TLF	9M DS 29.6±2.0 vs 24±2 (non-inferiority 0.001) LLL 0.26±0.42 vs 0.30±0.35 (0.41)	12M 9.6 vs 9.6 (1.0) 24M -	12M TLF 4.4 vs 2.6 (0.72) 24M 5.2 vs 2.8 (0.5)
BASKET-SMALL2, 2018,2020	1:1 RCT Open-label non-inferiority Corelab CEC	Sequent Please PCB	TAXUS PES and XIENCE EES	758	CCS, ACS Successful pre-dilatation	Concomitant PCI in a large (>3mm) on same epicardial artery Restenosis, LE<1Y, pregnancy	100 vs 100 5%	RVD 2-3	12M MACE (non inferiority)	12-36M adverse events, clinical benefit	6M LLL 0.13 (-0.14 to 0.57) vs 0.10 (-0.16 to 0.34) (0.72)	12M 8 vs 8 (0.918; non-inferiority 0.015) 36M 15 vs 15 (ns)	12M 3.4 vs 4.5 (0.438) 36M 9 vs 9 (ns)
BIORISE CHINA, 2022	1:1 RCT Open-label, superiority Corelab CEC	BA9 BCB	POBA	212	CCS or UA (DS>70 or >50 with ischemia)	MI<1M, severe HF, shock, LVEF<35, allergies, LE<1Y, severe CKD, stroke, GI bleeding<6M, severe liver failure Thrombus, >=2 non target lesions, CTO, ISR, severe calcification	100 vs 100 2.8%	RVD 2-2.75 Length≤25	PP 9M LLL In-segment	9M ISR, device, lesion, procedure-success 9-12M MACE, TLR, TLF, POCE, St	9M LLL 0.16±0.29 vs 0.30±0.35 (0.001) Positive remodeling 29 vs 9 %(0.007)	12M TLF 6.7 vs 13.9 (0.088)	12M 5.7 vs 10.9 (0.177)

PICCO LETO II, 2022	1:1 RCT Open-label, non-inferiority Corelab CEC	Elutax SV/E mpero r PCB (dextr an)	Xience EES	232	CCS or ACS, DS>70%	LE<12M, MI<72H, LVEF<30%, GFR<30 Ostial, LM, CTO, tortuosity, severe calcification, thrombus	84 vs 69% 6.7%	RVD 2-2.75 Length≤25	6M LLL In-segment	6M MLD, DS 12-36M MACE	6M LLL 0.04 vs 0.17 (non inferiority 0.001; superiority 0.03)	12M 5.6 vs 7.5 (0.55) 36M 10.8 vs 20.8 (0.046)	12M 5.6 vs 5.6 (0.80) 36M 8.8 vs 14.8 (0.18)
PEPCA D I, 2010	Prospectiv e, observatio nal multi-center trial	Seque nt please	-	118	UA or CCS, single de-novo	MI<48H, GFR<30, allergies, LE<2Y	30%	2.25-2.8	6M LLL	6M ISR 12M MACE, TLR	6M LLL 0.28 ± 0.53 ISR 17%	12M 15%	12M 12%

Same as Table 2.

Supplementary Table 4. Clinical trials evaluating the performance of DCBs in large vessels, myocardial infarction and high bleeding risk patients

LARGE VESSEL DISEASE													
Study name	Design	DCB	Comparator	n	Inclusion	Exclusion	Predilatation	Reference vessel	Primary endpoint	Secondary endpoints	Angiographic follow-up (p value)	MACE (p value)	TLR (p value)
SCBDNMAL NCT04017364	1:1 RCT Open-label non-inferiority Corelab CEC	Sequent SCB	Sequent please PCB	70	De novo, CCS or UA (≥70% or ≥50% with ischemia)	MI<72H, allergies, LVEF<30%, RVD<2.5	Scoring recommended	RVD>2.5	6M LLL ITT	Procedural success 6M-12M MACE, St, MI, CD, TLR, ISR	6M LLL 0.10±0.32 vs 0.01 ±0.33 (0.08 non inferiority margin 0.35)	12M 0 vs 6% (0.493)	12M 0 vs 0 (1)
Nishiyama et al 10.1016/j.ijcard.2016.07.156	1:1 RCT Open-label observational Single-center Autonomous QCA	Sequent please PCB	EES	60	De novo lesions with good preparation (IVUS based)	ACS, ISR	Non-slip (NSE) recommended	Length <25mm	8M TLR and LLL	-	8M LLL 0.25±0.25 vs 0.37±0.40 (0.185)	-	8M 0 vs 6.1 (0.193)
MYOCARDIAL INFARCTION													
REVELATION,2019 10.1016/j.jcin.2019.04.016	1:1 RCT Open-label non-inferiority Single-center Corelab CEC	Pantera Lux	Orsiro	120	STEMI referred to PCI Good predilatation result (DS<50%)	Previous Mi, recent stent implantation, controindication to DAPT, cardiogenic shock	.	Any	9M FFR	9M LLL, 9M MACE, St, bleeding	9M FFR 0.92± 0.05 vs 0.91±0.06 (0.027)	9M 0 vs 0 (1)	9M 3 vs 2 (1)
DEBAMI, 2012 10.1016/j.jacc.2012.02.027	1:1:1 RCT Open-label non-inferiority Two-center Corelab CEC	DIOR+BMS	BMS vs DES	150	STEMI referred to PCI Good predilatation result (DS<50%)	Controindication to DAPT, LE<12M,3VD, LM, DM+typeC lesion	60	2.5-4 Length<25	6M LLL	6M ISR, MACE 6M OCT and endothelial function	6M LLL DCB+BMS 0.74±0.57 vs BMS 0.64±0.56 vs DES 0.21±0.32 (<0.01) ISR 26.2 vs 28.6 vs 4.7 (0.01)	6M 23.5 vs 20 vs 4 (0.02)	-
Gobic et al, 2017 10.1016/j.amjms.2017.07.005	Single center prospective 1:1 RCT Autonomous QCA	Sequent Please	SES	75	STEMI with de novo lesion	Allergies, stroke<6M, GFR<30, LE<12M, ISR, PCI/CABG<6M, tortuosity,	-	2.5-4	6M MACE	6M LLL	6M LLL-0.09±0.09 vs 0.10±0.19 (0.05)	6M 0 vs 5.4 (0.29)	-
PEPCAD NSTEMI, 2019 10.4244/EIJ-D-19-00723.	1:1:1 RCT Open-label non-inferiority Multi-center	Sequent Please and sequent please neo	BMS (56%) and DES (44%)	210	NSTEMI and identifiable culprit lesion	Large thrombus	99.2% (bailout 15%)	Any	9M TLF	9M MACE	-	9M ITT 6.7 vs 14.2 (0.11) PP 5.9 vs 14.4 (0.056)	9M TLF ITT 3.8 vs 6.6 (0.11) PP 4.7 vs 6.3 (0.75)

Hao et al, 2021 10.1186/s13019-021-01525-8	1:1 Randomized single center prospective trial Autonomous QCA	Biotech Bingo	DES	80	STEMI<12H	Severe calcification, history of bleeding, intracranial disease, cardiogenic shock ISR, stent<6M, contraindication to DAPT	-	2.5-4	12M LLL	12M MACE	12M LLL -0.11±0.45 vs 0.13±0.3 (<0.05)	12M 11 vs 12% (ns)	-
PEBSI, 2017 10.4244/EIJ-D-16-00128	1:1 RCT Open-label non-inferiority Multi-center Corelab CEC	BMS + Pantera Lux	BMS	223	STEMI	Cardiogenic shock, LE<12M LM, bifurcation with SB>2.5, St, more than one stenosis in same artery, referred to CABG within 30D	18%	2.5-4mm Length<30mm	9M LLL	9M ISR and struts coverage (OCT), 9M MACE	9M LLL 0.31 vs 0.80 (0.001) ISR 2.2 vs 29.8 (0.001)	9M 3.6 vs 12.5 (0.016)	9M 1.8 vs 7.1 (0.06)
Besic, 2014 10.1016/j.jjcc.2014.05.007	Single center prospective 1:1 RCT Autonomous QCA	Elutax or Sequent Please + BMS	BMS	85	NSTEMI/UA	STEMI, cardiogenic shock, major bleeding<2W, haemorrhagic diathesis, contraindication to DAPT ISR, LM	39%	Any	6M LLL and ISR	6M TLR, St, ACS	6M LLL 0.22 vs 0.68 (0.002) ISR 17 vs 22 (0.593)	6M 24 vs 29 (0.835)	6M 19.5 vs 22.7 (0.770)
HIGH BLEEDING RISK													
DEBUT RCT, 2019 10.1016/ S0140-6736(19)31126-2 See	1:1 RCT Open-label non-inferiority Multi-center Corelab CEC	Sequent Please	BMS	208	De novo ischemic with at least one risk factor for bleeding	STEMI, cardiogenic shock, bifurcation (2 stents), ISR, LE<1Y, CTO, LM, suboptimal predilatation	100	2.5-4	9M MACE	9M TLR, procedural success 36M TLR, MACE	-	1 vs 14% (0.00034 superiority)	0 vs 6% (0.015 superiority)
Shin et al, 2019 10.1097/MCA.0000000000000755	1:1 RCT Open-label non-inferiority Autonomous QCA	Sequent Please	BMS	40	De novo HBR with FFR>0.80 post-predilatation	Cardiogenic shock, LVEF<35%, STEMI<72H, LM, 3VD, CTO, grafts, LE<12M	100	>2.8	9M LLL	9M functional restenosis 12 M cardiac death, MI, lesion thrombosis, TLR	9M LLL 0.2±0.3 vs 1.2±0.8 (<0.001) 9M functional restenosis 0 vs 25% (0.049)	0 vs 0	0 vs 0

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; NSTEMI, non-ST segment elevation myocardial infarction; remaining as for Table 2.

Supplementary Table 5. Image the vulnerable plaque

	TCFA	VULNERABLE PLAQUE
OCT	Large necrotic core, covered by a thin rim of fibrous tissue (typically ≤75 μm)	• MLA <3.5 mm2, • Fibrous cap thickness of <75 μm • Lipid arc of >180° • Macrophages
VH-IVUS	>10% confluent necrotic core at the lumen on three consecutive frames	• MLA ≤4 mm2 • Plaque burden ≥70%, • TCFA phenotype
IVUS-NIRS	Lipid rich plaque: max lipid core burden index (LCBI) within any 4 mm ($LCBI_{4mm}$) ≥325 LCBI is the number of pixels with probability of lipid >0.6 divided by all analysable pixels multiplied by 1000	• Plaque burden ≥70% • Lipid-rich plaque ($maxLCBI_{4mm}$≥325)
CCTA	-	• Positive remodeling • Low-attenuation plaque • Spotty calcification • Napkin-ring sign

CCTA, Coronary computed tomography angiography; IVUS, intravascular ultrasound; MLA, minimal lumen area; NIRS, near-infrared spectroscopy; OCT, optical coherence tomography; TCFA, thin-cap fibroatheroma; VH, virtual histology

Supplementary Table 6. Clinical trials evaluating the performance of DCBs bifurcation lesions

Study name	Design	DCB	Comparator	n	Inclusion	Exclusion	Pre-dilatation	Bailout stenting	Reference vessel	Primary endpoint	Secondary endpoints	Angiographic follow-up (p value)	MACE (p value)	TLR (p value)
DEBIUT, 2012 **10.1002/ccd.23499**	1:1:1 RCT Open-label superiority Multi-center Corelab CEC PROVISIONAL T • MV DCB+BMS and SB DCB • MV BMS +POBA SB • MV DES + POBA SB	Dior	PES	117	CCS, UA, ischemia De novo (DS 50-100)	LVEF<30, MI<72H, LM, previous PCI in TV, severe calcification, bleeding diathesis, TIA/Stroke<3M, Major surgery planned<9M, LE<12M, contraindication to DAPT	DCB predilatation	10 vs 5 vs 5 (0.68)	>2.5 in MV >2 in SB	6M LLL	6M ISR 12M MACE	6M MV LLL 0.58±0.65 vs 0.60±0.65 vs 0.13±0.45 (0.87) SB LLL 0.19±0.55 vs 0.21±0.57±0.11±0.43 (0.92) Restenosis 24 vs 28vs15 (0.79)	12M 20vs29vs17 (0.32)	12M 20 vs 27 vs 15 (NS)
BABILON, 2014 **10.4244/EIJV10I1A10**	1:1 RCT Open-label non-inferiority Multi-center PROVISIONAL T • MV DCB+ BMS and SB DCB • MV DES + POBA SB	Sequent please	EES	108	CCS, US, ischemia De novo (DS 50-100)	STEMI<48H, LM, ISR, allergies, bleeding diathesis, crea>2, LVEF<35%, cardiogenic shock, stroke<6M, contraindication to DES, LE<12M	DCB predilatation in MV and SB	7.8 vs 8.9 (1.0)	>3 in MV >2 in SV	6M LLL	9M MACE	9M MV LLL 0.31±0.48 vs 0.16±0.38 (0.15) SB LLL -0.04±0.76 vs 0.03±0.51 (0.98) Restenosis MV/SB 13/6 vs 1.8/3.6 (0.027/0.67)	9M 17.3 vs 7.1 (0.11)	9M 15.4 vs 3.6 (0.045)
PEPCAD V, 2011	Observational, dual-center prospective, single-arm Pilot study Corelab CEC MV DCB+BMS and SB DCB	Sequent please	-	28	CCS or UA or ischemia De novo (DS>70 or >50 with ischemia)	MI, NYHA IV, cardiogenic shock, stroke, GFR<30	DCB predilatation in MV and SB	14.3	MV 2.5-3.8 SB 2-3.5 LL<20	9M LLL	9M TLR	9M MV LLL 0.38±0.46 SB LLL 0.21±0.48 Restenosis MV/SB 3.8/7.7%	9M 10.7%	9M 3.8%
HERRADOR 2013	Comparative observational non randomized cohort single center Autonomous QCA PROVISIONAL T • MV DES and SB DCB • MV DES	Sequent Please	Taxus	100	DS>50% in MV and SB	Cardiogenic shock, akinetic territory, LVEF<30%, contraindication to DAPT	DCB predilatation in SB	?	>2.5 in MV and SB Sb LLL <10	12M LLL	12M MACE	12M MV LLL 0.49±0.6 vs 0.62±0.7 (0.39) SB LLL 0.09±0.4 vs 0.4±0.5 (0.01) Restenosis MV/SB 12/7 vs 18/20 (0.44/0.08)	12M 11 vs 24 (0.76)	12M 12 vs 20 (0.16)

DEBSIDE, 2015	Multicenter observational Corelab CEC PROVISIONAL T • SB predilatation followed by MV DES and KB and final SB DCB	Danubio	Nile PAX	52	CCS or UA or ischemia	PCI to TV<6M, LM, MI<72H	DCB final dilatation in SB (after provisional)	excluded	MV2.5—3.5 SB 2-3 SB LL<6	6M LLL	6M ISR 6M MACE	6M MV LLL 0.54±0.6 SB LLL -0.04±0.34 Restenosis MV/SB 0/0%	6M 10%	6M 8%
BIOLUX-1, 2015 **10.1016/j.carrev.2015.07.009**	Prospective, multi-center, single arm pilot study DCB dilatation to SB and DES to MV, final KBI with POBA	Pantera lux	-	35	DS>50%	Graft, significant stenosis prox or distal, tortuousity, aorto-ostial, LM, severe calcification, thrombus	DCB for SB treatment after pre-dilatation	11.4%	MV 2-4	9M LLL	12M MACE	9M MV LLL 0.28±0.59 SB LLL 0.10±0.43 Restenosis MV/SB 0/0%	12M 5.7%	12M 2.9%
SARPEDON, 2015 **10.1016/j.ijcard.2015.04.002**	Single center, prospective observational cohort study Autonomous QCA DCB in SB after Provisional DES and KBI	Pantera Lux	-	58	De novo DS>50% in MV or SB	LVEF<30, heavy calcification, contraindication to DAPT, LE<2Y	-	Excluded	MV>2.25 SB>2	6M LLL	12M MACE, TVR	6M MV LLL 0.21±0.35 SB LLL 0.09±0.21 Restenosis MV/SB 4/6%	12M 19%	12M 5.2%
Schulz, 2014 **10.1007/s00392-014-0671-9**	Prospective single center observational study DCB in SB, MB, SB/MB	Sequent please	-	39	De novo after appropriate pre-dilatation with 0.8/1:1 balloon (DS<30%MV, <75%SB)	None	100	12.8	Any	4M ISR	4M MACE	4M Restenosis MV/SB 6.7/3.3	4M 7.7	4M 7.7
PEPCAD BIF **10.1007/s00392-015-0957-6**	Prospective, multicenter, 1:1 RCT Provisional DES After successful pre-dilatation (recoil<30%, Diss<C) randomization to - SB DCB - POBA DCB	Sequent please	POBA	64	De novo Medina 0,0,1 or 0,1,1 CCS or UA, ischemia	MI<48H, NYHA IV, SVHD, LE<12M LM, CTO	100	0	SB >2-3.5 and lesion<10mm	9M LLL	9M ISR	9M LLL 0.13±0.31 vs 0.51±0.66 (0.045) 9M ISR 6 vs 26% (0.045)	-	-

Okutsu, 2022 **10.1007/s00380-021-02000-z**	Observational, single center Direct coronary atherectomy + DCB LM 59% Autonomous QCA/IVUS/OCT	Sequent please	-	25	De novo True bif of proximal Left coronary	STEMI, CTO, shock, severe calcification, diffuse disease	-	5%	MV>3, SB>2 (and relevant)	Number of stents used In-hospital MACE	3M MACE 3M LLL	3M 0.2 ± 0.6 mm	0	0
DCA/DCB registry, 2020 **10.1002/ccd.29185.**	Multicenter retrospective registry Direct coronary atherectomy + DCB in bifurcation LM 81%	Sequent please	-	129	Major bifurcation (SB>2mm) suitable for DCA delivery	LVEF<30, grafts, severe tortuosity, calcification, ISR, CTO, thrombus, MI<7D, dissection D-F	.	?	SB>2	12M TVF	Procedure-related MACE 12M ISR 12M MACE, TLR, TVR	6-15M LLL 0.29 ± 0.51 mm 12M ISR 2.3%	12M TVF 10.9%	12M 3.1%
BEYOND, 2020 **10.1097/CM9.0000000000000743**	Prospective, multicenter RCT DCB vs POBA in non-LM bifurcations after provisional with DES in MV (1:1 Randomization after pre-dilatation)	Bingo PEB	POBA	222	CCS or UA, ischemia, old MI De novo bifurcation with SB DS>70, <50 after pre-dilatation	LM ISR, LVEF<35%, LE<12M	100%	0	SB 1.25-5, lesion length<40mm	9M DS	TLR, TVR, TVF, MACE	9M DS 28.7±18.7 vs 40±19 (0.001 superiority)	9M 0.9 vs 3.7 (0.16) MI 0vs 0.9 (0.49)	-
Liu et al, 2022 **10.1155/2022/8250057**	Retrospective single center observational LM with DES to MV and DCB to SB	Bingo	2 stent strategy	100	True LM bifurcation	CABG, severe calcification, CTO, MI acute	98	-	-	6M LLL	MACE, TLR	6M SB LLL -0.17 vs 0.43 (0.001) ISR 7 vs 30 (0.093)	6M No difference	6M 6 vs 12 (0.485)

MV, main vessel; SB, side-branch; QCA, quantitative coronary analysis; IVUS, intravascular ultrasound; OCT, optical coherence tomography; KBI, kissing balloon inflation. Others as in Table 2 and 5