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Rationale and design of a prospective, open-label, randomized, multicentric clinical trial on the role of drug-coated balloons for bifurcation coronary lesions: the PRO-DAVID study (NCT04403048)

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Abstract

Background

Coronary bifurcation lesions (CBL) are associated with impaired outcome. The role of drug-coated balloons (DCB) in this setting has been only investigated in small studies so far.

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Aim

We here describe the design of PRO-DAVID study, aiming at investigating the clinical outcomes of a “provisional DCB” versus a "standard" approach (provisional or upfront two stent techniques) for the treatment of complex CBL.

Methods and results

The PRO-DAVID trial is a prospective, open-label, randomized, multicentric clinical trial of the interventions with true CBL (Medina 1,0,1; 1,1,1; 0,1,1) of unprotected left main (LM), and non-left main (non-LM) CBL with affected significant side branche (SB). The study hypothesis is that a “provisional DCB approach” with PCI using first DCB in SB after optimal predilatation and then DES implantation in the main vessel will be non-inferior to standard bifurcation-PCI as per EBC recommendations. The calculated sample size is 602 patients in total, and allocation is 1:1. The primary study endpoint is a composite of cardiac death, target vessel MI, or clinically-driven target lesion revascularization (TLR) at 12 months, and patients will be followed up for up to 3 years.

Implications

CBL management with stents only is associated with impaired outcome, and some preliminary data on the performance of DCB show their safety and efficacy in this setting. PRO DAVID study is an adequately powered randomized trial with clinical endpoints aimed to test DCB use in true CBL.

Keywords: DCB; coronary bifurcations; study design.

Introduction

Preferred and gold standard approach for the majority of patients with non-true and non- left main coronary bifurcation lesions (CBL), or true CBL with a side branch (SB) length <10mm, is the stepwise provisional stenting (PS).[1,2] The PS strategy is a treatment philosophy, rather than a technique[3], recommended by the European Bifurcation Club (EBC) since its inception[4] as the preferred strategy to treat CBL, not only when the use of a single stent is planned but also when a final use of 2 stents is required during the procedure. PS is layered and sequential, with the aim of performing an optimal treatment with a single stent whenever possible and performing stenting of the SB or assigned SB (aSB) when necessary, using the T, T and small protrusion (TAP), or culotte

implantation techniques.[1,2] This recommendation is based on clinical research which compared various implantation techniques of two stents with provisional technique [5-13] as well as meta-analyses of data from these studies.[14-20] The results of EBC MAIN trial[21] proved that PS approach should be the first choice for the majority of patients with true left main CBL with an SB lesion length <10 mm, and these patients are treated equally well as with a more complex upfront two-stent technique, with reduced number of balloons and stents, complexity and duration of the procedure, contrast dye use, fluoroscopy time and total X-ray dose.

Optimal strategy to treat true complex CBL (Medina classification 1,0,1; 1,1,1; 0,1,1) is still a subject of debate. As bifurcation lesion complexity increases, an intentional (upfront) 2-stent strategy appears more favorable, especially with a long (>10 mm) diseased SB/aSB.

Chinese physicians pioneered DK crush technique and established practical, easy-to-use classification criteria to differentiate simple from complex bifurcation lesions in the DEFINITION trial.[22] Main idea of this approach is that inclusion of lesion complexity as a parameter might have led to different stenting strategies. Benefit of 2-stent techniques for complex bifurcation lesions was confirmed in DEFINITION II study[23], where a systematic 2-stent approach was associated with a significant improvement in clinical outcomes compared with PS. Two-stent strategies and especially DK crush, are complex and demanding techniques that require extensive technical skills and experience, knowledge of technical steps, and the ability to identify and correct complications.

Based on the results of a single randomized study, DKCRUSH-V,[24] in which planned DK crush reduced TLF at 1-year compared with PS strategy in patients with true distal LM bifurcation lesions, EAPCI/EACTS revascularization guidelines[25] gave a Class IIb recommendation, level of evidence B, for double-kissing crush (an upfront two-stent technique) over a provisional approach.

Data for DK crush studies originate from a single group of expert operators,[26] thus in a daily clinical practice where less experienced operators with a limited number of true bifurcations performed annually are faced with the challenge of treating complex CBL, it is imperative to find a standardized and universal approach that would be simple, quick and safe, with a high percentage of procedural success, with a small number of complications, good long term results, with a small expenditure of material and contrast volumes, and shorter procedure and fluoroscopy times.

The role of drug-coated balloons for coronary bifurcation lesions

The drug-coated balloon (DCB) technology allows bringing a high concentration of an antiproliferative drug with immediate and rapid local delivery even with short contact times between the balloon surface and the vessel wall, sufficient for effective drug delivery without a durable polymer and further permanent metal prosthesis. The application of DCB in SB is an attractive and intriguing solution for treating complex BL (Table 1).[27,28]

Table 1. Potential advantages of DCB use for CBL.
potentially easier procedure including fewer steps
homogeneous drug distribution at all segments of bifurcation
reduced risk of carina distortion
no risk of late events related to: stent malapposition, under-expansion, fracture, and struts protrusion or double layer
unnecessary or easier wire recrossing of branches
unnecessary kissing balloon inflation and proximal optimization technique
potential late lumen enalrgement at all segments

The rationale for such an approach lies in the many theoretical advantages of DCB. The application of DCB in SB respects the original anatomy of bifurcation, which is especially important in the carina area, and allows for an homogeneous application of a high dose of the antiproliferative drug on the entire blood vessel surface and avoids the risk of incomplete coverage of the bifurcation area. In the case of a successful DCB application in the SB, unnecessary use of the stent is avoided, obviating long-term stent failure related to stent malapposition, under-expansion, and fracturing, the scaffolding of the SB ostium, overlapping and crushing of multiple metal layers and polymers

with uncontrolled drug release. Further, from the technical standpoint wire jailing, rewiring, and deformation of the stent with kissing balloon inflation may be avoided with DCB .[29]

The application of DCB has a theoretical advantage over the application of a regular balloon, with an expected positive remodelling of the vessel and plaque stabilization, better late angiographic results[30-34] as well reduced risk of neoatherosclerosis. Studies with intravascular ultrasound and optical coherence tomography,[35,36] have shown a trend toward positive remodelling with the use of DCB. A meta-analysis including 349 patients[37] showed that DCB use in SB was associated with lower SB late lumen loss compared with balloon angioplasty.

Another advantage of using DCB in CBL is the possibility to reduce the PCI complexity and the rate of two or more stents implantation. PCI strategies for complex coronary bifurcation lesions should be individualized, considering the anatomical differentiation of coronary bifurcation lesion differences, disease burden, and definition of complexity.

To investigate the possible role of DCB in CBL, a certain number of small-sized clinical studies were conducted. There is a high level of heterogeneity regarding treatment strategies and the procedural phase where DCB was used. Some studies in fact combined DCB and bare-metal stent (BMS),[38-41] others DCB and POBA ,[42,43] or DCB-only strategies;[44-48] however, in the majority of the cases a combination of DCB and DES was investigated[49-53]. Unfortunately, all these studies are of small size, with only four being randomized. Moreover, precise description of lesion characteristics are often missing, or the type and complexity of CBL according to Medina classification, and finally only surrogate endpoints were used in the majority of these studies. Notably, so far all the CBL studies investigating DCB used a paclitaxel-coated balloon. In the end, we believe that a well known and described DCB, with solid clinical background, should be used for this trial[54-57].

Expert opinion is that in general the use of DCB appears effective and safe when deployed in the SB and that larger randomized trials are required and that provisional stenting with DES in the main branch and DCB in the side branch could be a valuable treatment option.[29]

Ongoing studies and future directions

The available studies that examined the performance of a DCB strategy for CBL unfortunately share the aforementioned limitations. Future well-designed randomized clinical trials with strict inclusion criteria, a clear flowchart for lesion predilatation, and criteria for bail-out stenting are a true necessity. We believe that DCB should be compared to best-in-class DES with "hard" clinical endpoints and a follow-up of at least 5 years.

One interesting, ongoing trial is DCB-BIF,[58] where investigators are randomizing a total of 784 patients with true CBL (maximum SB length 10 mm) to DCB or POBA for SB after provisional stenting in MB.

Another potentially interesting strategy for the management of CBL is the use of DCB applications in both branches (the so-called "full-DCB approach"). This strategy implies sequential predilatation and final drug application of SB followed by MB. This strategy seems appealing and modern, however, there are some limitations that need to be addressed, including the fate and management of eventual residual dissections, and the need for expert DCB users. A pilot study with surrogate endpoints (B. Cortese, study design of PICCOLETO V RCT) has been proposed for the EBC meeting in 2022, to test the feasibility and safety of such a full-DCB approach.

PRO-DAVID study design

We here present the rationale and design of the PRO DAVID study (**PRO**spective, open label, randomized, multicentric clinical trial: **D**rug-coated balloon for side br**A**nch treatment **V**s. standard stenting **I**n true complex bifurcation coronary **D**isease, NCT04403048) in patients with true CBL (Medina 1,0,1; 1,1,1; 0,1,1) of unprotected left main CBL, and non-left main CBL with prognostically significant, severely involved SB. We aim to demonstrate how a “provisional DCB approach” with PCI using first DCB in SB after optimal predilatation and then DES implantation in the main vessel will be non-inferior to standard bifurcation-PCI as per EBC recommendations.

Study design

The PRO DAVID trial is a prospective, open-label, randomized, trial with a planned enrolment of 602 patients at 20 European centers. The study will include patients with either stable angina pectoris or stabilized non–ST elevation myocardial infarction (NSTEMI) requiring percutaneous coronary interventions with true CBL (Medina 1,0,1; 1,1,1; 0,1,1) of unprotected left main (LM)

CBL, and non-left main (non-LM) CBL with affected important SB (most likely to supply at least 10% of fractional myocardial mass by angiographic criteria alone). The SB should have a proximal reference size ≥2,5 mm and ≥70% diameter stenosis in the ostium of LM CBL and ≥90% in non-LM CBL, by visual estimation. Lesion length in both LM and non-LM CBL will be 10 mm or longer (Figure 1). Complete clinical and angiographic inclusion and exclusion criteria are listed in Tables 2 and 3.

Figure 1

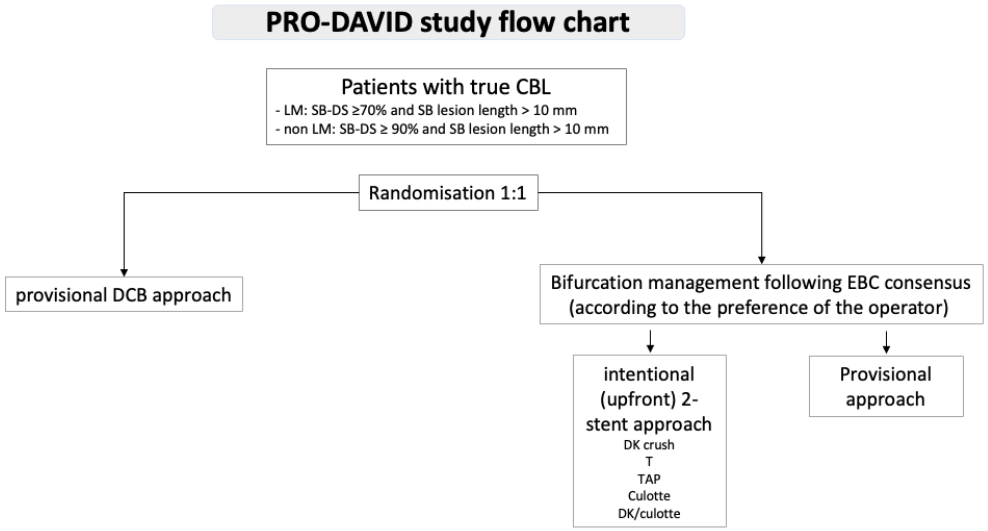


TABLE 2 Clinical inclusion and exclusion criteria for PRO DAVID study	
Clinical inclusion criteria: • stable CAD • ACS (either unstable angina or stabilized NSTEMI) • age ≥18 years	Clinical exclusion criteria: • STEMI <72 hours preceding • cerebrovascular accident within 6 months • surgical procedure within one week • pregnant/nursing women

• clinical and anatomical eligibility for PCI (local Heart Team) • patients with mental and logistical conditions for further monitoring and follow-up for 3 years • written informed consent	• LV ejection fraction <30% • cardiogenic shock • severe valvular disease • unfavorable long-term prognosis - patient life expectancy less than 12 months • creatinine > 2,0 mg/dl (>177 mmol/L) • active bleeding or coagulopathy • untreatable hypersensitivity, allergy or contraindication to: aspirin, heparin, clopidogrel, prasugrel, steel, sirolimus, everolimus, zotarolimus, biolimus or contrast agents • treatment of hyperthyroidism, administration of immunosuppressives or anticoagulant therapy, addiction to alcohol or drugs • patients included in another clinical trial

CAD: coronary artery disease; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; LV: left ventricle.

TABLE 3 Angiographic inclusion and exclusion criteria for PRO DAVID study

Inclusion criteria:	Angiographic exclusion criteria:
• de novo CBL with affected side branch (Medina classification 1,0,1; 1,1,1; 0,1,1) • side branch diameter ≥2,5 mm (visual estimation) • LM SB-DS ≥70% and SB lesion length > 10 mm • non-LM: SB-DS ≥ 90% and SB lesion length > 10 mm • side branch length ≥ 10mm	• high thrombotic burden (angiographic definition: spheric, ovoid, or irregular intraluminal filling defect or lucency surrounded on three sides by contrast medium seen just distal or within the coronary stenosis in multiple projections or a visible embolization of intraluminal material downstream) • severe tortuosity • chronic total occlusion of either vessel • SYNTAX score >32 • severe calcification (intravascular imaging or angiographic definition: multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion) • patients who had a stent implanted ≤15 mm from the lesions included in the study

	• lesions on the aortocoronary venous or arterial grafts • in-stent restenosis or restenosis in a segment closer than 4 mm from the target lesion

CBL: coronary bifurcation lesion; LM: left main stem; SB: side branch; DS: diameter stenosis.

Study endpoints

Study primary endpoint will be target lesion failure (TLF) assessed during clinical visit at 1 year. TLF is defined as a composite of cardiac death, target vessel MI (TV-MI), or clinically-driven target lesion revascularization (TLR).

The study's bifurcation-oriented composite endpoint includes cardiac death, target bifurcation MI, and ischemia-driven target bifurcation revascularization. The patient-oriented composite endpoint is all-cause mortality, MI, any revascularization, and stroke. Study endpoints are listed in Table 4.

Additional variables that will be included in the electronic case report form are listed in the supplement material.

TABLE 4 Primary and secondary endpoints
Primary and point • Combined endpoint of target lesion failure (TLF) (composite of cardiac death, target vessel MI (TVMI), or clinically-driven target lesion revascularization (TLR) at 12 months Secondary end points • Study bifurcation-oriented endpoint: composite of cardiac death, target bifurcation MI, target bifurcation revascularisation

- Patient-oriented composite endpoint: all-cause mortality, MI, any revascularisation, stroke
- Clinical endpoints at 1,12, 24 and 36 months
    - All-cause mortality
    - Cardiac death
    - MI
    - Stent thrombosis (definite, possible,probable)
    - Target lesion MI
    - Target bifurcation revascularisation
    - Any revascularisation
    - CCS angina class

MI: myocardial infarction; CCS: Canadian Class of angina System.

Study procedure

Patients are enrolled according to clinical inclusion and exclusion criteria, and only fully eligible patients are randomized (Figure 2). Patients are randomized to the provisional DCB approach, or to the conventional approach. The principal structure of the provisional DCB approach is shown in Figure 3, and procedural details about the provisional DCB approach can be found in the supplement material. In the conventional approach, according to the preference of the operator, patients can be treated with the standard provisional approach or intentional (upfront) 2-stent approach. According to EBC consensus document, any of the following techniques can be used in this group: DK crush, T, TAP, Culotte, DK/culotte.[1,2]

Figure 2

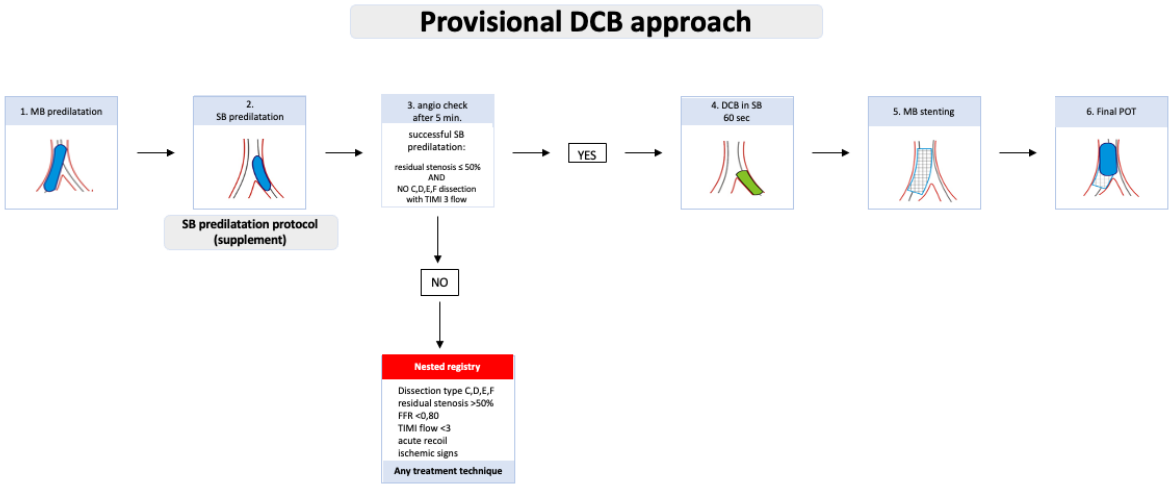
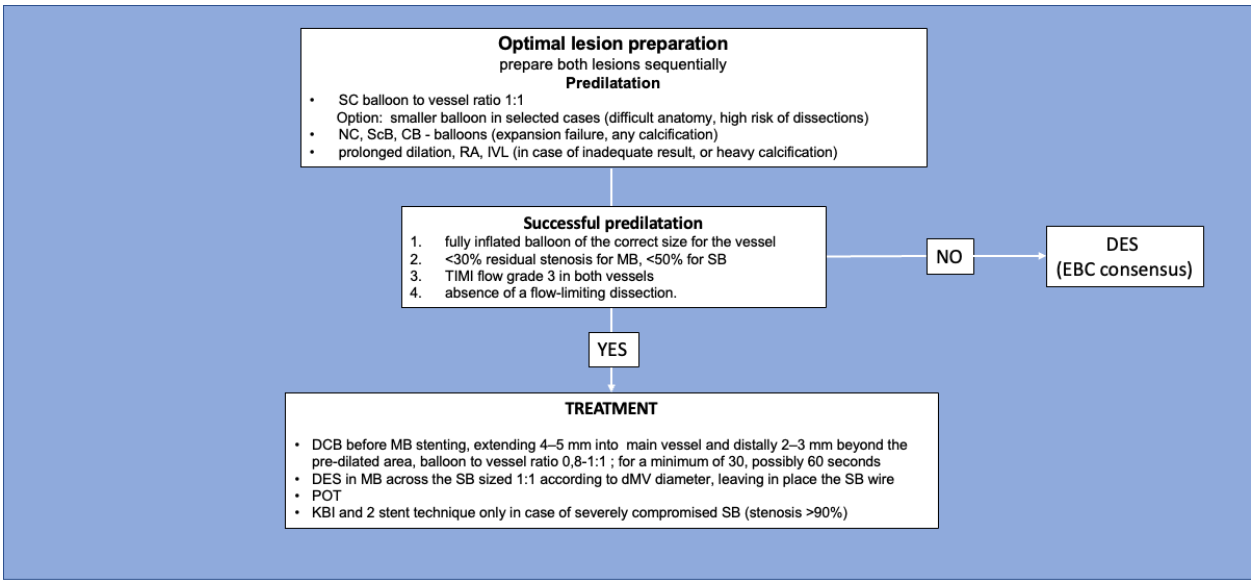


Figure 3



Core laboratory analysis

The angiographic analysis is performed for all patients in both treatment arms. The target bifurcation is analyzed by applying a 7-segment model. Balloon-treated segments are analyzed as stented segments. Analysis of pre-PCI includes reference size, percent diameter stenosis, minimal lumen diameter, lesion length, and angulations. The pre and post-PCI angiograms are analyzed by observers blinded to treatment allocation. All analyses are performed by an independent core laboratory.

Sample size calculation

Estimates for median 1-year rates of TLF are based on the following evidence and assumptions. In DKCRUSH V[24] which included patients with complex CBL, TLF within 1 year occurred in 10.7% assigned to a PS strategy. To test the non-inferiority of the DCB group, with an alpha error probability of 0.05 with power of 0.90, and allocation ratio of 1:1, SD 0.04, non-inferiority margin of 0.03 we calculated a total sample size of 602 patients (301 in each group) also taking in account a potential attrition rate of 10%. We estimate starting of enrollment of patients in Q3/2023.

Follow-up

Patients will be followed up by in-hospital visit at 12 months, and by telephone interview at 1, 24 and 36 months. During visits, the following parameters will be assessed: angina symptoms (CCS class), medications (angina index), and clinical endpoints. Angina index is a scoring system where a point is scored for each of the following medications being taken by the patient: nitrate (sublingual or spray) used ≥ 1 during the week prior to question, nitrate (oral), blocker or ivabradine, calcium antagonist, nicorandil or other antianginals. The maximum angina index score on this system is therefore 5.

Study conduction, data collection, and monitoring

The study will be submitted to the local or national ethics committees as appropriate and to the Danish Data Protection Agency covering all sites within the European Union. The trial is registered with Clinicaltrials.gov NCT04403048. Only CE-marked equipment will be used and only for the approved indications. The principles in the Declaration of Helsinki will always be followed, and all patients will provide written informed consent for participation in the trial.

Data will enter directly a dedicated e-CRF in the secure Web-based trial management system. Imaging data including angiographic image runs will be uploaded to the study database, enabling remote monitoring and procedure feedback by the centralized core laboratory. The study is monitored according to the Good Clinical Practice guidelines. During the study period, monitors will ensure that the trial is conducted in compliance with the protocol, Good Clinical Practice, and applicable regulatory requirements. All events will be adjudicated by an independent Clinical Events Committee.

Conclusions

Coronary bifurcation lesion management is still associated with impaired outcome, mostly for a not negligible higher risk of SB failure with currently available techniques. The role of DCB in this setting is interesting, and showed promising results in small, clinically underpowered studies. PRO DAVID is the first adequately powered clinical trial aimed to test DCB use in true CBL.

Potential advantages of the techique described in this manuscript include the simplicity of the procedure, an acceptable crossover rates to bailout stenting, shorter procedure times, shorter radiation, and reduced consumption of contrast agents, wires, balloons, and stents. From PRO DAVID study we expect to encounter the non-inferiority between standard-of-care and a "provisional DCB approach" in terms of TLF at 12 months, and a sequential superiority during the upcoming years of follow up.

Declarations

Acknowledgments

None.

Conflict of Interest

The Authors declare that there is no conflict of interest.

Funding

None.

Running head

DCB use for coronary bifurcations.

Figures legend

Figure 1: PRO DAVID study flow chart (NCT04403048).

SC: semicompliant balloon; NC: noncompliant balloon; ScB: scoring balloon; CB: cutting balloon; RA: Rotational atherectomy; IVL: Intravascular lithotripsy; TIMI: thrombolysis in myocardial infarction; DES: drug-eluting stent; DCB: drug-coated balloon; EBC: European bifurcation club; LM: left main; CBL: coronary bifurcation lesion; SB: side branch; MB: main branch; POT: proximal optimisation technique; KBI: kissing balloon inflation.

Figure 3: Provisional DCB approach in PRO DAVID trial.

MB: main branch; SB: side branch; DCB: drug coated balloon; POT: proximal optimization technique; FFR: fractional flow reserve; TIMI: thrombolysis in myocardial infarction.

Figure 4: Provisional DCB approach.

SC: semicompliant balloon; NC: noncompliant balloon; ScB: scoring balloon; CB: cutting balloon; RA: Rotational atherectomy; IVL: Intravascular lithotripsy; TIMI: thrombolysis in myocardial infarction; DES: drug-eluting stent; DCB: drug-coated balloon; EBC: European bifurcation club; LM: left main; CBL: coronary bifurcation lesion; SB: side branch; MB: main branch; POT: proximal optimisation technique; KBI: kissing balloon inflation.

References

1. Albiero R, Burzotta F, Lassen J, Lefèvre T, Banning A, Chatzizisis Y, Johnson T, Ferenc M, Pan M, Darremont O, Hildick-Smith D, Chieffo A, Louvard Y, Stankovic G.Treatment of Coronary Bifurcation lesions, part I: implanting the first stent in the provisional pathway. The 16th expert consensus document of the European Bifurcation Club. EuroIntervention. 2022;18:e362-76.

2. Lassen JF, Albiero R, Johnson TW, Burzotta F, Lefèvre T, Iles TL, Pan M, Banning AP, Chatzizisis YS, Ferenc M, Dzavik V, Milasinovic D, Darremont O, Hildick-Smith D, Louvard Y, Stankovic G. Treatment of coronary bifurcation lesions, part II: implanting two stents. The 16th expert consensus document of the European Bifurcation Club. EuroIntervention. 2022 Aug 19;18(6):457-470. Doi: 10.4244/EIJ-D-22-00166. PMID: 35570753

3. Lassen JF, Burzotta F, Banning A, Lefèvre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm N, Louvard Y, Stankovic G. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus

4. Thomas M, Hildick-Smith D, Louvard Y, Albiero R, Darremont O, Stankovic G, Pan M, Legrand V, Debruyne B, Lefèvre T. Percutaneous coronary intervention for bifurcation disease.A consensus view from the first meeting of the European Bifurcation Club. EuroIntervention. 2006 Aug;2(2):149-53. PMID: 19755253

5. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, Maccarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. Circulation. 2010;121:1235-43.

6. Colombo A, Bramucci E, Sacca S, Violini R, Lettieri C, Zanini R, Sheiban I, Paloscia L, Grube E, Schofer J, Bolognese L, Orlandi M, Niccoli G, Latib A, Airoldi F. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. Circulation. 2009;119:71-8.

7. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation. 2004;109:1244-9.

8. Ferenc M, Gick M, Kienzle RP, Bestehorn HP, Werner KD, Comberg T, Kuebler P, Buttner HJ, Neumann FJ. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. Eur Heart J. 2008;29:2859-67.

9. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, Niemela M, Kervinen K, Jensen JS, Galloe A, Nikus K, Vikman S, Ravkilde J, James S, Aaroe J, Ylitalo A, Helqvist S, Sjogren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Lassen JF, Thuesen L; Nordic PCI Study Group. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. Circulation. 2006;114:1955-61.

10. Pan M, de Lezo JS, Medina A, Romero M, Segura J, Pavlovic D, Delgado A, Ojeda S, Melian F, Herrador J, Urena I, Burgos L. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. Am Heart J. 2004;148:857-64.

11. Lin QF, Luo YK, Lin CG, Peng YF, Zhen XC, Chen LL. Choice of stenting strategy in true coronary artery bifurcation lesions. Coron Artery Dis. 2010;21:345-51.

12. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, Kan J, Paiboon C, Zhou Y, Ding SQ, Kwan TW. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. J Am Coll Cardiol. 2011;57:914-20.

13. Kumsars I, Niemela N, Erglis A, Kervinen K, Christiansen EH, Maeng M, Dombrovskis A, Abraitis V, Kibarskis A, Steigen TK, Trovik T, Latkovskis G, Sondore D, Narbute I, Terkelsen CJ, Eskola M, Romppanen H, Thayssen P, Kaltoft A, Vasankari T, Gunnes P, Frobert O, Calais F, Hartikainen J, Jensen SE, Engstrem T, Holm NR, Lassen JF, Thuesen L. Randomized comparison of provisional side branch stenting versus a two-stent strategy for treatment of true coronary bifurcation lesions involving a large side branch, the Nordic-Baltic Bifurcation Study IV. TCT 2013, San Francisco, CA, USA.

14. Brar SS, Gray WA, Dangas G,et al. Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials. EuroIntervention. 2009 Sep;5(4):475-84.

15. Zhang F, Dong L, Ge J. Simple versus complex stenting strategy for coronary artery bifurcation lesions in the drug-eluting stent era: a meta-analysis of randomised trials. Heart. 2009 Oct;95(20):1676-81.

16. Hakeem A, Khan FM, Bhatti S, et al. Provisional vs. complex stenting strategy for coronary bifurcation lesions: meta-analysis of randomized trials. J Invasive Cardiol. 2009 Nov;21(11):589-95.

17. Zimarino M, Corazzini A, Ricci F, Di Nicola M, De Caterina R. Late thrombosis after double versus single drug-eluting stent in the treatment of coronary bifurcations: a meta-analysis of randomized and observational Studies. JACC Cardiovasc Interv. 2013 Jul;6(7):687-95

18. Gao XF, Zhang YJ, Tian NL, et al. Stenting strategy for coronary artery bifurcation with drug-eluting stents: a meta-analysis of nine randomised trials and systematic review. EuroIntervention. 2014 Sep;10(5):561-9

19. Di Gioia G, Sonck J, Ferenc M, Chen SL, Colaiori I, Gallinoro E, Mizukami T, Kodeboina M, Nagumo S, Franco D, Bartunek J, Vanderheyden M, Wyffels E, De Bruyne B, Lassen JF, Bennett J, Vassilev D, Serruys PW, Stankovic G, Louvard Y, Barbato E, Collet C.Clinical Outcomes Following Coronary Bifurcation PCI Techniques: A Systematic Review and Network Meta-Analysis Comprising 5,711 Patients. JACC Cardiovasc Interv 2020;13:1432-44

20. Ford TJ, McCartney P, Corcoran D, Collison D, Hennigan B, McEntegart M, Hildick-Smith D, Oldroyd KG, Berry C.Single- Versus 2-Stent Strategies for Coronary Bifurcation Lesions: A Systematic Review and Meta-Analysis of Randomized Trials With Long-Term Follow-up. J Am Heart Assoc 2018;7:e008730

21. Hildick-Smith D, Egred M, Banning A, Brunel P, Ferenc M, Hovasse T, Wlodarczak A, Pan M, Schmitz T, Silvestri M, Erglis A, Kretov E, Lassen JF, Chieffo A, Lefèvre T, Burzotta F, Cockburn J, Darremont O, Stankovic G, Morice MC, Louvard Y.The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). Eur Heart J 2021;42:3829-39

22. Chen SL, Sheiban I, Xu B, Jepson N, Paiboon C, Zhang JJ, Ye F, Sansoto T, Kwan TW, Lee M, Han YL, Lv SZ, Wen SY, Zhang Q, Wang HC, Jiang TM, Wang Y, Chen LL, Tian NL, Cao F, Qiu CG, Zhang YJ, Leon MB. Impact of the complexity of bifurcation lesions treated with drug-eluting stents: the DEFINITION study (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts). JACC Cardiovasc Interv. 2014 Nov;7(11):1266-76. doi: 10.1016/j.jcin.2014.04.026. Epub 2014 Oct 15. PMID: 25326748.

23. Zhang JJ, Ye F, Xu K, Kan J, Tao L, Santoso T, Munawar M, Tresukosol D, Li L, Sheiban I, Li F, Tian NL, Rodríguez AE, Paiboon C, Lavarra F, Lu S, Vichairuangthum K, Zeng H, Chen

L, Zhang R, Ding S, Gao F, Jin Z, Hong L, Ma L, Wen S, Wu X, Yang S, Yin WH, Zhang J, Wang Y, Zheng Y, Zhou L, Zhou L, Zhu Y, Xu T, Wang X, Qu H, Tian Y, Lin S, Liu L, Lu Q, Li Q, Li B, Jiang Q, Han L, Gan G, Yu M, Pan D, Shang Z, Zhao Y, Liu Z, Yuan Y, Chen C, Stone GW, Han Y, Chen SL. Multicentre, randomized comparison of two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: the DEFINITION II trial. Eur Heart J. 2020 Jul 14;41(27):2523-2536. doi: 10.1093/eurheartj/ehaa543. PMID: 32588060

24. Chen SL, Zhang JJ, Han Y, et al. Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions: DKCRUSH-V Randomized Trial. J Am Coll Cardiol. 2017;70(21):2605–2617. doi:10.1016/j.jacc.2017.09.1066

25. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87–165. doi:10.1093/eurheartj/ehy394

26. Pan M, Ojeda S. Complex Better Than Simple for Distal Left Main Bifurcation Lesions: Lots of Data But Few Crushing Operators. JACC Cardiovasc Interv. 2020;13(12):1445-1447. doi:10.1016/j.jcin.2020.04.039

27. Cortese B, Piraino D, Buccheri D, Alfonso F. Treatment of bifurcation lesions with drug-coated balloons: A review of currently available scientific data. Int J Cardiol. 2016 Oct 1;220:589-94. doi: 10.1016/j.ijcard.2016.06.079. Epub 2016 Jun 28. PMID: 27390995.

28. Elwany M, Palma GD, Cortese B. Treatment of coronary bifurcation lesions: current knowledge and future perspectives. Future Cardiol. 2018 Mar;14(2):165-179. doi: 10.2217/fca-2017-0068. Epub 2018 Jan 26. PMID: 29372810.

29. Rathore S, Tehrani S, Prvulovic D, Araya M, Lefèvre T, Banning AP, Burzotta F, Rigatelli G, Gutierrez-Chico JL, Bonaventura K, Chevalier B, Kinoshita Y, Sikic J, Alfonso F, Louvard Y,

Stankovic G. Drug coated balloons and their role in bifurcation coronary angioplasty: appraisal of the current evidence and future directions. Expert Rev Med Devices. 2020 Oct;17(10):1021-1033. doi: 10.1080/17434440.2020.1831385. Epub 2020 Oct 14. PMID: 330009529.Ann SH, Singh GB, Lim KH, Koo BK, Shin ES. Anatomical and physiological changes after paclitaxel-coated balloon for atherosclerotic de novo coronary lesions: serial IVUS-VH and FFR study. PLoS One. 2016;11:e0147057

30.Ann SH, Singh GB, Lim KH, Koo BK, Shin ES. Anatomical and physiological changes after paclitaxel-coated balloon for atherosclerotic de novo coronary lesions: serial IVUS-VH and FFR study. PLoS One. 2016;11:e0147057

31.Her AY, Ann SH, Singh GB, et al. Comparison of paclitaxel-coated balloon treatment and plain old balloon angioplasty for de novo coronary lesions. Yonsei Med J Yonsei Univ Coll Med. 2016;57:337

32.Jing QM, Zhao X, Han YL, Gao LL, et al. A drug-eluting Balloon for the treatment of coronarY bifurcatiON lesions in the side branch: a prospective multicenter ranDomized (BEYOND) clinical trial in China. Chin Med J. 2020 Apr 20;133:899-908.

33. Kleber FX, Schulz A, Waliszewski M, Hauschild T, Böhm M, Dietz U, Cremers B, Scheller B, Clever YP. Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. Clin Res Cardiol. 2015 Mar;104(3):217-25. doi: 10.1007/s00392-014-0775-2. Epub 2014 Oct 28. PMID: 25349065.

34. Cortese B, Silva Orrego P, Agostoni P, Buccheri D, Piraino D, Andolina G, Seregni RG. Effect of Drug-Coated Balloons in Native Coronary Artery Disease Left With a Dissection. JACC Cardiovasc Interv. 2015 Dec 28;8(15):2003-2009. doi: 10.1016/j.jcin.2015.08.029. Epub 2015 Nov 25. PMID: 26627997.

35.Poerner TC, Duderstadt C, Goebel B, Kretzschmar D, Figulla HR, Otto S. Fractional flow reserve-guided coronary angioplasty using paclitaxel-coated balloons without stent implantation: feasibility, safety and 6-month results by angiography and optical coherence tomography. Clin Res Cardiol. 2017 Jan;106(1):18-27. doi: 10.1007/s00392-016-1019-4. Epub 2016 Jul 5. PMID: 27379610; PMCID: PMC5226992.

36. Ann SH, Balbir Singh G, Lim KH, Koo BK, Shin ES. Anatomical and Physiological Changes after Paclitaxel-Coated Balloon for Atherosclerotic De Novo Coronary Lesions: Serial IVUS-VH and FFR Study. PLoS One. 2016 Jan 29;11(1):e0147057. doi: 10.1371/journal.pone.0147057. PMID: 26824602; PMCID: PMC4733051.

37. Megaly M, Rofael M, Saad M, Shishehbor M, Brilakis ES. Outcomes With Drug-Coated Balloons for Treating the Side Branch of Coronary Bifurcation Lesions. J Invasive Cardiol. 2018 Nov;30(11):393-399. Epub 2018 Sep 15. PMID: 30218555.

38. Mathey DG, Wendig I, Boxberger M, Bonaventura K, Kleber FX. Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial. EuroIntervention. 2011 May;7 Suppl K:K61-5. doi: 10.4244/EIJV7SKA11. PMID: 22027730.

39. Stella PR, Belkacemi A, Dubois C, Nathoe H, Dens J, Naber C, Adriaenssens T, van Belle E, Doevendans P, Agostoni P. A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. Catheter Cardiovasc Interv. 2012 Dec 1;80(7):1138-46. doi: 10.1002/ccd.23499. Epub 2012 Mar 15. PMID: 22422607.

40.López Mínguez JR, Nogales Asensio JM, Doncel Vecino LJ, Sandoval J, Romany S, Martínez Romero P, Fernández Díaz JA, Fernández Portales J, González Fernández R, Martínez Cáceres G, Merchán Herrera A, Alfonso Manterola F; BABILON Investigators. A prospective randomised study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results. EuroIntervention. 2014 May;10(1):50-7. doi: 10.4244/EIJV10I1A10. PMID: 24832638.

41.Sgueglia GA, Todaro D, Bisciglia A, Conte M, Stipo A, Pucci E. Kissing inflation is feasible with all second-generation drug-eluting balloons. Cardiovasc Revasc Med. 2011 Sep-Oct;12(5):280-5. doi: 10.1016/j.carrev.2010.12.001. Epub 2011 Jan 26. PMID: 21273144.

42. Herrador JA, Fernandez JC, Guzman M, Aragon V. Drug-eluting vs. conventional balloon for side branch dilation in coronary bifurcations treated by provisional T stenting. J Interv Cardiol. 2013 Oct;26(5):454-62. doi: 10.1111/joic.12061. PMID: 24106744.

43.Li Y, Mao Q, Liu H, Zhou D, Zhao J. Effect of Paclitaxel-Coated Balloon Angioplasty on Side Branch Lesion and Cardiovascular Outcomes in Patients with De Novo True Coronary Bifurcation Lesions Undergoing Percutaneous Coronary Intervention. Cardiovasc Drugs Ther. 2022 Oct;36(5):859-866. doi: 10.1007/s10557-021-07225-8. Epub 2021 Jul 9. PMID: 34241730.

44.Kleber FX, Rittger H, Ludwig J, Schulz A, Mathey DG, Boxberger M, Degenhardt R, Scheller B, Strasser RH. Drug eluting balloons as stand alone procedure for coronary bifurcational lesions: results of the randomized multicenter PEPCAD-BIF trial. Clin Res Cardiol. 2016 Jul;105(7):613-21. doi: 10.1007/s00392-015-0957-6. Epub 2016 Jan 14. PMID: 26768146.

45.Schulz A, Hauschild T, Kleber FX. Treatment of coronary de novo bifurcation lesions with DCB only strategy. Clin Res Cardiol. 2014 Jun;103(6):451-6. doi: 10.1007/s00392-014-0671-9. Epub 2014 Feb 14. PMID: 24522798.

46.Bruch L, Zadura M, Waliszewski M, Platonic Z, Eränen J, Scheller B, Götting B, Herberger D, Palmieri C, Sinicròpi G, Motz W. Results From the International Drug Coated Balloon Registry for the Treatment of Bifurcations. Can a Bifurcation Be Treated Without Stents? J Interv Cardiol. 2016 Aug;29(4):348-56. doi: 10.1111/joic.12301. Epub 2016 May 31. PMID: 27242273.

47. Vaquerizo B, Fernández-Nofreiras E, Oategui I, Suarez de Lezo J, Rumoroso JR, Martín P, Routledge H, Tizón-Marcos H. Second-Generation Drug-Eluting Balloon for Ostial Side Branch Lesions (001-Bifurcations): Mid-Term Clinical and Angiographic Results. J Interv Cardiol. 2016 Jun;29(3):285-92. doi: 10.1111/joic.12292. Erratum in: J Interv Cardiol. 2016 Oct;29(5):553. PMID: 27245124.

48.Her AY, Ann SH, Singh GB, Kim YH, Okamura T, Garg S, Koo BK, Shin ES. Serial Morphological Changes of Side-Branch Ostium after Paclitaxel-Coated Balloon Treatment of De Novo Coronary Lesions of Main Vessels. Yonsei Med J. 2016 May;57(3):606-13. doi: 10.3349/ymj.2016.57.3.606. PMID: 26996558; PMCID: PMC4800348.

49. Berland J, Lefèvre T, Brenot P, Fajadet J, Motreff P, Guerin P, Dupouy P, Schandrin C; DEBSIDE trial investigators. DANUBIO - a new drug-eluting balloon for the treatment of side branches in bifurcation lesions: six-month angiographic follow-up results of the DEBSIDE trial. EuroIntervention. 2015 Dec;11(8):868-76. doi: 10.4244/EIJV11I8A177. PMID: 26696455.

50. Worthley S, Hendriks R, Worthley M, Whelan A, Walters DL, Whitbourn R, Meredith I. Paclitaxel-eluting balloon and everolimus-eluting stent for provisional stenting of coronary bifurcations: 12-month results of the multicenter BIOLUX-I study. Cardiovasc Revasc Med.

2015 Oct-Nov;16(7):413-7. doi: 10.1016/j.carrev.2015.07.009. Epub 2015 Aug 10. PMID: 26346023.

51. Jim MH, Lee MK, Fung RC, Chan AK, Chan KT, Yiu KH. Six month angiographic result of supplementary paclitaxel-eluting balloon deployment to treat side branch ostium narrowing (SARPEDON). Int J Cardiol. 2015;187:594-7. doi: 10.1016/j.ijcard.2015.04.002. Epub 2015 Apr 2. PMID: 25863309.

52. Liu H, Tao H, Han X, Lu Y, Xue X, Feng R, Lv F, Liu Y, Jin H, Li L, Gu H. Improved Outcomes of Combined Main Branch Stenting and Side Branch Drug-Coated Balloon versus Two-Stent Strategy in Patients with Left Main Bifurcation Lesions. J Interv Cardiol. 2022 Jan 11;2022:8250057. doi: 10.1155/2022/8250057. PMID: 35095348; PMCID: PMC8767379.

53. Pan L, Lu W, Han Z, Pan S, Wang X, Shan Y, Peng M, Qin X, Sun G, Zhang P, Dong J, Qiu C. Drug-coated balloon in the treatment of coronary left main true bifurcation lesion: A patient-level propensity-matched analysis. Front Cardiovasc Med. 2022 Nov 3;9:1028007. doi: 10.3389/fcvm.2022.1028007. PMID: 36407423; PMCID: PMC9669294.

54. Cortese B, Pellegrini D, Latini RA, Di Palma G, Perotto A, Orrego PS. Angiographic performance of a novel sirolimus-coated balloon in native coronary lesions: the FAtebenefratelli SIrolimus COated NATIVES prospective registry. J Cardiovasc Med (Hagerstown). 2019 Jul;20(7):471-476. doi: 10.2459/JCM.0000000000000806. PMID: 30994510.

55. El-Mokdad R, di Palma G, Cortese B. Long-term follow-up after sirolimus-coated balloon use for coronary artery disease. Final results of the Nanolutè study. Catheter Cardiovasc Interv. 2020 Nov;96(5):E496-E500. doi: 10.1002/ccd.28863. Epub 2020 Mar 19. PMID: 32191384.

56. Cortese B, Testa L, Di Palma G, Heang TM, Bossi I, Nuruddin AA, Ielasi A, Tespili M, Perez IS, Milazzo D, Benincasa S, Latib A, Cacucci M, Caiazzo G, Seresini G, Tomai F, Ocaranza R,

Torres A, Perotto A, Bedogni F, Colombo A. Clinical performance of a novel sirolimus-coated balloon in coronary artery disease: EASTBOURNE registry. J Cardiovasc Med (Hagerstown). 2021 Feb 1;22(2):94-100. doi: 10.2459/JCM.0000000000001070. PMID: 32740442.

57. Cortese B, Testa L, Heang TM, Ielasi A, Bossi I, Latini RA, Lee CY, Perez IS, Milazzo D, Caiazzo G, Tomai F, Benincasa S, Nuruddin AA, Stefanini G, Buccheri D, Seresini G, Singh R, Karavolias G, Cacucci M, Sciahbasi A, Ocaranza R, Menown IBA, Torres A, Sengottvelu G, Zanetti A, Pesenti N, Colombo A; EASTBOURNE Investigators. Sirolimus-Coated Balloon in an All-Comer Population of Coronary Artery Disease Patients: The EASTBOURNE Prospective Registry. JACC Cardiovasc Interv. 2023 Jul 24;16(14):1794-1803. doi: 10.1016/j.jcin.2023.05.005. PMID: 37495352.

58. Gao XF, Ge Z, Kan J, Kong XQ, Wang Y, Qiu CG, Tresukosol D, He YQ, Wu Q, Li JF, Yuan HT, Shen C, Chen X, Munawar M, Hanif B, Santoso T, Shin ES, Sheiban I, Ye F, Zhang JJ, Chen SL; DCB-BIF investigators. Rationale and design for comparison of a non-compliant balloon with drug-coating balloon angioplasty for side branch after provisional stenting for patients with true coronary bifurcation lesions: a prospective, multicentre and randomised DCB-BIF trial. BMJ Open. 2022 Mar 11;12(3):e052788. doi: 10.1136/bmjopen-2021-052788. PMID: 35277400; PMCID: PMC8919455.