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DEFINITION criteria for left main bifurcation stenting – from clinical need to a formula

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KEYWORDS

- coronary bifurcation lesion
- drug-eluting stent
- lesion complexity
- risk stratification

Abstract

Percutaneous coronary intervention using drug-eluting stents for coronary bifurcation lesions is associated with higher rates of in-stent restenosis, myocardial infarction, and revascularisation as compared with non-coronary bifurcation lesions. The increased percentage of suboptimal results after stenting bifurcation lesions is largely, if not always, due to the extreme complexity of the anatomy. Obviously, one weapon (stenting technique) does not suit all enemies (bifurcation lesions with different anatomies), and it underscores the importance of establishing a stratification system.

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Abbreviations

CABG	coronary artery bypass graft
LMCA	left main coronary artery
MV	main vessel
PCI	percutaneous coronary intervention
SB	side branch
ST	stent thrombosis

Introduction

BIFURCATION STRUCTURE AND THE COMPLEXITY OF BIFURCATION LESIONS

Bifurcated vessels involve 3 segments (the proximal and distal main vessels [MV], and the side branch [SB]), which are part of the polygon of confluence and have an irregular contour. Vessel diameter and lesion length are 2 key factors that influence stent selection and predict clinical outcomes, while the impact of the bifurcation angle on clinical results remains controversial[1-3]. The Medina classification was proposed as a simple, easy-to-remember scheme that labels bifurcation lesions by plaque involvement in 3 anatomic segments[4]. However, this classification also has limitations because it doesn't include important descriptive features of bifurcation lesions that could be helpful in determining the optimum stent treatment strategy[5,6]. Therefore, the lack of a comprehensive stratification system defining the complexity of bifurcation lesions remains an unmet clinical need.

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"IS THE LEFT MAIN A DIFFERENT ANIMAL?"[7]

Compared to the non-left main coronary artery, the left main coronary artery (LMCA) is characterised by a large calibre, a wide distal bifurcation angle, and the perfusion of a large amount of myocardium[7]. As a result, the occurrence of restenosis or stent thrombosis (ST) in the LM can be a disaster. Coronary artery bypass grafting (CABG) is the standard of care for LM disease[1]. However, because of marked advancements in percutaneous coronary intervention (PCI) techniques with stenting and CABG, as well as adjunctive pharmacologic therapy, a new evaluation and review of the current indications for the optimal revascularisation therapy for LM disease may be required to determine the standard of care for these patients[8,9]. The available current evidence suggests that the only difference between PCI with stenting and CABG is the rate of repeat revascularisation during long-term follow-up. Whilst PCI can be successfully performed in most LMCA lesions, the "high-risk" anatomic subsets, especially those with distal LMCA bifurcation lesions, continue to present interventional cardiologists with unique technical challenges[7]. In the EXCEL trial, which included 342 patients with distal LM bifurcation disease that did not involve both major side branch vessels, the 3-year primary endpoint was found to be lower with a provisional 1-stent versus with a planned 2-stent technique (13.8% vs 23.3%; p=0.04). There was no notable difference in the primary endpoint present in the 182 patients with distal LM bifurcation disease that involved both side branch vessels (14.3% vs 19.2%; p=0.6)[10]. Thus, it appears that lesion complexity in the LM is directly correlated with clinical events.

RISK STRATIFICATION SYSTEMS FOR LM LESIONS

The 2018 European Society of Cardiology (ESC) Guidelines on myocardial revascularisation recommend that a planned 2-stent approach with upfront SB stenting may be preferable in bifurcation lesions with an SB ≥2.75 mm in diameter, an SB lesion length ≥5 mm, or when difficulty in accessing the SB before stenting the MV is anticipated[1]. This stratification is not yet accepted globally.

The SYNTAX Study randomly assigned 1,800 patients with 3-vessel or LM coronary artery disease to undergo CABG or PCI. At 12 months, the rate of major adverse cardiac or cerebrovascular events was significantly higher in the PCI group (17.8%, vs 12.4% for CABG; p=0.002), mostly due to an increased rate of repeat revascularisation (13.5% vs 5.9%; p<0.001). As a result, the criterion for non-inferiority was not met. The rates of mortality and myocardial infarction (MI) were similar between the 2 groups at 12 months; however, the rate of stroke was notably increased with CABG (2.2% vs 0.6% [with PCI]; p=0.003)[11]. Subsequently, the initial anatomical-based SYNTAX score[12] was further modified to become the SYNTAX score II[13], including 8 predictors: anatomical SYNTAX score, age, creatinine clearance, left ventricular ejection fraction, presence of unprotected LM coronary artery disease, peripheral vascular disease, female sex, and chronic obstructive pulmonary disease. Farooq et al wrote, "Long-term (4-year) mortality in patients with complex coronary artery disease can be well predicted by a combination of anatomical and clinical factors included in the SYNTAX score II. The SYNTAX score II can better guide decision-making between CABG and PCI than the original anatomical SYNTAX score"[14].

The New Risk Stratification Score (NERS) consists of 54 variables (17 clinical, 4 procedural, and 33 angiographic) and was derived from 260 patients with unprotected LM stenosis who underwent PCI; it was tested in a validation group consisting of 337 patients with LM disease undergoing PCI in a prospective, multicentre trial. A NERS score ≥25 demonstrated a sensitivity of 92.0% and a specificity of 74.1%, significantly higher than SYNTAX intermediate risk (20.5% and 25.4%) or SYNTAX highest risk (70.5% and 35.2%; p for all <0.001). At follow-up, the rates of myocardial infarction, cardiac death, and target vessel revascularisation were 3.0%, 5.6%, and 13.1%, respectively, and the composite of major adverse cardiac events (MACE) was 26.0%[15]. Similarly, in order to overcome the complicated calculation, the NERS score II was derived from our previous 2 studies and was externally compared with the NERS and SYNTAX scores in 1,463 patients with unprotected LM disease who had undergone implantation of a drug-eluting stent (DES) in a prospective, multicentre registry trial. The NERS score II system consists of 16 variables: 7 clinical and 9 angiographic. A NERS score II ≥19 demonstrated enhanced MACE sensitivity and specificity of 84.0% and 76.0% (with MACE as the stated variable), respectively, which were similar to the NERS scores but significantly higher than the SYNTAX score. A NERS score II ≥19 was the sole independent predictor of cumulative MACE (hazard ratio [HR] 3.27, 95% confidence interval [CI]: 1.86-5.23; p≤0.001) and

stent thrombosis (odds ratio [OR] 22.15, 95% CI: 12.47-57.92; p≤0.001) at follow-up[16].

While both the SYNTAX (II) scores and NERS (II) scores demonstrated their prediction for clinical events in patients with LM disease, a dedicated risk stratification scoring system is urgently required for patients with LM distal bifurcation lesions.

DEFINITION CRITERIA

The DEFINITION criteria, a dedicated stratification system for coronary bifurcation lesions, were developed from 1,550 patients with coronary bifurcation lesions by multivariate regression and were further validated in an external cohort of 3,660 patients with varied bifurcated disease[17]. The DEFINITION criteria aimed to differentiate between simple and complex bifurcation lesions and to help interventional cardiologists select an appropriate technique. The DEFINITION criteria consist of 2 major and 6 minor angiographic criteria **(Table 1)**. The major criteria are (1) for distal LM bifurcations, SB lesion length ≥10 mm and SB diameter stenosis ≥70%; and (2) for non-left main bifurcation lesions, SB lesion length ≥10 mm and SB diameter stenosis ≥90%. The 6 minor criteria include (1) moderate-to-severe calcification, (2) multiple lesions, (3) bifurcation angle <45° or >70°, (4) MV reference vessel diameter (RVD) <2.5 mm, (5) thrombus-containing lesions, and (6) MV lesion length ≥25 mm. A bifurcation lesion is defined as complex if it meets 1 major criterion plus any 2 minor criteria. For complex bifurcation lesions, provisional stenting is associated with a higher risk of cardiac death and MACE compared with a systematic 2-stent approach[17]. On the contrary, for simple bifurcation lesions, a systematic 2-stent strategy results in a higher risk of MACE compared with provisional stenting **(Table 1)**.

Table 1. Components of the DEFINITION criteria.

Major criteria	Minor criteria
For left main distal bifurcation lesions 1. SB lesion length ≥10 mm AND 2. SB diameter stenosis ≥70%	Moderate to severe calcification
	Multiple lesions
	Bifurcation angle <45° or >70°
For non-left main distal bifurcation lesions 3. SB lesion length ≥10 mm AND 4. SB diameter stenosis ≥90%	Main vessel reference vessel diameter <2.5 mm
	Thrombus-containing lesions
	Main vessel lesion length ≥25 mm
Complex coronary bifurcation lesions = 1 major criterion + any 2 minor criteria	
SB: side branch	

The DEFINITION II trial[18] was the first randomised clinical trial aimed at comparing the clinical outcomes between a systematic 2-stent approach and provisional stenting (PS) in 653 patients with complex bifurcation lesions as defined by the DEFINITION criteria[17]. The primary endpoint was the composite of target lesion failure (TLF) at 1-year follow-up, including cardiac death, target vessel myocardial infarction (TVMI), and clinically driven target lesion revascularisation (TLR). The safety endpoint was definite or probable stent thrombosis. At 1-year follow-up, TLF occurred in 37 (11.4%) and 20 (6.1%) patients in the provisional and 2-stent groups, respectively (HR 0.52, 95% CI: 0.30-0.90; p=0.019), largely driven by increased rates of TVMI (7.1%, HR 0.43, 95% CI: 0.20-0.90; p=0.025) and clinically driven TLR (5.5%, HR 0.43, 95% CI: 0.19-1.00; p=0.049) in the provisional group. At 1 year after the index procedure, the incidence of cardiac death was 2.5% in the provisional group, which was not significantly different from the 2.1% in the 2-stent group (HR 0.86, 95% CI: 0.31-2.37; p=0.772). At 3 years, 52 (16.0%) patients in the PS group and 34 (10.4%) patients in the 2-stent group experienced TLF (HR 0.63, 95% CI: 0.41-0.97; p=0.035), for the most part, driven by increased rates of TVMI (8.0% vs 3.7%, HR 0.45, 95% CI: 0.23-0.89; p=0.022) and TLR (8.3% vs 4.3%, HR 0.50, 95% CI: 0.26-0.96; p=0.038)[19]. There was no difference in TLF between year 1 and year 3 in the 2 groups. Recently, a meta-analysis further confirmed that an SB lesion length ≥10 mm is a key predictor of provisional stenting failure[20]. Therefore, an assessment of lesion complexity based on an already accepted scoring system is crucial to decision-making for bifurcation lesions.

COMPARISON OF STENTING APPROACHES FOR LM BIFURCATIONS STRATIFIED BY RISK SCORES

The DKCRUSH-III trial[21] enrolled a total of 419 patients with LM bifurcation lesions who were randomly assigned to double kissing (DK) or culotte treatment. The primary endpoint was the occurrence of MACE at 1 year, and stent thrombosis served as a safety endpoint. Patients were stratified by SYNTAX and NERS scores. Patients in the culotte group had a significantly higher 1-year MACE rate (16.3%), mainly driven by increased target vessel revascularisation (TVR; 11.0%), compared with the DK group (6.2% and 4.3%, respectively; all p<0.05). The in-stent restenosis (ISR) rate in the SB was 12.6% in the culotte group and 6.8% in the DK group (p=0.037). The definite ST rate was 1.0% in the culotte group and 0% in the DK group (p=0.248). Among patients with a bifurcation angle ≥70°, a NERS score ≥20, and a SYNTAX score ≥23, the 1-year MACE rate in the DK group (3.8%, 9.2%, and 7.1%, respectively) was significantly different from those in the culotte group (16.5%, 20.4%, and 18.9%, respectively; all p<0.05). At 3 years, 49 patients in the culotte group and 17 patients in the DK crush group experienced MACE (cumulative event rates of 23.7% and 8.2%, respectively; p<0.001), largely driven by increased rates of MI (8.2% vs 3.4%, respectively; p=0.037) and target vessel revascularisation (18.8% vs 5.8%, respectively; p<0.001). The rates of definite ST were 3.4% in the culotte group and 0% in the DK crush group (p=0.007). Patients with complex left main distal bifurcation lesions (LMDBL) were associated with a higher rate of MACE (35.3%) at 3 years compared with patients with simple LMDBL (8.1%) (p<0.001), with a much higher rate in the culotte group (51.5% vs 15.1%; p<0.001)[22].

Currently, only 2 randomised trials have compared provisional stenting with the 2-stent strategy in LM bifurcation lesions: the DKCRUSH-V and the EBC MAIN trials. The DKCRUSH-V Trial compared the clinical outcomes of provisional stenting with the

DK crush technique for true distal LM bifurcation lesions. The primary endpoint was target lesion failure (TLF) at 1-year follow-up. A total of 482 patients with LM true bifurcation lesions were randomised to either the DK crush or the PS group. At 1 year, TLF occurred in 10.7% of the PS group versus 5.0% of the DK crush group (p=0.02). Compared with the PS strategy, DK crush resulted in a lower incidence of patients with target vessel myocardial infarction (TVMI) (2.9 vs 0.4%; p=0.03) or definite or probable ST (3.3 vs 0.4%; p=0.02). The rates of clinically driven TLR (7.9 vs 3.8%; p=0.06) and angiographic restenosis (14.6 vs 7.1%; p=0.10) were also lower with DK crush compared with PS[23,24]. Notably, DK crush stenting was associated with a further significant reduction in the primary endpoint for patients with complex LM bifurcation lesions, according to the DEFINITION criteria, compared with provisional stenting. In addition, the superiority of DK crush stenting over PS continued during the 3-year follow-up[25]. On the other hand, the EBC MAIN trial enrolled 467 patients with true distal LM bifurcation lesions who were randomly assigned to the provisional or planned 2-stent groups. The primary endpoint was a composite of death, MI, and TLR occurring in 14.7% of the provisional group versus 17.7% of the planned 2-stent group (p=0.34) at 1-year follow-up. Secondary endpoints included death (3.0% vs 4.2%; p=0.48), MI (10.0% vs 10.1%; p=0.91), TLR (6.1% vs 9.3%; p=0.16), and ST (1.7% vs 1.3%; p=0.90), respectively[24].

While the neutral results that came from the EBC MAIN trial are the main concerns about its design, insightful analyses of the comparison of the DKCRUSH-V and the EBC MAIN trials have shown that there are many similarities but several differences between these 2 trials: more simple lesions and low-risk patients were included in the EBC MAIN trial, for example, with lower SYNTAX scores, shorter SB lesion lengths, no acute myocardial infarctions or chronic totally occluded lesions, when compared with the DKCRUSH-V Trial.

WHY DO DEFINITION CRITERIA-DEFINED BIFURCATION LESIONS INCREASE WORSE EVENTS?

Given the results mentioned above, it remains unclear what the mechanisms are that underlie the increased rate of periprocedural MI after provisional stenting for complex bifurcation lesions. A study on OCT bifurcation prospectively analysed a total of 405 patients with 405 bifurcation lesions who underwent preprocedural OCT imaging of both the MV and the SB. Using quantitative analysis, patients were divided into long SB lesion (SB lesion length ≥10 mm) and short SB lesion (SB lesion length <10 mm) groups. They were also stratified by the presence of vulnerable plaques identified by OCT. The primary endpoint was the occurrence of TVMI after provisional stenting at 1-year follow-up. A total of 178 (43.9%) patients had long SB lesions. Vulnerable plaques were found more frequently in the long SB lesion group (42.7%) than in the short SB lesion group (24.2%; p<0.001) and were predominantly localised in the MV. At 1-year follow-up after PS, there were 31 (7.7%) TVMI, of which 21 (11.8%) were found in the long SB lesion group and 10 (4.4%) were found in the short SB lesion group (p=0.009). Using multivariate regression analysis, it was shown that a long SB lesion length (p=0.011), the absence of vulnerable plaques in the polygon of confluence (p=0.001), and true coronary bifurcation lesions (p=0.004) were the 3 independent factors of TVMI[26]. Coronary bifurcation lesions with a longer SB lesion length are definitively associated with more frequent vulnerable disease, leading to increased TVMI rates, and this finding is consistent with reports by the DEFINITION II trial.

Conclusions

In conclusion, the DEFINITION criteria were formulated to help differentiate between simple and complex coronary bifurcation lesions, and they have a strong potential for predicting clinical outcomes after provisional treatment. Future trials using intravascular imaging to guide the stenting selection and to assess the stent expansion are warranted.

Conflict of interest statement

The author has no conflicts of interest to declare.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. *EuroIntervention.* 2019;14(14):1435-534.

2. Kassab GS, Finet G. Anatomy and function relation in the coronary tree: from bifurcations to myocardial flow and mass. *EuroIntervention.* 2015;11 Suppl V:V13-7.

3. Huo Y, Finet G, Lefevre T, Louvard Y, Moussa I, Kassab GS. Which diameter and angle rule provides optimal flow patterns in a coronary bifurcation? *J Biomech.* 2012; 45:1273-9.

4. Medina A, Surez de Lezo J, Pan M. Una clasificación simple de las lesiones coronarias en bifurcación. [A new classification of coronary bifurcation lesions]. *Rev Esp Cardiol.* 2006;59:183.

5. Louvard Y, Thomas M, Dzavik V, Hildick-Smith D, Galassi AR, Pan M, Burzotta F, Zelizko M, Dudek D, Ludman P, Sheiban I, Lassen JF, Darremont O, Kastrati A, Ludwig J, Iakovou I, Brunel P, Lansky A, Meerkin D, Legrand V, Medina A, Lefèvre T. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! *Catheter Cardiovasc Interv.* 2008;71:175-83.

6. Sanborn TA. Bifurcation classification schemes: impact of lesion morphology on development of a treatment strategy. *Rev Cardiovasc Med.* 2010;11 Suppl 1:S11-6.

7. Park SJ, Park DW. Left main stenting: is it a different animal? *EuroIntervention.* 2010;6 Suppl J:J112-7.

8. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N Engl J Med.* 2016;375:2223-35.

9. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RB, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sørensen HT, Nielsen PH, Niemelä M, Kervinen K, Lassen JF, Maeng M, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Fröbert O, Graham AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH; NOBLE study investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet.* 2016;388:2743-52.

10. Kandzari DE, Gershlick AH, Serruys PW, Leon MB, Morice MC, Simonton CA, Lembo NJ, Banning AP, Merkely B, van Boven AJ, Ungi I, Kappetein AP, Sabik JF 3rd, Généreux P, Dressler O, Stone GW. Outcomes Among Patients Undergoing Distal Left Main Percutaneous Coronary Intervention. *Circ Cardiovasc Interv.* 2018;11: e007007.

11. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-72.

12. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1:219-27.

13. Takahashi K, Serruys PW, Fuster V, Farkouh ME, Spertus JA, Cohen DJ, Park SJ, Park DW, Ahn JM, Kappetein AP, Head SJ, Thuijs DJ, Onuma Y, Kent DM, Steyerberg EW, van Klaveren D; SYNTAXES, FREEDOM, BEST, and PRECOMBAT trial investigators. Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation. *Lancet.* 2020; 396:1399-412.

14. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet.* 2013;381:639-50.

15. Chen SL, Chen JP, Mintz G, Xu B, Kan J, Ye F, Zhang J, Sun X, Xu Y, Jiang Q, Zhang A, Stone GW. Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. *JACC Cardiovasc Interv.* 2010;3:632-41.

16. Chen SL, Han YL, Zhang YJ, Ye F, Liu HW, Zhang JJ, Xu B, Jiang TM, Zhou YJ, Lv SZ. The anatomic- and clinical-based NERS (new risk stratification) score II to predict clinical outcomes after stenting unprotected left main coronary artery disease: results from a multicenter, prospective, registry study. *JACC Cardiovasc Interv.* 2013; 6:1233-41.

17. 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;7:1266-76.

18. 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;41: 2523-36.

19. Kan J, Zhang JJ, Sheiban I, Santoso T, Munawar M, Tresukosol D, Xu K, Stone GW, Chen SL; DEFINITION II Investigators. 3-Year Outcomes After 2-Stent With Provisional Stenting for Complex Bifurcation Lesions Defined by DEFINITION Criteria. *JACC Cardiovasc Interv.* 2022;15:1310-20.

20. 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.

21. Chen SL, Xu B, Han YL, Sheiban I, Zhang JJ, Ye F, Kwan TW, Paiboon C, Zhou YJ, Lv SZ, Dangas GD, Xu YW, Wen SY, Hong L, Zhang RY, Wang HC, Jiang TM, Wang Y, Chen F, Yuan ZY, Li WM, Leon MB. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol.* 2013;61:1482-8.

22. Chen SL, Xu B, Han YL, Sheiban I, Zhang JJ, Ye F, Kwan TW, Paiboon C, Zhou YJ, Lv SZ, Dangas GD, Xu YW, Wen SY, Hong L, Zhang RY, Wang HC, Jiang TM, Wang Y, Sansoto T, Chen F, Yuan ZY, Li WM, Leon MB. Clinical Outcome After DK Crush Versus Culotte Stenting of Distal Left Main Bifurcation Lesions: The 3-Year Follow-Up Results of the DKCRUSH-III Study. *JACC Cardiovasc Interv.* 2015;8:1335-42.

23. Chen SL, Zhang JJ, Han Y, Kan J, Chen L, Qiu C, Jiang T, Tao L, Zeng H, Li L, Xia Y, Gao C, Santoso T, Paiboon C, Wang Y, Kwan TW, Ye F, Tian N, Liu Z, Lin S, Lu C, Wen S, Hong L, Zhang Q, Sheiban I, Xu Y, Wang L, Rab TS, Li Z, Cheng G, Cui L, Leon MB, Stone GW. Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions: DKCRUSH-V Randomized Trial. *J Am Coll Cardiol.* 2017;70:2605-17.

24. 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.

25. Chen X, Li X, Zhang JJ, Han Y, Kan J, Chen L, Qiu C, Santoso T, Paiboon C, Kwan TW, Sheiban I, Leon MB, Stone GW, Chen SL; DKCRUSH-V Investigators. 3-Year Outcomes of the DKCRUSH-V Trial Comparing DK Crush With Provisional Stenting for Left Main Bifurcation Lesions. *JACC Cardiovasc Interv.* 2019;12: 1927-37.

26. Li X, Kan J, She L, Shrestha R, Pan T, You W, Wu Z, Ge Z, Zhang JJ, Gogas BD, Ye F, Chen SL. Optical coherence tomography predictors of target vessel myocardial infarction after provisional stenting in patients with coronary bifurcation disease. *Catheter Cardiovasc Interv.* 2021;97:1331-40.