Stenting Left Main and Bifurcation Disease: From DK crush to Risk Assessment

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Left main (LM) disease is reported with angiography to be ~10%[1]. LM is segmented by ostial (proximal 3-5 mm), body (mid-segment, 5 mm in length), and distal (distal 5 mm). When LM length is <10mm, from the standpoint of percutaneous coronary intervention (PCI), most interventional cardiologists prefer to cover the whole LM segment using a drug-eluting stent (DES) unless a proximal landing zone is pretty clear. Among isolated distal LM lesions, >80% of disease[2] is extended to left anterior descending artery (LADN). Of overall LM lesions, ~85% involves both LAD and left circumflex (LCX), forming distal LM bifurcation lesions[3].

Criteria for LM treatment[2,4] are: 1) LM diameter stenosis ≥70% by angiography; 2) minimal luminal area (MLA) ≤6.0 mm^2 by intravascular ultrasound (IVUS) or optical coherence tomography (OCT); or 3) fractional flow reserve (FFR) ≤0.80. While the impact of LM disease locations on clinical outcome after coronary artery bypass graft (CABG) can be largely ignored, how to stenting distal LM lesions is a key issue. Of a total of 2,775 patients with isolated ostial/midshaft lesions in an unprotected LM disease enrolled in the DELTA multinational registry[5], at a median follow-up period of 1,293 days, there were no significant differences in the propensity score-adjusted analyses for the composite endpoint of all-cause death, myocardial infarction (MI), and cerebrovascular accident between PCI and CABG groups, with an exception of higher rate of target vessel revascularization (TVR) in the PCI arm. For entire cohort of LM disease, in a recent meta-analysis[6] including 29 studies extracted with 21,832 patients (10,424 in PCI vs 11,408 in CABG), the pooled analysis demonstrated remarkable differences in ≥1 year follow-up major adverse cardiac and cerebrovascular event, TVR, and MI, favoring CABG over PCI. Obviously, it is resumed that LM distal lesions is mainly correlated with increased clinical events after PCI. This finding is in line with more recent two large clinical trials[7, 8] with >3-year follow-up. In the EXCEL trial[7], in which 1905 patients with ULMCAD and low or intermediate SYNTAX scores were randomized to PCI with second-generation everolimus-eluting stents vs. CABG, ~80% of patients had disease of the distal LM bifurcation, most commonly treated with a provisional stenting (PS) approach. Although PCI provided comparable 3-year composite rates of death, myocardial infarction (MI) or stroke compared to CABG, repeat revascularization rates after 30 days were higher with PCI. In the NOBLE trial[8], ~80% of patients also had distal LM involvement, again most often treated with PS strategy. In NOBLE, PCI with an earlier generation DES resulted in a higher composite rate of death, MI, stroke or TVR at 5 years than CABG.

The PS approach to true bifurcation lesions consists of a DES to the main branch and balloon angioplasty of the side branch (SB), with stenting of the SB (usually with a T technique) reserved for a suboptimal balloon result. Therefore, whether alternative approaches to the distal LM bifurcation might afford superior results is unknown. In this issue of AsiaIntervention, Dr. Stankovic and coworker[9] have systematically analyzed the similarities and differences between PS and upfront two-stent approaches for LM bifurcation. In this writing there is no more “disclosures” about the comparison of PS versus two-stent treatments. However, the following issues remain to be programmatic.

Is LM bifurcations’ complexity influencing clinical outcome after PCI? 2018 ESC/EACTS guidelines on myocardial revascularization[10] recommended the use of systematic two-stent for true coronary bifurcation lesions if large SB (≥2.75 mm in diameter) with a long ostial SB lesion (>5 mm), anticipated difficulty in accessing an important SB after MV

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stenting, and true distal LM bifurcations. Widespread agreement is lacking. In 2014, the DEFINITION criteria of complex bifurcation lesions[11] were developed from a large bifurcation cohort (n=1550 patients) and subsequently validated in a 3660-patient study. Significant reductions in mortality and in-hospital adverse events were observed in patients with complex bifurcation lesions so defined treated with routine two-stent techniques. Subsequent DEFINITION II trial[12] showed that a planned 2-stent strategy significantly reduced the incidence of 1-year target lesion failure (TLF) compared with provisional stenting, driven by fewer target vessel MI (TVMI) and clinically-driven target lesion revascularization (TLR). In that study, ~80% of two-stent techniques was DK crush, leading to the conclusion that DK crush is the winner. In fact, DKCRUSH V[13], the 2nd randomized trial comparing DK crush with PS for LM distal bifurcation lesions, has reported the significant reduction of 1- to 3-year TLF in patients with complex bifurcations stratified by DEFINITION criteria, supported by a recently published retrospective study[14]. Altogether, DEFINITION criteria consisting of angiographic parameters provide the reliability of separating simple from complex bifurcation lesions and the prediction value for the occurrence of clinical events after LM bifurcation PCI.

What is the internal difference between culotte and double kissing (DK) double crush? Culotte stenting is used to be and continues to be the main techniques of systematic two-stent approach for true coronary bifurcation lesions. In the DKCRUSH III study[15], patients in the Culotte group had significant higher 1-year major adverse cardiac event (MACE, including cardiac death, MI, and TVR), mainly driven by increased TVR, compared with the DK crush. Interestingly, the 1-year MACE rate after culotte for LM bifurcation lesions was similar between DKCRUSH III (16.3%) and EBC Main (17.7%, all-death in this trial)[16] trials. Furthermore, at 3-year follow-up of DKCRUSH III study[17], the difference in MACE between culotte and DK crush group was widened, accompanied with extreme higher rate of stent thrombosis in the culotte arm. As a result, culotte stenting approach should be moved from the list of upfront two-stent techniques for treatment of LM bifurcation lesions.

Why higher rate of periprocedural MI (PMI) after PS approach? Post-stenting MI consists of PMI and spontaneous MI. Spontaneous MI rate is comparable between PS and two-stent[12-16], however, PMI was significantly higher in the PS arm from DKCRUSH V[13] and DEFINITION II[12] trials. In a total of 405 patients with 405 bifurcation lesions who underwent pre-procedure OCT imaging of both the main vessel (MV) and the SB[18], vulnerable plaques were predominantly localized in the MV and were more frequently in the long SB (≥10 mm) lesion group (42.7%) than in the short SB lesion group (24.2%, $p < 0.001$). At 1-year follow-up after provisional stenting, there were 31 (7.7%) TVMIs, with 21 (11.8%) in the long SB lesion group and 10 (4.4%) in the short SB lesion group ($p = 0.009$). Multivariate regression analysis showed that long SB lesion length, vulnerable plaques in the polygon of confluence, and true coronary bifurcation lesions were the three independent factors of TVMI. Obviously, SB lesion length plays an important role in stenting selection and predicting worse events (Table I), consistent with recent meat-analysis[19].

Table-I

Correlation of side branch lesion length with worse event at 1-year after provisional stenting

1-year F/U	Cardiac death	TVMI	TLR	TLF	ST
SB lesion length < 5-mm	0.8%	0	2.1%	2.5%	0
SB lesion length = 5 mm but <10-mm	1.3%	3.3%	4.5%	6.6%	0
SB lesion length ≥10 mm	2.2%	6.1%	8.4%	13.4%	2.7%

Unpublished data from DKCRUSH II, DKCRUSH V, and DKCRUSH VI studies.

What is the correlation of PMI with mortality after bifurcation stenting? PMI refers to myonecrosis following PCI using DES. Its rate varies from 1.1% to 55.9% depending on the types and cut-off values of biomarkers and additional EKG criteria or clinical symptoms. The pathophysiology of PMI is multifactorial and includes distal embolization of thrombus or plaques, dissection, spasm, and occlusion of small SBs. In 1,971 patients with true coronary bifurcations who underwent DES implantation in the DEFINITION trial[11], we reported that 1-year mortality was significantly higher in the PMI group (defined as creatinine kinase [CK]-myocardial band [CK-MB]>3 times over the upper normal limit [UNL], 6.4%) group than in the non-PMI group (1.7%). Among 1300 patients with both CK and CK-MB measurements pre- and post-stenting were evaluated from four DKCRUSH studies[20], Sheiban and coworkers reported that 56 (4.3%) patients had PMI. According to SYNTAX, 4th UDMI or ISCHEMIA, SCAI, and EXCEL definitions (Table II), PMI occurred in 21 (1.6%), 56 (4.3%), 29 (2.2%), and 32 (2.5%) patients, respectively. All definitions were significantly correlated with unadjusted mortality at the end of follow-up but not at 30 days or 1-year after stenting. PMI using SYNTAX, SCAI, and EXCEL definitions rather than 4th UDMI definition was strongly associated with adjusted all-cause death. By adjusted analysis, PMI according to 4th UDMI, SCAI, and EXCEL definitions but not SYNTAX definition was positively correlated with cardiac death at a median of 5.58 years of follow-up. CK-MB ≥5 x UNL strongly enhanced the correlation of CK-MB values with mortality (Table III). Accordingly, intravascular imaging-guidance of bifurcation stenting is critical in improving clinical outcomes.

Table-II

Components of definitions for peri-procedural myocardial infarction

	Component of definitions
SYNTAX definition	New Q waves in ≥2 leads
	- peak CK-MB/peak total CK >10%
	- CK-MB > 5 x UNL
4th UDMI definition	CK-MB > 5 x 99% percentile UNL
	- new ischemic ECG changes
	- new Q waves
	- flow-limiting complications
	- new loss of viable myocardium
	- new wall motion abnormally
ISCHEMIA definition	CK-MB > 5 x UNL
	- ST-segment elevation or depression
	- new Q waves
	- persistent LBBB
	- new TIMI flow 0/1 in major vessel or SB
	- NHLBI ≥type C dissection
	CK-MB > 10 x UNL
SCAI definition	CK-MB ≥5 x UNL
	- new Q waves
	- persistent LBBB
	CK-MB > 10 x UNL
EXCEL definition	CK-MB > 5 x UNL
	- new Q waves
	- persistent LBBB
	- occlusion, new thrombosis or TIMI <3
	- new loss of viable myocardium
	- new regional wall motion abnormally
	CK-MB > 10 x UNL

Table-III

Association of CK-MB values with all-cause or cardiac death at the end of follow-up

CK-MB increases (x ULN)	All-cause death			Cardiac death		
	Event, N (%)	HR	95% CI	Event, N (%)	HR	95% CI
CK-MB < 1 x UNL	46/577 (8.0)	-	-	25/577 (4.3)	-	-
1 x UNL ≤CK-MB < 3 x UNL	61/598 (10.2)	0.63	0.36-1.10	38/598 (6.4)	0.59	0.30-1.13
3 x UNL ≤CK-MB < 5 xUNL	8/68 (11.8)	1.08	0.49-2.35	4/68 (5.9)	0.81	0.28-2.32
CK-MB ≥5 x UNL	11/57 (19.3)	2.07	1.02-4.18	9/57 (15.8)	2.79	1.28-6.06

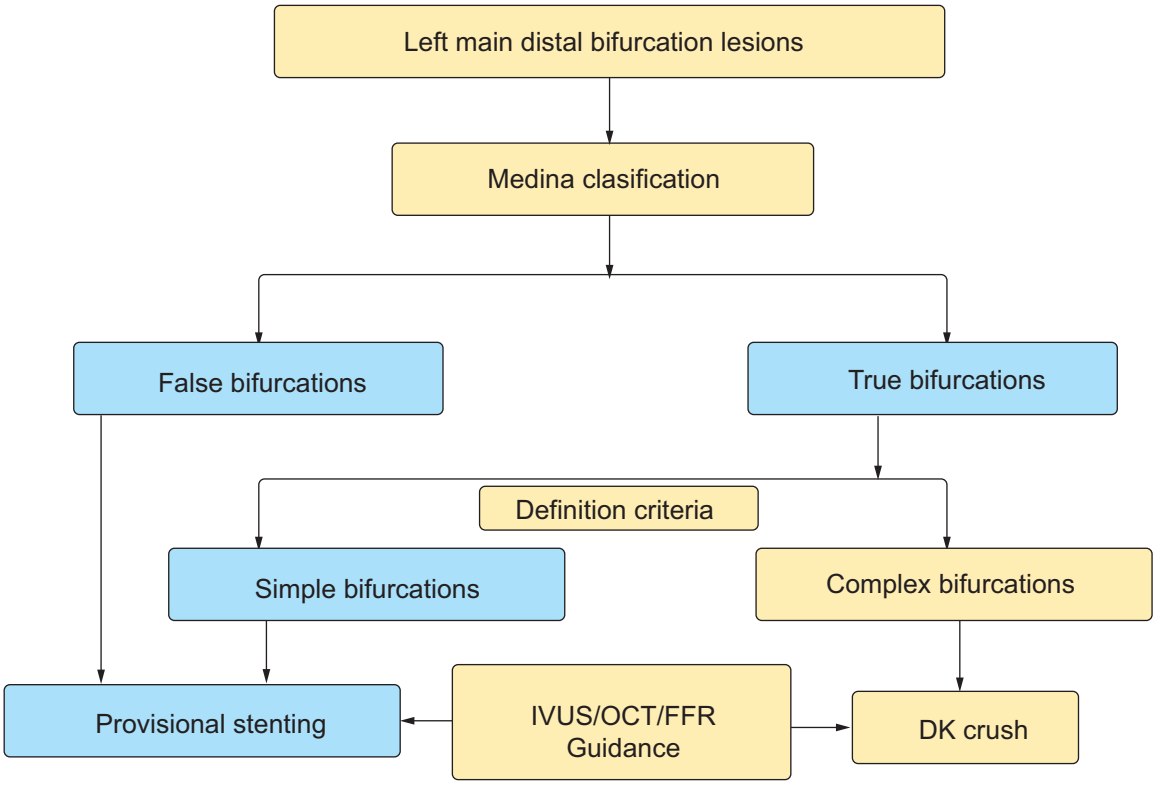

Fig.-1: *Algorithm of stenting left main distal bifurcation lesions*

In conclusion, stenting LM bifurcation lesions is technically demanding. Careful assessments according to angiography, intravascular images, and or FFR are key points of device and approach selection (Figure 1). Quality of stenting procedures determines the short- and long-term clinical outcomes. DK crush is associated with less frequent worse clinical events, particularly for complex bifurcation lesions defined by DEFINITION criteria.

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