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EDITORIAL

A Frequentist Opting for the Road Less Traveled

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Bifurcation lesions account for 15% to 20% of all lesions managed by percutaneous coronary intervention and their optimal treatment remains a challenge both in terms of procedural success and longer-term cardiovascular outcomes. Bifurcation lesions vary both by their distribution and extent of disease in the main vessel and side branch (SB), as well as through differences in the relative sizes of the main vessel and SB, their angulation, lesion characteristics such as lesion length, calcification, and thrombus burden and whether they are left main (LM) or non-LM lesions.[1] This makes treatment of bifurcation lesions challenging.

See Article by Park et al.

The optimal treatment strategy for bifurcations remains under debate, with trials such as the EBC TWO (European Bifurcation Coronary TWO), CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents), BBC ONE (British Bifurcation Coronary Study) randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions, and EBC MAIN (European Bifurcation Club Left Main Coronary Stent Study) demonstrated greater major adverse cardiovascular event rates (MACE) including death, myocardial infarction (MI), and target vessel revascularization (TVR) associated with an upfront systematic 2-stent strategy.[2–6] As such the European Society of Cardiology guidelines opted for a default stepwise provisional strategy for both non-LM and LM bifurcation disease.[7] Nevertheless, mounting evidence suggests that an upfront 2-stent approach in patients with more complex bifurcations as defined by the DEFINITION II criteria (Figure) may be the preferred approach.[8] However, there is also further debate around which is the preferred 2-stent technique when an upfront 2-stent approach is adopted.

Previously published bifurcation trials comparing provisional versus 2-stent strategy approaches, as well as different techniques either in comparison to each other or to the provisional approach have multiple caveats such as strict inclusion criteria that exclude many of the types of multimorbid patients encountered in routine clinical practice, variable inclusion of true versus nontrue bifurcations, significant heterogeneity in the use of stent optimization techniques such as proximal optimization technique, intravascular imaging, final kissing balloons, and variable use of newer generation drug-eluting stent platforms. This makes comparison across studies difficult, particularly in network meta-analyses where the comparative efficacy of several interventions often depends on indirect comparisons obtained through one or more common comparators that will be highly heterogenous.

While recognizing the limitations of such analyses, in this issue of the *Journal of the American Heart Association (JAHA)*, Park et al. have undertaken a network meta-analysis of 29 contemporary bifurcation randomized controlled trials including a total of 8318 patients using frequentist and Bayesian techniques to

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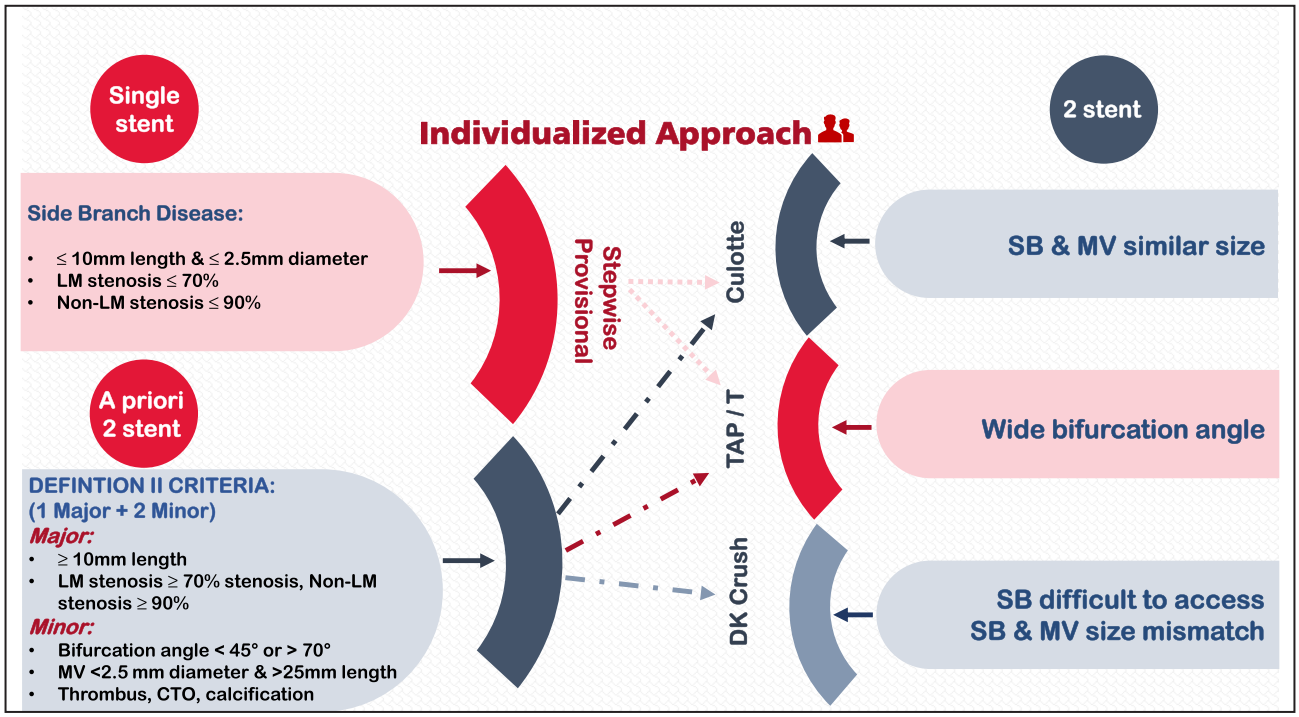

Figure. Selection of bifurcation strategy (true bifurcation 1,1,1 or 1,0,1 or 0,1,1).
CTO indicates chronic total occlusion; DK, double kissing; LM, left main; MV, main vessel; SB, side branch; and TAP/T, T and small protrusion/T-stenting.

compare provisional versus 2-stent approaches and define the optimal 2-stent technique. The analysis is well conducted and provides an in-depth overview of both the different trials in this arena as well as the variability in trial designs, lesion characteristics and disease distribution, heterogenous populations recruited, and wide variation in pharmacological regimes used, techniques employed in relation to intravascular imaging, final kissing balloon, proximal optimization technique, and stent platforms used.[9]

The authors report no significant differences in all-cause mortality, cardiac death, MACE, MI, stent thrombosis (ST), target lesion revascularization (TLR), and TVR between provisional and 2-stent approaches. A subgroup analysis undertaken in accordance with one of the currently accepted components of complexity using DEFINITION II criteria showed that 2-stent strategies were associated with reduced cardiac death (risk ratio [RR], 0.60; 95% CI, 0.40–0.90), MACE (RR, 0.68; 95% CI, 0.50–0.93), TLR (RR, 0.55; 95% CI, 0.39–0.78), and TVR (RR, 0.58; 95% CI, 0.36–0.95) compared with the provisional approach when the lesion length in the SB was ≥10 mm.

When comparing different 2-stent techniques and the provisional approach, the authors report significantly lower rates of cardiac death (RR, 0.57; 95% CI, 0.38–0.84), MACE (RR, 0.50; 95% CI, 0.39–0.64), MI (RR, 0.60; 95% CI, 0.39–0.90), ST (RR, 0.50; 95% CI, 0.28–0.88), TLR (RR, 0.44; 95% CI, 0.33–0.59), and TVR (RR, 0.48; 95% CI, 0.34–0.66) with the double kissing (DK) crush technique. Interestingly, T-stenting/T and small protrusion (TAP) technique, which are the simplest and most commonly adopted 2-stent techniques particularly during bailout, had a higher rate of ST (RR, 2.37; 95% CI, 1.02–5.51). Finally, comparing the different 2-stent techniques the authors report DK crush was associated with lower risk of cardiac death, MACE, MI, ST, TLR, and TVR compared with the crush technique and lower risk of MACE, MI, ST, TLR, and TVR compared with the culotte technique and also better outcomes compared with dedicated bifurcation stents and the T/TAP technique. These findings are consistent with findings from the DKCRUSH II, III, and V trials and persisted when analyzing LM and non-LM disease.[10–12]

Nevertheless, there are a number of caveats that are needed to place these findings into context. Although the better outcomes associated with a 2-stent approach in SB where lesion length was ≥10 mm would at first sight be consistent with the findings of the DEFINITION II trial, the authors did not have access to individual patient data and so are able to analyze trial data only by mean SB lesion length in the overall population rather than at the individual patient level. Furthermore, the findings are confounded by differences in 2-stent techniques used between

the groups of trials where SB lesion length was either ≤10 or ≥10 mm and year of publication (where the latter group are more contemporary trials using more contemporary stent platforms, intravascular imaging, and proximal optimization technique more commonly).

Comparisons of outcomes among the different 2-stent approaches in this analysis are by necessity confounded by the publication level data used. This is particularly relevant for many of the non-DK crush trials that included more than 1 bifurcation technique in the 2-stent arm, where outcomes were attributed by the authors to the predominantly used technique in that study. This is particularly problematic in trials such as BBC ONE where culotte was used in 68% of cases (crush in 30% of cases), EBC MAIN where culotte was barely used in more than half of cases (culotte 53%, T/TAP 32%), and NBBS IV (Nordic Baltic Bifurcation Study IV) where culotte was used in 66% of cases and yet outcomes from all 3 of these trials were "assigned" to the culotte technique.[6,13,14] Similarly, the crush technique accounted for only 50% of cases in the NBBS and yet data from the 2-stent approach in this trial were assigned to the crush technique. The finding that T/TAP technique was associated with worst outcomes of all the 2-stent techniques studied is surprising and may relate to the fact that 2 of the trials used to inform this analysis are close to 20 years old, used dual antiplatelet therapy for only 3 months, and were undertaken in an era before proximal optimization technique technique that has been show to improve bifurcation outcomes was first described, where intravascular imaging was not used and first-generation Cypher drug-eluting stents were used.[15–17] Robust contemporary randomized data for T/TAP are lacking to guide current practice and therefore the findings of this analysis in relation to T/TAP based on older data, using non-contemporary optimization techniques and obsolete first-generation drug-eluting stent platforms, are difficult to interpret.

The frequentist analysis certainly suggests that the more complex DK crush technique is superior in terms of hard outcomes as well as TLR and TVR to both provisional and other 2-stent approaches. A point to bear in mind is that many of the DKCRUSH trials that studied outcomes of the DK crush technique such as the DKCRUSH V trial used expert operators, where participating primary operators were required to have performed >300 percutaneous coronary interventions/year for 5 years, including at least 20 LM percutaneous coronary interventions per year. In addition, each operator performed 3 to 5 DK crush cases, which were reviewed by the steering committee before they were allowed to recruit into the study. It is unclear whether the outcomes associated with the DK crush technique observed in these trials can be replicated in the real world by operators who are less experienced than the highly selected group of operators in the DKCRUSH series of trials.

So where does this leave us? The findings of Park et al. support the findings of the DEFINITION II trial whereby 2-stent approaches may be better for more complex groups of lesions than the provisional approach and that outcomes of the DK crush technique are favorable in comparison to other 2-stent approaches. Nevertheless, the findings of Park do not mandate a one-size-fits-all approach. Given the wide range of bifurcation lesions routinely encountered in clinical practice, we believe an individualized approach that takes into account the complexity of the bifurcation and experience of the operator is ideal (Figure). The analysis by Park and colleagues highlights the heterogeneity of bifurcation techniques. It also emphasizes the lack of contemporary data for many of the most common 2-stent bifurcation strategies, including the T-stent and TAP technique. This analysis should serve as a call to generate the highest level of evidence for the optimal treatment of bifurcations using a more personalized approach; one size really does not fit all, particularly in bifurcations.

ARTICLE INFORMATION

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Disclosures

None.

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