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Commentary on the TRYTON Dedicated Bifurcation Stent: 5-Year Clinical Outcomes

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Bifurcations constitute up to 20% of all percutaneous coronary interventions. Both the NORDIC I and British Bifurcation Coronary trials compared a two-stent strategy with main vessel (MV) stenting and provisional stenting of the side branch (SB). They consistently revealed a higher peri-procedural rate of myocardial infarction (MI) in the two-stent strategy, making provisional stenting the default strategy [1,2].

Nevertheless, many patients will require a two-stent a strategy for bailout or true bifurcations involving a large SB. Challenges remain in the simplification and widespread adoption of the different two-stent techniques. As such, the TRYTON dedicated bifurcation technology was designed. The randomized pivotal TRYTON trial examined this stent in *de novo* true bifurcations. The primary endpoint, powered to non-inferiority, was target vessel failure (TVF) at nine months. This was defined as a composite of cardiac death, target vessel MI, and clinically driven target vessel revascularization (TVR). The secondary endpoint, powered for superiority, included SB restenosis at nine months, procedure success, target lesion revascularization (TLR), stent thrombosis and absence of in-hospital major adverse cardiac events (MACE). The results revealed a 17.4% TVF (driven by peri-procedural MI) in the TRYTON stent arm and 12.8% in the provisional stent arm. There was no statistical difference in the secondary endpoint of binary late restenosis. Several conclusions can be drawn. Firstly, it did not meet its primary endpoint of non-inferiority with regard to TVF. Secondly, SB restenosis, although numerically lower with the TRYTON stent, did not reach statistical significance. Subgroup analysis suggested that both TVF due to peri-procedural MI and non-significant SB restenosis may have been due to enrollment of patients with SB smaller than 2.25 mm, which was an exclusion criterion for the initial study design. Both strategies were safe, with low stent thrombosis and cardiac death rates [3,4]. Based on an *ad hoc* analysis of the pivotal trial, the investigators conducted a prospective extension confirmatory trial that only enrolled bifurcations with SB > 2.25 mm. This met the non-inferiority primary endpoint, with a peri-procedural MI of 10.5% (lower than the reported 11.9% rate for the provisional arm in the pivotal trial). This led to the US Food and Drug Administration approval of the TRYTON stent for treatment of bifurcation lesions involving large SBs.

The primary limitation of the initial pivotal and confirmatory studies was the short follow-up. This observational cohort addresses long-term outcomes at five years post-TRYTON stent implantation. The primary endpoints addressed were major adverse cardiac events (MACE), major adverse cardiac and cerebral event (MACCE) and all-cause mortality at 5 years. Sub-group analysis of diabetic patients and small SBs was also described.

The reported results at five years demonstrate a low rate of non-hierarchial major adverse cardiac events (MACE) (9.8%) and non-hierarchial major adverse cardiac and cerebral event (MACCE) (13.9%) [5]. These results appear to be more positive than those at nine months. It is important to acknowledge that the definition of MI has changed since the initial TRYTON pivotal trial, which used Q waves and CK-MB measurements. This cohort included a mixed definition of MI that included the old definition and the new Society for Cardiovascular Angiography and Interventions definition in some of the centers [6]. The non-uniform definition of MI could account for the reported reduction in major adverse cardiac events (MACE) at five years. Comparing these data to trials such as the Nordic Bifurcation Study's five-year outcomes has little clinical relevance today. Nordic investigators used a first-generation Cypher stent that is no longer available for clinical use [7]. More contemporary trials addressing bifurcation strategies include the DKCRUSH-V and CELTIC trials. They suggest an *a priori* two-stent strategy is superior to provisional stenting in true bifurcations. The CELTIC trial employed the Culotte technique using new-generation everolimus-eluting stents in Medina 1,1,1 bifurcation lesions. The primary endpoint, a composite of death, MI, TVF, stroke and binary restenosis at nine months, was 16% and 19%, respecitvely. Of all the two-stent strategies, Culotte closely resembles the TRYTON deployment

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technique. The DKCRUSH-V study employed an *a priori* two-stent strategy for *de novo* distal left main (Medina 1,1,1 or 0,1,1) disease using the latest-generation drug-eluting stents. It was also guided by intravascular ultrasound in 41% of the interventions. The primary endpoint of TLF, cardiac death, and TLR at 12 months was 5% for DKCRUSH and 10.7% for provisional stenting [8,9]. These contemporary trials raise several important questions not addressed by the TRYTON trials including this five-year outcome study: namely, the potential superiority of a two-stent strategy in true bifurcation disease, treatment of left main bifurcation disease, utility of intracoronary imaging to guide revascularization, the adoption of a proximal optimization technique Proximal Optimisation Technique (POT), as recommended by the latest European Bifurcation Consensus Document, and the duration of dual antiplatelet therapy [10]. It is noteworthy that the TRYTON deployment technique mandates proximal balloon dilatation Proximal Optimisation Technique (POT) before re-crossing with the wire.

Subgroup analyses addressed the size of the SB and diabetes. Diabetics constituted only 19.7% of the total studied population. They had a higher rate of TLR, cardiac death and bleeding. This may be confounded by the fact that they also had a higher rate of other atherosclerotic cardiovascular risk factors, including hypertension and hyperlipidemia. It is not apparent if they had smaller-size SB. Often, diabetic patients have diffuse atherosclerosis, which was not reflected in this trial. The lesion type and location were not statistically different in diabetics compared to non-diabetics. A question to consider is whether the event rate would change with better glycemic control using the novel anti-diabetic agents reported to have positive cardiovascular outcome data. Additionally, introduction of tight lipid control with intensive therapy addressed in the recent American Heart Association/American College of Cardiology Lipid Management Guidelines may impact overall major adverse cardiac events (MACE).

Small SB, found in 68.8% of the study population, showed no difference in major adverse cardiac events (MACE) or major adverse cardiac and cerebral event (MACCE) at five years. This is in contradistinction to the initial randomized trial demonstrating a higher TVR in the TRYTON arm (4.7%) compared to the provisional stent arm (3.6%). This comes as a surprise given that it is a bare metal stent. The investigators explain that it is due to the updated definition of MI (discussed above) and using a cutoff of 2.5 mm for the SB. Hence, TVF in the TRYTON and provisional arms was 11.3% and 15.6%, respectively. In the initial trials, the TRYTON stent was intended for use in bifurcations with a large side branch >2.5 mm. Similar to the Absorb Registry, in the pivotal trial, up to 60% of the treated SB were smaller than intended, resulting in higher clinically driven TVF. Unlike the five-year results, these were based on quantitative coronary analysis (QCA).

The results obtained represent those from a non-randomized cohort. The dataset is multi-centric, making inter-observer variability in the visual assessment of the stenosis a notable limitation. QCA was not uniformly performed in all participating centers. Additionally, operator expertise cannot be ascertained across multiple centers. Since routine follow-up angiography was not mandated for the study population, only clinically driven TVF can be extracted from the data.

Overall, the five-year outcomes of the TRYTON technology are promising. We remain in need for a randomized trial that standardizes adjunctive risk modifying medical therapy, antiplatelet regimen, mandates intracoronary imaging at the time of deployment, uses QCA at a core lab for stenosis assessment, and establishes uniform definitions of MI. Furthermore, it is important to evaluate its performance in left main disease, diabetes, and various clinical presentations, including acute coronary syndromes.

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