JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 9, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.02.038

EDITORIAL COMMENT

In-Stent CTO, Not as Easy as it Looks*

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Percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) represents the most technically challenging procedure in contemporary interventional cardiology (1). Although large, definitive randomized trials are lacking, a growing body of evidence suggests that successful percutaneous CTO revascularization relieves symptoms, improves left ventricular systolic function, reduces the need for surgical coronary bypass, and, in the context of complete coronary revascularization, may improve survival (2).

Historically, the success rate of CTO PCI has been approximately 70% (3). More recently, with the use of the "hybrid" approach for the percutaneous treatment of CTOs, success rates continued to improve and led, in the latest studies, to success rates within the 90% range (4).

Despite these improvements, specific patient and lesion subsets still represent a challenge. One such lesion subset is in-stent CTOs (IS-CTOs), which have traditionally been associated with suboptimal procedural success rates (63% to 71%) (5). In more recent experience, such as that shown in the PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) registry, procedural success rates of IS-CTO PCI have improved and, although numerically lower, were comparable to de novo CTO PCI (86.0% vs. 90.3%; p = 0.31) (6). While these recent findings are encouraging, IS-CTO remains an important concern considering that CTO-PCI of in-stent occlusive segments has been identified as an independent predictor of the need for repeat revascularization after CTO PCI (7).

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In this issue of *JACC: Cardiovascular Interventions*, Azzalini et al. (8) explore the procedural and long-term outcomes of percutaneous coronary intervention for IS-CTOs. They analyzed a total of 991 procedures that were performed in 899 patients by experienced CTO PCI operators (>80% success rate) between January 2009 and December 2015 in 3 different high-volume PCI centers. The final analysis compared 111 IS-CTOs with 788 de novo CTOs. The prevalence of IS-CTO PCI for that period was 12.3%, which is comparable to that encountered in the published data. Baseline clinical, angiographic, and procedural characteristics as well as clinical outcomes on follow-up were compared between the 2 groups. After multivariate Cox regression, although IS-CTO was not associated with lower procedural success, it was found to be independently associated with a higher risk of major adverse cardiac events (MACE) (driven by target vessel revascularization) on follow-up (hazard ratio: 2.16; 95% confidence interval: 1.18 to 3.95; p = 0.01). This finding is not unexpected, as it is well known that PCI for non-occlusive in-stent restenosis, even in the era of DES, yields inferior outcomes compared to PCI for de novo lesions (9,10).

The strengths of the current report include the large sample size and the availability of data on long-term clinical outcomes (median follow-up was 471 days), which makes this observational study very relevant to the contemporary interventional cardiologist. Moreover, the procedural success rates of IS-CTO in this study are similar to other large registries such as the PROGRESS-CTO registry and showcases the improvement in overall success rates of CTO-PCI in the last few years. Unfortunately, the

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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use of intravascular ultrasound or imaging modalities was quite low (12.9% overall) in this study. This represents a missed opportunity to shed more light on the mechanisms of IS-CTO, as well as potentially improving procedural success and long-term outcomes. One of the strategies that has consistently been associated with better procedural and even clinical outcomes in CTO-PCI, is intravascular ultrasound-guided PCI (11).

There are different anatomic variations in IS-CTO. The easiest subtype to treat is one in which the CTO's proximal and distal caps are within the stent. In this situation, wires and particularly, the CrossBoss device (Boston Scientific, Marlborough, Massachusetts), have a high success rate in crossing the occlusion. The toughest subset is one in which the CTO's proximal and distal caps are proximal and distal to the stent itself.

There is a common misconception that IS-CTO may be easier to cross than de novo CTOs due to the fact that the stent is more readily visible with IS-CTO and, therefore, may remove some of the ambiguity regarding vessel assessment to facilitate wiring and tracking of the CTO segment. However, the current study supports prior reports (6) that this may not be the case, but only with additional expertise and improvements in technology can the results of IS-CTO be comparable to de novo CTOs. Possible explanations for the increased difficulty with IS-CTO are the following: 1) occluded stents, especially DES, tend to be grossly underexpanded, which makes wiring through the stent much more difficult since the wire tends to follow the path of least resistance and enter the subintimal space at the proximal cap; 2) there may be a stent fracture or disruption of the original stent architecture or the mere presence of a metallic scaffold may make wiring and delivery of equipment challenging, especially in a tortuous vessel segment; and 3) CTOs of long chronicity are often associated with hard fibrous tissue and high calcium content, which once again pose unique challenges to the operator.

Given the target vessel revascularization rate of IS-CTO (16.7% in this study), it is imperative that realistic expectations be set with patients upfront. However, if IS-CTO PCI is to be undertaken, it imperative to strive for the best procedural outcomes through the use of multimodality imaging to understand the etiology of the prior stent failure and subsequently use adjunctive methods to optimize stent expansion, such as laser or rotational atherectomy. The use of drug-eluting balloons, current-generation drug-eluting stents, or even a combination of both may also be considered, although data are lacking. The use of brachytherapy is a potential additional option, but its availability is limited to a few centers worldwide. Nevertheless, newer and more innovative technologies are clearly needed. Finally, in some circumstances, such as IS-CTO of long stents with poor outflow or small diameter single-vessel runoff, it may be more prudent to allocate the patient to medical therapy.

In our experience, when counseling patients who have undergone successful IS-CTO PCI it is imperative that they seek immediate medical evaluation from their interventionalist as soon as they have any recurrence in symptoms. Frequently in these situations, the patient may be experiencing a focal, nonocclusive lesion, which may be easier to treat than one from a delayed presentation, which is likely to have a recurrent, long IS-CTO.

In conclusion, despite the encouraging procedural success rates encountered in the last few years in high-volume CTO centers, and as this study shows, acceptable long-term outcomes, IS-CTO PCI remains a challenging lesion subset and has to be dealt with the utmost care and precaution. However, this lesion subset can and should be tackled by taking the extra time and effort to apply meticulous PCI technique during the index procedure.

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KEY WORDS chronic total occlusions, chronic total occlusions percutaneous interventions, in-stent restenosis