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EDITORIAL COMMENT

Percutaneous Revascularization of Chronic Total Coronary Occlusions

Are the Benefits Underappreciated?*

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Chronically totally occluded coronary arteries (CTOs) are common and represent the most technically challenging subset of lesions in contemporary interventional cardiology (1). The presence of a CTO on coronary angiography has a powerful impact on treatment decisions, leading to more frequent referral to coronary artery bypass grafting (CABG) and medical therapy when compared with when only stenotic lesions are present.

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In carefully selected patients, successful percutaneous CTO revascularization leads to a meaningful reduction in symptoms (2–7), improved left ventricular function (8), and a reduction in the need for subsequent CABG (9). In addition, a mounting number of registry studies (5–7,9–20) (Table 1) demonstrate, with a few exceptions, that successful CTO revascularization is associated with improved survival (9,18) particularly in the setting of multivessel disease when complete revascularization is achieved (4).

In this issue of *JACC: Cardiovascular Interventions*, Jones et al. (19) report their single-center experience with long-term survival in patients with chronic stable angina who had undergone attempted percutaneous CTO revascularization. Patients (n = 836) who underwent CTO percutaneous coronary intervention (PCI) between 2003 and 2010 were followed for up to 5 years (median of 3.8 years). They achieved approximately a 70% acute success rate, with low in-hospital major adverse cardiac events (2.1% in successful cases, and 3.1% in failures). The authors were able to capture all deaths through the U.K. Office of National Statistics. Procedural success compared with failure was associated with improved all-cause mortality at 5 years of follow-up (4.5% vs. 17.2%, $p < 0.0001$), a survival on par with non-CTO PCI (6.7%). Drug-eluting stent use (76.1% of cases) was associated with a trend toward improved mortality when compared with patients treated with bare-metal stents. Furthermore, after regression analysis procedural success remained a powerful independent predictor of survival (hazard ratio: 0.28, 95% confidence interval: 0.15 to 0.52). In addition subsequent target vessel revascularization (CABG and PCI) was significantly lower for patients with successful CTO PCI versus those with unsuccessful CTO PCI (11.5% vs. 22.1%, $p < 0.0001$). Previous PCI and CABG were more frequent in the unsuccessful group, but otherwise the reported clinical and demographic characteristics were well matched between the 2 groups.

Despite the acknowledged limitations of selection bias impacting both the initial treatment selection as well as subsequent treatment after unsuccessful CTO PCI, inherent to all observational registry studies, the rigorous follow-up in this report is a welcome addition to the existing data indicating that CTO revascularization improves survival (Table 1). However, one must be mindful that all registry data are subject to potential confounders, for example: 1) complications related to CTO PCI failure can lead to death (20) (unlikely in this report, given the low in-hospital major adverse cardiac events); 2) PCI failure can be a marker of disease burden and other comorbidities such as frailty and chronic kidney disease; and 3) other diseases that shorten lifespan might limit the vigor of the CTO attempt. A more detailed understanding of the differences in causes of death in the Jones et al. report (19) could have lent more insight to this important issue.

It is of interest that Jones et al. (19) demonstrated this survival benefit in a population predominantly comprising patients with single-vessel disease (SVD) with the majority of the treated vessels involving the right coronary artery. The Kaplan-Meier curves diverge early and continue to diverge throughout the duration of the study, which is similar to other recent reports (18). Other studies suggesting survival impact include the presence of left anterior descending coronary artery CTO in SVD (21) or the presence of a CTO in post-myocardial infarction (MI) patients (22).

The possible mechanisms of survival benefit after successful CTO revascularization are not fully understood. However, several possibilities can be considered: 1) reduction in future arrhythmic events (23); 2) improvement in left ventricular function (8); 3) reduction in ischemic burden (24); 4) potentially better tolerance of future MIs in a non-CTO artery (22); 5) less referral to CABG (9); and 6) reduced incidence of future acute coronary syndromes, although in 2 large recent reports, there were differences in

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Table 1. Effect of Successful Versus Failed CTO PCI in All-Cause Mortality During Long-Term Follow-Up

First Author, Year (Ref. #)	Follow-Up (yrs)	PCI Success (n)	PCI Failure (n)	OR/HR, 95% CI
Finci et al., 1990 (5)	2	100	100	OR: 1.70, 0.40–7.32
Warren et al., 1990 (10)	2.6	26	18	N/A
Ivanhoe et al., 1992 (6)	4	317	163	OR: 0.21, 0.05–0.83
Angioi et al., 1995 (11)	3.6	93	108	OR: 0.37, 0.10–1.40
Noguchi et al., 2000 (12)	4.3	134	92	OR: 0.28, 0.11–0.72
Suero et al., 2001 (13)	10	1,491	514	OR: 0.67, 0.54–0.83
Olivari et al., 2003 (7)	1	289	87	OR: 0.19, 0.03–1.14
Hoye et al., 2005 (14)	4.5	567	304	OR: 0.52, 0.32–0.84
Drozd et al., 2006 (15)	2.5	298	161	OR: 0.74, 0.23–2.37
Aziz et al., 2007 (16)	1.7	377	166	OR: 0.31, 0.13–0.76
Prasad et al., 2007 (17)	10	914	348	OR: 0.82, 0.62–1.08
Valenti et al., 2008 (4)	1	344	142	OR: 0.38, 0.19–0.77
de Labriolle et al., 2008 (20)	2	127	45	OR: 1.25, 0.25–6.27
Mehran et al., 2011 (18)	2.9	1,226	565	HR: 0.63, 0.40–1.0
Jones et al., 2012 (19)	3.8	582	254	HR: 0.28, 0.15–0.52
Joyal et al., 2010* (9)		5,056	2236	OR: 0.56, 0.43–0.72

Successful PCI is associated with large reductions in the risk (OR) of death over several years. *Meta-analysis including 13 studies (4–7,20,25–32).
CI = confidence interval(s); CTO = chronically totally occluded coronary artery; HR = hazard ratio; N/A = not applicable; OR = odds ratio(s); PCI = percutaneous coronary intervention.

subsequent MI during the follow-up period between these subgroups (9,18).

The fact that the presence of a CTO is one of the major anatomic predictors for referral to CABG leads one to conclude that a large majority of cardiologists believe CTOs should be revascularized. However, in the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial, approximately one-third of the CTOs referred for CABG were not surgically revascularized (25). Thus it should not be taken for granted that full revascularization will occur simply by referring a patient with CTO for CABG.

Three main arguments against CTO PCI include: 1) the negative results of the OAT (Occluded Artery Trial) (26); 2) the assumption that well-developed collaterals supplying the CTO territory provide adequate blood flow to the myocardium at risk under situations of increased oxygen demand; and 3) the lack of a randomized trial that would definitively address the question of whether successful CTO PCI improves survival.

In the first instance, OAT was by design a non-CTO trial (26), because the mean period from MI to randomization was 8 days, whereas by definition chronicity is defined by its presence for a minimum of 3 months. A closer look at the population in OAT reveals that the vast majority of the patients (83%) had either mild or no symptoms and, of the 27% who had a functional ischemic assessment (the balance were presumed to have "completed" infarcts), 90% had either mild or no ischemia. In addition, with 82% of the patients having SVD (50% right coronary artery), it is no surprise that there was no survival benefit. On the second point, Werner et al. (27), in an elegant study, assessed the collateral fractional flow reserve in 62 patients with CTOs, after successful wire crossing. This study found not a single patient with a collateral fractional flow reserve >0.80 (the current accepted ischemic threshold), suggesting that although collaterals might be adequate for preservation of myocardial viability, they rarely prevent stress-induced ischemia. This of course leads to the paradox that, under current appropriate use criteria, PCI is appropriate for a 99% proximal left anterior descending coronary artery but not for 100% (28).

Several recent publications have shown that with contemporary techniques consistently high success rates can be achieved with acceptable rate of complications in very complex lesions (29,30). So there is good news: we have the right setting for a U.S.-based randomized trial. But designing such a trial raises many issues. Chronically totally occluded coronary arteries occur in a variety of scenarios: SVD, multivessel disease, associated with different degrees of ischemic burden, in patients with chronic stable angina, asymptomatic patients with abnormal function studies, and acute coronary syndromes. Which patient population do we need to focus on? Are mortality and/or MI the only primary endpoints of significance? Are there really enough expert centers that could participate in the trial and complete it in a reasonable time period? Who would fund such an expensive trial?

The Euro CTO Group and a group from Korea (Decision CTO) are currently randomizing patients with chronic stable angina to PCI versus medical therapy with combined primary endpoint of mortality, MI, stroke, and revascularization at 36 months. The investigators should be commended for undertaking such a Herculean task; their results

are highly anticipated, and the progress of the trial will be very informative with regard to the feasibility of a similar U.S.-based trial. Even in the best-case scenario the results from these trials are not expected before 2018.

How should patients with CTOs be treated until then? On the basis of the available evidence, it is reasonable to revascularize symptomatic CTOs, CTOs associated with significant ischemic burden (>10% of myocardium at risk), and CTOs in the setting of multivessel disease to achieve complete revascularization and to improve left ventricular function.

In summary, when confronted with a CTO, given the current body of knowledge, should not the patient be given the benefit of the doubt? Unfortunately, in the contemporary environment of searching for definitive evidence of cost effectiveness before recommending a procedure, weighing the odds of benefit from the perspective of the patient is not in vogue. A fair and complete presentation of the state of the art can empower patients and allow them a stronger voice in the decision-making process.

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