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EDITORIAL COMMENT

# Chronic Total Occlusion Intervention

## The Case for More Evidence*

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The past decade has witnessed significant improvement in the success rates of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) with the introduction of advanced, specialized techniques (1). As procedural success rates of CTO PCI improved, so did clinical investigations exploring its application and potential benefits. Naturally, it was hoped that successful revascularization to a viable, ischemic myocardium would improve its function and possibly patient survival. Several international registries sought to better understand techniques, outcomes, and variables associated with success. Although observational and single-arm studies have been many, randomized trials addressing this question are rare.

Nonrandomized studies have suggested improved survival in patients undergoing successful PCI of CTO compared with those treated medically or in whom PCI has failed (2,3). In addition to reduction in ischemic burden, such benefit has been theorized to be related to an improvement in left ventricular function. Kirschbaum et al. (4) used magnetic resonance imaging to demonstrate improvements in segmental wall thickening and left ventricular ejection fraction (LVEF) 5 months and 3 years after successful revascularization of a CTO involving viable myocardium. In an observational study, Galassi et al. (5) demonstrated significant improvement in LVEF after CTO revascularization in patients with baseline LVEFs of <35%.

The first contemporary randomized trial to test whether LVEF might improve after CTO revascularization, the EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Segment Elevation Myocardial Infarction) trial (6), yielded negative results. In that trial, patients who were stable after successful revascularization of the infarct-related artery underwent randomization to PCI versus medical management of a non-infarct-related CTO. Although there was no improvement in LVEF at 4 months, there was a signal for positive results in the subset of patients with left anterior descending CTOs. There was no assessment of baseline viability or ischemia in the EXPLORE trial, and the adjudicated success rate was 73%, less than what is currently achieved in experienced hands. Two other randomized trials, the EURO-CTO (A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) (7) and the recently presented DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusions), tested angina relief and quality of life as endpoints. Although the EURO-CTO trial showed improvement in health status as assessed using the Seattle Angina Questionnaire, the DECISION-CTO trial was essentially negative. Neither trial showed a difference in major adverse cardiovascular events. Both trials recruited patients with multivessel disease and with relatively low symptom severity at baseline.

On the heels of the aforementioned data comes the REVASC (A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion) trial, published in this issue of *JACC: Cardiovascular Interventions* (8). The primary goal of the REVASC trial was to investigate

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the effect of CTO PCI on left ventricular function, as assessed by changes in cardiac magnetic resonance imaging-derived segmental wall thickening at 6 months after PCI. The investigators randomized 205 patients to CTO PCI versus medical management. Treatment of other non-CTO lesions was at the discretion of the treating physician. At 6 months, there was no difference in segmental wall thickening change or in the LVEF between the 2 groups. Clinically driven repeat revascularization was less frequent in the CTO PCI group at 1 year.

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How should one interpret the results of the REVASC trial? Would it be reasonable to conclude that the REVASC and the EXPLORE trials, leading to similar conclusions, have provided the proof that left ventricular function does not improve after PCI CTO? Should that dampen the interventional community's enthusiasm to continue to push for CTO revascularization? Before these questions are answered, one needs to interpret the results in light of the recruited patient population, the implemented treatments, and the measured outcome.

First, and similar to the other CTO randomized trials, the REVASC patients had multivessel disease; 56% of patients had 3-vessel disease. Importantly, there was a considerable imbalance in non-CTO revascularization between the groups: 60% of the non-CTO PCI group had PCI of non-CTO segments compared with 16% in the CTO PCI group. In the former group, more than two-thirds of PCIs were of arteries that provided collateral paths to the CTO segment (donor arteries), potentially alleviating some of the ischemia in the occluded territory. To what extent such an imbalance could have played a role in tampering with the outcome remains to be determined. In fact, when the investigators limited the analysis to those patients with a single CTO lesion and no other diseased vessels, the PCI group showed an improvement in wall thickening compared with the medically managed group.

Second, baseline LVEF was >50% in the REVASC patient population. With a relatively healthy ventricle at baseline, it is hard to prove additional benefit from revascularization. Had the study population consisted of patients with reduced ejection fractions, one might have seen different results, in line with an observational study published by the same investigators (5) that revealed a significant improvement in LVEF after revascularization of CTO in patients with ejection fractions <35%.

Third, CTO PCI in REVASC was not guided by demonstrable viability or ischemia in the CTO territory, a limitation already seen in the EXPLORE trial. In fact, 23% of the CTO segments were nonviable and thus not expected to benefit from revascularization (4). The reader is also left without much information about the presence and location of objective ischemia on invasive or noninvasive study. The trial reflects the interventional cardiology practice prevalent more than 10 years ago, when the trial was conceived, when interventions were guided mostly by angiography.

Given these limitations, and although the REVASC trial is an important addition to the published research given the paucity of large randomized trials in the CTO field, it does not provide the final answer to the question of improvement in ventricular function after CTO PCI. To answer such a question will require a randomized trial in patients with low LVEFs and documented viability and/or large areas of ischemia in the CTO territory. As it is uncommon for an isolated right coronary artery or nondominant left circumflex CTO to be responsible for a significant impairment in left ventricular systolic function in the absence of mitral regurgitation, it is not reasonable to expect an intervention on such an isolated lesion to result in significant improvement in LVEF. Thus, a randomized trial will also have to include patients with left anterior descending or combination right coronary and circumflex artery occlusions, preferably treated by high-volume operators with proven high success and low complication rates. Until such a trial is performed, which at this point seems quite unlikely, the interventional community should not be treating CTO with the sole indication of improving left ventricular function or reducing major adverse events. As of 2018, CTO PCI should be performed only in patients with viable myocardium who continue to have symptoms on medical management, after other ischemic non-CTO segments have been treated, and with the sole goal of symptom relief.

If we are not treating CTO to improve ventricular function, do we need additional evidence to prove that treating ischemic myocardium in symptomatic patients relieves angina and improves quality of life? In the era of the ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial (9), the answer is probably yes. Appropriate patient

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selection (moderate or severe symptoms on medical management, absence of other stenoses) and a sham control arm, as in the ongoing SHINE-CTO (Sham-Controlled Intervention to Improve QOL in CTOs; NCT02784418) trial, will be important to answer this question.

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