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EDITORIAL COMMENT

Chronic Total Occlusion Trials

A Step in the Right Direction*

Manesh R. Patel, MD, J. Antonio Gutierrez, MD

Coronary chronic total occlusions (CTOs) are routinely found in 18% to 52% of patients undergoing coronary angiography (1-6). Despite their prevalence, only 8% to 15% of CTOs are treated with percutaneous coronary intervention (PCI) (7). Over the past decade, advances in both interventional technique and tools have led to higher rates of procedural success, among experienced operators, without sacrificing patent safety (8). Regardless of such improvements, when compared to non-CTO PCI, the rate of CTO PCI in the United States remains stagnant. The key barriers limiting the transition of CTO PCI from a niche to conventional procedure are widespread interventional expertise and a limited amount of randomized trial-generated evidence to support its use. The majority of current data on CTO PCI is primarily derived from registry and meta-analyses; which suggest the benefit of CTO PCI to reside in the amelioration of anginal symptoms, with improvement in exercise capacity and left ventricular ejection fraction (LVEF) (9-12).

SEE PAGE 2158

In this issue of *JACC: Cardiovascular Interventions*, Galassi et al. (13) present a prospective, longitudinal observational multicenter study in which symptomatic patients underwent CTO PCI (13). Revascularization was only performed if viable myocardium of hemodynamic significance was found in the territory of the respective CTO. Outcomes were presented according to degree of left ventricular function (≥50%, 35% to 50%, and ≤35%), and at 2 years, major cardiac and cerebrovascular event-free survival were similar among the 3 cohorts, although notably reduced in the lower ventricular function groups (86%, 82.8%, 75.2%; all p = NS). Successful CTO PCI was associated with reduced dyspnea among patients with a LVEF ≤35% and improvement in anginal symptoms among patients with a LVEF ≥50% (13).

Galassi et al. (13) should be congratulated because they provide a few important steps forward to the field. They reaffirm that in the hands of experienced operators, CTO PCI can be executed with a high degree of success (>90%) with minimal complications (<3%) (14,15). The study is limited by the fewer patients with LVEF <35 (<10%), the intendant selection biases from observational studies analyzed with multiple comparisons, and importantly, the lost to follow-up rate of 53 patients. Nevertheless, the present study extends prior findings regarding the benefit of successful CTO PCI and left ventricular function by demonstrating a mean improvement in LVEF of >10 units in patients with a baseline LVEF ≤35%. The authors infer, that such an improvement in ventricular function has the potential to lead to improved survival, because LVEF has long been identified as a key predictor of survival in patients with ischemic heart disease (16-18). Such studies are needed for percutaneous intervention as they are present in patients with low EF going to coronary artery bypass grafting surgery.

This past year, 2 randomized trials involving CTO PCI versus optimal medical therapy (OMT) in patients in stable condition were completed; the DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion, NCT01078051) trial and the EURO-CTO trial (A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Occlusions, NCT01760083). Presented at the American College of Cardiology 2017 Scientific

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From the Duke Clinical Research Institute, Division of Cardiology, Duke University, Durham, North Carolina. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

TABLE 1 Recent CTO Studies

Trial/First Author (Ref.#)	N	Study Type	Population	Outcomes and Measures
EXPLORE (19)	304	Randomized: CTO PCI vs. no CTO PCI	• STEMI with concurrent CTO of native coronary artery • Reference vessel ≥2.5 mm • CTO PCI performed 7 days of successful primary PCI	Primary • 4-month mean LVEF and LVEDV per cardiac MRI comparable in both groups Secondary • 4-month cardiac death, MI, or CABG comparable in both groups
DECISION-CTO*	834	Randomized: CTO PCI + OMT vs. OMT	• Silent ischemia, SA, or ACS • De novo CTO in proximal to mid-coronary artery • Reference vessel ≥2.5 mm	Primary • 3-year death, MI, stroke, or repeat revascularization comparable in both groups Secondary • Quality-of-life measures were similar in both groups
EURO-CTO*	396	Randomized: CTO PCI + OMT vs. OMT	• Stable angina or anginal equivalent • CTO of native coronary artery • Reference vessel ≥2.5 mm • Myocardial ischemia in territory supplied by CTO and viability in akinetic myocardium	Primary • PCI group experienced lower angina frequency per SAQ Secondary • 1-year death or nonfatal MI comparable in both groups
Galassi et al. (13)	839	Observational: CTO PCI	• Symptomatic patients undergoing elective PCI of CTO • Inducible ischemia (10%) in CTO territory and viability • Patients subdivided into 3 groups: LVEF ≥50%, 35%–50%, and ≤35%	• 2-year cardiac death, MI, stroke, or revascularization free survival similar among all groups • Patients with LVEF ≤35% had significant improvement in LVEF following successful CTO PCI

*Not yet published in a peer-review journal.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CTO = chronic total occlusion; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SA = stable angina; SAQ = Seattle Angina Questionnaire; STEMI = ST-segment elevation myocardial infarction.

Sessions (March 17 to 19, Washington, DC), the DECISION-CTO trial found that CTO PCI + OMT to not be superior to OMT in mitigating the primary endpoint of major cardiac cerebrovascular events (MACCE) or improving the secondary endpoint of quality of life, as measured by the Seattle Angina for Questionnaire (SAQ) score, among patients with CTO lesions (Table 1). Presented at EuroPCR 2017 (May 16 to 19, Paris, France), the EURO-CTO trial found CTO PCI + OMT, compared with OMT alone, to be associated with a significant improvement in the primary endpoint of quality of life as measured by the SAQ score and no difference in the secondary endpoint of MACCE, among patients with CTO lesions. Although both studies did not show an improvement in MACCE, it is likely that the DECISION-CTO trial did demonstrate an improvement in quality of life due to the fact that patients were randomized before treatment of symptomatic non-CTO lesions. At the time of this editorial, both the DECISION-CTO and EURO-CTO trials have not been published, and all the initial trial findings are based on their respective scientific proceeding presentations.

The findings by Galassi et al. (13), and the DECISION-CTO and EURO-CTO trials spark a necessary debate regarding the optimal primary endpoint for CTO PCI trials. Many experienced CTO operators favor symptoms, such as angina and dyspnea, to be the ideal primary endpoints in such trials because these are often the driving factors for intervention. Proponents of symptomatic endpoints also argue that in light of the difficulties by both the DECISION-CTO and EURO-CTO trials in reaching the target enrollments, future trials will likely experience a similar predicament and may never uncover the true effect, if any, of CTO PCI on ischemic events due to a shortage of clinical events. It is possible that the present findings by Galassi et al. (13) may resolve this dilemma by identifying a cohort of CTO patients that stand to benefit from CTO PCI, both in symptoms and clinical endpoints: those with a LVEF ≤35%. As such, Galassi et al. have provided a strong rationale for the next era of randomized trials evaluating the potential benefits of CTO PCI. As with all interventional therapies, the onus is on the physicians, companies involved with CTO products, and patients who will need to partner and advocate for the right trials with right endpoints.

ADDRESS FOR CORRESPONDENCE: Dr. Manesh R. Patel, Duke Clinical Research Institute, Duke University Medical Center, 2400 Pratt Street, Room 0311 Terrace Level, Durham, North Carolina 27705. E-mail: manesh.patel@duke.edu.

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