JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 11, NO. 14, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Percutaneous Coronary Intervention of Chronic Total Occlusions

Conquering the Final Frontier*

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Chronic total occlusions (CTOs) are often referred to as the "final frontier" of percutaneous coronary intervention (PCI), representing the lesion subtype with (by far) the lowest procedural success rates and the most common cause of incomplete revascularization and referral to coronary artery bypass graft surgery. During my fellowship at the Mid-America Heart Institute in Kansas City, Missouri, I reviewed the PCI procedural outcomes of 971 CTO lesions in 905 consecutive patients performed by 5 expert operators between 1980 and 1989 (1). In hindsight, their technical success rate of 72% achieved solely with antegrade wire escalation is remarkable given the archaic PCI equipment of the time (poorly steerable wires that not infrequently fractured, high-profile balloons, and no support devices, atherectomy, or stents). Procedural complications included death (0.8%), myocardial infarction (0.6%), and emergency coronary artery bypass graft surgery (0.8%). The past 3 decades have witnessed remarkable improvements in CTO PCI equipment (especially guidewires, but also microcatheters, intracoronary support guides, and more) and the introduction of new techniques (antegrade dissection and re-entry and retrograde approaches), which, coupled with drug-eluting stents, the selective use of atherectomy, intravascular imaging, and optimal pharmacotherapy have markedly improved the early and late outcomes of CTO PCI. These developments were made possible by international alliances (with major contributions originating from the United States, Japan, and Europe) and close collaboration with industry to guide development of the unique tools enabling the present-day outcomes. Indeed, CTO PCI has developed into its own subspecialty of interventional cardiology, with a novel nomenclature and training requirements, worldwide member-based organizations, and dedicated live case demonstration courses.

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The current state of the art is reflected in the multicenter PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) registry study reported in this issue of *JACC: Cardiovascular Interventions* (2), describing the outcomes of 3,122 CTO PCI procedures performed in 3,055 patients at 20 dedicated centers in the United States, Europe, and Russia between 2012 and 2017. Acute technical and procedural success rates were 87% and 85%, respectively. Achieving success rates this high required facility with the 3-pronged hybrid approach (3), with successful wire crossing achieved by antegrade wire escalation, antegrade dissection and re-entry, and retrograde techniques in 46%, 19%, and 24% of cases, respectively; the initially selected CTO crossing strategy was successful in only 55% of cases. Other multicenter studies of highly skilled operators have reported similar technical success rates (e.g., 86% from the U.S.-based Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures (OPEN-CTO) registry [4], 86% from the European REgistry of Crossboss and Hybrid procedures in FrAnce, the NetheRlands, BelGium and UnitEd Kingdom (RECHARGE) registry [5], and 89% from the Japanese J-CTO registry [6]). The increase in technical success rates from 72% at Mid-America Heart Institute to 87% in the PROGRESS CTO registry is

*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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ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2018.03.031

TABLE 1 Randomized Trials of Chronic Total Occlusion Percutaneous Coronary Intervention Versus Medical Therapy

	EXPLORE (9,10)	EURO-CTO (11)	DECISION-CTO (12)
Planned number and type of patients	300 patients with STEMI status post-successful primary PCI with ≥1 non-infarct artery-related CTOs*	1,200 patients with stable CAD with ≥1 CTOs*	1,284 stable patients with CAD or ACS with ≥1 CTOs*
Total number of patients enrolled	304	396	834
Period of enrollment	November 2007 through April 2015	March 2012 through May 2015	NR (enrollment concluded September 2016)
Longest follow-up duration reported	5 yrs	12 months	5 yrs
Crossovers (excluding failed PCI)	No CTO PCI to CTO PCI: 3.2% CTO PCI to no CTO PCI: 0.7%	No CTO PCI to CTO PCI: 7.3% CTO PCI to no CTO PCI: NR	No CTO PCI to CTO PCI: 19.9% CTO PCI to no CTO PCI: 7.1%
PCI success	77% (investigator) 73% (core laboratory)	86.3%	91.1%
PCI complications	Death: 0% Stroke: 0% MI: 2.7% Tamponade: 0.7% Emergency CABG: 0%	Death: 0% Stroke: NR MI: 0% Tamponade: 1.5% Emergency CABG: 0%	NR
Primary endpoint results	CMRI LVEF and LVEDV at 4 months (superiority): no differences between groups; positive interaction noted with LAD vs. non-LAD CTO	Follow-up SAQ angina frequency and QOL improved with CTO PCI; 3 other SAQ domains not significantly different; 3-yr primary safety endpoint pending	5-yr composite death, MI, stroke, or any repeat revascularization: PCI 20.6% vs. MT 19.6% (p = 0.67); no subgroup interactions
Other outcomes	4-month MACE: PCI 5.4% vs. MT 2.6% (p = 0.25) 5-yr MACE: PCI 13.5% vs. MT 12.3% (p = 0.93)	12-month MACE: PCI 5.7% vs. MT 6.5% (p = 0.55) EQ-5D QOL scales improved more in the PCI group than the MT group	No differences in the components of the primary endpoint or follow-up SAQ AF or QOL measures

*With reference vessel diameter ≥2.5 mm.

ACS = acute coronary syndrome(s); CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CMRI = cardiac magnetic resonance imaging; CTO = chronic total occlusion; EQ-5D = EuroQol-5D; LAD = left anterior descending coronary artery; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; MACE = major adverse cardiac event(s); MI = myocardial infarction; MT = medical therapy; NR = not reported; QOL = quality of life; SAQ = Seattle Angina Questionnaire; STEMI = ST-segment elevation myocardial infarction.

especially notable given the fact that case selection was unquestionably more restrictive in the 1980s. "Back in the day" we would rarely if ever tackle a flush occlusion of the ostial right coronary artery that recanalized 10 cm distally at the crux and other CTOs that are no longer rejected. However, notwithstanding the progress achieved at dedicated centers, contemporary CTO PCI success rates among the universe of operators are lower (e.g., 59% in 22,365 patients from the U.S. National Cardiovascular Data Registry between 2009 and 2013 [7]). Higher annual CTO PCI volumes have been strongly correlated with procedural success rates in both PROGRESS CTO and the National Cardiovascular Data Registry report (2,7).

The incidence of complications in the PROGRESS CTO registry bears notice. In-hospital major adverse cardiovascular events (MACE) occurred in 3.0% of patients, including death in 0.9% and stroke in 0.3% of patients. The 1.1% incidence of myocardial infarction would likely had been higher had periprocedural biomarkers been routinely assessed. Perforation has become the most common serious procedural complication of CTO PCI and in the present series resulted in pericardial tamponade in 0.9% of patients, although rarely emergency coronary artery bypass graft surgery (0.2%). The in-hospital complication rate correlated with anatomic lesion complexity and technique (known to be higher, for example, with the retrograde approach and use of epicardial collateral vessels), but not center CTO PCI volume. Procedural complications are now more frequent after CTO PCI than non-CTO PCI (7), and along with contrast nephropathy, bleeding, radiation exposure, and costs must be taken into account when considering the risk-benefit balance of complex CTO procedures.

Acknowledging the present report as the magnum opus of CTO PCI technique, the focus now needs to shift to 1) appropriate patient selection and demonstration of clinical utility; and 2) ensuring that most patients with CTOs who can derive benefit are provided access to expert care. Potential benefits of CTO PCI include reduced ischemia and angina, improved left ventricular (LV) function and exercise capability, improved quality of life (QOL), and enhanced survival (8). Improved outcomes of patients undergoing CTO PCI were initially demonstrated from uncontrolled registries and nonrandomized comparisons of patients in whom CTO PCI was versus was not successful. Only 3 randomized trials of CTO PCI versus

conservative management have been completed (9–12), 2 of which recruited fewer than their planned number of patients (11,12) and only 1 of which is published (9,10). The design specifications and results of these trials are summarized in **Table 1**. The CTO PCI success rates in these studies ranged from 73% to 91%, and periprocedural complications occurred infrequently. Two of the 3 trials produced negative results. The EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Segment Elevation Myocardial Infarction) trial (9) was unable to demonstrate that recanalization of a CTO in a non-infarct-related artery after successful primary PCI in patients with ST-segment elevation myocardial infarction improved LV function or reduced LV volumes at 4 months. A positive interaction was present such that LV function was improved in the subset of patients undergoing PCI of an occluded left anterior descending coronary artery, but such interactions need to be cautiously interpreted when the primary endpoint is negative. There were no differences in the 5-year rates of MACE between the CTO PCI and medical therapy (MT) groups in this trial (10). 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) trial (11) did demonstrate improvement in angina frequency and QOL as assessed by the Seattle Angina Questionnaire (SAQ) 12 months after CTO PCI compared with MT, and in several additional QOL measures assessed by the EuroQol-5D instrument. MACE rates through 1 year were not significantly different between the groups, however. Finally, DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusions) trial (12) was the largest of the 3 trials (834 randomized patients) and the only study powered for clinical events, although it was (curiously) designed to demonstrate noninferiority of MT compared with CTO PCI. The 5-year rates of MACE were 26.3% with CTO PCI versus 25.1% with MT ($p = 0.67$); nor were between-group differences in follow-up QOL observed. However, crossover rates in this study were higher than the others, and the baseline SAQ angina frequency scores of >80 are consistent with enrollment of a minimally symptomatic population (13). In this regard, both DECISION-CTO and EURO-CTO trials enrolled less symptomatic patients than other registries that have reported greater QOL improvements after successful CTO PCI (4). All 3 trials also enrolled patients with multivessel disease undergoing PCI of non-CTO lesions, adverse events from which during follow-up would likely occur to a similar degree in both arms, thereby diluting the power of the trial to elicit differences between the groups.

Of note, none of these trials were sham controlled, a topic that has received a great deal of attention since the publication of The ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial (14). Placebo, nocebo, and Hawthorne effects (as well as other biases) will doubtless affect outcomes in unblinded CTO trials, especially of softer QOL endpoints. Although sham procedures are logistically challenging, they provide an important measure of quality control (and serve to quiet the naysayers). In this regard, the SHINE-CTO (SHam-controlled INtErvention to Improve QOL in CTOs trial) (NCT02784418) is an ongoing, 142-patient, single-center, sham-controlled, randomized study with a 1-month QOL primary endpoint assessed by the 7-item SAQ summary score.

Incorporating all these lessons, the ideal multicenter randomized trial would enroll only highly symptomatic patients with at least moderate inducible ischemia or wall motion abnormalities (with viability), without prior (or planned) PCI of non-CTO lesions within 1 year, with 1 or more CTO lesions involving a large myocardial territory (preferably the left anterior descending coronary artery in a high proportion), be sham controlled and include guideline-directed MT in both arms, keep crossovers to a minimum (<5%), and be powered for QOL (requiring hundreds of patients) or mortality (thousands of patients) at 1 year or later rather than MACE. The participating operators should be capable of obtaining procedural success rates approaching 90%. Technical failures (which are more likely to be accompanied by complications [2]) are a form of internal crossover that bias outcomes toward the null unless the sample size is accordingly increased. The hurdles of completing such a trial are daunting but with perseverance (and adequate funding) should be feasible for at least the QOL endpoint. Until such a definitive trial is performed, a growing choir of increasingly vocal critics doubting the use and cost-effectiveness of CTO PCI should be anticipated.

Finally, additional imperatives include implementing more widespread training to grow the numbers of expert operators and expand their geographic reach, continuing to improve PCI equipment and techniques to enhance success rates (and simplicity) for non-expert as well as expert operators,

and ultimately revise reimbursement pathways so referral considerations are no longer an impediment to all patients with CTOs receiving proficient intervention. We have a long journey ahead before the final frontier of PCI is conquered, although at last this event horizon is in sight.

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KEY WORDS complications, coronary occlusion, prognosis, quality of life, stent