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EDITORIAL

An Open (Up the Vessel) and Shut (Up the Critics) Case or Fake News?

Long-Term Outcomes Following Percutaneous Coronary Intervention of Chronic Total Occlusions

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Percutaneous coronary intervention (PCI) for stable ischemic heart disease (SIHD) has made tremendous strides over the past several decades. On the one hand, the diversity and complexity of lesions treatable with PCI has increased significantly. At the same time, our understanding of the appropriateness of PCI in SIHD has been refined with the results of trials, such as COURAGE (Optimal Medical Therapy with or without PCI for Stable Coronary Disease), ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina), FAME (Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention), and ISCHEMIA (Initial Invasive or Conservative Strategy for Stable Coronary Disease). Overall, PCI along with optimal medical therapy (OMT) appears to result in significant improvements in anginal symptoms compared with OMT alone. At ≈5 years of follow-up, PCI for SIHD does not lower mortality. The effect on myocardial infarction (MI) appears to be neutral: a long-term reduction in nonprocedural MI is balanced by a higher risk of periprocedural MI, although the prognostic implications of the 2 are likely different.[1] Patients with chronic total occlusion (CTO) of a coronary artery present a challenging and somewhat enigmatic subset of patients with SIHD. Although CTOs are highly prevalent among patients with SIHD, CTO PCI was typically excluded from these landmark trials. Furthermore, these patients typically have a higher burden of comorbidities and are at higher risk of future cardiac events compared with similar patients with non-CTO SIHD.[2,3] In addition, there are significant technical complexities and lower success rates with CTO PCI compared with non-CTO PCI, with success rates only recently improving in the setting of technological advances and operator skill set (75%–80% earlier, now ≈90%–95%). In addition, procedural complication rates remain higher than for non-CTO PCI.[3–5]

See Article by Park et al.

One of the biggest challenges in the CTO field is that most data on a possible benefit with CTO PCI are registry based or derived from meta-analyses of observational studies, and for the most part, centered around improvements in refractory angina, exercise capacity, and left ventricular ejection fraction.[4,6,7] In addition, some observational studies have suggested short-term mortality benefit from successful CTO PCI. For instance, Tsai and colleagues previously reported that, compared with failed CTO PCI, successful intervention was associated with a 2-year reduction in mortality, but with no reduction in hospitalization or MI risk.[3] Despite these promising data, data from 3 dedicated CTO PCI randomized controlled trials suggest that CTO PCI does not improve hard outcomes, but may improve quality-of-life measures. DECISION-CTO (Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion) showed

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that CTO PCI in addition to OMT was not superior to OMT alone at improving major adverse cardiovascular events (MACEs) or quality of life over 3 years of follow-up.[5] EURO-CTO (A Randomized Multicentre Trial to Compare Revascularization with Optimal Medical Therapy for Chronic Total Coronary Occlusions) similarly found that CTO PCI in addition to OMT was not superior to OMT alone on future 1-year MACEs, but that it did significantly improve quality-of-life factors (the primary end point of this study).[8] Finally, the EXPLORE (Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI) trial investigated the role of CTO PCI in patients with ST-segment–elevation MI after successful primary PCI, who were not in cardiogenic shock. A similar null result for MACEs and improvement in left ventricular function at 4 months were noted.[9] Thus, the randomized controlled trial evidence base does not support routine CTO PCI beyond for possible symptomatic benefit, but the trials were small (total sample size of the 3 trials ≈1400 patients) and had limited follow-up. Long-term outcomes remain unknown.

In this study, Park et al[10] present an observational, single-center, propensity-matched cohort of consecutive patients with symptomatic angina or a positive functional study undergoing either CTO PCI or routine care. The initial cohort included 1547 patients (883 in CTO PCI group, 664 in OMT group) enrolled between 2003 and 2012; median follow-up was 7.9 years. Patients in both groups underwent routine PCI for obstructive non-CTO stenoses, as needed. OMT was not standardized, and left to individual physicians. The success rate for CTO PCI was 79%. The primary end point, cardiac death at 10 years, was significantly lower in the CTO PCI group compared with the routine care group (10.4% versus 22.3%, respectively; $P<0.001$). This remained significant on multivariable Cox regression analysis. A landmark analysis was performed at 3 years after index procedure. There was no benefit of CTO PCI for the primary end point between baseline and 3 years (4% versus 6.5%; $P=0.61$), but between 3 and 10 years, there appeared to be a mortality benefit with CTO PCI (6.7% versus 16.9%; hazard ratio [HR], 0.47 [95% CI, 0.31–0.70]; $P<0.001$). Cardiac mortality, MI, and revascularization were all also lower in the CTO PCI group between 3 and 10 years. All of these findings were similar using a propensity score–matched analysis as well.[10]

The authors should be congratulated for presenting one of the largest observational studies in CTO PCI, and also to date one of the only studies focusing on long-term outcomes (>5 years) following CTO PCI (Table).[2–4,6,7,11–15] Although the conclusions of this observational study differ from the available randomized data, there are several points worth noting. This study actually examines an area that the randomized data cannot at this time point: there may be long-term benefits from CTO PCI that are not evident before 3 years. Second, both DECISION-CTO and EURO-CTO had a shortage of clinical events, with both trials stopped before completion of planned enrollment secondary to slow recruitment, and a high rate of crossover throughout the trial.[5,8] Given this, null findings need to be analyzed with caution. The total sample size of this cohort was also larger than all 3 trials put together. Also, hard end points are less prone to error and bias compared with surrogate or subjective outcomes. Finally, results from this study are concordant with several other observational studies and meta-analyses addressing similar outcomes of MACEs and cardiac death.[14–16]

There may be some biologic plausibility to the improvement in hard outcomes seen in this study. Among patients with left anterior descending (LAD) CTO, the cardiac death rate at 10 years was lower in the CTO PCI group than the OMT group (9.9% versus 21.2%; HR, 0.39 [95% CI, 0.21–0.75]; $P=0.004$) and was not significantly different in those without left anterior descending CTO. Because of a greater amount of myocardium potentially at risk with left anterior descending CTOs compared with other distributions, this makes intuitive sense. In addition, a subgroup analysis of the EXPLORE-CTO trial noted an improvement in left ventricular ejection fraction on cardiovascular magnetic resonance imaging assessment in the subset of patients undergoing left anterior descending CTO PCI compared with conservative management.[9] Also, in the current study, analysis of failed versus successful CTO PCI yielded results showing lower risk of cardiac death in the successful CTO PCI group, and that cardiac death risk was comparable in the failed CTO PCI group and routine care group, further providing internal validity to the reported findings.

There are also important limitations to this study. The major limitation is the possibility of selection bias in the absence of randomization. This seems likely in this study given patients undergoing PCI were younger, were more likely to be men, and had fewer comorbidities, including diabetes mellitus, prior MI, prior PCI, and a higher ejection fraction compared with patients who were conservatively managed. Although the comparison group is listed as "OMT," it more accurately represents a cohort of patients who were conservatively managed/received no intervention. In fact, the use of statins, aspirin, and P2Y12i was lower in the OMT group at baseline; no data are available on longitudinal use of these medications over the duration of follow-up.[17] Data on frailty are also not available, which is an important unmeasured confounder, particularly for observational studies comparing patients with and without a procedural intervention.[18] The authors are successful in addressing this to some extent with propensity score

Table **Recent CTO PCI Studies**

Study or Author	Study Type	Comparators	Study Population	Outcome of Interest	Results
EXPLORE (n=304)[9]	RCT	CTO PCI vs no CTO PCI	Post-PCI STEMI patients with concurrent CTO	4 mo LVEF and LVEDV assessed on cMRI	No difference between groups
DECISION-CTO (n=834)[5]	RCT	CTO PCI+OMT vs OMT alone	Stable angina, nonsymptomatic ischemia, or ACS with CTO	3 y death, MI, stroke, or repeated revascularization	No difference between groups
EURO-CTO (n=396)[8]	RCT	CTO PCI+OMT vs OMT alone	Stable angina or equivalent with CTO in viable territory	QOL by SAQ score (primary) 1 y death or nonfatal MI (secondary)	Improved QOL in CTO PCI arm (primary) No difference between groups (secondary)
Galassi et al 2017 (n=839)[4]	Observational	CTO PCI in patients with LVEF ≥50%, 35%–50%, and ≤35%	Symptomatic patients undergoing elective CTO PCI with inducible ischemia in CTO territory	2 y cardiac death, MI, stroke, or revascularization-free survival	No difference among groups; highest benefit in LVEF ≤35% group
Jang et al 2014 (n=738)[14]	Observational	CTO treated with OMT alone vs OMT+CABG or PCI	CTO on angiogram with Rentrop 3 collateral circulation	42 mo cardiac death, MACE (cardiovascular death, MI, repeated revascularization)	Significant lower incidence of cardiac death and MACEs in revascularization compared with OMT group
George et al 2014 (n=13 443)[11]	Observational	Successful vs unsuccessful CTO PCI	At least 1 CTO intervention	Procedural success (primary) 5 y mortality (secondary)	Procedural success of 70.6%; decreased mortality in those with successful revascularization compared with failed revascularization
Yang et al 2016 (n=1547)[13]	Observational	CTO PCI vs OMT	Symptomatic angina or +functional ischemia study with CTO	Cardiac death at follow-up (median follow-up, 45.8 mo)	No difference in rate of cardiac death between OMT and PCI groups
Goel et al 2018 (n=632)[12]	Observational	CTO PCI success vs failure	Consecutive cases with at least 1 CTO	Survival free of all adverse outcomes (death, MI, repeated PCI or CABG, recurrent angina) (median follow-up, 2.9 y)	Significantly higher event-free survival in successful vs unsuccessful CTO PCI No difference in death or MI individually (subgroup analysis)
Tomasello et al 2015 (n=1777)[15]	Observational	CTO PCI vs OMT or CABG	At least 1 CTO	1 y MACE, cardiac death	Significant lower incidence of MACEs and cardiac death in PCI compared with OMT or CABG group

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; cMRI, cardiac magnetic resonance imaging; CTO, chronic total occlusion; DECISION-CTO, Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion trial; EURO-CTO, A Randomized Multicentre Trial to Compare Revascularization with Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions trial; EXPLORE, Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI trial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; QOL, quality of life; RCT, randomized controlled trial; SAQ, Seattle angina questionnaire; and STEMI, ST-segment–elevation MI.

adjustment, although this also remains prone to bias, and does not account for unknown confounders. A comparison of noncardiac mortality between the 2 groups and/or a falsification end point analysis may have helped to some extent, but these are not perfect tools either. Another limitation is the use of the 3-year time frame for landmark analysis. Although the authors provide some speculative discussion, it is unclear why the 3-year mark was chosen for this analysis: was this a fortuitous finding borne out of multiple testing, or was it prespecified at the outset? What is the biological rationale for this finding, particularly for the MI signal? Similar findings have not been reported with SIHD PCI in contemporary trials. Many CTO operators prefer quality end points, including angina, decrease in dyspnea on exertion, or exercise tolerance, compared with hard end points as these are what drive CTO interventions. It is widely accepted that the expected benefits of CTO PCI should be symptomatic improvement as opposed to changes in MACEs.[19,20] Procedural success in this study (79%) was lower than what has been reported recently in similar observational studies (≈90%–95%); this may have an impact on long-term outcomes as well. Finally, there appeared to be significant attrition in follow-up beyond 3 years, which may have also biased the results. All of these issues need to be factored in when considering these results.

Future studies, especially randomized controlled trials, should incorporate longer-term follow-up to validate (or refute) these findings. On the basis of the experience from sham-controlled trials, such as ORBITA and SYMPLICITY (A Controlled Trial of Renal Denervation for Resistant Hypertension), future CTO trials will ideally also incorporate a sham PCI arm, so that the true utility of CTO PCIs can be systematically assessed. At the current time, it remains unclear whether CTO PCI can truly positively affect long-term outcomes, particularly hard end points, such as mortality and MI.

ARTICLE INFORMATION

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Disclosures

None.

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