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Chronic Total Occlusion Percutaneous Coronary Intervention

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Abstract Patients with a chronic total occlusion (CTO) often present with stable exertional angina resulting from insufficient blood flow through collaterals to meet myocardial oxygen demand during stress. The objectives of percutaneous coronary intervention (PCI) on these lesions include relief of symptoms, improvement in left ventricular function and remodeling, and potential decrease in mortality. There are currently no randomized trials that have assessed outcomes in patients with CTOs treated with complex PCI compared to medical therapy or coronary artery bypass graft surgery. However, several ongoing investigations aim to evaluate a large range of outcomes and new technology and techniques in CTO PCI, offering the promise of stronger evidence-based guidelines for the care of these complex patients. In this article, we assess the current knowledge regarding prevalence, indications, and outcomes of CTO PCI and provide an up-to-date review of the literature.

Keywords Chronic total occlusion · Complex percutaneous coronary intervention · Outcomes · Review

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Introduction

A chronic total occlusion (CTO) is defined as a 100 % obstructive coronary lesion present for at least 3 months with less than or equal to Thrombosis in Myocardial Infarction (TIMI) grade I flow. The estimated prevalence of chronic total occlusions (CTOs) is around 30 % in high-risk patients referred for coronary angiography [1, 2].

Patients with a CTO often have stable exertional angina resulting from insufficient blood flow through collaterals to meet myocardial oxygen demand during stress [3]. In addition to management of symptoms, referral for percutaneous coronary intervention (PCI) may be prompted by significant ischemia on noninvasive imaging.

In this article, we provide an appraisal of current knowledge regarding the prevalence, success rates, indications, and outcomes of CTO PCI. We also examine specific management scenarios in CTO PCI and provide an up-to-date review of the literature.

Current CTO Intervention Rates and Operator Volume

Although CTOs are highly prevalent in patients with known CAD, the rate of attempted interventions on these lesions varies greatly depending on geographic location and regional practice patterns. In Japan—where many of the techniques for CTO PCI were originally developed—interventions on this complex subset of lesions encompasses nearly 12 % of all coronary cases. This is in stark contrast to recent practice in the USA, where an analysis of procedural outcomes in elective patients between 2009 and 2013 in the National Cardiovascular Data Registry (NCDR) demonstrated that CTO PCI comprised 3.8 % of interventions performed for stable coronary artery disease (CAD). The procedural success rate was 59 %, compared to 96 % in those without CTOs [4, 5, 6••]. Greater procedural success was associated with patient factors, including younger age, absence of current tobacco use, past myocardial infarction, and previous coronary artery bypass grafting (CABG), as well as operator experience. There is also significant regional variation in practice patterns within the USA, with CTO PCI comprising anywhere from 0 to 44 % of cases at different centers [6••].

Overall, CTO PCI is becoming increasingly common in the USA, and with greater rates of procedural attempts has come greater rates of technical success. Data from the NCDR shows that as rates of CTO PCI increased from 3.2 to 4.8 % from 2009 to 2013, the likelihood of procedural success improved from 55.5 to 61.9 %. Commensurate with increased case volumes are increased numbers of interventionalists attempting CTO PCI [6••]. Higher volume operators have higher rates of technical success, and interventionalists performing more than 10 CTO PCIs per year have significantly improved outcomes (75 vs. 53 %; $p < 0.001$) compared to those performing fewer than five cases per year [7]. Average success rates for the highest volume operators were greater than 80 % [6••].

The inherent complexity and technical challenges of CTO PCI generate a steep learning curve. To achieve the best outcomes, patients should undergo CTO interventions at high-volume centers by experienced operators. There may also be benefit from the creation of multidisciplinary CTO teams specially versed in the peri-procedural care of these patients, similar to those now common in the management of patients undergoing transcatheter valve interventions [8, 9].

The Hybrid Algorithm for CTO PCI

Unlike the treatment of non-occlusive coronary artery disease, which is associated with a consistently high likelihood of procedural success, recanalization of a CTO is often thwarted by failure to cross the lesion. To improve success rates, a stepwise approach to CTO PCI—the "hybrid algorithm"—has been developed to provide operators with a step-by-step method to cross CTO lesions (Fig. 1). Routine use of two guide catheters for dual coronary injection is now the standard of care, as it allows assessment of the proximal cap (facilitated in many cases by intravascular ultrasound), the length of the occlusion, and the anatomy of collaterals as well as the distal vessel. The presence of two guide catheters then allows fluid application of wire escalation or dissection/re-entry techniques via either an antegrade or retrograde approach [5].

A retrospective analysis of procedural outcomes at two high-volume CTO PCI centers revealed significantly higher rates of successful revascularization after adoption of the hybrid algorithm [10]. In one particularly dramatic instance, by providing a systematic approach to crossing CTOs, the hybrid algorithm facilitated a procedural success rate of 95.5 % when utilized by a non-CTO operator at one center [11].

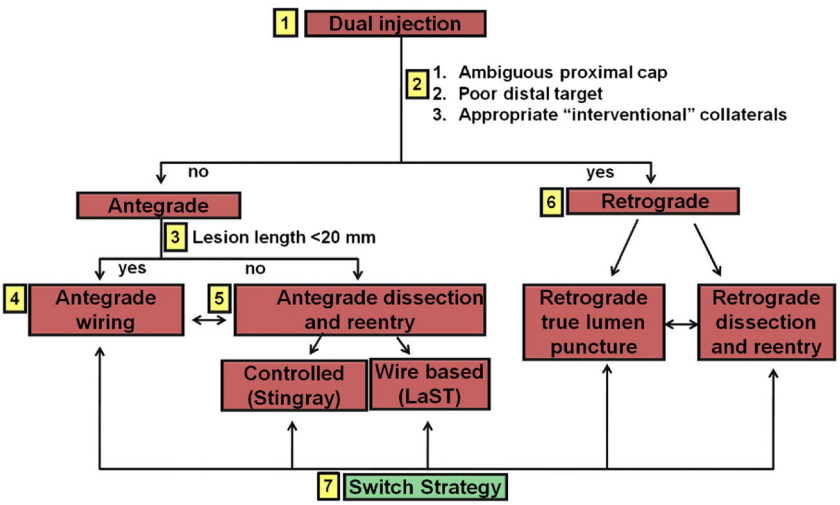

Fig. 1 The hybrid approach to CTO PCI: algorithm for choosing the initial procedure strategy, and subsequently, a secondary strategy if the upfront approach fails. Reproduced with permission from [5]

Indications for CTO PCI

The objective of CTO PCI includes relief of symptoms, improvement in left ventricular function and remodeling, and potential decrease in mortality. It is crucial to note that there are currently no randomized clinical trials that have assessed outcomes in patients with CTOs treated with complex PCI compared to medical therapy or coronary artery bypass graft surgery (CABG). The existing data is primarily gleaned from registries, which are inherently limited by the inability to control for patient and operator heterogeneity. Despite the limitations, registry data plays an important role in revealing trends in practice patterns and patient outcomes.

Symptom Relief

TOAST-GISE was a prospective, observational study that sought to describe the impact of CTO PCI on relief of angina. Authors evaluated 376 consecutive patients who underwent CTO PCI of 390 lesions at 29 different centers. At 1 year of follow-up, patients who had successful revascularization reported significantly less angina and were more likely to complete an exercise stress test without limiting symptoms than their counterparts whose PCI was unsuccessful [12•].

More recently, the FACTOR trial enrolled 125 patients undergoing CTO PCI and tracked patient-reported health status using the Seattle Angina Questionnaire. At 30-day follow-up, mean scores for angina frequency, physical limitation, and quality of life were significantly improved in patients whose CTO PCI ended in successful recanalization compared to those whose procedures were unsuccessful [13].

Even in patients with an isolated CTO in the absence of additional occlusive CAD, revascularization is associated with resolution of angina and significant relief of symptoms as defined by improvement of two or more classes in the Canadian Cardiovascular Society (CCS) classification system [14].

Improvement of Left Ventricular Function

Successful revascularization of CTOs is associated with improved left ventricular (LV) function and attenuated remodeling, particularly in patients with viability in the region subtended by the occluded artery [15]. Immediate and sustained increases in regional contractility and myocardial blood flow in territory supplied by treated CTOs has been demonstrated using cardiovascular magnetic resonance imaging (CMRI) [16]. A recent meta-analysis revealed that after successful CTO PCI, LV ejection fraction increased by 4.4 % ($p < 0.001$), whereas those with failed revascularization did not experience any change in LV systolic function [17]. Kirschbaum et al. demonstrated significant decreases in mean end-diastolic and end-systolic volume indexes as well as improved segmental wall thickening at 3 years after successful CTO PCI [18]. The transmural extent of infarction seen on CMRI prior to treatment was the best predictor of functional recovery.

Major Adverse Cardiac Events, Safety, and Survival Benefit

In the TOAST-GISE study described earlier, the rate of successful revascularization was high at 77.2 % and overall incidence of MACE was 5.1 % in the 376 CTO patients enrolled. Those who underwent successful CTO PCI had a lower incidence of MACE and cardiac death at 12 months than those with failed attempts at recanalization [12•].

In the contemporary era, the innovative guidewire techniques previously mentioned, as well as the use of newer-generation drug-eluting stents, have further improved procedural outcomes. In the EXPERT CTO trial, Kandzari et al. conducted a prospective, multi-center registry evaluating outcomes of CTO PCI using everolimus-eluting stents. Successful recanalization was accomplished in 89 % of 250 consecutive patients. At 1 year, death occurred in 1.9 % and major adverse cardiac events (MACE) in 18.5 % of patients; the latter outcome was primarily driven by myocardial infarction (MI), with an event rate of 13.9 % according to the Academic Research Consortium (ARC) criteria [19•]. However, when MI was defined according to a more conservative definition predefined in the study, the adjudicated rate of events dropped to 3.4 %. Despite the increased complexity of the interventions studied in EXPERT CTO, the exceedingly low rates of definite stent thrombosis (0.9 %) and clinically driven target lesion revascularization (5.8 %) were comparable to those reported in similar stent trials in non-occlusive CAD [19•]. These results provide compelling evidence that CTO PCI in the modern era can be accomplished safely and effectively.

The SYNTAX trial showed that incomplete revascularization is associated with greater mortality, MACE, and cerebrovascular events in patients treated with either PCI or CABG [20]. The adverse clinical outcomes associated with incomplete revascularization are strongly predicted by the presence of a total occlusion. Though uncommon for a CTO to be the cause of an acute coronary syndrome (ACS) [12•], in patients who do present with ACS, a CTO in a non-infarct-related artery predicts adverse outcomes. Choi et al. recently demonstrated that patients with acute myocardial infarction who undergo successful PCI of a CTO in a non-infarct-related artery have decreased all-cause mortality compared to those who receive medical therapy for such lesions or who have a failed CTO PCI (16.7 vs. 32.3 %, hazard ratio 0.459, $p = 0.012$) [21].

Compared to those with non-occlusive CAD, patients undergoing CTO PCI have increased prevalence of risk factors including higher rates of LV dysfunction, history of MI and stroke, prior PCI, diabetes, and active smoking [5, 22]. As presence of a CTO indicates greater severity and complexity

of underlying CAD, it is not surprising that higher rates of adverse cardiac events including mortality are seen in patients with these lesions compared to those with non-occlusive CAD [6••, 23]. However, when patients with CTO lesions are compared to one another, mortality in those who undergo successful PCI is significantly lower than in those whose attempts at recanalization are unsuccessful (14.3 vs. 17.5 %, OR 0.56, 95 % CI 0.43–0.72) [24, 25].

Complications of CTO PCI

Due to the increased complexity of treating CTO lesions, the rate of complications associated with CTO PCI is generally higher than for other coronary interventions. Major complications associated with CTO PCI include coronary artery perforation, cardiac tamponade, loss of collaterals resulting in ischemia or infarction, radiation injury, contrast-induced nephropathy, and vascular complications at access sites.

In a meta-analysis of over 18,000 patients, Patel et al. demonstrated a rate of coronary perforation of 2.9 % in patients undergoing CTO PCI (Table 1). However, this did not correspond to a markedly elevated rate of tamponade, suggesting the majority of cases of perforation do not result in clinically significant hemorrhage [25]. In an unadjusted analysis of data from the NCDR, the rate of tamponade was 0.3 % in CTO PCI and 0.1 % in non-CTO PCI ($p < 0.001$), without accounting for significant baseline differences seen in these two distinct populations [6••]. Typically, bivalirudin and GpIIb/IIIa inhibitors are avoided in CTO PCI to mitigate the risk of bleeding should a perforation occur. Despite decreased utilization of aggressive anticoagulation regimens, rates of stent thrombosis have historically been low and have remained low, comparable to those seen in cases of non-CTO PCI [19•].

Radiation injury is a rare but potentially morbid complication of CTO PCI, as these cases are associated with longer procedure times and greater radiation exposure. Up to one in three patients will receive a radiation dose greater than 4.5 Gy (Gy), the threshold at which increased rates of radiation dermatitis are seen [1, 26]. Patients with exposure to greater than 5 Gy of radiation or fluoroscopy times longer than 60 min are recommended to receive radiation counseling and evaluation by Dermatology [1].

Contrast-induced nephropathy (CIN) is another complication seen more frequently in CTO PCI than in interventions in patients with non-occlusive CAD. It is defined as an increase in serum creatinine of 25 to 50 % from baseline, or an increase in absolute value of 0.5 to 1.0 mg/dL, within the first 48–72 h after a procedure. CTO PCI requires greater contrast utilization (on average, 258 mL in CTO PCI vs. 223 mL in non-CTO PCI, $p < 0.001$), and is thus associated with up to 4 % overall risk of CIN [25]. Christakopoulos et al. recently examined contrast utilization in 1330 CTO patients in the PROGRESS CTO registry. In adjusted analyses, moderate to severe calcification, distal cap at vessel bifurcation, use of eight French catheters, and antegrade dissection re-entry or retrograde approaches were associated with significantly higher contrast utilization [27]. Operators should exercise particular caution when attempting CTO PCI in patients with a baseline creatinine greater than 2 mg/dL and in those at higher risk of developing CIN due to DM or a history of previous renal failure.

Collateral loss due to shifting plaque, stenting of long segments, and dissection re-entry techniques has also raised concerns about the safety of CTO PCI. However, Werner et al. demonstrated that only 7 % of patients with a CTO have sufficient flow reserve from collaterals. Thus, despite the transient ischemia that accompanies any coronary intervention, the vast majority of patients will ultimately experience overall alleviation of ischemia after successful CTO PCI [3]. There is currently limited data assessing MACE and mortality associated with collateral loss after CTO PCI; this is a potential target of future research.

Approach to the Treatment of Patients with Chronic Total Occlusion

Despite the absence of randomized controlled trials to guide clinical decision-making, current evidence suggests that patients with persistent angina despite optimization of antianginal medications and those with a significant burden of ischemia should be considered for revascularization through either percutaneous intervention or bypass surgery.

Table 1 Unadjusted complication rates in studies of CTO PCI

	Brilakis et al. Non-CTO Total $N = 572,145$	Brilakis et al. Successful CTO Total $N = 22,365$	Patel et al. Pooled CTO Total $N = 18,061$
Tamponade	0.1 %	0.3 %	0.3 %
Perforation	–	–	3.7 %*
Radiation injury	–	–	<0.01
Contrast-induced nephropathy	–	–	3.8

*Successful CTO only

Management of an Isolated CTO

When a CTO occurs in the absence of significant occlusive disease in the rest of the coronary vasculature, PCI is warranted when the patient's symptoms are attributable to the occluded artery, the myocardium subtended by the CTO is viable, and there is a moderate to high likelihood of successful recanalization [28].

Role of CABG in the Treatment of CTOs

CABG has long been considered the primary method of revascularization for patients with a CTO in the setting of significant left main disease or severe multi-vessel CAD. In light of the controversy surrounding treatment of CTOs, a panel representing the views of the major American cardiovascular professional organizations developed appropriate use criteria in 2009 with an update published in 2012. In the case of complex multi-vessel coronary artery disease, such as that due to the presence of a CTO, the panel rated use of PCI of "uncertain" benefit but treatment with CABG as "appropriate" [29].

One potential benefit of CABG over PCI for treatment of CTOs is that distal placement of anastomoses enables bypass grafts to treat both proximal and distal CTOs [30]. Current CTO trials generally exclude patients with distal CTOs, in whom the smaller diameter of the target vessel may raise concerns about outflow after placement of a stent. Utilization of CABG is associated with a greater likelihood of complete revascularization [20]. However, in the SYNTAX trial, patients in both treatment arms had an equivalent proportion of CTOs (24.2 % in those randomized to PCI vs. 22.2 % in those randomized to CABG, $p = 0.33$) with no difference in all-cause mortality at 1 year [31]. There is evidence that saphenous vein grafts (SVGs) are more likely to fail when used to bypass CTO lesions compared to non-occlusive lesions. In the Prague-4 trial, only 23 % of SVGs used to bypass CTOs in locations other than the left anterior descending artery were patent 1 year after CABG [32].

Despite the historical preference for CABG for management of complex multi-vessel CAD including CTOs, the improved safety and efficacy of CTO PCI have resulted in a growing subset of patients for whom percutaneous intervention has become the preferred method to achieve complete revascularization. Widespread use of second-generation drug-eluting stents, advances in wire technology and techniques, as well as establishment of centers of expertise with high-volume operators have resulted in improved rates of successful revascularization over time [33]. Analyzing outcomes of patients undergoing CTO PCI between 2012 and 2013 at five high-volume centers, Christopoulos et al. found rates of successful revascularization greater than 90 % compared to rates around 75 % in pooled results from 39 previously published CTO PCI series [34]. These results further support the utilization of CTO PCI as an effective alternative to CABG in the modern era.

2016 Update and Future Directions in CTO PCI

Despite the significant progress mentioned above, challenges to the widespread use of PCI in the treatment of CTOs remain. Intense resource utilization due to long procedure times and use of numerous guidewires, increased exposure to radiation and contrast, and rates of procedural success that lag behind those seen with PCI of non-CTO lesions continue to raise important questions about the benefits and risks of CTO PCI. Recent research has attempted to address a number of these questions. The most groundbreaking efforts in the past year were aimed at three major themes: outcomes related to technical approach (i.e., retrograde vs. antegrade and wire escalation vs. dissection re-entry), outcomes related to CTO interventions in patients with prior coronary bypass grafts, and novel techniques for crossing CTO lesions.

Two analyses from the PROGRESS CTO registry provide thorough evaluation of outcomes related to CTO PCI technique. First, the use of antegrade dissection re-entry (ADR) was compared to other techniques for crossing lesions. Despite higher utilization of radiation and contrast, ADR was associated with similar rates of technical success (92.7 vs. 94.2 %; $p = 0.43$) and MACE (2.1 vs. 0.6 %; $p = 0.12$) compared to other methods [35]. Second, the retrograde and antegrade approaches to CTO PCI were compared to one another. Retrograde CTO attempts were associated with significantly greater lesion complexity according to the Japan-CTO score (3.1 vs. 2.1, with a higher score indicating greater lesion complexity; $p < 0.001$) and lower success rates (85 vs. 94 %; $p < 0.001$). Procedures utilizing retrograde approaches were associated with higher rates of MACE (4.3 vs. 1.1 %; $p < 0.001$) than those solely relying on antegrade techniques. This outcome was largely driven by higher rates of MI (2.1 vs. 0.3 %; $p < 0.001$) and perforation (5.5 vs. 1.9 %; $p < 0.001$). The authors comment that although associated with higher MACE and lower success rates, the retrograde approach remains a critical tool in enabling overall success of recanalization in patients with CTOs [36].

A second major focus of study over the past year was on outcomes in patients with prior coronary bypass grafts and CTO lesions. Dautov et al. compared CTO patients with and without a history of CABG and demonstrated that the presence of bypass grafts was associated with a higher rate of MACE after CTO PCI. In an interesting secondary analysis, authors examined the safety and feasibility of utilizing SVGs as the primary conduit to access the CTO lesion compared to antegrade or collateral approaches that did not involve an SVG. The study showed that SVG use to access CTO lesions resulted in a similarly high rate of success compared to alternative approaches without a difference in MACE [37].

Table 2 Planned and Ongoing CTO studies

Prinicpal investigator	Design	Question	Expected completion	Identifier
Park et al.	RCT	Outcomes in CTO PCI vs. medical therapy	2023	NCT01078051
Thiele et al.	RCT	Bioabsorbable stents in CTO PCI	2018	NCT02739685
Verma et al.	Prospective cohort	EXERTION trial: change in peak VO2 with CTO PCI	2016	NCT02499666
Yangsoo et al.	RCT	Effect of pre-procedure coronary CT on outcomes	2016	NCT02037698
Keeble et al.	Prospective cohort	Effect of CTO intervention on FFR and iFR	2017	NCT02643940

RCT randomized, *FFR* fractional flow reserve, *iFR* instantaneous wave-free ratio

Further advancement in techniques to improve success rates was another major theme within the field of CTO PCI over the past year. In a retrospective analysis of 59 patients, Carlino et al. described a novel technique to facilitate crossing highly complex CTO lesions. The study involved injection of <1 cc of contrast into a microcatheter to create a hydraulic dissection plane to enable CTO crossing. The technique led to a success rate of 81.4 % in a cohort with a high rate of prior failed attempts at CTO PCI. There were no complications directly attributable to use of the technique [38]. A second novel approach named "the Mother-Daughter-Granddaughter technique" was recently described to facilitate access of distal CTO lesions. The technique involves using a six French GuideLiner catheter inside an eight French GuideLiner catheter to allow access to the retrograde limb of a bypass vessel [39].

Future and Ongoing Studies

In addition to the aforementioned recently published trials, there are several ongoing investigations that will shape the future of CTO PCI. These trials aim to evaluate a large range of outcomes and new technology and techniques in CTO PCI (Table 2). As previously mentioned, there is a need for randomized controlled trials to definitively establish a significant benefit of CTO PCI over medical therapy alone in patients with stable CAD. The DECISION-CTO trial (NCT01078051) is currently enrolling in Korea and will randomize CTO patients with stable angina to PCI or optimal medical therapy. The primary endpoint will be mortality and MACE at 5 years. The EURO-CTO trial (NCT01760083), which recently completed enrollment, will evaluate quality of life at 12 months and MACE at 3 years in patients with symptomatic CTOs treated with PCI compared to optimal medical therapy. Results from these two trials are expected to bolster evidence-based decision-making in the care of patients with CTOs.

Conclusion

As a large body of literature attests, advancements in technique, technology, operator, and center experience have made CTO PCI an increasingly safe, effective, and viable method of treating patients with complex coronary disease. With the knowledge gained from ongoing studies, we expect CTO PCI to play an increasingly important role in the treatment of chronic CAD.

Compliance with Ethical Standards

Conflict of Interest Drs. Chung, Hatem, Green declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain studies with human or animal subjects performed by the author.

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