Percutaneous Treatment of Coronary Chronic Total Occlusions Part 1: Rationale and Outcomes

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Abstract

Coronary chronic total occlusions (CTOs) are commonly encountered in patients with coronary artery disease. Compared to patients without coronary CTOs, those with CTO have worse clinical outcomes and lower likelihood of complete coronary revascularisation. Successful CTO percutaneous coronary intervention (PCI) can significantly improve angina and improve left ventricular function. Although currently unproven, successful CTO PCI might also reduce the risk for arrhythmic events in patients with ischaemic cardiomyopathy, provide better tolerance of future acute coronary syndrome, and possibly improve survival. Evaluation by a heart team comprised of both interventional and non-interventional cardiologists and cardiac surgeons is important for determining the optimal revascularisation strategy in patients with coronary artery disease and CTOs. Ad hoc CTO PCI is generally not recommended, so as to allow sufficient time for (a) discussion with the patient about the indications, goals, risks, and alternatives to PCI; (b) careful procedural planning; and (c) contrast and radiation exposure minimisation. Use of drug-eluting stents is recommended for CTO PCI, given the lower rates of angiographic restenosis compared to bare metal stents.

Keywords

Percutaneous coronary intervention, chronic total occlusions, outcomes

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Section A Coronary Chronic Total Occlusions – Prevalence and Pathophysiology

A chronic total occlusion (CTO) is defined as a completely occluded coronary artery with no antegrade flow (thrombolysis in myocardial infarction [TIMI] 0 flow) for at least three months.¹ CTOs are present in 15–30 % of patients undergoing coronary angiography.^{2–5} In a Canadian prospective registry of 14,439 patients undergoing coronary angiography a CTO was present in 18.4 % of all patients with significant coronary artery disease (CAD).² Approximately 1/3–1/2^{6,7} of patients undergoing CTO percutaneous coronary intervention (PCI) have had a prior acute myocardial infarction (MI). This suggests acute onset of the occlusion, whereas in the remaining patients gradual development of CTO from high-grade lesions likely occurred.

The basic histopathologic feature of a CTO is a proximal cap of the occlusion. This is often fibrotic or calcified and may provide considerable resistance to wire advancement during CTO PCI. Distal to the proximal cap and along the occlusion length follows a segment of loose fibrous tissue or organised thrombus, with various extent of calcification.^{8,9} In several of these lesions, residual channels may be observed that are not visible under angiography. In addition, microchannels may appear during the CTO's consolidation process, however these are mostly located in the adventitia with extremely tortuous courses and do not generally traverse the entire occluded segment.¹⁰ A recent autopsy study of 95 CTO lesions from 82 patients reported frequent negative remodelling of the CTO body (more frequent with longer duration of the occlusion), very rare presence of microchannels and more frequent tapering of the distal cap as compared with the proximal cap (79 % vs. 50 %, $P < 0.0001$).¹¹

Table 1: Rentrop and Werner Classification of Coronary Collateral Circulation

Rentrop Classification ¹⁵ (Developed for Occluded and Non-occluded Arteries)	
0	no filling of collateral vessels
1	filling of collateral vessels without any epicardial filling of the target artery
2	partial epicardial filling by collateral vessels of the target artery
3	complete epicardial filling by collateral vessels of the target artery (In CTOs, Rentrop 3 is prevalent in 85% of lesions)
Collateral Connection Grade ¹³	
CC0	no continuous connection
CC1	threadlike continuous connection
CC2	side branch-like connection (≥ 0.4 mm)
CC3	>1 mm diameter of direct connection (not included in the original description)

CTO = chronic total occlusion.

Collaterals are interarterial connections that provide blood flow to a vascular territory whose original supply vessel is obstructed. Thus, the integrity of the myocardium supplied by the obstructed vessel may be preserved, or to a certain degree impaired, but would not become necrotic. Collaterals develop through arteriogenesis, i.e. the recruitment of preformed and preexisting interarterial connections, which is driven mainly by shear forces along the pressure gradient that develops when the native vessel is occluded.¹² The functional assessment of collaterals revealed that, in patients without well-developed preexisting collateral connections, collaterals require between 2–12 weeks to fully develop their functional capacity.¹³ The collateral supply provides a perfusion pressure in the range of 30–40 mm Hg at the occluded territory, a pressure that leads to the functional reduction of distal vessel size, which then leads to the underestimation of the vessel dimensions during a recanalisation procedure.¹⁴

The most widely used angiographic grading system for collaterals (described by Rentrop et al. in 1985) does not actually rate the collaterals themselves but rather their effect in filling the occluded arterial segment¹⁵. Recently, a grading of collateral connections was introduced specifically for CTOs, which can help plan the retrograde approach^{13,16} (see Table 1). Collateral function can develop to a similar functional level in patients with prior MI and large akinetic territories, as in patients with preserved regional function, i.e. viability is not required for collateral development.¹⁷

The direct assessment of collateral function shows that the functional competence of collaterals in CTOs is limited, even in patients without a prior Q-wave MI. During a standard stress protocol with systemic infusion of adenosine, the coronary flow velocity and pressure changes distal to an occlusion (after CTO crossing but before stent implantation) were well below the cut-off values for assessing the functional reserve in non-occlusive coronary obstructions, i.e. a fractional flow reserve (FFR) above 0.75. Therefore, even well-developed collaterals do not prevent ischaemia during exercise.^{18–20}

Collaterals will regress once the native artery that was replaced by the collaterals is revascularised.²¹ This process starts immediately after re-establishing antegrade flow with immediate loss of collateral conductance and lasts for many months after the revascularisation procedure.

Section B
Clinical Presentations and Timing of Intervention
Clinical Presentation

The symptoms attributable to CTOs are no different than those of non-total occlusions. Patients may report characteristic angina or anginal equivalents, including dyspnoea and fatigue. CTO symptoms are by definition chronic and may sometimes be minimised through accommodation and denial.

Stable angina is present in many patients with CTO. Data from the FlowCardia's approach to chronic total occlusion recanalisation (FACTOR) trial²² suggests that two thirds of the patients referred for the trial (which required symptoms and/or abnormal stress testing) had angina, that significantly impaired their quality of life (QoL). Dyspnoea is the most common anginal equivalent among patients with CTO. Safley et al.²³ compared 98 patients with single-vessel CTO with 687 patients undergoing non-CTO PCI and reported similar alleviation in both dyspnoea and angina.

Numerous patients with CTO have been identified after presenting with other culprit lesions (46 % of patients with CTO presented with an acute coronary syndrome (ACS) in the Canadian Multicentre CTO Registry).² Among patients presenting with ST-segment elevation acute myocardial infarction, approximately 10 % also have a CTO.² The same study showed that 13 % of the CTO patients were asymptomatic or had minimal angina (Canadian classification angina class 0 and/or 1).² The decision to revascularise the CTO in these patients depends on the indications discussed in section C. A careful search should be conducted for residual symptoms of myocardial ischaemia such as poor progression in cardiac rehabilitation, activity avoidance, residual dyspnoea, fatigue and angina, as well as residual ischaemic burden.

Timing of CTO-PCI

In most patients CTO-PCI should be performed electively and not ad hoc.²⁴ Separating diagnostic angiography and CTO-PCI allows for a detailed discussion with the patient about the indications, goals, risks, and alternatives (such as medical therapy and coronary artery bypass graft surgery) to PCI.

Risks that are more specific to CTO PCI warrant discussion. These include the risk of radiation injury, perforation, tamponade and donor vessel injury. There is controversy on whether CTO PCI provides clinical benefit to asymptomatic patients, which should be discussed with the patient (section C, part 6).²⁵ Finally, adequate pre-procedural planning, which is critical to maintaining high procedural success, is more challenging when performed on an ad hoc basis. On rare occasions, the clinical situation may force ad hoc CTO PCI. An example would be a patient who presents with an ACS due to a severely degenerated saphenous vein graft (SVG) with no option for embolic protection. Native vessel CTO-PCI might be preferable and required if the patient cannot be stabilised with medical therapy.²⁶

Section C
Outcomes after CTO Interventions

CTO PCI can improve angina and left ventricular (LV) function. Although registry data are promising, the potential role of CTO PCI to decrease the risk for ventricular arrhythmias, improve tolerance of subsequent ACS and improve survival has not yet been demonstrated.

Angina

In a meta-analysis of six observational studies²⁷⁻³² that evaluated angina post-CTO PCI, patients undergoing successful PCI experienced a significant reduction in recurrent angina during a six-year follow-up compared with patients undergoing unsuccessful PCI (odds ratio, 0.45; 95 % confidence interval, 0.30 to 0.67).³³

LV Dysfunction

Left ventricular systolic function has been demonstrated to improve after CTO PCI in patients with baseline LV dysfunction,³⁴⁻⁴² while no change in ejection fraction can be expected when the baseline LV function is normal.⁴² Left ventricular function improvement is dependent on the maintenance of CTO target vessel patency^{37,38} and on the viability of the perfused myocardial territory,^{39,40} therefore an assessment of left ventricular viability should be performed in case of left ventricular dysfunction. Theoretically, an improvement in LV function should improve heart failure symptoms, but this has not yet been demonstrated. A magnetic resonance imaging study of 170 consecutive patients with coronary CTO revealed prior myocardial infarction by late gadolinium enhancement in 86 %, a much higher proportion that previously recognised, although only 25 % of patients had Q waves on their electrocardiogram.⁴³

Ventricular Arrhythmias

Ischaemia may predispose to ventricular arrhythmias. Among 162 patients with ischaemic cardiomyopathy who received an implantable cardioverter defibrillator, 44 % had at least one CTO.⁴⁴ During a median follow-up of 26 months, the presence of CTO was associated with higher ventricular arrhythmia and mortality rates ($p < 0.01$).⁴⁴ The preventive effect of CTO revascularisation on subsequent arrhythmias remains to be shown.

Tolerance of Future ACS

The presence of a CTO has been associated with worse outcomes in patients presenting with ACS, possibly due to the greater extent of myocardial injury during the initial ACS presentation.⁴⁵

Among 3,277 patients with acute ST-segment elevation myocardial infarction treated with primary PCI, the presence of a CTO was an independent predictor for 30-day mortality (hazard ratio (HR), 3.6; 95 % confidence intervals (CI), 2.6–4.7; $p < 0.01$), a stronger predictor than multivessel disease (HR, 1.6; 95 % CI, 1.2–2.2; $p = 0.01$). Among patients who survived at least 30 days, the presence of a CTO (but not multivessel disease without CTO) remained a strong predictor of death (HR, 1.9; 95 % CI, 1.4–2.8, $p < 0.01$).⁴⁶

Similar results were obtained from the 3,283 patients who participated in the Harmonising outcomes with revascularisation and stents in acute myocardial infarction (HORIZONS-AMI) trial, where 8.6 % had a CTO in a non-infarct-related artery.⁴⁵ A CTO in a non-infarct-related artery was an independent predictor of both 0- to 30-day mortality (HR 2.88; 95 % CI, 1.41–5.88; $p = 0.004$) and 30-day to three-year mortality (HR 1.98; 95 % CI 1.19–3.29; $p = 0.009$), while multivessel disease without a CTO was associated with higher early (0- to 30-day) (HR 2.20; 95 % CI, 1.00–3.06; $p = 0.049$) but not late (30-days to three years) mortality.⁴⁵

A similar adverse impact of CTO was observed in patients with ST-segment elevation acute myocardial infarction presenting with cardiogenic shock⁴⁷ and in a series of patients with non-ST segment elevation acute coronary syndromes.⁴⁸ A small retrospective study

demonstrated better outcomes for patients who underwent successful vs failed CTO PCI after primary PCI for acute ST-segment elevation MI.⁴⁹ The ongoing Evaluating XIENCE V® and left ventricular function in percutaneous coronary intervention on occlusions after ST-elevation myocardial infarction (EXPLORE) trial is assessing whether PCI of a CTO in a non-infarct-related artery within one week from primary PCI can improve LV dimensions and function.

Survival

There are no published, randomised controlled trials comparing CTO PCI with medical therapy or with surgical revascularisation. However, there are several observational studies that have consistently shown better survival among patients who underwent successful vs failed CTO PCI. In a meta-analysis of 13 observational studies^{7,27-32,50-55}, mortality over a weighted mean follow-up of six years was 14.3 % among 5,056 patients with successful CTO recanalisation compared with 17.5 % among 2,232 patients with failed CTO recanalisation (odds ratio [OR] 0.56; 95 % CI, 0.43–0.72).³³ Similar results were observed in two more recent studies^{56,57} but no difference was observed in a third study.⁵⁸ In a large, single-centre, retrospective study, a mortality benefit was only observed among patients in whom the CTO target vessel was the left anterior descending artery.⁵⁹

Completeness of Coronary Revascularisation and Outcomes

Patients with incomplete coronary revascularisation have worse clinical outcomes compared to those with complete revascularisation.⁶⁰ Research in this area has been hampered by the lack of universal definition of complete revascularisation. Anatomic definitions often require revascularisation of all stenotic vessels whereas functional definitions usually require revascularisation of ischaemic myocardial territories only.⁶¹ The presence of a CTO has been one of the major reasons for incomplete revascularisation,⁶² suggesting (but not proving) that providing complete revascularisation by recanalising the CTOs could improve clinical outcomes.^{63,64} The presence of moderate or severe ischaemia is associated with worse clinical outcomes in patients with⁶⁵ or without⁶⁶⁻⁶⁸ a CTO. In a study of 301 patients who underwent myocardial perfusion imaging before and after CTO PCI, a baseline ischaemic burden of >12.5 % was optimal in identifying patients most likely to have a significant decrease in ischaemic burden post-CTO PCI, suggesting that the highest benefit of CTO PCI is more likely to be achieved in patients with significant baseline myocardial ischaemia.⁶⁹

Ongoing Clinical Trials

To date no randomised-controlled clinical trials of CTO PCI vs medical therapy or coronary artery bypass graft surgery have been reported. Importantly, the Open artery trial (OAT) was not a CTO trial, as it included patients within 30 days from acute myocardial infarction.² Two clinical trials comparing CTO PCI with optimal medical therapy (OMT) are ongoing.⁷⁰ The Drug-eluting stent implantation vs optimal medical treatment in patients with chronic total occlusion (DECISION-CTO, <http://clinicaltrials.gov/show/NCT01078051>) trial is evaluating whether compared to OMT, CTO PCI will reduce the composite endpoint of all cause death, myocardial infarction, stroke and any revascularisation at three years after randomisation. The European study on the utilisation of revascularisation vs optimal medical therapy for the treatment of chronic total coronary occlusions (EURO-CTO) trial (<http://clinicaltrials.gov/ct2/show/NCT01760083>) is randomising patients to CTO PCI with biolimus-eluting stent implantation and OMT vs OMT alone and has as primary endpoints the

QoL at 12 months and the composite of death or non-fatal myocardial infarction during a follow-up of 36 months. Finally, the Evaluating Xience V and left ventricular function in percutaneous coronary intervention on occlusions after ST-elevation myocardial infarction (EXPLORE) trial (<http://www.exploretrial.com/>) is randomising 300 patients presenting with ST-segment elevation acute myocardial infarction and a CTO in a non-infarct vessel to either CTO PCI within seven days of presentation or standard medical therapy. The study's primary endpoint is left ventricular ejection fraction and end-diastolic volume, measured using cardiac magnetic resonance imaging at four months.

Section D

Stent Selection

Clinical Rationale for Drug-eluting Stents in Percutaneous Revascularisation of Coronary Occlusions

The appeal of drug-eluting stents (DES) for improving long-term vessel patency following CTO recanalisation is related not only to the success of DES in other complex lesion morphologies, but also to the clinical inadequacies of bare metal stents in sustaining restenosis-free patency in this particular lesion subset.⁷¹ As an example, in the Total occlusion study of Canada 1 (TOSCA-1) trial, rates of restenosis and re-occlusion six months after bare metal stent revascularisation exceeded 50 % and 10 %, respectively.⁷²

The failure to achieve or sustain patency after CTO recanalisation has been associated with an impairment in the regional and global left ventricular systolic function, recurrent angina and target vessel revascularisation, and a greater need for late bypass surgery.⁷³ Therefore, improving long-term, restenosis-free patency in coronary occlusions may have a potentially significant clinical impact.

Contemporary DES Trials in CTO Revascularisation

In the randomised Primary stenting of totally occluded native coronary arteries (PRISON) II trial (N=200), treatment with sirolimus-eluting stents (SES) was associated with statistically significant reductions in angiographic restenosis at six months (in-stent, 36 % versus 7 %, $p<0.0001$), reocclusion at six months (13 % versus 4 %, $p<0.04$) and repeat revascularisation at one year (21 % versus 5 %, $p<0.0001$).⁷⁴ At five years, the benefit of SES was sustained, demonstrating significant reductions in target lesion revascularisation (TLR, 30 % versus 12 %, $p=0.001$) and major adverse cardiac events, despite a greater number of cases of definite or probable stent thrombosis (ST).⁷⁵ Similar clinical and angiographic benefit using first-generation DES has been supported in non-randomised studies.^{76–84} Among the 200 CTO patients treated with SES in the prospective Approaches to chronic occlusions with sirolimus-eluting stents/total occlusion study of coronary arteries-4 (ACROSS/TOSCA-4) trial, the three-year rate of TLR and ST remained favourable at 10.9 % and 1.0 %, respectively, with no occurrences of ST beyond one year.⁸³ However, stent fracture was associated with higher restenosis rates.

The growing clinical trial experience with DES in CTO revascularisation has also enabled meta-analyses of angiographic and clinical outcomes.^{85,86} Among 17 studies evaluating SES and/or paclitaxel-eluting stents (PES) against bare metal stents in CTO revascularisation, treatment with DES was associated with a significant reduction in angiographic restenosis (odds ratio (OR) 0.15; 95 % CI, 0.08–0.26) and repeat revascularisation (OR 0.13; 95 % CI, 0.06–0.26), with a similar long-term incidence of death, myocardial infarction and ST.⁸⁵

While these findings further support the safety and efficacy of DES following CTO recanalisation, they also have implications regarding procedural technique. For example, restenosis in the entire treated segment after recanalisation occurs nearly twice as often beyond the stent margins than in-stent. Therefore, DES treatment of the entire segment exposed to pre-dilatation angioplasty may yield greater reductions in restenosis and subsequent TLR than with balloon angioplasty alone or in combination with bare metal stents.^{83,87} Nevertheless, percutaneous revascularisation of CTOs is routinely associated with more extensive stent placement. As a consequence, it is unclear whether the improvement in restenosis is offset by a potentially higher risk of thrombotic occlusion, by complications associated with stent fracture or by acquired late malapposition.^{83,88}

The question as to whether disparities in angiography and clinical outcome arise in more complex lesion morphologies is an issue of ongoing study and is especially relevant to coronary total occlusions. At present, at least five comparative trials of SES and PES in CTOs have been performed.⁸⁹ In general, these studies have been limited by their small study populations, which limit statistical comparisons – variability in trial design and limited clinical and angiographic follow-up. The demonstration of differences in clinical outcomes across the individual trials has been less consistent. More recently, the PRISON III trial randomised 300 CTO patients to receive either SES or two different zotarolimus-eluting stents, Endeavor and Resolute, Medtronic CardioVascular (Santa Rosa, CA).⁹⁰ Compared with SES, the primary endpoint of in-segment late lumen loss at the eight-month angiographic follow-up was significantly higher with Endeavor but similar with Resolute. Given the overall small sample size, the clinical outcomes did not vary statistically according to the DES assignment.

Additional studies have evaluated everolimus-eluting stents (EES) compared with PES,^{91,92} reporting lower angiographic and clinical restenosis with EES. In the Non-acute coronary occlusion treated by everolimus eluting stent (CIBELES) randomised trial that compared SES with EES (N=207), the nine-month in-stent late loss (primary endpoint, 0.13 ± 0.69 mm EES versus 0.29 ± 0.60 mm SES, $p=0.12$) and angiographic restenosis were similar between the stent types.^{93,94} At 12 months, TLR and ST were numerically, but not significantly, higher among SES-treated patients. In a recent meta-analysis, compared with first-generation DESs, second-generation DESs were associated with lower incidence of death (odds ratio [OR], 0.37; 95 % confidence intervals [CI], 0.15–0.91), target vessel revascularisation (OR, 0.59; 95 % CI, 0.40–0.87), binary angiographic restenosis (OR, 0.68; 95 % CI, 0.46–1.01) and reocclusion (OR, 0.35; 95 % CI, 0.17–0.71), but similar incidence of myocardial infarction (OR, 0.45; 95 % CI, 0.10–1.95) and stent thrombosis (OR, 0.34; 95 % CI, 0.07–1.59).⁹⁵

Additional studies evaluating EES in CTO revascularisation are forthcoming and include the Angiographic evaluation of the everolimus-eluting stent in chronic total occlusions (ACE CTO, clinicaltrials.gov identifier NCT01012869) and the evaluation of the XIENCE PRIME™ LL and XIENCE Nano™ everolimus eluting coronary stent coronary stents, performance, and technique in chronic total occlusions (EXPERT CTO, NCT01435031).

Section E

Clinical Summary and Recommendations

The aim of revascularisation in CTOs is to improve symptoms and/or prognosis, thus recanalisation attempt of a CTO should be considered

in the presence of symptoms or objective evidence of viability/ ischaemia in the territory of the occluded artery.

In the 2011 American College of Cardiology/American Heart Association PCI guidelines, CTO PCI carries a class IIA recommendation: "PCI of a CTO in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise".⁹⁶ The 2010 European Society of Cardiology state that "similar to nonchronically occluded

vessels, revascularisation of CTO may be considered in the presence of angina or ischaemia related to the corresponding territory".⁹⁷ In the 2012 statement on Appropriate Use Criteria for Coronary Revascularisation, coronary revascularisation was given a lower level recommendation compared with patients with 1–2 vessel CAD without a CTO in 5 of 18 assessed clinical scenarios.²⁵ It is the authors' opinion that the presence of a CTO should not have an impact on the revascularisation decision, as long as appropriate expertise in CTO PCI is locally available. ■

The authors support the following summary statements and specific recommendations regarding indications and performance of CTO PCI:

1. Compared to patients without coronary CTOs, those with CTO have worse clinical outcomes and lower likelihood of complete coronary revascularisation.
2. Successful CTO PCI can significantly improve angina and improve left ventricular function. Although currently unproven, successful CTO PCI might also reduce the risk for arrhythmic events in patients with ischaemic cardiomyopathy, provide better tolerance of future acute coronary syndrome and possibly improve survival.
3. Patients with an ischaemia-causing culprit CTO lesion who either (a) have had prior coronary artery bypass graft surgery and patent left internal mammary graft to the left anterior descending artery or (b) have single vessel coronary artery disease with a right coronary artery CTO are best treated with CTO PCI than with coronary artery bypass graft surgery.
4. Evaluation by a heart team comprised of both interventional and non-interventional cardiologists and cardiac surgeons is important for determining the optimal revascularisation strategy in patients with coronary artery disease and CTOs.
5. Ad hoc CTO PCI is generally not recommended, so as to allow sufficient time for (a) discussion with the patient about the indications, goals, risks, and alternatives to PCI; (b) careful procedural planning; and (c) contrast and radiation exposure minimisation.
6. Use of drug-eluting stents is recommended for CTO PCI, given the lower rates of angiographic restenosis compared to bare metal stents.

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