



Indications for Percutaneous Coronary Intervention (PCI) in Chronic Total Occlusion (CTO): Have We Reached a DECISION or Do We Continue to EXPLORE After EURO-CTO?

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A coronary chronic total occlusion (CTO) is a common finding during coronary angiography and is associated with increased mortality and poorer cardiovascular prognosis. Technological developments in percutaneous strategies for revascularisation have resulted in increased interest in this area. However, until recently, there has been a paucity of robust scientific randomised data comparing the efficacy of medical management with percutaneous strategies. Both observational data, and to a lesser extent, randomised data, suggest that CTO percutaneous coronary intervention (PCI) should be considered in symptomatic patients. However, in the absence of any randomised data, CTO PCI should not be performed for prognostic benefit. Ongoing trials are needed to confirm these findings as well as to identify the optimal timing and strategy of such interventions.

Keywords

Chronic total occlusion • Percutaneous Coronary Intervention • Interventional cardiology • Coronary artery disease • Revascularisation

Introduction

Coronary chronic total occlusions (CTO) are often referred to as the final frontier in interventional cardiology owing to their relative frequency and prognostic importance coupled with the paradoxical low adoption of revascularisation. Having been previously consigned to specialised operators in a few select centres, CTO percutaneous coronary intervention (PCI) is becoming increasingly adopted and is of mounting relevance to the wider cardiology community with advances in wire

types, device technology and treatment approaches [1]. With this increasing interest comes increasing scientific scrutiny. As a result, patient advocates, cardiologists and hospital administrators increasingly demand robust evidence for this often resource intense procedure. In the last 2 years, three trials: Percutaneous intervention for concurrent Chronic Total Occlusion in patients with ST-Elevation Myocardial Infarction (EXPLORE) [2]; A randomised multicentre trial to compare revascularisation with optimal medical therapy for the treatment of chronic occlusions (Euro-CTO) [3]; and DECISION-

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CTO [4] have added much needed randomised data. The aim of this review is to critique these studies and existing non-randomised data and to provide perspective within the established evidence base for CTO PCI.

Background

A CTO is the complete or near-complete occlusion of a coronary artery, defined as Thrombosis in Myocardial Infarction (TIMI) grade 0 flow, present for greater than 3 months [5]. Radiographically, this is appreciated by the filling of the distal occluded vessel by collaterals, within the aforementioned historical timing. The incidence of CTOs ranges between 18–52% depending on the cohort presenting for coronary angiography [6–9], with 6.6% of patients with an ST elevation myocardial infarction (STEMI) having a concurrent CTO [10]. The presence of a CTO is independently associated with poorer prognosis, with an almost 2.9-fold increased risk of mortality in patients presenting with a STEMI and concurrent CTO [10]. Similarly, the presence of a CTO in stable disease is also associated with a higher mortality [7], greater recurrence of ventricular arrhythmia [11] and ongoing anginal symptoms due to insufficient collaterals to prevent ischaemia during increased demand [12].

Observational Data

Until recently, the evidence base for the utility and effectiveness of CTO PCI was derived solely from registry data and non-randomised observational studies comparing successful PCI with failed PCI. A number of clinical benefits with CTO revascularisation had been observed with CTO PCI in these non-randomised studies.

Mortality

A number of non-randomised studies have shown that successful CTO PCI, compared to either medical management, or failed CTO PCI is associated with a significant improvement in survival [13–15]. Often, this is attributed to a reduction in ischaemic burden, with successful CTO PCI resulting in a greater reduction in ischaemia in those with a greater degree of ischaemia at baseline [16]. Indeed, both CTO specific studies, as well as general stable coronary disease studies, suggest that there is a survival benefit with revascularisation when the ischaemic territory is greater than 12.5% of at risk myocardium [16,17]. It is thus unsurprising that the mortality benefit appears to be particularly related to PCI of the left anterior descending artery (LAD), rather than the right coronary artery [18,19]. In a meta-analysis of almost 30,000 CTO PCI procedures, successful CTO PCI as compared to unsuccessful CTO PCI, remained an independent predictor of improved survival [20].

Reduced Anginal Symptoms and Improved Quality of Life

Despite the hallmark presence of coronary collaterals supplying the myocardial territory subtending the CTO, these are often insufficient to prevent ischaemia. Invasive pressure

wire testing has confirmed that less than 10% of collaterals provide sufficient functional reserve during pharmacological stress [12,21]. It follows, that in non-randomised data, successful CTO PCI, as compared to unsuccessful CTO PCI, is associated with less limitation of physical activity, reduction in angina and improved treatment satisfaction [22]. The degree of baseline ischaemia also predicts the degree of symptomatic improvement following PCI [16]. In the Primary Setting of Totally Occluded Native Coronary Arteries II (PRISON II) trial in which 200 patients with a CTO were randomised to PCI with either a sirolimus eluting stent or a bare metal stent following crossing of the occluded segment, there was a reduction in the proportion of patients with class 3 or 4 angina from 62 to 25% at 6 months [23]. Similarly, in the registry-based FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) trial, patients with successful CTO PCI had a significant reduction in angina, improvement in functional capacity and better quality of life scores as compared to those with unsuccessful CTO PCI [24].

Improved LV Function

In patients with left ventricular (LV) dysfunction in a viable territory subtended by a CTO, revascularisation with PCI has been associated with short-term [25] and long-term [26] improvement in objective parameters of ventricular function. In a recent meta-analysis [27] of studies documenting left ventricular ejection fraction (LVEF) pre and post CTO recanalisation in 2,243 patients, successful PCI was associated with an absolute improvement of 4% in LVEF. Magnetic resonance imaging (MRI) studies have shown that successful recanalisation of the CTO results in improved LVEF and regional wall motion [28], presumably attributed to viable hibernating myocardium which improves following restoration of antegrade blood flow and improved perfusion.

Decreased Ventricular Arrhythmia

One of the proposed mechanisms of the increased mortality seen in patients with a CTO is that of sudden cardiac death due to ventricular arrhythmias [11,29]. Mechanistically this may be explained either by chronic microvascular ischaemia resulting in abnormal electrical automaticity of myocytes or else by re-entrant circuits at the border of infarcted myocardium. However, there have been conflicting reports as to whether successful CTO PCI results in lower arrhythmia burden [29] or not [30].

Reduction in Ischaemia Burden

The putative advantage of PCI for the indication of a reduction in ischaemia long has been an area of significant controversy in both the setting of a CTO as well as stable coronary disease in general. In a study of 301 patients undergoing CTO PCI [16], a reduction in ischaemic myocardium of $\geq 5\%$ was associated with a mortality advantage in those with baseline ischaemia of $\geq 12.5\%$, most commonly seen in those with a CTO of the LAD. This finding is similar to that seen in stable coronary artery disease, whereby a reduction in ischaemia of $\geq 5\%$ with PCI is associated with improved prognosis

compared with optimal medical therapy (OMT) alone [31]. Similarly, following CTO PCI, there is a significant improvement in myocardial blood flow and reduction in ischaemia, which is similar to the effect of PCI on haemodynamically significant non-CTO lesions [32].

However, these studies are highly selective sub-analyses of larger studies, and are retrospective in their analysis. Consequently, a precise cut-off for ischaemia may be difficult to entertain, and may better serve as a guide as to what a large ischaemic territory may be quantified as.

The Importance of Randomised Data

The majority of available data in respect to the clinical benefit of CTO PCI is from non-randomised data, with which comes inherent bias. Furthermore, comparing outcomes in patients with successful CTO PCI with unsuccessful CTO PCI is fraught with bias, in that these two groups may reflect different patient populations, with patients who are more likely to have unsuccessful PCI having more complex disease and less collaterals [33]. Furthermore, it is also conceivable that undergoing an unsuccessful attempt at PCI to a CTO in itself could be potentially harmful, in that important collateral branches subtending the myocardium distal to the occlusion could be disrupted. Consequently, to ascertain if there is a clinical benefit of CTO PCI, randomised data are imperative.

Randomised Trials

In the EXPLORE trial [2], patients undergoing PCI for STEMI, who were found to have a concurrent CTO in a non-infarct related artery were randomised to either CTO PCI ($n = 150$) or medical therapy alone ($n = 154$) within 7 days of the index presentation. The primary endpoint was cardiac MRI determined LVEF and left ventricular end diastolic volume (LVEDV) at 4 months. Procedural success was 77% by operator adjudication but 73% by core laboratory assessment. At 4 months, there was no difference in LVEF or LVEDV between the 2 groups, although in sub-group analysis, in patients with a CTO of the LAD, PCI resulted in a higher LVEF compared to OMT (47.2% vs 40.4%, $p < 0.05$). Similarly, the longer term follow-up (median follow-up 3.9 years) showed no difference in LVEF, cardiac death or MACE, although freedom from angina was greater in the CTO PCI group [34].

Whilst this appeared to be a negative study for CTO PCI, a number of factors must be considered for the interpretation and external validity of this study. Firstly, this study was assessing only ventricular remodelling in patients presenting with a STEMI with concurrent CTO, and hence does not reflect the majority of patients considered for CTO PCI. Furthermore, the success rate of this study was relatively low, particularly compared to the other randomised trials published in the last few years, which may reflect either more complex disease, or recruitment in less experienced centres. Finally, the finding of benefit

with CTO PCI of the LAD is in keeping with previous studies [18,19], and requires further assessment.

The Euro-CTO trial [3], was a prospective, randomised, multi-centre, open-labelled control trial comparing treatment between CTO PCI and OMT in a 2:1 randomised ratio in 396 patients. The primary endpoint was the change in health status as assessed by the Seattle angina questionnaire (SAQ) at 12 months. Optimal medical therapy was defined as the use of aspirin, an angiotensin converting enzyme inhibitor and a statin, along with at least two anti-anginals. Of note, complete revascularisation was mandated in the study, with 52.2% of patients undergoing drug eluting stent (DES) to other vessels prior to randomisation of the CTO. Of the 259 patients randomised to PCI, 220 patients (86.6%) had procedural success. Adverse events related to PCI were few in this cohort. At 12 months, in the intention to treat analysis, a greater improvement in SAQ subscales was seen in patients undergoing PCI as compared to OMT. This corresponded with significantly lower angina frequency, higher rates of freedom from angina and higher quality of life scores. Whilst not powered for clinical endpoints, there was a lower rate of ischaemia driven revascularisation in the PCI group compared to OMT (2.9% vs 6.7%, $p < 0.05$), suggesting a role for CTO PCI with respect to both symptoms, quality of life and clinically relevant endpoints. However, patients and clinicians were not blinded to the treatment type which may have impacted on the treatment effect.

The DECISION-CTO trial [4] was also a prospective, open-labelled randomised trial comparing CTO PCI with OMT (in a 1:1 fashion) with respect to clinical endpoints. The protocol in the study included patients with non-CTO lesions requiring PCI, and hence the study was therefore plagued by the “noise” from events related to the non-CTO PCI and this must be considered when appraising this study. Inclusion criteria were patients with stable angina, acute coronary syndrome (ACS) and silent ischaemia with the primary endpoint the composite of all-cause mortality, myocardial infarction, stroke or repeat revascularisation. Examination of the data set also revealed that the CTO lesions were short and were easily wired, which may suggest that some of these lesions may have been sub-acute occlusions rather than true CTOs. The study was designed as a non-inferiority trial with respect to OMT compared to PCI, with the initial power calculations mandating 1,284 patients. However, due to slower than anticipated recruitment, the study was stopped prematurely after enrolment of only 834 patients. Of the 459 patients randomised to PCI, the success rate was 91.1%. In the intention to treat analysis, at 3 years they reported no difference between the CTO PCI group compared to the OMT group with respect to the cumulative primary endpoint (20.6% vs 19.6%, $p = 0.54$). Similarly, no difference in quality of life scores was observed between the groups. However, there was significant cross-over within groups (18.1% in the OMT group underwent PCI whilst 15.6% of the PCI group were only treated with OMT). When analysed based upon treatment received, OMT did not meet the pre-specified non-inferiority margin, suggesting symptomatic benefit with CTO PCI.

Clearly, both EURO-CTO and DECISION CTO were well conducted studies in experienced centres with expert CTO operators. However, these contradictory results have increased the

confusion for many with regard to which patients would benefit from PCI. Looking closely at the studies, however, a number of points must be considered. Firstly, with respect to the design of DECISION-CTO, complete revascularisation was not mandated prior to randomisation, with 77% of patients having multivessel disease which may have been treated percutaneously following randomisation. This may explain some of the symptomatic benefit observed in the OMT group. Secondly, in the DECISION-CTO trial, the number of patients recruited was 450 fewer than necessary for the power calculation performed, in spite of the fact that patients with an ACS and silent ischaemia were included. Despite this, the under-powered study showed a trend toward a reduction in cardiovascular death (1.9% vs 3.6%, $p=0.22$) and all-cause death (3% vs 4.4%, $p=0.25$) at 3 years, as well as stroke (1% vs 5%, $p=0.11$) at 5 years in the PCI group compared to OMT. Whilst only hypothesis generating, the finding of an almost 50% reduction in cardiac death and other clinical outcomes provides support for the long-standing observational data described above. Clearly, there is a need for an appropriately powered study with adequate numbers to further investigate whether this signal may translate into meaningful outcomes.

Local Centre and Operator Experience

Another important factor to consider when contemplating whether to refer a patient for CTO PCI is the expected success rates. Whilst numerous scoring tools based upon angiographic and case factors may help predict this, operator experience strongly influences success rates. Whilst the success rate is over

90% [4] in high volume centres, it is considerably lower in less experienced centres, with an analysis from the National Cardiovascular Data Registry (NCDR) procedural success of CTO PCI between 2009 and 2013 was 59% [35]. This may also influence where and when to refer a patient for CTO PCI.

Current Guidelines and Ongoing Trials

Both the European Society of Cardiology/Europan Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines on Myocardial Revascularization [36] and the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) Guidelines for Percutaneous Coronary Intervention [37], published prior to the randomised studies into CTO PCI, give a class IIa recommendation for CTO PCI, in the setting of symptoms. Whilst there appears to be some increasing evidence that PCI may reduce symptoms and improve quality of life, there remains some conflicting data.

In the current state of play, we believe CTO PCI should be reserved for alleviation of symptoms in patients despite medical management. Based upon current observational studies and randomised trial data, it cannot currently be advocated that CTO PCI be performed purely with the aim of improving LV function. Consequently, PCI should not be offered for prognostic benefit, although in the setting of extensive ischaemia (>12.5%) this could be considered and discussed with the patient during the decision making process (Figure 1).

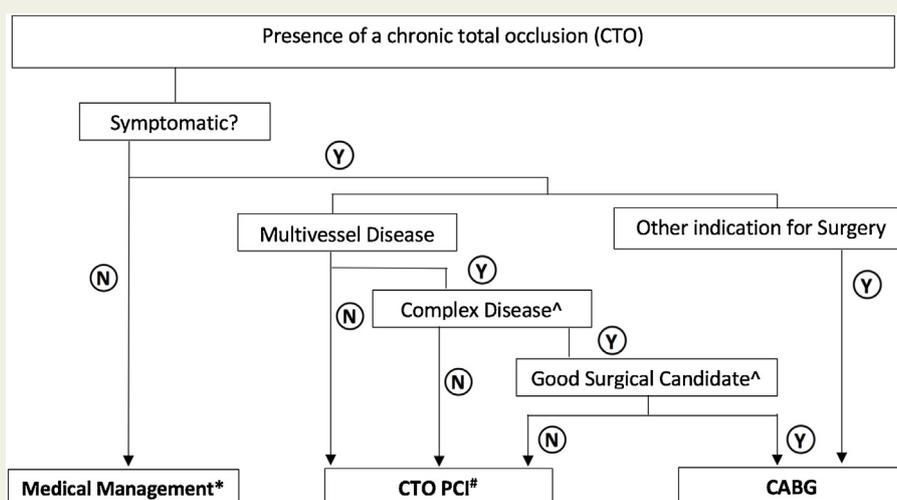


Figure 1 Treatment algorithm for CTO.

*In the setting of >12.5% ischaemia or similarly large territory of ischaemia, CTO PCI could be considered on an individualised patient basis. ^ Assessment of complex disease and surgical candidate must be individualised and ideally discussed in a heart team meeting. Disease complexity may be guided through CTO scoring tools, such as the J-CTO score, the Syntax score, as well as surgical morbidity and mortality predictive tools. #CTO PCI should only be considered when operators are experienced in performing this, or are proctored, and the centre has appropriate experience in managing complications as they occur.

Abbreviations: CTO, chronic total occlusion; PCI, percutaneous coronary intervention

Whilst randomised data has finally entered the sphere of CTO PCI, there remains the need for adequately powered, well designed and executed studies to build on the trends and existing evidence base. The SHINE-CTO trial [38] is currently enrolling patients whereby CTO PCI will be compared with a sham CTO procedure to determine changes in quality of life measures at 1 month as well as clinical and economic assessments. This is particularly important in that one previous study found that, even in patients with fixed perfusion defects, as assessed by nuclear perfusion imaging, in the territory supplied by the CTO, PCI resulted in a symptomatic benefit [39]. As has been seen with the recently published sham control trials, Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) [40], SYMPPLICITY HTN-3 [41] and Catheter Ablation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA) [42], the importance of a sham comparator is all the more vital to limit any placebo or trial effect of intervention. Furthermore, the optimal timing and strategy for CTO PCI for optimal long-term results also remains an area of ongoing research.

Conclusions

The presence of a CTO is associated with significant morbidity and mortality above and beyond that of other forms of stable coronary artery disease. With ever improving percutaneous strategies and success rates for revascularisation, the importance of appropriateness criteria and valid indications are vital. Chronic total occlusion PCI should be reserved for management of symptoms not responding to medical management. However, further appropriately powered and designed studies remain necessary to further elucidate any further benefit from PCI.

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