Evidence for Benefit of Percutaneous Coronary Intervention for Chronically Occluded Coronary Arteries (CTO) – Clinical and Health Economic Outcomes

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Abstract

Percutaneous revascularisation of a coronary chronic total occlusion (CTO) remains one of the technical frontiers of interventional cardiology. CTOs are common, and yet intervention is only attempted in 10 % of cases. CTO procedures are perceived to be technically challenging, lengthy, associated with significant risk and have only limited data to support the practise. Recent technical advances have dramatically increased the success rate, shortened procedural time and improved clinical outcomes. The aim of this article is to critically examine the data that supports CTO intervention, including specifically an appraisal of procedural safety, benefit and overall cost effectiveness.

Keywords

Chronic total occlusions (CTO), benefits, economic outcomes

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A chronic total occlusion (CTO) in a coronary artery is defined as “the presence of TIMI 0 flow within an occluded arterial segment of greater than three months standing.”¹ The successful percutaneous revascularisation of CTO vessels represents one of the dominant remaining technical challenges in interventional cardiology.

CTOs are common, found in between 20 %² and 50 %³ of all patients with significant coronary artery disease (defined as a stenosis of >70 % in a single epicardial vessel). However, despite the frequency with which they are encountered, an attempt at revascularisation is made in only 10 % of cases.⁴ There remains a perception that CTO intervention is lengthy, costly, associated with significant risk and offers only limited clinical benefit. This is rooted in historical data demonstrating that both the procedural success and the long-term patency of CTO percutaneous coronary intervention (PCI) has been significantly lower when compared to non-CTO PCI.⁴ Almost certainly because of these data and reservations about CTO PCI, the culture has developed that only a minority of CTO cases are considered for angioplasty. Most patients are therefore treated with simply medical therapy, thus condemning them to ongoing angina or coronary artery bypass surgery (CABG) surgery. Whilst surgery is an effective therapy for most patients, this is a longer procedure, with higher risk, longer recovery and there are recent concerns regarding long term graft patency specifically in the context of CTO.⁵

The traditional technical approach to CTO PCI is progressive antegrade wire escalation strategy. This remains technically challenging and has a high failure rate even in expert hands.⁴ Procedures are often lengthy and associated with high radiation doses for both patient and operator, as well as large volumes of radiographic contrast. Recent technical advances, including the adoption of dissection/re-entry⁶ and equipment

to enable a retrograde approach⁷, have significantly increased procedural success rates. In addition, the new hybrid strategies (see *Figure 1*) have shortened procedure time, reduced contrast load, and decreased the need for repeat procedures^{7,8} (see *Figure 1*). Despite the perceived complexity of these techniques, they can be taught extremely effectively using an experienced proctor – and adopting such an approach can significantly improve success rates.⁹

Despite these advances, controversy persists regarding the objective clinical value of successful CTO PCI. The aim of this article is to critically examine the data that supports contemporary percutaneous CTO intervention, specifically including an evaluation of procedural safety and cost effectiveness.

Clinical Safety

A perception persists that the percutaneous treatment of coronary CTOs is associated with significant procedural and patient risk.⁴ This however is not reflected in the published data in the modern literature that reflects contemporary practise. In the largest published meta-analysis, examining over 18,000 patients undergoing a CTO PCI procedure from 65 studies in the era 2000–11, there was an overall rate of major adverse cardiovascular events (MACE) of 3.1 % (pooled estimate, 95 % CI: 2.4 %–3.7 %).¹⁰ Specifically, the overall procedural mortality was 0.2 %, with the commonest procedural complications being perforation (2.9 %, 95 % CI: 2.2 %–3.6 %) and contrast nephropathy (3.8 %, 95 % CI: 2.4 %–5.3 %). Overall, the success rate across the cohort was 77 %, with evidence that this has improved progressively year on year during the duration of the study (see *Figure 2*). The authors were able to study the impact of the retrograde approach in over 886 lesions (884 patients), and reported an similar overall MACE rate (3.1 %), driven predominately by periprocedural

MI (2.8 %), but with a lower rate of procedural mortality (0.1 %). The success rate of the retrograde approach is comparable to that of the overall cohort at 79.6 %.

The incorporation of Bridgepoint™ technology into the hybrid strategy for the treatment of CTOs has led to its adoption in CTO practice despite no large scale published data on the safety of controlled dissection re-entry using the system.¹¹ The largest single-centre series published to date utilised the approach in 62 consecutive cases (60 patients) and have reported follow-up data for a median duration of 1.8 years. When compared to a demographically similar cohort of patients that underwent a CTO procedure over the same time scale that did not utilise Bridgepoint™ technology, overall success rates were similar to that quoted in the wider literature (Bridgepoint™ vs Non-Bridgepoint™: 74.2 % vs 75.4 %; $p=0.99$) and there were no significant differences in immediate procedural complication rates (Bridgepoint™ vs Non Bridgepoint™: overall complication rate 8.2 % vs 8.3 % ($p=0.99$); Perforation rate 1.6 % vs 3.2 % ($p=0.99$); vascular site complication 7.6 % vs 3.6 %: $p=0.27$). There was a higher (non-significant) rate of procedural MI reported in the Bridgepoint™ group (13.2 % vs 7.2 %, $p=0.25$) but the clinical impact of this remains uncertain. It is important to note, however, that within the Bridgepoint™ group, a significantly higher proportion of patients had already had one unsuccessful attempt (1.6 % vs 13.1 %; $P=0.01$) at CTO PCI by an alternative strategy. This indicates that controlled dissection-re-entry using Bridgepoint technology is a safe and effective technique that offers a reproducible way to facilitate procedural success in CTOs that in many cases would remain untreatable.¹¹ However, long-term multicentre clinical outcome data remains unavailable, as do randomised controlled trials.

When compared to an overall procedural mortality rate of 0.65 % for all PCI undertaken outside of ST segment elevation myocardial infarction (STEMI) (excluding cardiogenic shock)¹², CTO PCI using both traditional and hybrid techniques can be considered safe. Of course, such published data is derived from a series of cohort analysis in whom the operators were expert practitioners. Given the learning curve for new CTO PCI techniques, the current recommendations advocate that CTO intervention should be undertaken by those individuals that have a specific interest in CTO intervention and who have undergone specialist training.¹ There is evidence that having procedural guidance by visiting highly experienced proctors in the catheter lab significantly improves procedure success rates and shortens the learning curve⁹ Conceptually, however, CTO PCI (including retrograde techniques) is safe, with a low overall complication rate.

Clinical Benefits

The underlying justification behind an attempt at CTO recanalisation is the relief of myocardial ischaemia in an area supplied by an occluded artery. This may manifest either as symptomatic angina/angina equivalent, or if asymptomatic, to involve a sufficient extent of myocardium be of sufficient quantity on a non-invasive ischaemia test as to carry prognostic significance. Whilst the relief of symptoms is clear cut, the objective data to support a prognostic benefit for CTO PCI purely on the grounds of the amount of reversible ischaemia is circumstantial and derived from indirect cohort analysis rather than from prospective randomised studies. The following section will describe the data that supports CTO intervention:

- I. firstly, in those patients with symptomatic angina – with the goal of symptom relief, and

Figure 1: Algorithm Summarising the Hybrid Strategy for the Crossing and Successful Treatment on Coronary Chronic Total Occlusion

Algorithm summarising the Hybrid strategy for the crossing and successful treatment of Coronary chronic total occlusions. Adapted from Brilakis et al.⁸

Figure 2: Temporal Trends In Cumulative Angiographic Success Rates and Major Procedural Complication Rates

Temporal trends in cumulative angiographic success rates and major procedural complication rates, presenting according to study publication year. Reproduced from Patel et al. with kind permission of the American College of Cardiology Foundation.¹⁰

- II. secondly in patients with demonstrable ischaemia on a non-invasive test (who may be asymptomatic) – in whom the document goal is to improve prognosis.

Symptomatic Angina

Numerous studies have demonstrated that successful CTO intervention is effective at reducing angina.^{13,14} Specifically, in patients with clear angina symptoms (CCS 3–4), successful CTO intervention is associated with an early improvement in angina frequency, physical limitation and quality of life (QoL),¹⁴ when compared to those patients in which CTO recannulisation was unsuccessful.

However, amongst patients who have minimal symptoms of angina (defined in one study as having an angina frequency score of <100 and termed asymptomatic), only modest non-significant improvements in both angina frequency and QoL were noted after successful PCI. Amongst this group, there were no significant differences noted in angina frequency or QoL score if the PCI procedure was successful or not, along with no differences in 30-day mortality (see Figure 2).¹⁴ There remains no long-term systematic follow-up data

Figure 3: Effect of Procedural Success on Adjusted Health Status Outcomes Among Patients Without (Asymptomatic) and with (Symptomatic) Pre-procedural Angina

Variables used in this model included age, sex, prior MI, hypertension, hyperlipidaemia, diabetes, smoking status, prior CABG, number of diseased vessels, ejection fraction, pre-procedural creatinine, B-blocker, calcium channel blocker, and nitrate use. Data expressed as point estimate of change in outcome from baseline to follow-up with 95% confidence intervals. Reproduced from Grantham et al. by kind permission of the American Heart Association.¹⁴

Figure 4: Markov Model for Comparing Chronic Total Occlusions-Percutaneous Coronary Intervention (CTO-PCI) with Optimal Medical Treatment in Patients With Chronic Stable Angina

*= Risk of stent thrombosis only pertains to patients post successful CTO-PCI. CABG = coronary artery bypass graft; CVA = Cerebrovascular accident (stroke); OMT = optimal medical therapy; TVR = Target vessel revascularisation. Reproduced from Gada et al. by kind permission of the British Cardiovascular Society.²⁷

to assess the overall impact on mortality/prognosis in this cohort of asymptomatic patients.

In addition to the improvement in symptoms, successful CTO intervention can lead to demonstrable improvements in left ventricular function,¹⁵⁻¹⁷ and a reduction in ventricular arrhythmias¹⁸ when completed in patients with impaired left ventricular systolic function. In addition, a number of observational studies have demonstrated a reduction in the need for coronary bypass surgery in those patients who have undergone a successful CTO PCI procedure.¹ All these data were derived from patients who presented with symptomatic angina. By contrast, there are, at present, no specific data to support CTO revascularisation with the aim of improving left ventricular function

or preventing ventricular arrhythmias in patients who do not have manifest angina. There are ongoing trials in this area that are due to report in 2016-17 (see below).

Prognostic Impact

The identification of ischaemia in patients with coronary artery disease (CAD) is likely a key determinant of prognosis.¹⁹ Furthermore, reducing the overall ischaemic myocardial burden (i.e. effective re-vascularisation) is effective at long-term improvement prognosis.^{13,20,21} Contemporary data looking specifically at non-invasive measures of ischaemia suggest that in symptomatic patients with demonstrable ischaemia of greater than 10 % of viable myocardium, a reduction in ischaemic burden by more than 5 % is associated with a significant improvement in overall mortality, as well as a reduction in the incidence of MI.²² This effect is marked most amongst patients who have the greatest ischaemic burden pre-revascularisation.²² It could be inferred, that in patients with at least one CTO and demonstrable ischaemia on a non-invasive test, revascularisation may be of significant clinical benefit.

In patients with a CTO, an ischaemia burden of more than 12.5 % on myocardial perfusion scanning was associated with a greater probability of a successful reduction in ischaemia (greater than 5 % improvement noted in 34.7 % with mild ischaemia vs 86.7 % in severe ischaemia $P<0.001$) following successful CTO intervention with a sensitivity and specificity of 80 % respectively. Paradoxically, amongst this group of 301 patients, those with a low ischaemia burden before CTO intervention (less than 6.25 %), were more likely to have an increase in ischaemia post PCI.²³ This maybe due to restenosis, loss of collateral circulation, loss of side branches, or progression of coronary artery disease in other territories.

Further evidence that the presence and extent of ischaemia is a determining factor in defining patient prognosis can be derived from examining outcomes after an attempt at PCI. Overall, incomplete revascularisation is associated with worse clinical outcomes when compared to patients in whom complete revascularisation has been achieved.²¹ The presence of a CTO is a predictor of incomplete revascularisation in those patients treated with PCI. For example, in a cohort of over 11,000 PCI patients treated in the DES era, 69 % ($n=7795$) were incompletely revascularised. These individuals had a higher mortality rate at 18 months (adjusted HR 1.23, 95 % CI 1.04-1.45), that increased if greater than two vessels (including a CTO) remained unrevascularised (HR 1.44 95 % CI 1.14-1.82, adjusted survival 94.9 % vs 92.9 % $p=0.002$). Hence, within the context of symptomatic angina, successful CTO intervention which leads to complete revascularisation (and relief of underlying ischaemia) may offer a substantial mortality benefit.²⁰ It is also important to appreciate that CABG is not certain to produce complete revascularisation. For example, in the Syntax trial CTO subset, successful bypass grafting to an occluded arterial segment occurred in only 69 %, with complete revascularisation (in the context of a CTO) being achieved in only 49 %²⁴, albeit by a very strict definition. Interpretation of these data requires care, of course.

There remains a paucity of a large scale randomised trial data that specifically addresses the outcomes after successful ischaemia-driven CTO intervention. The bulk of data currently available to support CTO interventional practice is derived from registries that compare patients in whom CTO intervention has been successful with those in whom it

has not. For example, when comparing 582 successful CTO procedures with 282 cases in which revascularisation was not achieved, Jones et al. report a 12.7 % decrease in mortality at five years.²⁵ A meta-analysis of data available up until 2010, including over 7,000 patients across 13 studies found a 3.2 % lower mortality with successful CTO intervention¹³ (14.3 % vs 17.5 % OR 0.56, 95 % CI 0.43–0.72). In addition, a significantly lower rate of CABG was observed (OR 0.22, 95 % CI 0.17–0.27), but no differences in MI or other major adverse cardiac events were noted. Overall, successful CTO intervention does appear to offer a prognostic advantage, but only when compared to those in whom a CTO procedure was unsuccessful. These data provide circumstantial evidence at best: a randomised trial of CTO PCI versus optimal medical therapy (OMT) with an intention-to-treat analysis is required for definitive proof of benefit.

The reasons behind the difference between successful and unsuccessful CTO PCI remain undefined. Certainly, the differences observed can only partly be explained by adverse events in the unsuccessful PCI arms, the rates of which are broadly similar across reported data.¹³ The observed prognostic benefit may relate partly to a reduction in ischaemia driven arrhythmia,¹⁸ and possibly improved outcome amongst patients who go on to have an acute myocardial infarction of a non-CTO artery, on the basis of the “double jeopardy” theory. This was demonstrated in one large series of over 3,200 STEMI patients where the presence of a CTO, distinct from the culprit artery, was an independent predictor of 30-day mortality (HR 3.6, 95 % CI 2.6–4.7; $p < 0.01$). In those alive at 30 days, the presence of a CTO remains a predictor of overall five year mortality.²⁶

To summarise, although the current data are encouraging, Despite these favourable indicators, CTO interventional practice is still lacking a large scale randomised trial to formally demonstrate prognostic benefit for the procedure. However, to answer this criticism, two large scale randomised trials comparing CTO intervention with optimal medical therapy are ongoing, EURO-CTO and DECISION-CTO, both of whom are still recruiting and due to report in 2017 & 2018 respectively.

Cost Effectiveness

As is detailed above, objective evidence from properly conducted randomised trials that CTO intervention decreases mortality is not available at present. As such, a formal assessment of cost effectiveness of CTO intervention versus medical therapy is difficult. Indeed, CTO PCI in the majority of cases is only offered to those patients who continue to be symptomatic despite optimal medical

therapy. However, utilising a Markov model examining a hypothetical cohort of 10,000 patients (see Figure 3), Gada et al. have constructed a detailed analysis of the relative cost benefits of CTO intervention in patients with CCS class III-IV angina. Based on a mean age of 60 years, with a procedural success rate (68 %) and overall complication rate derived from contemporary published literature and based upon costs derived from CTO procedures conducted in an outpatient setting, the authors were able to calculate cost benefit model over a five-year period.²⁷ They concluded that a successful CTO PCI strategy incurred higher costs than optimal medical therapy (\$31,512 vs \$27,805), but accumulated more quality-adjusted life-years (QALYs). Overall, CTO-PCI appeared to be cost effective, with a ratio of \$9,505/QALY, which is well below the accepted conventional threshold of \$50,000/QALY.

With the addition of further variables, including the costs of a repeat CTO procedure that increased the overall procedure success rate to 80 %, the cost per QALY rose to \$14,047/QALY, which is still dominant.

Importantly, however, the cost calculations are based on procedures conducted in a single centre between 2010–11. This is before the more widespread adoption of technology such as the Corsair[®] microcatheter and the Crossboss[™] dissection re-entry system. The use of these technologies demonstrably increases the overall rate of procedure success^{6,7}, but they are associated with a increase in overall procedural cost. This may be balanced with a reduced need for a second CTO-PCI procedure and reduced rate of target lesion revascularisation (TLR) but data is not available to fully establish true cost effectiveness of these technical advances in CTO revascularisation.

Conclusions

CTO intervention remains a technically challenging process, but recent advances in technology and technique have increased procedural success rates and safety. Despite the complexity of the hybrid CTO techniques, these are readily teachable to experienced PCI operators with an interest in CTO. However, given the learning curve for these technically challenging techniques, it is clear that CTO PCI should be concentrated on a relatively few specialist operators. In patients with significant angina, CTO intervention is proven to be highly effective at relief of symptoms. This is likely to be cost effective – even allowing for increases in procedural costs associated with newer hybrid strategies. In patients with demonstrable ischaemia in a territory supplied by an occluded vessel, CTO intervention is likely to offer prognostic benefit but this has not yet been confirmed in a large scale randomised trial. ■

1. Sianos G, Werner GS, Galassi AR, et al. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. *EuroIntervention* 2012;8:139–45.
2. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 2012;59:991–7.
3. Christofferson RD, Lehmann KG, Martin GV, et al. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol* 2005;95:1088–91.
4. Grantham JA, Marso SP, Spertus J, et al. Chronic total occlusion angioplasty in the United States. *JACC Cardiovasc Interv* 2009;2:479–86.
5. Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. *Circulation* 2004;110:3418–23.
6. Werner GS, Schofer J, Sievert H, et al. Multicentre experience with the Bridge-Point devices to facilitate recanalisation of chronic total coronary occlusions through controlled subintimal re-entry. *EuroIntervention* 2011;7:192–200.
7. Joyal D, Thompson CA, Grantham JA, et al. The retrograde technique for recanalization of chronic total occlusions: a step-by-step approach. *JACC Cardiovasc Interv* 2012;5:1–11.
8. Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv* 2012;5:367–79.
9. Sharma V, Natsios A, Harcombe A, Smith W. Impact of proctoring and new techniques on success rates for operators undertaking percutaneous intervention of chronic total occlusions. *Heart* 2013;99:A39.
10. Patel V, Brayton K, Tamayo A, et al. Angiographic Success and Procedural Complications in Patients Undergoing Percutaneous Coronary Chronic Total Occlusion Interventions. *J Am Coll Cardiol Interv* 2013;6:128–36.
11. Mogabgab O, Patel VG, Michael TT, et al. Long-term outcomes with use of the CrossBoss and Stingray coronary CTO crossing and re-entry devices. *J Invasive Cardiol* 2013;25:579–85.
12. Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2010;55:1923–32.
13. Joyal D, Afilaio J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J* 2010;160:179–87.
14. Grantham JA, Jones PG, Cannon L, Spertus JA. Quantifying the early health status benefits of successful chronic total occlusion recanalization: Results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) Trial. *Circ Cardiovasc Qual Outcomes* 2010;3:284–90.
15. Kirschbaum SW, Baks T, van den Ent M, et al. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. *Am J Cardiol* 2008;101:179–85.
16. Melchior JP, Doriot PA, Chatelain P, et al. Improvement of left ventricular contraction and re-laxation synchronism after recanalization of chronic total coronary occlusion by angioplasty. *J Am Coll Cardiol* 1987;9:763–8.
17. Cheng AS, Selvanayagam JB, Jerosch-Herold M, et al. Percutaneous treatment of chronic total coronary occlusions improves regional hyperemic myocardial blood flow and contractility: insights from quantitative cardiovascular magnetic resonance imaging. *JACC Cardiovasc Interv* 2008;1:44–53.
18. Nombela-Franco L, Mitroli CD, Fernández-Lozano I, et al.

- Ventricular arrhythmias among im-plantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coro-nary occlusion (VACTO Primary Study). *Circ Arrhythm Electrophysiol* 2012k;5:147–54.
19. Longman K, Curzen N. Should ischemia be the main target in selecting a percutaneous coro-nary intervention strategy? *Expert Rev Cardiovasc Ther* 2013b;11:1051–9.
 20. Valenti R, Migliorini A, Signorini U, et al. Impact of complete revascularization with percutane-ous coronary intervention on survival in patients with at least one chronic total occlusion. *Eur Heart J* 2008c;29:2336–42.
 21. Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascu-larization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol* 2013d;62:1421–31.
 22. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Re-vascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008e;117:1283–91.
 23. Safley DM, Koshy S, Grantham JA, et al. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. *Catheter Cardiovasc Interv* 2011f;78:337–43.
 24. Thompson C. Percutaneous revascularisation of coronary chronic total occlusions: the new era begins. *JACC Cardiovasc Interv* 2010;3(2):152–4.
 25. Jones DA, Weerackody R, Rathod K, et al. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovasc Interv* 2012d;5:380–8.
 26. Claessen BE, van der Schaaf RJ, Verouden NJ, et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 2009j;2:1128–34.
 27. Gada H, Whitlow PL, Marwick TH. Establishing the cost-effectiveness of percutaneous coro-nary intervention for chronic total occlusion in stable angina: a decision-analytic model. *Heart* 2012m;98:1790–7.