CONTEMPORARY EVIDENCE, TREATMENT STRATEGIES, AND INDICATIONS FOR CHRONIC TOTAL OCCLUSION-PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

Chronic total occlusions (CTOs) are detected incidentally in ~20% of patients undergoing coronary angiography and are often associated with significant morbidity and mortality. CTOs can manifest with worsening symptoms, reduced left ventricular function, and increased incidence of ventricular arrhythmias. Despite this, according to USA, Italian, and Japanese national registry data, only ~5–22% of CTO lesions are treated by percutaneous coronary intervention (PCI). CTO-PCI is a particularly challenging technique for this subset of lesions and has traditionally been associated with increased risks and complications compared to conventional PCI. However, increased experience, the development of novel techniques, and dedicated equipment have revolutionised CTO-PCI. USA, Italian, and Japanese registry data have shown success rates of between 85% and 90%, with diminishing complication rates when performed by experienced operators. Moreover, observational studies have suggested that there are significant benefits of using CTO-PCI, including fewer symptoms, improved quality of life, reduced need for coronary artery bypass surgery, and reduction in ischaemic burden and mortality. In addition, when there is demonstrable ischaemia and viable myocardium in the CTO territory, there is further potential prognostic benefit from complete revascularisation. However, there has so far been a relative lack of randomised trial data to support the routine use of CTO-PCI. This paper reviews the current evidence surrounding this subject and discusses the arguments for and against CTO-PCI. It includes an exploration of the interventionalist's 'toolbox' and the techniques used in CTO-PCI, including a section on 'tips and tricks' for the most challenging cases. Finally, there is a discussion on the future of CTO-PCI including promising ongoing clinical trials and novel equipment that may improve outcomes and help to establish a more widespread adoption of CTO-PCI.

Keywords: Percutaneous coronary intervention (PCI), chronic total occlusion (CTO), drug-eluting stents (DES), retrograde, antegrade dissection/re-entry technique (ADR), microcatheter.

BACKGROUND AND HISTORICAL PERSPECTIVE

"If I had an enemy I would teach him angioplasty,"[1] were the words uttered by Andreas Gruentzig in 1980, 3 years after he performed the first percutaneous coronary intervention (PCI) in September 1977. Andreas Gruentzig would have witnessed the clinical benefits subside over time and, as the reality dawned that adverse events do occur post PCI, the initial honeymoon period and optimism of using PCI would have been diminished. Through further technological development, operator skill, and pharmacotherapy, PCI has now become the mainstream of treatment and the default choice for most revascularisation procedures. However, the last frontier of PCI that fills most operators with trepidation is chronic total occlusion (CTO)-PCI. There has been a large increase of innovations that have allowed the interventional cardiologist to treat diseases that were once only amenable to surgery.

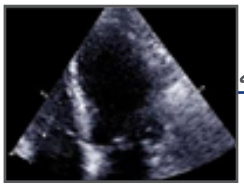
CHRONIC TOTAL OCCLUSIONS

PCI  VS  Medical Therapy

REDUCED ISCHAEMIC BURDEN
Reduction in ischaemic burden associated with reduction in death/MI in COURAGE nuclear substudy[7,17]

IMPROVED QOL AND SYMPTOMS
Observational studies show improvements in angina/dyspnoea symptoms, functional ability, and QOL, especially in symptomatic patients[23]

IMPROVED LVEF[43,44]



REDUCED NEED FOR CABG[47]

BETTER TOLERANCE OF FUTURE ACS
The presence of a non-IRA CTO has been shown to be an independent predictor of short and long-term mortality after STEMI[57]

HIBERNATING MYOCARDIUM CAN RECOVER AND REMODEL AFTER CTO-PCI
CTO-PCI had positive effects on LV remodelling in viable myocardium in CMR studies[43,44,57]

COMPLETE REVASCULARISATION
Observational data has found that mortality reduces with increasing completeness of revascularisation in those undergoing CTO-PCI[46]

IMPROVED SURVIVAL
Observational studies and meta-analyses suggests CTO revascularisation is associated with reduction in mortality[4,46]

LACK OF EVIDENCE
There is a lack of RCT or hard cardiovascular outcome data supporting use of CTO-PCI. Recent RCTs have had conflicting results[21,22]

Many observational studies supporting CTO-PCI have compared successful vs. unsuccessful PCI, which is not equivalent to comparing with medical therapy[4]

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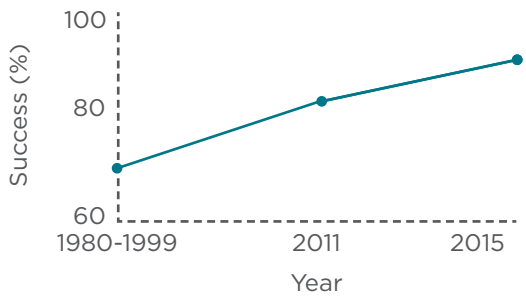
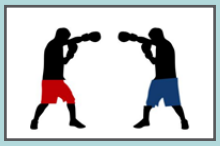
CTO-PCI IS A LONG PROCEDURE[51]
CTO procedures are longer than conventional PCI, and require more equipment and resources

CTO-PCI HAS HIGHER RISK
CTO-PCI has traditionally been associated with lower technical success and greater complication rates, including the risk of coronary perforation and cardiac tamponade[51]

However, procedural success is improving and complication rates are decreasing as operator experience increases, and with advanced techniques and equipment.[21,23,48,50]



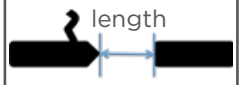


HIGHER RADIATION AND CONTRAST EXPOSURE[51]
CTO-PCI procedures involve increased fluoroscopy times, radiation doses, and contrast load

Figure 1: The boxers' guide to CTO-PCI: A selection of arguments for and against CTO-PCI.[4,8,44-54]

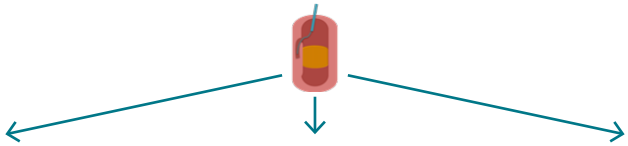
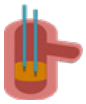
PCI: percutaneous coronary occlusion; MI: myocardial infarction; IRA: infarct related artery; CTO: chronic total occlusion; CABG: coronary artery bypass grafting; ACS: acute coronary syndrome; RCT: randomised controlled trial; LVEF: left ventricular ejection fraction; QOL: quality of life.

A) J-CTO SCORING SYSTEM

Entry shape of lesion		Calcification	Lesion bending >45°	Length of occlusion	Previous failed attempt
Tapered	Blunt				
					
Tapered=0 Blunt=1 Tapering at proximal cap scores 1		None=0 Present=1	No=0 Yes=1	<20 mm=0 ≥20 mm=1	No=0 Yes=1

0=Easy	1=Intermediate	2=Difficult	≥3=Very difficult

B) ANTEGRADE TECHNIQUES

CONVENTIONAL		ANTEGRADE DISSECTION AND RE-ENTRY		
Single wire Over-the-wire microcatheter Single wire penetrates lesion using wire escalation with controlled drilling and penetration/step up-step down wire approach 	**Side branch anchor** Wire anchored in proximal side-branch +/- balloon to increase guide catheter support 	Intentional subintimal dissection using loop of wire tip or blunt micro-dissection catheter 		
Parallel wires  First wire anchored in subintimal space, acts as marker A second stiffer wire advanced into true lumen via micro-catheter		STAR  Advance wire in subintimal space until spontaneous re-entry of wire to true lumen	MiniSTAR/LAST  Wire re-entry as early as possible after occlusion using loop of wire tip (MiniSTAR) or specialised guide wire with distal bend (LAST)	Stingray  Uses specialised Stingray balloon in subintimal space, with two exit ports, one directed towards true lumen for wire to pass through
Seesaw wires  Uses two wires, each with an over the wire microcatheter				

C) RETROGRADE TECHNIQUES

Use both antegrade and retrograde (via collaterals) wire with aim of connecting passages made by each wire

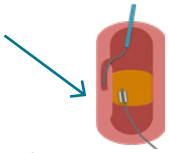
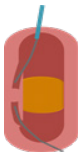
Kissing wire cross  Both wires are in the true lumen and are each gradually advanced through lesion until they overlap	**Antegrade balloon dilatation (1)**  Similar to Kissing wire cross but uses balloon to dilate and expand antegrade channel towards retrograde channel	**CART**  Antegrade wire is in subintimal space Retrograde ballooning to advance and connect passages
Intentional antegrade dissection  Antegrade penetration of subintimal space and balloon inflation until connection to retrograde channel	**Antegrade balloon dilatation (2)**  Antegrade wire in true lumen, retrograde wire in subintimal space Antegrade ballooning to disrupt body of occlusion and connect channels	**Reverse CART**  Both wires are in the sub-intimal space Progressive advancement of antegrade wire to connect channels

Figure 2: A) J-CTO score is calculated by addition of individual scores, allowing lesions to be categorised as easy, intermediate, difficult, or very difficult; B) and C) Antegrade and retrograde techniques in CTO-PCI.[52,53] CTO: chronic total occlusion; PCI: percuateous coronary intervention; CART: controlled antegrade and retrograde tracking.

Adapted from Morino et al.[24]

CTOs are a subset of coronary artery disease (CAD) defined as coronary arteries with absent anterograde flow over >12 weeks duration.[2] They have been found in ≤20% of coronary disease cases diagnosed at angiography.[3] The technical difficulty associated with treatment of CTOs has led to the conclusion that it is the 'final frontier' in interventional cardiology.[3-5] The low intervention rates are commonly due to the misconception that intervening on a CTO will have limited benefit, with higher complication rates. CTO-PCI is no enemy, but a friend, and we present here the evidence, treatment strategies, and indications that allied to newer devices and techniques, ensure safe and effective treatment of these complex lesions, and often forgotten patients.

JUSTIFICATION

Werner et al.[6] demonstrated that regardless of the degree of collateralisation, the area of myocardium distal to the CTO lesion is always ischaemic. Ischaemia is effectively relieved by a successful CTO-PCI, although success depends on the vessel intervened upon.[7,8] Additionally, complete, as opposed to incomplete, revascularisation has mortality benefits regardless of whether surgical or percutaneous revascularisation is used, supporting the notion that CTO-PCI reduces ischaemic myocardial burden (Figure 1).[2]

Intervention has been linked to a lower incidence of ventricular arrhythmias,[9] improved left ventricular (LV) function,[10] and improvements in quality of life (QoL).[11] A 2017 study by Sotomi et al.[12] examined the effects of CTO-PCI on electrical stability and LV function in a single-centre, prospective, observational study. It evaluated electrical stability as a surrogate marker for ventricular arrhythmias, using signal-averaged electrocardiogram (SAECG), and assessed systolic and diastolic function using speckle tracking echocardiography. They found no improvements in electrical stability following CTO-PCI, but did find some evidence of enhancements in systolic and diastolic function.

ISCHAEMIA

Clinically, the primary driver towards CTO-PCI is symptomatic angina with associated coronary ischaemia. The American cardiovascular societies' appropriate use criteria (AUC) outlines 180 clinical scenarios aiming to guide clinicians in making decisions about intervention in patients with CAD including CTOs.[13] The AUC heavily emphasise ischaemic burden as a reason for revascularisation when there is a large area of ischaemia, even in the absence of symptoms. The 2014 European revascularisation guidelines recommend that CTO-PCI be considered when there is an expected reduction in myocardial ischaemia (Class IIa, Level of Evidence B).[14,15] CTO-PCI has been shown to significantly decrease the ischaemic burden from 13.1% to 6.9%. Moreover, mortality has been shown to increase in several studies if the percentage of myocardium at risk is >7–10%.[16,17]

SYMPTOMS

A key objective of CTO-PCI is to induce relief of symptoms, improve exercise capacity, and improve QoL. Anecdotally there is a tendency to underestimate the symptoms attributable to CTOs. This is because there tends to be a higher prevalence of angina chest pain rather than shortness of breath.[2] Large observational studies looking at the impact of CTO revascularisation have found improvements in patient's angina and QoL (assessed by QoL indexes).[18-20] The beneficial effects include improved physical activity ($p=0.01$), rarer anginal episodes ($p<0.001$), and greater treatment satisfaction ($p=0.03$) compared with failed interventions.[20]

Considering the importance of symptom control on the benefit of CTO intervention, few studies exist that compare its efficacy with optimal medical treatment (OMT). DECISION CTO[21] is a randomised controlled trial (RCT) which began recruitment in 2010 and presented its findings at the American College of Cardiology (ACC) scientific sessions in March 2017. It recruited 834 patients and was due to follow-up for a total of 5 years; however, due to problems with recruitment it stopped at 3 years. The CTO-PCI success rate was 91.1%. At 3 years, the combined primary endpoint of all-cause death, myocardial infarction (MI), stroke, and repeat revascularisation in the intention-to-treat population was similar for patients on OMT and CTO-PCI (19.6% versus 20.6%; $p=0.008$ for non-inferiority). Furthermore, there were no differences in angina or QoL scores at 1-year.

This study contrasts that of the EUROCTO[22] club trial which began recruiting in 2012 and presented its 12-month findings in May 2017 at the EuroPCR congress. It was a multicentre RCT, which examined the symptomatic benefit of CTO-PCI versus OMT (aspirin, statin, angiotensin-converting-enzyme [ACE] inhibitor, and two anti-anginals at the

maximum tolerated dose). The study recruited 407 patients from 26 different countries. Using the Seattle Angina Questionnaire (SAQ) it showed a benefit of using CTO-PCI versus OMT (p=0.009) and reported improvements in the Canadian Cardiovascular Society (CCS) angina score (p<0.001). It also showed that improvements in QoL, angina stability, physical activity, and treatment satisfaction were numerically higher in CTO-PCI compared with OMT. There were comparable MACCE rates at 12 months.[23]

DECISION-CTO and EUROCTO highlighted the continued controversy about trial data which has led to a divergence in the real-world management of CTOs across different institutions and countries.

CLASSIFICATION AND SCORING SYSTEMS

Scoring systems help to predict the probability of procedural success. The 2011 Japanese CTO (J-CTO) is based on a multicentre retrospective analysis of nearly 500 CTO procedures. It identified five independent predictors of the ability of the guidewire to cross the lesion within the first 30 minutes.[24] It applies one point for each of these variables when present: i) calcification; ii) bending >45° in the CTO segment; iii) a blunt proximal cap; iv) when the length of the occluded segment is >20 mm; and v) a previously failed attempt. The CTO case complexity was further stratified into easy (J-CTO score=0), intermediate (J-CTO score=1), difficult (J-CTO score=2), and very difficult (J-CTO score=3–5) (Figure 2).

The J-CTO study had limitations, including the fact that the overall success rate was 72% versus the current standard of 85–90%,[24,25] and the under-representation of retrograde PCIs. Alessandrino et al.[26] proposed the Clinical and Lesion (CL) related score. This emerged from a single-centre prospective trial of 1,657 patients. It includes variables such as the anatomy of the proximal cap, grade of lesion calcification, left anterior descending (LAD) or non-LAD CTO, lesion length >20 mm, and history of coronary artery bypass grafting or MI. All variables are then adjusted on the basis of an odds ratio.

ORA,[27] PROGRESS-CTO,[28] and RECHARGE[29] are more contemporary scoring systems, taking into account the hybrid approach. The ORA scoring system uses ostial location, Rentrop Grade <2 (Grade 0 has no angiographic evidence of filling and 4 is fully filled), and age ≥75 years; with these measurements it is possible to assign each lesion a technical difficulty and therefore predict procedural success.[27] The PROGRESS-CTO score also uses four variables (proximal cap ambiguity, absence of retrograde collaterals, moderate or severe tortuosity, or a circumflex CTO). This was developed from the PROGRESS registry and was validated against the J-CTO scoring system. The RECHARGE[29] score uses six variables (blunt stump, calcification, tortuosity >45°, lesion length >20 mm, diseased distal landing zone, and previous CTO vessel bypass graft) and was validated against the PROGRESS and J-CTO scoring systems.

Yu et al.[30] have developed the Korean Multicentre CTO CT Registry (KCCT) score in 2017. Unlike the aforementioned scores, it uses computed tomography (CT) angiographic imaging to predict the difficulty of navigating the CTO within 30 minutes as well as procedural success. It analysed 684 CTO lesions with CT and identified proximal blunt entry, proximal side branch, bending, occlusion length >15 mm, severe calcification, whole luminal calcification, reattempt and >12 months or unknown duration of CTO as being independent predictors of success. A KCCT score <4 predicts the ability to cross the lesion within 30 minutes (p<0.05).

'THE KIT'

Vascular Access

The femoral approach allows larger and more supportive guiding catheters; however, radial access increases patient comfort and reduces the incidence of vascular complications. With complex lesions (J-CTO >3) we recommend long 8 Fr and 7 Fr femoral sheaths. The Arrow® long armoured-style sheath is particularly useful for this and also has great trackability in patients with peripheral vascular disease. This will ensure a hybrid approach is feasible, if necessary, and will also allow the insertion of intravascular ultrasound (IVUS), microcatheters, guideliners, anchor balloons, and multiple wires and balloons if required.

Guide Catheters

Guide catheter selection is extremely important; if the procedure requires additional support to prevent prolapse then a larger diameter catheter should be used (AL1 for the right coronary artery, and EBU for the left coronary artery, usually with preference to size up [e.g. use EBU4 in preference to EBU3.5]). Softer tip catheters are emerging such

as Hyperion™ (Asahi Intecc, Aichi, Japan), which may cause less trauma to the ostia and are marginally more steerable. In general, two guide catheters are used for each CTO-PCI case to allow the operator to seamlessly switch between antegrade and retrograde approaches. A mandatory dual coronary injection is performed to assess: i) a clear understanding of the location of the proximal cap; ii) occlusion length; iii) the presence of side branches and size and quality of the distal vessel; and iv) the presence of collaterals suitable for retrograde technique.

Wires and Microcatheters

Failed CTO-PCI is frequently caused by the inability to cross the CTO with a guidewire. There are three separate steps required to cross a CTO: i) penetrating the proximal fibrous cap; ii) traversing the body of the CTO to reach the distal fibrous cap; and iii) penetrating the distal fibrous cap. Dedicated guidewires for crossing CTOs have been developed. They are broadly divided into two groups:

- Hydrophilic (polymer coated) wires (e.g. Fielder™, Fielder XT [Asahi], Pilot 200® [Abbott, Illinois, USA]) – offer manoeuvrability in tortuous vessels and passage through micro-channels into the true lumen. They can, however, increase the incidence of sub-intimal perforation.
- Non-hydrophilic (non-polymer coated) wires (e.g. Miracle Bros® 3-12 [Asahi], Confianza Pro [Asahi]), are typically more controllable, provide better tactile feel, and are less likely to cause vessel dissection. They can be used to cross the fibrous cap as they have greater penetration force. They are graded in grams according to the penetration force they can withstand in grams during bench testing. This does give an idea of penetrability *ex vivo,* but operators should be cautious that, in regard to *in vivo* with microcatheter support, these values are only a guide and can be higher if used with anchor balloons or differing microcatheters. There are also newer steerable intra-occlusion wires such as the Gaia family (Asahi) (first, second, and third). The unique property of these wires is their ability to steer the wire with the use of a microcatheter within the occlusion.

It is possible to cross the CTO with a guidewire alone, although in the majority of J-CTO >2 cases a microcatheter for support is considered mandatory (e.g. Corsair [Asahi], FineCross® [Terumo, Leuven, Belgium], M-CATH [Accrostak, Geneva, Switzerland], NHancer [IMDS, Roden, Netherlands], Turnpike [Vascular Solutions, Minnesota, USA]). This allows the operator to provide increased wire force to the proximal fibrous cap. An alternative is an over-the-wire (OTW) balloon catheter (e.g. 1.25–1.5 balloon diameter), which, allied to increase force, allows pre-dilation once the CTO is crossed. OTW has more or less disappeared from use in CTO-PCI work and is essentially historic because the main limitation is the inability of OTW to track through complex CTOs.

'TIPS AND TRICKS' AND CHRONIC TOTAL OCCLUSION TECHNIQUES

The Stingray Balloon and Wire

When unable to penetrate the fibrous cap, a dissection flap can be created to circumnavigate the occlusion. The Stingray™ LP balloon (Boston Scientific, Massachusetts, USA) is a flat balloon that can be inflated in an intended dissection plane. There are two radiopaque markers on the Stingray balloon and an exit hole just proximal to each marker on the opposite face of the balloon. One exit port will lead the wire into the adventitial side of the artery distal to the occlusion and the other to the luminal side, therefore allowing re-entry and bypass of the CTO. The Stingray Wire (Boston) is a stiff wire with a pre-shaped 28° tip and a barb on the end to facilitate re-entry. It can be carefully advanced in the Stingray balloon and directed towards either the adventitia or luminal layer.

Anterograde

Anterograde is the most common approach to CTO-PCI. Progressively stiffer hydrophilic/non-hydrophilic wires are used sequentially until the proximal cap is penetrated or the wire advanced within the lesion. Failure after initial wire entry in the lesion has led to specialised techniques for recanalisation of CTOs. The antegrade dissection/re-entry technique (ADR) and subintimal tracking and re-entry (STAR) techniques (Figure 2) were pioneered by the work of Colombo et al.[31] and Carlino et al.[32] The STAR technique is a less well-controlled method of performing an ADR, where a hydrophilic wire in the shape of an 'umbrella handle' is knuckled though the intimal dissection planes until it enters the distal true lumen. ADR with the use of the aforementioned Stingray balloon and Crossboss™ (Boston) device allow the operator to perform a more precise and limited dissection than what was previously observed with the STAR

technique. These techniques have been essential in the remarkable improvements in the procedural success rates.

Retrograde

A retrograde approach can be broadly described as any approach that uses donor collaterals to deliver interventional equipment to facilitate the opening of a CTO. Unlike early procedures, this procedure has evolved to use septals (which have a straighter course) or the more tortuous epicardial vessels as the common conduit arteries.[33] The goal of the retrograde approach is to target the distal cap, which could be softer than the proximal one. It should be noted that the retrograde approach should only be performed by experienced operators who have mastered the anterograde approach. For all CTO-PCI, the activated clotting time (ACT) should be measured throughout ensuring an ACT >300, and further heparin introduced if required.

Various techniques have been described for retrograde CTO-PCI. These include passing the guidewire retrogradely through the distal cap within the true lumen with balloon dilatation before antegrade guidewire passage and PCI. Alternatively, passing the wire into the subintimal space and enlargement with sequential balloon dilatations before connecting with the true lumen retrogradely (controlled antegrade and retrograde tracking [CART] technique). If the subintimal space is enlarged from the anterograde then it is called the reverse CART technique (Figure 2). If the retrograde wire and microcatheter is eventually inserted into the antegrade guide then the RG3® (Asahi) wire is utilised to pass through the occlusion and is externalised in the opposite sheath. Conventional PCI can then be performed on the RG3 wire in an antegrade manner. It must be emphasised that at no time should contrast injections be performed in the antegrade guide prior to stenting, as this will only facilitate dissection planes and can cause large haematomas that could lead to compression of cavity and haemodynamic compromise.

The Hybrid Approach

The hybrid approach was proposed in 2012 and has been shown to be effective in ≤90% of cases with fewer complications (cardiac tamponade: 0.4%, periprocedural MI: 1.0%, death: 0.4%).[9,34] This is effectively a combination of the anterograde and retrograde techniques described above.

Future Directions in Chronic Total Occlusion-Percutaneous Coronary Intervention

Two further ongoing clinical trials should further clarify the benefits of CTO-PCI. OPEN-CTO[35] is a prospective observational registry of patients enrolled in North America utilising the hybrid approach. It aims to assess the safety, health and QoL, and cost effectiveness of the method. Initial results have been promising (Table 1).

Table 1: A summary of a selection of important studies relating to CTO-PCI.

Study	N	Design	Primary outcome	Key findings	Author comments
Shaw et al.[49]	314	Nuclear substudy of the COURAGE trial Compared PCI + MT vs. MT only in patients with stable CAD	≥5% reduction in ischaemic burden	PCI+MT resulted in greater reduction in ischaemic myocardium vs. MT alone Patients with moderate-to-severe ischaemic burden (≥10%) had even greater reductions with PCI+OMT (78% vs. 52%; p=0.007) Those with ≥5% ischaemia reduction had lower unadjusted risk of death/MI (p=0.037), especially if ≥10% ischaemic burden (p=0.001) Study recommended treatment target of ≥5% ischaemia reduction	This study emphasised the importance of ischaemic burden, and the effect of reduction on outcomes
Safley et al.[8]	301	Retrospective study of myocardial perfusion imaging in those undergoing CTO-PCI	Reduction in ischaemic burden	53.5% had significant (≥5%) reduction in ischaemic burden Average ischaemic burden reduced from 13.1% to 6.9% (p<0.001) Patients with ≥12.5% ischaemic burden most likely to benefit	Large study confirming beneficial effects on ischaemia reduction

Table 1 continued.

Study	N	Design	Primary outcome	Key findings	Author comments
Ladwiniec et al.[54]	34	Prospective study assessing effect of CTO-PCI on FFR in donor vessel (of collaterals)	FFR in donor vessel	Recanalisation of a CTO was associated with an improvement in donor artery FFR (0.782–0.810; p=0.001) Greater changes seen where donor vessel FFR ≤0.8	Even patients with well-collateralised CTOs may benefit from PCI
Dzavik et al.[55]	381	RCT of AMI patients with persistently occluded IRA-PCI vs. MT only	Vessel patency and LVEF	PCI associated with greater vessel patency at 1 year vs. MT (83% vs. 25%; p<0.001) but no difference in LVEF, LVESVI, or LVEDVI between groups	Very selected population that is not representative of many CTO-PCI candidates. Limited viability assessment
Grantham; Saint Luke's Health System[35]	1,000	Ongoing prospective multicentre observational registry assessing outcomes after CTO-PCI using the hybrid approach	Safety, health status outcomes, cost	6-month results showed that PCI was associated with improved quality of life, anginal stability, treatment satisfaction, and reduced angina frequency, physical limitation, SOB, and depression High technical success (89%) and low rate of complications	Large study showing significant QoL benefits. Due to complete in Dec 2017
Henriques et al.[56]	304	RCT of STEMI patients undergoing PPCI with concurrent CTOs, randomised to early PCI of CTO or MT	LVEF/LVEDV on CMR at 4 months	No significant difference in 4-month MACE (5.4% vs. 2.6%; p=0.25) Patients with CTOs in LAD had significantly higher LVEF with PCI vs. MT (47.2 vs. 40.4%; p=0.02). In other patients, there was no significant difference in LV function/volume Low numbers of adverse events, additional CTO-PCI <7 days following PPCI felt to be safe CTO-PCI procedural success was 73%	4 months perhaps not long enough to demonstrate significant benefit. Low success rates in PCI arm of trial compared to average experience
Lee et al.[47]	1,173	Registry study comparing successful vs. unsuccessful PCI	Mortality, need for CABG	Successful CTO-PCI not associated with reduction in all-cause mortality but significant reduction in need for CABG (HR: 0.02, CI: 0.006-0.06; p<0.001), and TVR (HR: 0.15, CI: 0.1-0.25; p<0.001)	High success rate and therefore small size of unsuccessful PCI group
George et al.[46]	13,443	Long-term follow-up of patients on UK Central Cardiac Audit Database undergoing elective CTO-PCI Compared successful vs. unsuccessful PCI and CR vs. IR	Cardiovascular outcomes and mortality	Successful revascularisation of at least one CTO associated with reduction in long-term mortality (HR: 0.72, CI: 0.62–0.83; p<0.001) Trend towards reduced mortality with increasing completeness of revascularisation (p<0.001) CR associated with reduction in mortality vs. IR (HR: 0.7; CI: 0.56–0.87; p=0.002)	Large study with long-term follow-up data. No data on lesion complexity or details of medical therapy were available
Galassi et al.[45]	1,914	In-hospital outcomes from the ERCTO registry (16 centres)	Success, technical information, and cardiovascular outcomes	CTO-PCI procedural success was 82.9%. Antegrade approach more successful compared to Retrograde approach (83.2% vs. 64.5%; p<0.001) Retrograde approach also associated with higher rates of coronary perforation, procedural and fluoroscopy times and contrast load Similar rates of 30-day MACE regardless of approach. Low rates of overall complications (CIN: 0.9%, stroke: 0.05%, death: 0.3%) that are comparable to non-CTO-PCI	Higher complications with retrograde approach may be partially explained by reduced experience with newer techniques
Sapontis et al.[48]	380	Retrospective study of patients undergoing Hybrid Approach CTO-PCI. Compared successful vs. unsuccessful PCI	Factors associated with failure	CTO-PCI procedural success was 91.3%. Lesions in failed CTO-PCI were longer, more tortuous, had more proximal cap ambiguity and blunt stumps, higher mean J-CTO scores, and were less likely to have collaterals amenable for retrograde approach	Findings demonstrate utility of J-CTO score in planning CTO-PCI

Table 1 continued.

Study	N	Design	Primary outcome	Key findings	Author comments
Pancholy et al.[4]	-	Meta-analysis of 13 studies comparing successful vs. unsuccessful CTO-PCI	All-cause mortality (short-term: n=3,932; long-term: n=6,403)	Successful CTO-PCI was associated with significant reduction in short-term (OR: 0.218, CI: 0.095–0.498; p<0.001) and long-term mortality (OR: 0.391; CI: 0.311–0.493; p<0.001)	Only included studies with high proportion of stent use. Low heterogeneity
Park et al.[21]	834	RCT of CTO-PCI vs. OMT	MACCE	Successful CTO-PCI was not associated with a reduction in MACCE at 3 years. There were no differences in angina or QoL at 1 year	Trial was stopped early due to poor recruitment
Werner et al.[22]	407	RCT of CTO-PCI vs. OMT	Symptom control	Successful CTO-PCI was associated with improved symptom control at 1 year There were numerical improvements in angina, physical activity, and treatment satisfaction. MACCE rates were comparable	The long-term safety evaluation is awaited. The trial didn't recruit the pre-planned number of patients

AMI: acute myocardial infarction; CAD: coronary artery disease; CI: confidence interval; CIN: contrast-induced nephropathy; CR: complete revascularisation, CTO: chronic total occlusion; ERCTO: European Registry of Chronic Total Occlusion; FFR: fractional flow reserve; IR: incomplete revascularisation; LVEDV: left ventricular end diastolic volume; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESVI: left ventricular end-systolic volume index; MACE: major adverse cardiovascular events; MT: medical therapy; n: number of patients; PCI: percutaneous coronary intervention; QoL: quality of life; RCT: randomised controlled trial; TVR: target vessel revascularisation; OMT: optimal medical therapy; MI: myocardial infarction; J-CTO: Japanese CTO; LAD: left anterior descending; HR: hazard ratio; OR: odds ratio; MACCE: major adverse cardiovascular and cerebrovascular event.

SHINE-CTO[36] is a USA single-centre RCT of CTOs to PCI versus sham procedure, and will assess the impact on QoL.

TECHNOLOGICAL DEVELOPMENTS AND THE SPECIFICS TO CHRONIC TOTAL OCCLUSION-PERCUTANEOUS CORONARY INTERVENTION

Technological developments may provide the 'knockout blow' for CTO-PCI. Some promising developments are described below.

Orbital Arthrectomy

Orbital atherectomy can facilitate plaque removal and softening, improve lesion compliance, and aid dilatation, especially in severely calcified lesions.[37] Though underused, it has been shown to be effective at facilitating angioplasty in resistant CTOs where device crossing is initially unsuccessful.[38]

Drug-eluting Balloons

Drug-eluting balloons have been the target of research looking at lowering the rates of in-stent restenosis. They also require a shorter duration of antiplatelet therapy. Koln et al.[39] investigated the feasibility and safety of its use in CTOs. They looked at 66 cases of anterograde CTO intervention (retrograde was not investigated due to the high prevalence of dissection). They found that restenosis (11.8%) and reocclusion (5.9%) rates were comparable to CTO-PCI. This was a small, non-randomised study and the lesions themselves had to have had good predilation results, which biased their selection. In view of its potential, further RCT evidence is required.

SoundBite

The SoundBite Crossing system[40] (SoundBite Medical Solutions, Inc, Quebec, Canada) is a novel device using shockwaves (short-duration, high amplitude pressure pulses) to facilitate crossing the proximal cap. It propagates shockwaves to its tip, using it as a micro 'jackhammer' to penetrate the lesion, and has recently undergone an *ex vivo* trial in an amputated leg. Further trials *in vivo* are expected. Although it is currently being used in peripheral vascular disease, it has potential for use in coronary disease.

Collagen and Collagenase

A collagen-rich matrix is present in CTO lesions and forms a barrier at the proximal cap. Collagenase is

an enzyme that degrades Type 1 collagen, and may facilitate lesion crossing. Phase I studies have shown it to be a feasible and safe therapy.[41]

CONCLUSIONS

CTO's have a significant impact on health and mortality, yet are undertreated. CTO-PCI offers potential benefits and should be considered for patients with symptoms of, or demonstrated, ischaemia, and viable myocardium in the CTO territory. Modern techniques and scoring sytems allow operators to successfully tackle complex and challenging CTOs. PCI success rates and safety are improving with contemporary trials providing evidence to challenge common misconceptions and allow patients, who may traditionally have been left untreated, to gain the potential benefits from CTO-PCI.

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