Contemporary overview and clinical perspectives of chronic total occlusions

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Abstract | Chronic total occlusions (CTOs) are often detected on diagnostic coronary angiograms, but percutaneous coronary intervention (PCI) for CTO is currently infrequently performed owing to high technical difficulty, perceived risk of complications, and a lack of randomized data. However, successful CTO–PCI can significantly increase a patient's quality of life, improve left ventricular function, reduce the need for subsequent CABG surgery, and possibly improve long-term survival. A number of factors must be taken into account for the selection of patients for CTO–PCI, including the extent of ischaemia surrounding the occlusion, the level of myocardial viability, coronary location of the CTO, and probability of procedural success. Moreover, in patients with ST-segment elevation myocardial infarction, a CTO in a noninfarct-related artery might lead to an increase in infarct area, increased end-diastolic left ventricular pressure, and decreased left ventricular function, which are all associated with poor clinical outcomes. In this Review, we provide an overview of the anatomy and histopathology of CTOs, perceived benefits of CTO–PCI, considerations for patient selection for this procedure, and a summary of emerging techniques for CTO–PCI.

Hoebers, L. P. *et al. Nat. Rev. Cardiol.* **11**, 458–469 (2014); published online 27 May 2014; doi:10.1038/nrcardio.2014.74

Introduction

Coronary artery disease (CAD) refers to atherosclerosis that might lead to narrowing of a coronary artery resulting in haemodynamically significant coronary lesions that induce ischaemia. Total coronary occlusions are coronary lesions that have become completely blocked. Over the past decade, remarkable progress has been achieved in the percutaneous management of CAD, such as the adoption of primary percutaneous coronary intervention (PCI) for acute myocardial infarction and the advent of drug-eluting stents (DESs).[1,2] Chronic total occlusions (CTOs) are often referred to as the final frontier for interventional cardiologists, who are often confronted with these complex lesions. The reported prevalence of CTOs varies widely from 16–50% in patients with clinically significant CAD, but is generally ~20% in large registries.[3–6] In a report from the Canadian multicentre CTO registry, a CTO was observed in 14.7% of patients without previous CABG surgery undergoing coronary angiography, and 18.4% in patients with clinically significant CAD.[4] In this registry, the majority of patients with a CTO underwent medical treatment (64%) or were referred for CABG surgery (26%)—only 10% were referred for CTO–PCI revascularization.[4] The disparity between the high prevalence of CTOs and the low rate of invasive treatment emphasizes the higher technical difficulty and perceived risk of complications compared with noninvasive treatment, but also the clinical uncertainties with regard to which patients benefit from CTO revascularization.[4,7] In this Review, we aim to provide an overview of the anatomy and histopathology of CTOs, patient and lesion characteristics, and patient selection criteria for CTO–PCI, with an emphasis on the current evidence regarding the clinical relevance and rationale of CTO–PCI.

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Competing interests
G.D.D. and R.M. are advisory Board members for Abbott Vascular and Boston Scientific. J.P.S.H. is principal investigator of the EXPLORE trial and has received a restricted research grant from Abbott Vascular. The other authors declare no competing interests.

Characteristics of CTOs

Definition

A uniform definition is essential for comparing the results of different studies. Consequently, a consensus document was published in 2005 in which a definition for CTOs was proposed.[8] A 'true' CTO arises owing to complete interruption of coronary flow (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0), whereas occlusions with minimal contrast penetration through the lesion without distal-vessel opacification (TIMI 1 flow) are classed as a 'functional' CTO. However, in the literature, the distinction between true and functional CTOs is rarely taken into consideration.[8] To be classed as a CTO, the lesion must have been present for ≥3 months. However, the period of time for which a CTO has been present is difficult to ascertain with complete certainty and, therefore, the age of the occlusion is often determined after careful assessment of a patient's medical history and cardiac symptoms in the previous 3 months.[8]

Before PCI was regularly used to treat acute myocardial infarction, a CTO could evolve after such an event in 30% of patients who received thrombolytic treatment,

Key points

- A chronic total occlusion (CTO) is observed in 14.7% of all coronary angiographies and in 18.4% of patients with coronary artery disease
- Most patients receive medical treatment without revascularization, owing to the complexity of percutaneous coronary intervention (PCI) for CTO, and the clinical uncertainties regarding those patients who might benefit
- Successful CTO–PCI can increase quality of life by alleviating symptoms, improve exercise tolerance and left ventricular function, reduce the need for CABG surgery, and improve survival
- CTO–PCI is indicated when an occluded artery leads to angina, ischaemia, left ventricular dysfunction, and electrical instability, especially when the left anterior descending coronary artery is involved
- Visible collateral arteries on an angiogram of patients with a CTO does not necessarily indicate an absence of ischaemia; additional evaluation is warranted to assess the need for revascularization
- Cardiac MRI with pharmacological stress testing, perfusion, and contrast enhancement is the optimal assessment for CTO–PCI indication in patients without severe symptoms or ischaemia

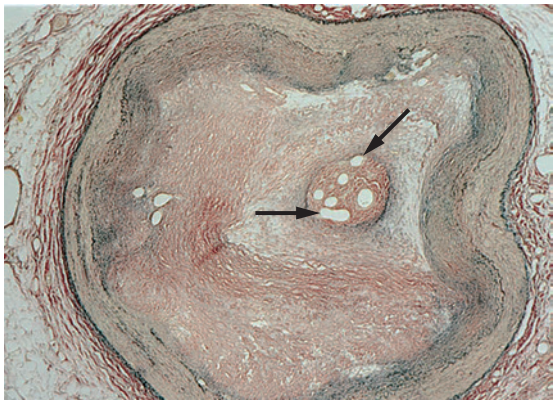

Figure 1 | Chronic total occlusion demonstrating lumen recanalization with small and intermediate neovascular channels (arrows). Permission obtained from Srivatsa, S. S. *et al.* Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J. Am. Coll. Cardiol.* **29**, 955–963 © Elsevier (1997).

and in 45% of those who did not receive pharmacological reperfusion therapy.[8–10] These rates have now dropped because of PCI, but a CTO might still develop after a failed intervention or subsequent vessel reocclusion in 5–10% of patients who have had a myocardial infarction.[11,12] However, the majority (~60%) of patients with a CTO do not have a history of myocardial infarction,[4] suggesting that an alternative mechanism can also lead to CTO. For example, the recruitment of collateral vessels to counterbalance the gradual progression to an occluded artery might limit myocardial damage resulting in the absence of, or only mild, clinical symptoms.[13]

Histopathology

In a post-mortem study of 61 patients in whom a CTO was identified on angiography in the 3 months before death (96 lesions in total), the thrombotic occlusion progressed over time from a 'soft' to a 'hard' lesion composition.[14] Soft plaques are composed of foam cells and cells with a high cholesterol content, and dense fibrous tissue at the proximal and distal ends (proximal and distal cap) with loose fibrous tissue in between.[14] Hard intimal plaques are characterized by calcification. The severity and extent of calcification increases with the duration of CTO, but is even present in 54% of occlusions <3 months old.[14] Nevertheless, with advancing CTO age, the calcium and collagen content of the intimal plaque increases.[14,15] Collagen is also a predominant component at the proximal fibrous cap and acts as an occlusive barrier.[16] This observation might partly explain the incremental procedural difficulty with advancing age of the occlusion, and the high procedural failure rate (15–32%) compared with that for nonocclusive lesions (~3%).[17,18]

Within CTO lesions, microchannels with an average diameter of 200 μm are often observed (Figure 1),[14] which might facilitate lesion crossing during CTO–PCI. In an animal study in which the timing and type of microvessel formation were evaluated in a rabbit model of total occlusion, two types of microvessels were observed: circumferentially oriented (extravascular) and longitudinally oriented (intravascular) microvessels.[19] In this study, extravascular microvessels grew to a maximum size by 2 weeks and then progressively decreased over time with very minimal microvessels evident beyond 12 weeks. By contrast, intravascular microvessel formation developed more slowly, with peak vascular volume at 6 weeks and was more prominent in the body compared with the proximal and distal ends of the CTO, probably owing to increased hypoxia. Channels that link extravascular and intravascular channels were observed at all time points. When the occlusion was 6 weeks old, intravascular neovascularization also occurred at both the proximal and distal ends of the lesion. As the occlusion further aged, only a single narrow intravascular channel with a small and tortuous pathway was present in 85% of lesions.[19] This observed temporal and geographical pattern of microvessel formation and the presence of connecting microvessels implies that the extravascular vessels might initiate formation of the intravascular channels within the centre of the occlusion.[19] The intravascular and extravascular communicating channels exit the lesion at an angle close to 90° to the path of the artery, which could be responsible for the often-observed diversion of guidewires into the extravascular space.[20,21] Post-mortem studies in humans support this mechanism —microchannels mostly lead into the adventitia, small side branches, or vaso vasorum; however, they might also extend from the proximal to the distal lumen.[14,20] Unfortunately, insufficient data from human CTO studies exist to confirm whether intravascular channels are actually initiated by extravascular channels. Other mechanisms might also be involved. The origin for neoangiogenesis within the CTO could be from the proximal and distal nonoccluded ends, or driven by the circulating endothelial progenitor cells, as reported in venous thrombi.[22] Extravascular channels might already be present and could, therefore, develop more easily than intravascular channels.

Clinical characteristics of CTO

In general, CAD is more prevalent in men than women. A total of 70% of patients with CAD without a CTO are

Table 1 | Positive effects of CTO revascularization

Effect	Measure	Outcome
Improved survival[28]	Risk ratio (95% CI)	0.54 (0.45–0.65)
Improved LVEF[29–34]	Change in LVEF	~4.0–4.5%
Improved health status[25]		
Symptom reduction	Change in SAQ score (SD)	14.8 (20.4)
Physical limitation	Change in SAQ score (SD)	17.3 (20.7)
Quality of life	Change in SAQ score (SD)	30.3 (23.1)
Ischaemic burden reduction[80]	Amount of ischaemic myocardium	6.2%
Fewer future cardiovascular events		
CABG surgery[28]	Risk ratio (95% CI)	0.25 (0.21–0.30)

Abbreviations: CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; SAQ, Seattle Angina Questionnaire.

men, a figure that rises to 80% for those with CAD and a CTO.[4] In patients receiving CTO–PCI, women tend to be older, have hypertension and diabetes mellitus, and are less likely to smoke, compared with male patients.[23] Moreover, female patients with a CTO are less likely to have multivessel disease and more often have a CTO located in the left anterior descending (LAD) coronary artery (although with a shorter CTO length, and fewer blunt stumps and bridging collaterals).[23] However, after multivariable adjustment for known predictors, sex was not associated with CTO–PCI failure.[23]

CTOs are most often observed in patients with a mean age of 66 ± 11 years, whereas patients with CAD but no CTO have a mean age of 64 ± 12 years.[4] Patients with a CTO have an increased cardiac risk profile compared with those with no CTO on their coronary angiogram, including a higher prevalence of diabetes mellitus (34% versus 26%), hypertension (75% versus 68%), hyperlipidaemia (82% versus 78%), heart failure (12% versus 9%), and peripheral artery disease (8% versus 4%).[4] Approximately 40% of patients with a CTO had a previous myocardial infarction, which is twice as high as in patients without a CTO.[4] Pathological Q waves indicative of myocardial infarction on an electrocardiogram correspond to the CTO territory in 32% of all CTOs in the right coronary artery (RCA), 13% in the LAD coronary artery, and 26% in left circumflex branch (LCx).[4] However, in an imaging study, the frequency of previous myocardial infarction was strikingly different based on clinical versus imaging criteria.[24] On electrocardiograms, Q waves were present in 25% of patients, 42% had experienced ischaemic symptoms consistent with myocardial infarction, whereas 86% of all patients had some evidence of scar tissue visualized by contrast-enhanced MRI.[24] The extent of transmural infarction in these patients was not reported. In the majority of the patients, the CTO was located in the RCA (47%), with the others in the LAD artery (20%), LCx artery (16%), or multiple locations (17%).[4]

Benefits of CTO–PCI

Successful CTO revascularization is associated with improved clinical outcomes for patients, and several retrospective studies have shown various beneficial effects (Table 1). Improvements in angina and quality of life,[25] a potential improvement in electrical myocardial stability,[26,27] a reduced need for CABG surgery,[28] enhanced tolerance of future coronary events, increased left ventricular function,[29–34] and a substantial increase in survival[25,28,34–58] have all been associated with successful CTO revascularization procedures.

A major limitation of studies designed to evaluate clinical outcomes after CTO–PCI is selection bias, which is inherent in observational research. To date, no randomized trial has been conducted to evaluate the effect of CTO–PCI on clinical outcomes. All data on clinical outcome after CTO–PCI are from registries of patients who have an indication for CTO revascularization, where a comparison is made between successful and failed PCI.[25,28,34–58] These nonrandomized studies do not include a control group of patients with CTO lesions being treated with optimal medical therapy alone.[25,28,34–58] Evidence from randomized trials is needed to confirm whether CTO revascularization is, indeed, associated with improved clinical outcome, or whether the perceived benefit of successful CTO–PCI results from complications related to procedural failure or comorbidities that reduce survival in the failed CTO–PCI group. Given that the mortality curves for successful and failed CTO–PCI diverge over time, procedural complications (which would manifest as a parting of the curves during the first week after the procedure with a parallel continuum) are unlikely to be contributory factors.[25,28,34–58] However, future randomized, controlled trials will provide the definite answer.

Myocardial viability

Myocardial viability is likely to be needed to improve left ventricular wall motion and function.[31,59] Several studies have shown an improvement in left ventricular ejection fraction (LVEF) after successful CTO revascularization.[29–34] The expected improvement or recovery of left ventricular function declines with the extent of nonviable myocardium, which correlates with the extent of infarction.[59] The effect of CTO–PCI ($n = 17$) versus medical treatment only ($n = 30$) on LVEF was compared using MRI in patients with nonviable myocardium.[60] Despite the lack of myocardial viability in these patients, local left ventricular wall motion and function improved at 6 months after PCI compared with preprocedural levels (LVEF +1.9 percentage points, SD 12.1), with a minimal increase in left ventricular end-diastolic volume (+3.0 ml, SD 34.6). Conversely, in patients who received only medical therapy, LVEF decreased (–3.7 percentage points, SD 11.5), with a substantial increase in left ventricular end-diastolic volume (+8.0 ml, SD 25.8), which indicates negative remodelling.[60] In 2011, the Surgical Treatment of Ischemic Heart Failure (STICH) investigators reported a prespecified substudy evaluating the interaction between myocardial viability and survival in 601 patients with ischaemic heart failure who were randomly assigned to CABG surgery or optimal medical therapy.[61] After correction of other prognostic variables, the presence of myocardial viability was no longer significantly

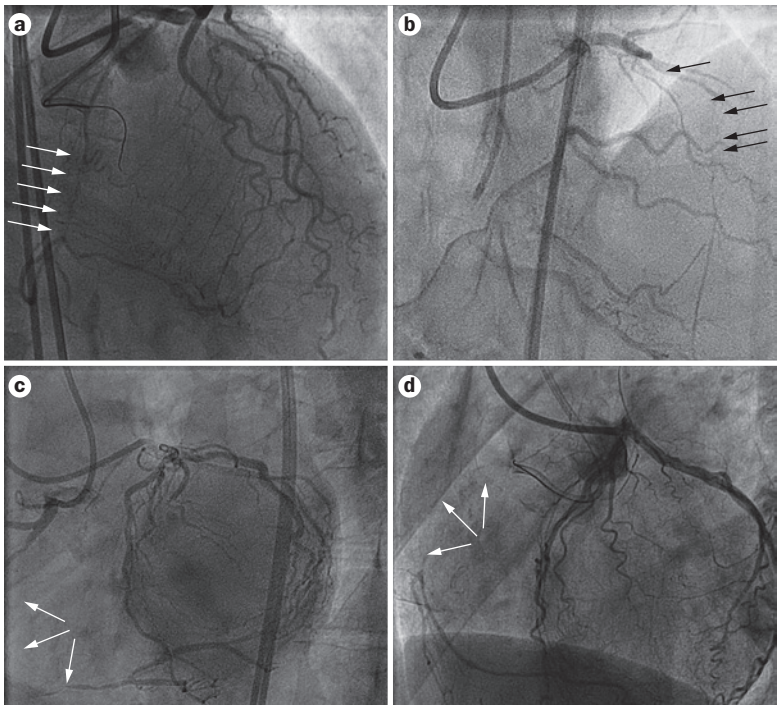

Figure 2 | CTO of the RCA and left anterior descending coronary artery with well-developed collateral circulation from the left coronary system. **a** | CTO of the RCA, which receives retrograde flow from septal collateral arteries. **b** | CTO of the left anterior descending coronary artery, which receives retrograde flow from the RCA through septal collateral vessels. **c** | CTO of the RCA with epicardial collateral vessels from the left coronary system. **d** | CTO of the RCA with epicardial collateral vessels from the left coronary system. Arrows indicate location of the CTO Abbreviations: CTO, chronic total occlusion; RCA, right coronary artery.

associated with mortality ($P = 0.21$). However, the cohort sizes were not powered to detect differences in mortality, which was much lower in those with viable myocardium (37% versus 51% patients with ischaemic heart failure who were randomly assigned to receive CABG surgery or optimal medical therapy).[61] Myocardial viability and treatment assignment did not have a significant interaction with respect to mortality. These findings bring into question whether LVEF recovery is completely dependent on myocardial viability, but might support the electrical or the 'reserve' hypothesis. In this hypothesis, patients with a CTO might be more prone to future cardiovascular events and have less reserve, especially during an acute occlusion in one of the remaining coronary arteries.

Ischaemic burden

The expected beneficial prognostic effect of CTO revascularization is thought to be associated with the amount of ischaemic myocardium, as has been observed in patients with CAD in general.[62–64] CTO–PCI might be beneficial in the absence of ischaemia. In one study, patients with successful CTO–PCI of the LAD coronary artery ($n = 99$) were stratified according to the presence of perfusion defects on nuclear imaging before the procedure.[33] Both those with reversible ($n = 40$) and those with fixed ($n = 50$) perfusion defects had significant improvement at 1 year in perfusion abnormalities (–20%, $P = 0.001$ and –15%, $P = 0.041$, respectively), LVEF (6%, $P = 0.002$ and 4.1%, $P = 0,006$), quality of life measured as improved 6 min walking distance (~50 m, $P < 0.05$ and ~25 m, $P < 0.05$), and frequency of angina measured with the Seattle Angina Questionnaire (mean score 18, $P < 0.05$ and mean score 15, $P < 0.05$). No benefit of CTO–PCI was observed in patients who had no perfusion defects ($n = 9$).[33] Adequately powered, randomized, controlled trials are needed to address the question of whether viable and ischaemic myocardium is required for improvement of clinical outcome.

Myocardial electrical stability

Currently, no evidence is available to show that myocardial electrical stability is improved after successful CTO–PCI. However, in patients with an implantable cardioverter–defibrillator (ICD) for ischaemic cardiomyopathy ($n = 162$), a CTO was significantly associated with ventricular arrhythmias requiring ICD therapy (HR 3.5, 95% CI 1.5–8.3, $P = 0.003$).[26] Two previously established arrhythmogenic factors might be responsible for the ventricular tachycardia: ischaemia owing to inadequate perfusion of the myocardium can lead to abnormal automaticity of the ventricular myocardial cells, and re-entry circuits in patients with a previous myocardial infarction and fibrous tissue interspersed with islands of viable tissue.[65] Restoring antegrade flow after successful CTO–PCI could resolve the ischaemia and might, therefore, enhance electrical stability in patients with ventricular arrhythmia, regardless of the presence of an ICD, which only treats the arrhythmic defect and not the cause of ischaemia.

Patient selection for CTO

Symptoms

In patients with a CTO, the presence of cardiac symptoms —despite optimal medical therapy—is an indication for CTO recanalization. In a study of 125 patients undergoing CTO–PCI, changes in health status outcomes between baseline and 1 month after the procedure were assessed using the Seattle Angina Questionnaire.[25] Significant improvements were observed in symptoms (15 ± 20, $P < 0.01$), physical function (17 ± 21, $P < 0.01$), and quality of life (30 ± 23, $P < 0.01$), but mainly in those patients who were symptomatic. Notably, in our own experience, patients with a CTO often complain about exertional dyspnoea rather than typical chest pain.

Collateral circulation

Collateral circulation is a natural bypass system providing retrograde flow to the myocardial perfusion area of the CTO, which can be visualized on an angiogram (Figure 2). In individuals with haemodynamically significant atherosclerotic lesions, well-developed collateral arteries are present in ~35% of patients.[66,67] Collateral vessels develop from pre-existing interarterial anastomoses owing to a pressure gradient generated when a vessel narrows or is occluded,[68,69] and might limit myocardial damage and maintain myocardial viability in patients with a CTO.[13] However, because the recruitment is based on a pressure gradient across the occluded lesion, the

presence of collateral circulation does not guarantee myocardial viability.[70] Conversely, well-developed collateral vessels are inversely correlated with the degree of transmural myocardial injury measured on contrast-enhanced MRI.[24] In a small study of 42 patients with 78 total occlusions, absent collateral vessels on angiography did not necessarily indicate a low probability of myocardial viability,[71] suggesting that regional myocardial perfusion (determined by PET) was sufficient to maintain viable myocardium.[71] This finding might be due to a limitation of angiographic assessment of collateral flow. Only channels >100–200 μm in diameter can be visualized with this technique, but many collateral vessels are smaller than this size.[14]

In >90% of patients with a CTO where collateral vessels provide adequate flow to maintain myocardial viability, the flow is insufficient to maintain adequate perfusion during pharmacological-induced stress, resulting in ischaemia.[72,73] Moreover, in approximately one-third of patients, the collateral supply is further reduced by coronary steal of the donor artery, defined as a drop in collateral coronary flow velocity reserve <0.85.[72,73] Consequently, the presence of collaterals in patients with CTOs is related neither to the extent of preserved left ventricular function, nor recovery of left ventricular function after successful CTO–PCI.[73] The presence of well-developed collateral vessels in symptomatic patients should not, therefore, be a reason to withhold CTO revascularization.

Ischaemic burden

Ischaemia is intrinsically linked to myocardial viability, and each factor must be interpreted in the context of the other. If ischaemia can be demonstrated by cardiac symptoms or stress testing, one can assume the associated myocardium is viable because a patient cannot experience symptoms or ischaemia from dead tissue. However, in patients with additional non-CTO lesions, establishing the lesion that is responsible for the symptoms and ischaemia is important.[74,75] The majority of patients with a CTO and collateral circulation experience ischaemia during exercise owing to inadequate perfusion distally of the occlusion, often resulting in cardiac symptoms.[72,73] However, an additional mechanism that might also contribute to ischaemic burden has also been proposed.[76] Immediately after successful CTO–PCI, the coronary segments distal to the occlusion have been shown to be severely dysfunctional to regulatory feedback mechanisms of acetylcholine and nitrate challenges. Also, an intense vasoconstrictive reaction in response to acetylcholine was observed.[76] A damaged or dysfunctional endothelium has been shown to be an initiator of vascular atherosclerosis and is a predictor of coronary events in patients with CAD.[77,78] The pathophysiological explanation for this finding is still unknown, and further research is needed to investigate whether these effects are sustained or reversible over time.

In patients without cardiac symptoms and definite ischaemia in the area of a CTO, testing of myocardial viability is required before considering CTO–PCI, because ischaemia can be present only when the myocardium is still viable. Ischaemia is often assessed as the degree of perfusion defect in stress versus rest: in the absence of perfusion defects, no ischaemia exists; reversible perfusion defects indicate ischaemia; whereas a fixed perfusion defect is most likely caused by scar tissue.[79] However, perfusion can be normal in nonviable myocardial areas after successful, but late, reperfusion treatment for an acute myocardial infarction, which can be evaluated using contrast-enhanced MRI.[31] Determining the extent of ischaemia that needs to be present to expect a beneficial effect of revascularization is difficult, especially in the absence of angina, because alleviation of symptoms is a valid reason for CTO–PCI. In asymptomatic patients, the achievable beneficial effects are improvement in physical activity, left ventricular function, electrical stability, and survival, and a reduced need for CABG surgery. In one study of 301 patients who underwent CTO–PCI, the level of ischaemia was assessed using serial myocardial perfusion imaging 12 ± 3 months before, and 12 ± 3 months after, the procedure.[80] Ischaemia was calculated using the difference between the summed stress and rest scores and converted to percentage of ischaemic myocardium. A meaningful improvement was defined as ≥5% decrease in ischaemic myocardium, because a change of this magnitude is known to be associated with reduced risk of death or myocardial infarction in patients with CAD.[64] In this cohort, the mean ischaemic burden decreased from 13.1 ± 11.9% at baseline to 6.9 ± 6.5% at follow-up after CTO–PCI.[80] Receiver operating characteristic analysis showed that 12.5% ischaemic burden at baseline was an optimal threshold to identify patients who would benefit from CTO–PCI in terms of a reduced ischaemic burden. Patients with a baseline ischaemic burden <6.25% were likely to have an increased ischaemic burden after PCI. Therefore, in asymptomatic patients with CTO, the ischaemic burden should be evaluated before CTO–PCI is considered.[64] In our opinion, a threshold of 12.5% can be used as a reference, but larger, prospective studies are needed to set a definitive cut-off value.

Myocardial viability

The presence and magnitude of myocardial viability is important to identify patients who might most benefit from CTO–PCI. A combination of viability parameters can predict improvement of myocardial function with more accuracy than the use of a single parameter including: dobutamine contractile reserve; transmural extent of infarction; and segmental wall thickening of normal remaining myocardium on cardiac MRI, especially in segments with intermediate extent of infarction.[31] Contractile reserve assessed with dobutamine seems to be one of the best predictors of myocardial improvement, because it directly unmasks the potential presence of contractile reserve in dysfunctional, noninfarcted myocardium.[81–85] Although intuitively logical, evidence that myocardial viability is absolutely necessary is limited and inconsistent. However, until an adequately powered, randomized clinical trial shows otherwise, the presence of myocardial viability is required to justify CTO–PCI.

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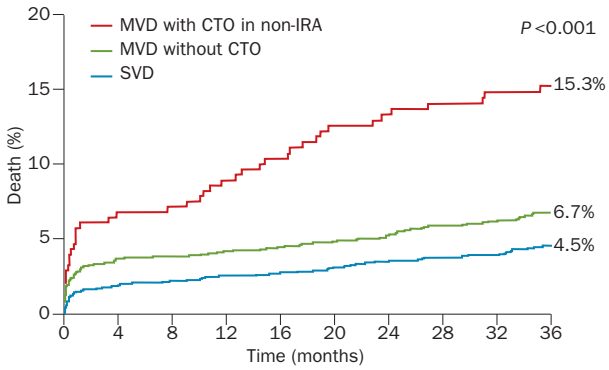

Number at risk										
MVD with CTO in non-IRA	283	260	258	253	243	237	231	224	221	148
MVD without CTO	1,477	1,403	1,389	1,377	1,351	1,345	1,330	1,295	1,286	911
SVD	1,524	1,479	1,468	1,454	1,433	1,426	1,413	1,391	1,381	939

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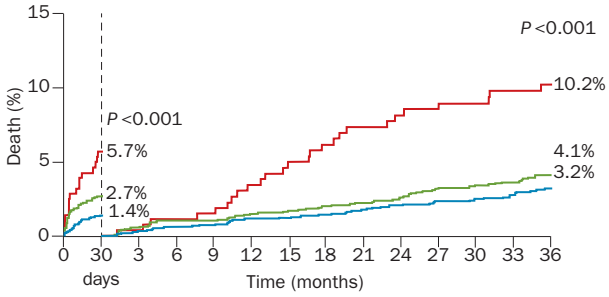

Number at risk								
MVD with CTO in non-IRA	283	265	259	253	240	231	223	148
MVD without CTO	1,477	1,429	1,399	1,377	1,347	1,330	1,291	911
SVD	1,524	1,494	1,474	1,454	1,429	1,413	1,388	939

Figure 3 | Time-to-event curves for all-cause mortality in patients with SVD, MVD without a CTO, or MVD with a CTO in a non-IRA. **a** | Mortality at 3 years. **b** | Mortality between 0 and 30 days, and 30 days and 3 years. Abbreviations: CTO, chronic total occlusion; IRA, infarct-related artery; MVD, multivessel disease; SVD, single-vessel disease. Permission obtained from Oxford University Press, Claessen, B. E. *et al.* Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur. Heart J.* **33**, 768–775 (2012).

Location of CTO

The location of a CTO in the coronary tree can be important for patient survival. In a study of 2,608 patients, successful versus failed CTO–PCI was beneficial only in patients with a CTO in the LAD artery (88.9% versus 80.2%; $P<0.001$), but not in those with a CTO in the LCx artery (86.1% versus 82.1%; $P=0.21$), or RCA (87.7% versus 84.9%; $P=0.23$) at 5 year follow-up.[86] However, these results might be influenced by an unconventional definition of procedural success—angiographic success with no in-hospital major adverse cardiac event (that is death, myocardial infarction with new Q waves on the electrocardiogram, or urgent target-vessel revascularization).[86] Consequently, all in-hospital deaths were considered procedural failures. From our own evaluation of the Kaplan–Meier curves of patients with a CTO in the LAD artery, the mortality difference seems to be determined in the first week, after which the slopes of the successful and failed curves seem similar.

However, data from another large, multinational registry with 1,734 patients with a CTO showed a survival benefit after successful CTO–PCI in either the LAD or the LCx arteries, but not in the RCA. At 5 years, mortality for successful versus failed CTO–PCI was 6.7% versus 11.0% in the LAD artery ($P=0.03$), 5.5% versus 13.9% in the LCx artery ($P=0.01$), and 6.6% versus 4.1% in the RCA ($P=0.80$).[87] Two potential explanations might account for this finding. First, the region of the myocardium supplied by the LAD artery is greater than the RCA or LCx territory; the effect of CTO–PCI in the LAD artery might, therefore, be more easily demonstrated. Secondly, sympathetic innervation is more pronounced in the anterior than in the inferior myocardial wall—vagal afferent receptors have a preferential distribution on the posterior wall of the left ventricle.[88,89] In the clinical setting, inferior myocardial infarction often leads to vagal activation.[88,89] Alterations in the balance of the autonomic nervous system owing to coronary occlusion has also been associated with life threatening ventricular arrhythmias and cardiac death in survivors of myocardial infarction.[90] In animal experiments, vagal stimulation or sympathetic inhibition reduces the threshold for ventricular fibrillation.[91] Therefore, patients with an inferior occlusion after myocardial infarction might be relatively protected from ventricular fibrillation, whereas patients with an anterior occlusion might have a higher frequency of ventricular arrhythmia. In a small cohort ($n=23$), CTO–PCI had a beneficial effect on the autonomic nervous system in the LAD artery, which was not observed after CTO–PCI of the RCA.[92] These findings suggest a potential antiarrhythmic effect after LAD revascularization, resulting from a shift in the autonomic balance in favour of the parasympathetic nervous system.

Until a randomized trial shows otherwise, all CTO locations should be evaluated for revascularization. However, data suggest that prognostic variability might be present. Consequently, in our opinion, revascularization of a CTO located in the LAD artery (and possibly the LCx artery) is highly recommended.

CTO in patients with STEMI

In the past decade, several papers have highlighted the importance of a concurrent CTO in patients with ST-segment elevation myocardial infarction (STEMI) who receive primary PCI.[93–96] A CTO in a noninfarct-related artery is present in approximately 10% of all patients with STEMI.[93,95] The presence of a CTO in a noninfarct-related artery in patients with multiple-vessel disease seems to explain to a large extent the adverse prognosis (compared with those patients with single-vessel disease) in these individuals (Figure 3). Patients with a CTO in a noninfarct-related artery have a high prevalence of cardiovascular risk factors and comorbidities compared with those with no CTO.[93–96] In addition, patients with STEMI and a CTO often have a higher increase in the level of cardiac enzymes than those without a CTO, which is indicative of a larger infarct size.[93,95] Interarterial connections between the CTO and infarct-related artery through collateral vessels might

increase the endangered myocardial area after acute closure of the culprit artery, because both its own supply and the myocardium served by that artery is at risk, leading to larger infarct size, increased end-diastolic left ventricular pressure, and suboptimal epicardial and myocardial reperfusion.[94,95] In substudies from the TAPAS and HORIZONS-AMI trials, the presence of a CTO in a noninfarct-related artery was associated with incomplete ST-segment resolution, lower myocardial blush grades, and lower post-procedural TIMI flow grades in the culprit artery (Figure 4).[95]

A distinction has also been made between patients with STEMI and the presence or absence of cardiogenic shock.[97] In patients with STEMI and multivessel disease who are not in cardiogenic shock, a coexisting CTO in a noninfarct-related artery is a predictor of both early and late mortality.[97] In patients with cardiogenic shock, multivessel with or without a CTO was a predictor of short-term mortality.[97] However, for long-term mortality, only the presence of a CTO seemed to be of importance. In our opinion, this observation might be explained by the reduced cardiac output and coronary blood flow in patients with cardiogenic shock, which might increase the functional importance of nonocclusive multivessel lesions, resulting in myocardial ischaemia in perfusion areas other than that of the culprit lesion.

The association between a noninfarct-related CTO and impaired outcome has also been reported in patients with non-STEMI.[98,99] However, whether a CTO is just an indicator of adverse prognosis, or whether additional CTO–PCI revascularization after a primary PCI for STEMI can improve clinical outcome remains unknown.

CTO and future adverse events

A CTO might increase the risk of future adverse cardiac events in another artery, especially in the setting of an acute myocardial infarction where only one coronary artery remains for blood supply. An artery with a CTO is unable to donate collateral vessels, which is normally associated with a reduction in infarct size, improved left ventricular function, and increased survival.[13,66,100] Conversely, when the myocardium of the CTO territory is dependent on collateral circulation of a remaining coronary artery, in theory, the amount of myocardium at risk after acute occlusion of the donor artery will extend beyond its own perfusion area, with an increased infarct size, major left ventricular dysfunction, heart failure, and even increased mortality. Consequently, patients with STEMI and a CTO in a noninfarct-related artery more often develop cardiogenic shock upon presentation to the catheterization laboratory than patients without a CTO.[97] This reduced myocardial reserve or lack of a collateral circulation 'back-up' system during a new coronary event might be another reason for a patient to undergo CTO–PCI revascularization. However, to test this hypothesis in a clinical trial would be extremely difficult owing to the very large number of patients required, and the need for extensive follow-up (>5 years).

In individuals without acute myocardial infarction, the presence of a CTO in the RCA was shown to be an

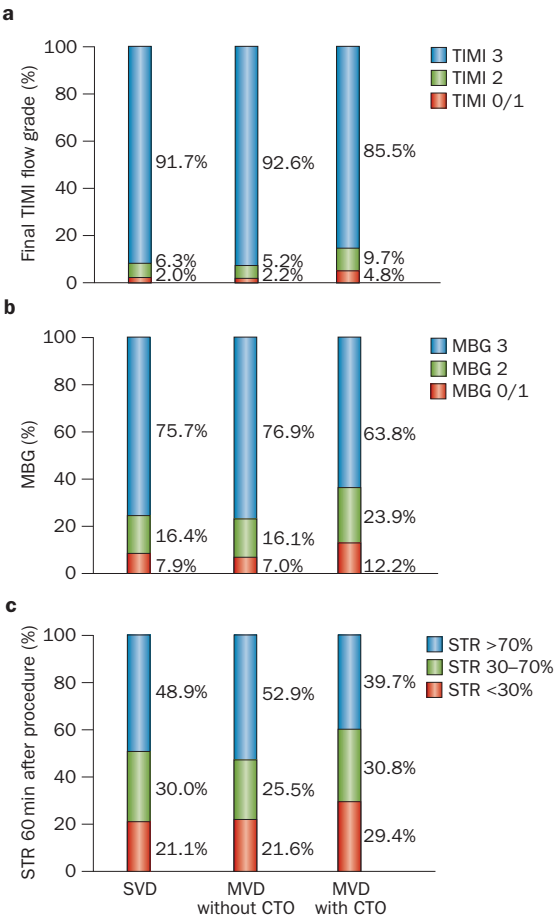

Figure 4 | Markers of reperfusion in patients with SVD, MVD without a CTO, or MVD with a CTO. Abbreviations: CTO, chronic total occlusion; MBG, myocardial blush grade; MVD, multivessel disease; STR, ST-segment resolution; SVD, single-vessel disease; TIMI, thrombolysis in myocardial infarction.

independent predictor of mortality in patients ($n = 330$) undergoing unprotected left main PCI (HR 2.15, 95% CI 1.02–4.50, $P = 0.043$).[101] Furthermore, successful CTO–PCI has been shown to reduce the need for CABG surgery compared with failed CTO–PCI (risk ratio 0.25, 95% CI 0.21–0.30, $P < 0.001$).[28]

Probability of successful PCI

Despite procedural complexity, increased operator volumes have led to an improved success rate of CTO–PCI from approximately 68% to 85%.[17,102] This improvement is accompanied by a low risk of procedural complications, regardless of procedural success.[17,18,102,103] These figures are similar to non-CTO procedures, with the exception of a significantly increased fluoroscopy time and use of contrast agent (Table 2).[18] However, complication rates are significantly higher in patients with failed CTO–PCI than in those with a successful intervention (Table 3).[102]

Several factors might increase procedural complexity and limit successful outcome. A number of angiographic features have been associated with a reduced success rate of CTO–PCI: increasing age of the CTO, presence of a

Table 2 | Complications of patients receiving PCI for CTO versus non-CTO lesions

In-hospital complication	CTO	No CTO	*P* value
Death (%)	0.3	0.2	0.35
Nonfatal myocardial infarction (%)	0.4	0.6	1.0
Stroke (%)	0.1	0.1	0.47
Resuscitation (%)	0.7	0.2	0.015
Others, for example, tamponade (%)	1.1	0.5	0.06
Emergency CABG surgery (%)	0	0.1	1.0
Median hospital stay days (quartile range)	2 (1–5)	2 (1–4)	0.72

Abbreviations: CTO, chronic total occlusion; PCI, percutaneous coronary intervention. Permission obtained from Werner, G. S. *et al.*, Contemporary success and complication rates of percutaneous coronary intervention for chronic total coronary occlusions: results from the ALKK quality control registry of 2006. *EuroIntervention* **6**, 361–366 © Europa (2010).

Table 3 | Complications in patients with CTO–PCI[102]

Procedural complication (%)	Successful CTO–PCI	Failed CTO–PCI	*P* value
Death	0.4	1.5	<0.0001
Stroke	0.07	0.4	0.04
Coronary perforation	3.7	10.7	<0.0001
Tamponade	0.0	1.7	<0.0001

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

blunt stump, presence of bridging collaterals, presence of calcium, excessive tortuosity, long occlusion length, and side branches at the occlusion entry.[51,52,104,105] The majority of these features are captured in the J-CTO (multicentre CTO registry in Japan) score (Table 4). This score was determined by assigning one point for each independent predictor of crossing the CTO lesion within 30 min of starting the procedure.[106] The summed value was then used to develop a model stratifying all lesions into four groups indicating the difficulty of the procedure: easy (score = 0); intermediate (score = 1); difficult (score = 2); and very difficult (score = 3–5). In our opinion, a high J-CTO score does not mean that no PCI attempt should be made, but might indicate whether a patient should be referred to an experienced centre or for CABG surgery, because operator experience determines successful outcome.

Treatment after CTO–PCI

Historically, CTO–PCI has been associated with a high rate of restenosis and reocclusion;[1,107–109] therefore, the implantation of a DES is recommended during a successful procedure.[110] The introduction of bare-metal stents (BMSs) in the 1990s led to a significant reduction in the need for repeat revascularization compared with balloon angioplasty alone.[107,109,111] In the first decade of the 21st century, DESs led to an incremental 60% reduction in the relative risk of repeat revascularization after CTO–PCI.[1] The risk of stent thrombosis tends to be higher with DESs compared with BMSs (relative risk 2.79, 95% CI 0.98–7.97, $P = 0.06$).[1] However, investigators from a multinational CTO registry reported similar rates of stent thrombosis with BMSs or DESs in a cohort of 1,160 patients up to 5 years after successful CTO–PCI (2.3% versus 1.7%; $P = 0.58$).[49,108] Only a small number of randomized trials have been conducted to investigate the safety and efficacy of various types of DES; therefore, no recommendations can be made specifying which DES should be used.[112–116] To date, no information is available about the performance of bioabsorbable stents in CTO lesions. The resorption of bioabsorbable scaffolds has been hypothesized to enable full restoration of vasomotion and autoregulation in the CTO territory.[117] The patency rate after CTO–PCI at 6–9 month follow-up is approximately 90% for first-generation DES, and 97% for everolimus-eluting stents.[118] The rate of 1-year graft patency is 80% for saphenous vein grafts, and 99% for internal mammary artery grafts.[119]

Table 4 | J-CTO score for predicting successful guidewire crossing within 30 min

Variables	OR (95% CI)	β coefficient	Point
Previously failed lesion	0.39 (0.15–0.97)	0.93	1
Blunt stump type	0.32 (0.18–0.55)	1.14	1
Bending	0.34 (0.20–0.58)	1.09	1
Calcification	0.26 (0.15–0.44)	1.36	1
Occlusion length ≥20 mm	0.19 (0.09–0.39)	1.65	1

Abbreviations: J-CTO, multicentre CTO registry in Japan. Permission obtained from Morino, Y. *et al.* Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc. Interv.* **4**, 213–221 © Elsevier (2011).

Forthcoming CTO trials

Investigators in the EXPLORE trial[120] will evaluate whether CTO–PCI in a noninfarct-related artery within 7 days of primary PCI can improve LVEF and reduce left ventricular end-diastolic volume, compared with optimal medical therapy. The trail rationale is based on the assumptions that recanalization of the CTO will restore contractile function to the myocardium and might improve the healing of the infarct border zone, protect against negative remodelling, and thereby preserve residual left ventricular function. Until a randomized controlled trial proves otherwise, subsequent CTO–PCI in the subacute setting after STEMI is not recommended in clinically stable patients. The EXPLORE trial is expected to complete enrolment in 2014. Investigators in two other randomized clinical trials powered for clinical end points are currently enrolling patients with CTO and stable CAD. Researcher in the EuroCTO trial[121] will randomly assign 1,200 patients to receive either PCI with DES and optimal medical therapy or optimal medical therapy alone. The primary end point is quality of life at 1 year and major cardiovascular events (a composite of all-cause death and nonfatal myocardial infarction) at 3 years. Similarly, investigators in the DECISION-CTO trial[122] will randomly assign 1,284 patients (in a 1:1 ratio) to receive PCI with DES and optimal medical therapy or optimal medical therapy alone. The primary end point is a composite of all-cause mortality, myocardial infarction, stroke, and any revascularization at 3-year follow-up.

Emerging treatments for CTO

Technical improvements in microcatheters, which have enabled enhanced antegrade and retrograde support, and

the development of dedicated guidewires for CTO have improved the success rate of CTO–PCI.[123] The success of CTO procedures is now >85% in centres with experienced interventional cardiologists and will probably improve further as technical developments continue.[123] 3D intravascular imaging with, for example, the forward-looking intravascular ultrasonography catheter, which enables a successful and safe crossing of the cap and occlusion, is a promising tool for CTO treatment.[124,125] Moreover, the CrossBoss™ catheter and Stingray™ devices (Boston Scientific, USA) can accurately target and re-enter the true lumen from a subintimal position, which is now incorporated in the 'hybrid' approach to CTO–PCI.[125,126] This approach focuses on opening the occluded vessel using all feasible techniques (antegrade, retrograde, true-to-true lumen crossing or re-entry) in the safest, most effective, and most efficient way.

A novel approach has been developed for complex CTO lesions with previous failed percutaneous revascularization attempts, and has been shown to be safe in a first-in-man study.[127] In 20 patients, CTOs in which guidewire crossing failed were pretreated with intracoronary collagenase for 30 min. The following day, another attempt was made to cross the lesion, which was successful in 75% of patients. Therefore, preliminary results suggest that collagenase facilitates guidewire crossing and might be a useful tool for the antegrade approach in difficult procedures; however, procedural efficacy still needs to be evaluated.[127]

Other strategies to restore compensatory blood flow to the myocardial territory of a CTO—such as stimulation of collateral growth through arteriogenesis or external counterpulsation—might also be alternative approaches to CTO–PCI. A detailed discussion of these non-PCI strategies is beyond the scope of this Review, and has been discussed extensively elsewhere.[67,128–132]

Conclusions

In patients with clinically significant CAD, a CTO is frequently observed on angiography, but the uptake of CTO–PCI by cardiologists is low, which reflects the procedural complexity and lack of randomized data. However, these factors alone do not justify withholding PCI in patients with a CTO. Careful selection of patients can improve clinical outcome in these high-risk patients. In experienced centres, the success rate is up to 85%, without an increased risk of complications compared with non-CTO–PCI. Evidence from observational studies suggests that the beneficial effects of CTO–PCI will finally be extended by evidence from adequately powered, randomized, controlled trials within the next few years.

Review criteria

A search of the PubMed database was performed for articles published between January 1990 and December 2013, using the following search terms: "chronic total occlusion", "chronic total coronary occlusion", "percutaneous coronary intervention", "angioplasty", "recanalization", and "revascularization", without further restrictions. Titles and abstracts were examined and potential studies were scrutinized in full text. We reviewed the reference lists of identified articles for additional papers. Selected articles identified through these methods published before 1990 were also considered.

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Author contributions

L.P.H., B.E.C. and J.P.S.H. researched data for the article and wrote the manuscript. All the authors substantially contributed to discussion of the content, reviewed, and edited the manuscript before submission.