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REVIEW

Clinical update

Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview

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Coronary chronic total occlusions (CTOs) are commonly encountered in patients undergoing coronary angiography. Several observational studies have demonstrated that successful CTO revascularization is associated with better cardiovascular outcomes and enhanced quality of life (QOL). However, in the absence of randomized trials, its prognostic benefit for patients remains debated. Over the past decade, the interest of the interventional community in CTO percutaneous coronary intervention (PCI) has exponentially grown due to important developments in dedicated equipment and techniques, resulting in high success and low complication rates. Both European and American guidelines have assigned a class IIa (level of evidence B) recommendation for CTO PCI. In the current review, we focus on the impact of CTO revascularization on clinical outcomes and QOL and on appropriate patient selection, and we provide a critical assessment of the current guidelines and recommendations on CTO PCI.

Keywords Chronic total occlusion • PCI • Guidelines • Cardiovascular outcome • Quality of life

Introduction

Coronary chronic total occlusions (CTOs) are defined as an occluded coronary segment with thrombolysis in myocardial infarction flow 0 for ≥3 months duration.[1,2] Coronary CTOs are commonly encountered in everyday catheterization laboratory practice, with a prevalence rate of 18–52% among patients undergoing coronary angiography.[3–5] Although several observational studies have demonstrated that successful CTO revascularization is associated with better cardiovascular outcome[6,7] and improved quality of life (QOL),[8,9] in the absence of randomized trials, its clinical benefit continues to be debated. In patients affected by CTOs, symptoms are often atypical and collaterals are generally well developed.[10] Furthermore, CTO percutaneous coronary intervention (PCI) is considered to be a cumbersome and costly procedure, and has been associated with a higher rate of complications, when compared with non-CTO lesions.[11,12] These reasons underlie the frequent clinician's reluctance to refer a patient for CTO PCI, particularly in the setting of single-vessel disease. On the other hand, the interest of the interventional community in CTOs has exponentially grown due to important developments in dedicated equipment and techniques.[13,14] High rates of success and low rates of complications are now achieved by expert operators, even in complex cases.[15,16] Despite this, the last European Society of Cardiology

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guidelines assigned a class IIa (level of evidence B) to CTO PCI in 'patients with expected ischaemia reduction in a corresponding myocardial territory and/or angina relief'.[17]

In the current review, we focus on the impact of CTO revascularization on clinical outcomes and QOL, in order to identify which patients would derive the most benefit from CTO revascularization according to the clinical scenario and to provide a critical assessment of the current guidelines regarding CTO PCI.

Chronic total occlusion revascularization and cardiovascular outcome

The presence of a coexisting CTO in patients undergoing primary PCI for ST-elevation myocardial infarction (STEMI) is associated with worse early and late clinical outcomes.[18,19] Similarly, in the setting of non STEMI, Gierlotka *et al.*[20] showed that the presence of an additional CTO was associated with higher mortality at 1-year follow-up.

Several observational studies have shown that successful CTO revascularization can provide clinical benefits[21–25] (*Table 1* and *Figure 1*). In recent years, tremendous progress has been achieved in the dissemination and application of CTO PCI techniques, as reflected in registries from around the globe[7,26–33] (*Table 2*). With growing CTO PCI experience, expert operators have achieved high rates of procedural success, using both antegrade and retrograde approaches.[26–31] Werner *et al.*[34] did not find a significant difference in complication rate between CTO and non-CTO PCI; in contrast, other reports showed that patients undergoing CTO PCI had a higher risk for in-hospital adverse events.[11,12] Use of the retrograde approach was associated with higher rates of coronary perforation and non-Q-wave myocardial infarction (MI) in comparison with antegrade techniques.[11,26] In Japan, the J-CTO registry (multicentre CTO registry in Japan) led to the development of J-CTO (Japanese Multicenter CTO registry) score to predict the likelihood of successful guidewire crossing within 30 min.[35] Independent angiographic predictors of failure (each given one point) that made up the J-CTO score included prior failed attempt, angiographic evidence of heavy calcification, bending within the occluded segment, blunt proximal stump, and occlusion length >20 mm. Chronic total occlusions were then graded as easy, intermediate, difficult, and very difficult (J-CTO scores of 0, 1, 2, and ≥3, respectively). Very recently, Galassi *et al.*[33] demonstrated that J-CTO scores ≥3 were independently associated with worse long-term outcome after retrograde CTO PCI.

The presence of well-developed collaterals often underlies the reluctance of clinicians to offer PCI in patients affected by CTOs. However, although the presence of collateral circulation has been associated with improved survival,[36] the collateral flow was sufficient to preserve ventricular function in only 5% of CTO patients.[37] Moreover, Sachdeva *et al.*[38] demonstrated resting ischaemia, defined as resting Pd/Pa < 0.80 (Pd = pressure distal to the CTO, Pa = pressure proximal to the CTO) in more than three-fourths of patients affected by CTOs. Recently, Jang *et al.*[39] compared the long-term clinical outcomes of patients with CTO and good collateral circulation (Rentrop 3) treated with revascularization vs. those conservatively managed by medical therapy. After propensity score matching, the incidence rate of cardiac death and major adverse cardiac events was significantly lower in the revascularization group when compared with the medical therapy-only group.[39]

Similar to the setting of acute coronary syndrome, operator's experience is highly related to the success of CTO attempts.[33] Indeed, in experienced hands, the outcome of CTO PCI is comparable to non-CTO PCI. When compared with successful procedures, failed PCI attempts for CTOs were associated with worse cardiovascular prognosis.[7,33] A meta-analysis by Joyal *et al.*[40] demonstrated a survival benefit for patients who underwent CTO recanalization (odds ratio [OR] 0.56), and a reduction of the need for subsequent coronary artery bypass graft (CABG) (OR 0.22) and residual/recurrent angina (OR 0.45). A more recent meta-analysis also confirmed that successful CTO PCI was also associated with reduced mortality in comparison with failed procedures (OR 0.52).[41] The fact that successful CTO PCI confers a long-term survival benefit might be driven by the differences in the outcome of patients with multivessel disease and who were completely revascularized in comparison with those incompletely revascularized.[42]

The negative results of the Open Artery Trial (OAT) are often cited as evidence against benefit of CTO PCI;[43] however, the OAT trial did not include patients with CTOs, but rather patients with a recent acute coronary syndrome, and hence the findings do not apply to CTO PCI.

Table 1 Observational studies showing the benefits of successful CTO PCI

	No. of patients	Follow-up	Findings
Chung *et al.*[21]	75	6 months	Improvement in LVEF and regional wall motion in patients without prior MI.
Nakamura *et al.*[22]	180	6 months	Improvement in LVEF in CTO patients revascularized with DES implantation.
Baks *et al.*[23]	27	5 months	Improvement of left ventricular volumes and LVEF as assessed by MRI.
Cheng *et al.*[24]	40	6 months	Successful CTO PCI increases hyperaemic myocardial blood flow with a greater and earlier improvement in regional contractility than after non-CTO PCI.
Cetin *et al.*[25]	114	24–48 h	Successful CTO PCI reduces the arrhythmic vulnerability on the basis of an analysis of the TpTe, the TpTe/QT ratio, and QTc dispersion.

CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; DES, drug-eluting stent; TpTe, T peak-T end; QTc, QT corrected.

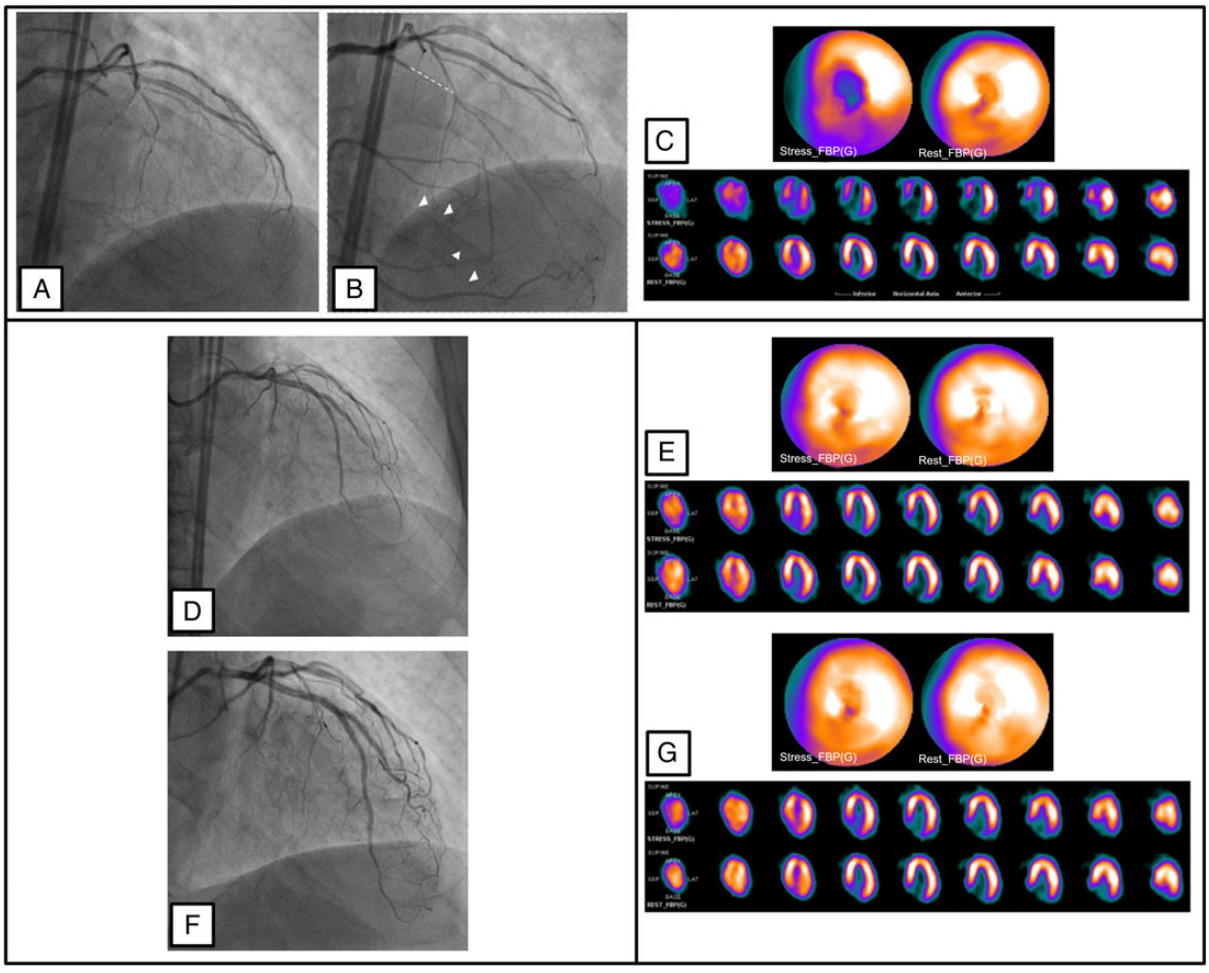

Figure 1 Example of a patient with a CTO percutaneously revascularized. A 58-year-old dyslipidaemic man was admitted for angina CCS class II and dyspnoea NYHA class III. Echocardiogram showed a preserved left ventricular function (EF = 50%) with antero-septal hypokinesia. At coronary angiography, a single-vessel disease was observed: a CTO of proximal left anterior descending (*A*) with distal filling Rentrop 3 from septal collaterals from the right coronary artery (*B*). Stress myocardial scintigraphy revealed an extensive area of hypoperfusion in both apical and septal regions (*C*). CTO PCI was successfully performed with DES implantation (*D*). At follow-up, the patient was asymptomatic, and no ischaemia was detected at 8 months myocardial scintigraphy after the index procedure (*E*). At 1-year angiographic control, neither reocclusion nor restenosis were observed (*F*). At 2-year follow-up, the patient remained asymptomatic with no perfusion defect at control scintigraphy (*G*). CCS, Canadian Cardiovascular Society; CTO, chronic total occlusions; DES, drug-eluting stents; EF, ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Chronic total occlusion revascularization and quality of life

The assessment of QOL is an important measure of the utility of revascularization in patients with coronary artery disease (CAD). In particular, the Seattle Angina Questionnaire (SAQ) has been extensively studied and validated in cardiac patients. The assessment is based on five domains: physical limitation, angina stability, angina frequency, disease perception, and treatment satisfaction.[44]

Quality-of-life assessment according to the SAQ has now been examined in four CTO revascularization studies (*Table 3*). Two of these studies have compared SAQ scores in patients with successful vs. failed PCI, demonstrating significant improvement in physical limitation, anginal episodes, and treatment satisfaction in successful vs. failed patients.[45,46]

After propensity matching, Safley *et al.*[8] compared QOL indices in patients who underwent PCI for CTO (147 patients) or non-CTO lesions (1616 patients) from 10 centres. There were similar increases in all SAQ domains at 6 months post-PCI in successfully treated lesions in both groups, despite a lower success rate in CTOs (85 vs. 98% in non-CTO).[8]

One study compared revascularization strategies with medical therapy in patients diagnosed with CTOs at coronary angiography.[9] The medical treatment group had no change in any SAQ domains, while patients in whom CTO was revascularized (either by PCI or CABG) showed improved physical limitation, angina frequency, and

Table 2 Data on CTO PCI outcomes from multicentre registries

Study	No. of patients	CTO techniques	Technical success (%)	In-hospital outcomes	Follow-up period	Mid-/long-term outcomes	Conclusions
Galassi *et al.*[26] ERCTO registry	1914	Antegrade and retrograde	82.9	Cardiac death (0.3%), Q-wave MI (0.1%), non-Q-wave MI (0.1%), ST (0.05%), TVR (0.05%), and stroke (0.05%).	–	–	– High rate of success with a low rate of complications. – Retrograde approach was associated with higher incidence of coronary perforations.
Morino *et al.*[27] J-CTO registry	498	Antegrade and retrograde	88.6	Cardiac death (0.2%), Q-wave MI (0.2%), and stroke (0%).	–	–	– High rate of success with a low rate of complications.
Karmpaliotis *et al.*[28]	462	Retrograde	81.4	Death (0.2%), Q-wave MI (0.4%), and emergency CABG (0.6%).	–	–	– Retrograde CTO PCI is associated with favourably high success and low complication rates.
Christopoulos *et al.*[29] PROGRESS CTO	497	Hybrid CTO PCI	91.5	Cardiac death (0.4%), MI (1%), and TVR (0.2%).	–	–	– Use of the hybrid approach to CTO PCI is associated with higher success and similar complication rates compared with prior studies
Alaswad *et al.*[30] PROGRESS CTO	650	Antegrade and retrograde	92.6	Cardiac death (0.3%), MI (0.7%), and TVR (0.1%).	–	–	– Transradial CTO PCI can be performed with similar success and complication rates with transfemoral CTO PCI.
Muramatsu *et al.*[31] J-PROCTOR registry	163	Dissection re-entry techniques	100	Cardiac death (0%), Q-wave MI (0%), non-Q-wave MI (1.8%) and emergency CABG (0%).	1 year	– Cardiac death (0%), MI (0%), ST (0%). – Similar TVR rate between intimal and subintimal groups (10.4 vs. 12.9%, respectively; $P = 0.75$).	– No negative clinical impact of subintimal tracking after mid-term follow-up.
George *et al.*[7] UK Central Cardiac Audit Database	13 443	Antegrade and retrograde	70.6	In-hospital death (0.25%), Q-wave MI (0.42%), cerebrovascular accident (0.06%), and emergency CABG (0.1%).	2.65 years	– Death (5.6%)	– Successful CTO PCI was associated with improved long-term survival. – Better outcome when complete revascularization was achieved.
Claessen *et al.*[32] Multinational CTO Registry	1791	Antegrade and retrograde	68.1	–	1178 days	– Cumulative long-term mortality: successful vs. unsuccessful *LAD: 6.7 vs. 11.0% ($P = 0.03$) *LCX: 5.5 vs. 13.9% ($P < 0.01$) *RCA: 6.6 vs. 4.1% ($P = 0.80$).	– Successful PCI of a CTO in the LAD and the LCX, but not in the RCA, is associated with improved long-term survival.
Galassi *et al.*[33] ERCTO registry	1395	Retrograde	75.3	Death (0.1%), Q-wave MI (0.1%), non-Q-wave MI (0.3%), ST (0.2%), emergency CABG (0.1%), TVR (0.1%), and stroke (0%).	24.7 months	Cardiac death (1.9%), MI (1.9%), stroke (0.6%), and further revascularization (13%).	– Retrograde CTO PCI was associated with high percentages of success, low rates of major complications, and good long-term outcomes.

CABG, coronary artery bypass graft; CTO, chronic total occlusion; LAD, left anterior descending; LCX, left circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; ST, stent thrombosis; TVR, target vessel revascularization.

Table 3 Summary of studies focusing on the impact of CTO revascularization on QOL

	Grantham et al.[45]	Borgia et al.[46]	Saffley et al.[7]	Wijeysundera et al.[8]
No. of CTO patients attempted percutaneously	125	302	167	46 (out of 387 CTO patients)
CTO PCI success rate (%)	55	78	84.7	78.8
Assessment tool	SAQ	SAQ-UK	SAQ	SAQ
Assessed parameters	– Angina frequency – Physical limitation – QOL	– Angina frequency – Physical limitation – Treatment satisfaction	– Angina frequency – Physical limitation – QOL – Rose Dyspnoea Score – EQ5D	– Angina frequency – Physical limitation – Angina stability – Treatment satisfaction – Disease perception – EQ5D
Follow-up	1 month	4 years	6 months	1 year
Compared groups	Successful vs. unsuccessful CTO PCI	Successful vs. unsuccessful CTO PCI	CTO lesions PCI vs. non-CTO lesions PCI	PCI to CTO vessel; PCI to non-CTO vessel; CABG; only medical therapy
Adjustment for group differences	Yes	Yes	Yes	Yes
Findings	– Significant improvement in all assessed parameters in the successful group when compared with failed procedures – The benefit was greatest in symptomatic patients	– Significant improvement in all assessed parameters in the successful group when compared with failed procedures	– Similar improvement in all assessed parameters in successfully treated patients in both groups	– Revascularization of the CTO (by either PCI or CABG) was associated with improvements in QOL

CABG, coronary artery bypass grafting; CTO, coronary total occlusion; PCI, percutaneous coronary intervention; QOL, quality of life; SAQ, Seattle Angina Questionnaire; EQ5D, European quality of life-5 dimensions.

disease perception domains.[9] Interestingly, the non-CTO PCI group (CTO left untreated), with an incomplete revascularization, showed improvement in some QOL domains (angina frequency and disease perception but not physical limitation), but to a lesser degree than the CTO PCI or CABG groups. However, these groups were not randomly assigned, and the CTO PCI group was younger with fewer co-morbidities. Moreover, the benefits in the CTO revascularization groups were present despite ~20% failure rate (failed PCI attempt or CTO not grafted).

Very recently, the EuroCTO club has reported the long-term outcome of 5-year retrograde experience showing a significant improvement in angina and dyspnoea status after a median follow-up period of 23 months.[33]

There remain some QOL domains in patients with CTOs that are not adequately assessed by currently available instruments. Although the SAQ focuses on physical limitation to various levels of activity, the questionnaire fails to capture whether the patient has been reducing his activity level to avoid angina. Indeed, patients with chronic symptoms tend to adapt to their condition, and will frequently avoid symptom-generating physical activity. In addition, many patients with CTOs will suffer from dyspnoea on exertion. While angina is attributed to underlying CAD, dyspnoea may be regarded as a normal consequence of ageing itself and not considered to be an angina-equivalent symptom. These interpretations need to be more formally studied in patients with chronic stable angina due to CTOs.

Clinical indications to attempt chronic total occlusion revascularization

Chronic coronary occlusions are frequent in patients with relevant CAD, >50% have well-preserved LV function, and ~80% have no Q-waves in the CTO territory suggesting viable myocardium.[1,3,26] Although collaterals may have prevented MI, they supply as much flow as a 95% coronary stenosis and often are insufficient during periods of increased oxygen demand, resulting in angina or reduced exercise capacity.[37] In the presence of a CTO lesion, the decision-making process leading to revascularization passes through three steps: the evaluation of symptoms, the assessment of ischaemic burden, and the demonstration of viability.[47]

Patients affected by CTOs sometimes show atypical symptoms; shortness of breath and exercise limitation are more frequently observed than typical angina.[10] Grantham *et al.*[45] showed that successful CTO recanalization was associated with angina relief, improved physical function, and enhanced QOL only in symptomatic patients at baseline.

Galassi *et al.*[48] reported a worse cardiovascular outcome in patients with non-revascularized CTO lesions and severe perfusion defect, when compared with those with normal or almost normal myocardial scan. On the other hand, Safley *et al.*[49] identified a baseline ischaemic burden of 12.5% as an optimal cut-off to identify

patients most likely to have a significant decrease in ischaemic burden post-CTO PCI.[49] Conversely, patients with baseline ischaemic burden <6.25% were more likely to have ischaemia worsening post-PCI,[49] suggesting that conservative strategy might be the most appropriate management in this patient subset.

In patients with CAD and left ventricular dysfunction, Gerber *et al.*[50] showed a higher 3-year survival rate among revascularized patients (by either PCI or CABG) when compared with medically treated patients when viability was demonstrated. Kirschbaum *et al.*[51] found that early and late improvements in regional function observed after revascularization in the territory subtended by the CTO were related to the transmural extent of infarction on baseline cardiac magnetic resonance imaging (MRI). Moreover, it was also reported that multiple MRI-derived viability parameters better identified CTO patients who would take more benefit from PCI revascularization.[52]

Figure 2 illustrates the most common approach to indicate revascularization in patients affected by CTO lesions.

Appropriate modality to revascularize chronic total occlusions

Appropriate use criteria (AUC) have been developed to assist clinicians in revascularization decision-making in a wide range of clinical scenarios, including CTOs. The AUC were determined by a 17 member panel comprised of cardiologists (predominantly non-interventional), cardiac surgeons, and health outcome researchers selected by several American cardiac organizations. The initial AUC report was published in 2009[53] and updated in 2012.[54] The decision about appropriateness was based on the relative benefits (symptoms, functional status, and/or QOL) and risks of revascularization using currently available literature and expert opinion. The main factors considered include symptom severity on maximal medical therapy, stress testing, extent of coronary disease, and anatomical location.

The AUC downgrade the recommendation for PCI of CTO vs. non-CTO lesions in several clinical scenarios (*Figure 3*). However, CTO PCI for patients who are symptomatic while receiving two anti-anginal medications is ranked as appropriate or uncertain.

The AUC revascularization for CTO has been critically examined in several recent articles.[10,55,56] Several aspects of the UAC methodology have been questioned.[55] The AUC also do not consider patient preferences, tolerance to medical therapy, or the expertise of the CTO PCI operator, which is a particularly important determinant of both the success rate and complications in complex CTO cases. An even more fundamental issue with the current AUC revascularization ratings is whether CTOs should be regarded as a separate entity from non-CTO lesions.

In Europe, there are no AUC separated from the guidelines. The decision for individual patients is left to the Heart Team, overcoming some of the limitations highlighted above, such as, for instance, the expertise of the PCI operator. Chronic total occlusion is included among the anatomical factors to be considered in the selection of the modality of revascularization, but the only factors mandating the need for a Heart Team discussion are the presence of proximal left anterior descending (LAD) involvement (if absent PCI can be

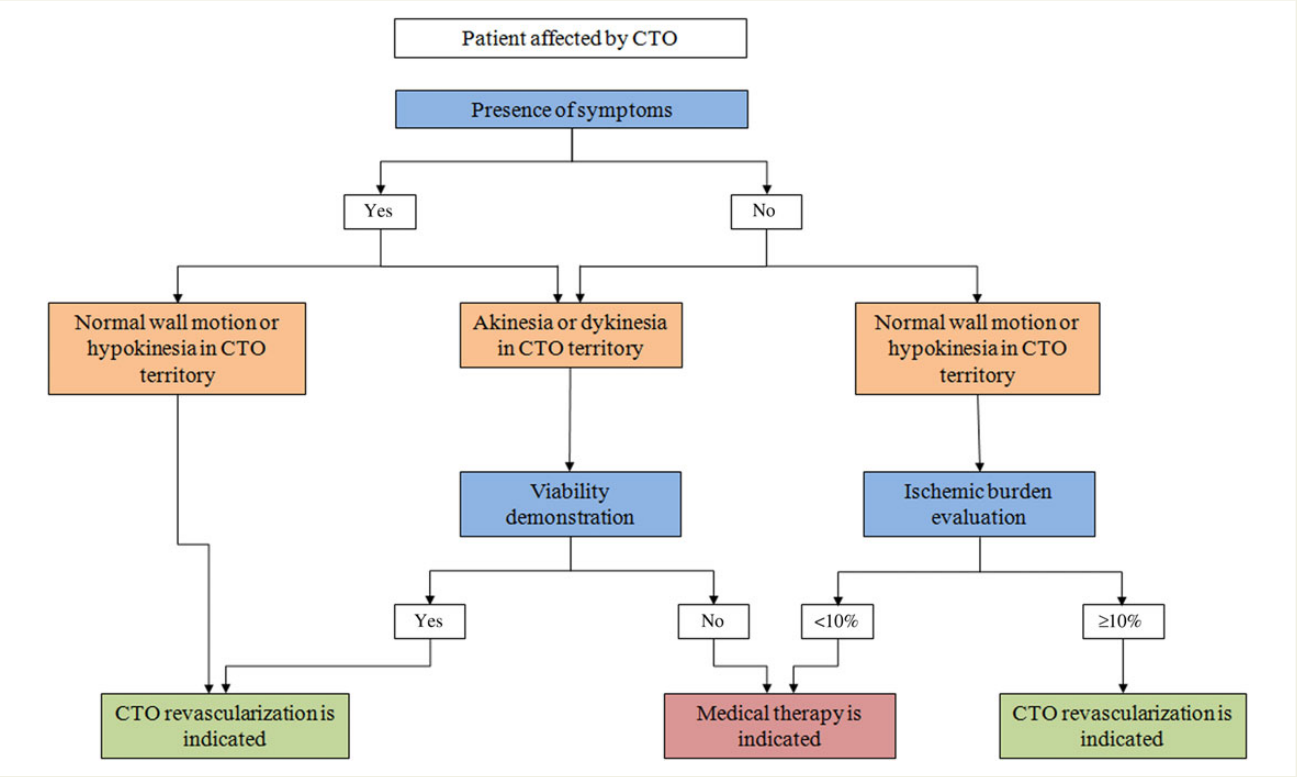

Figure 2 Indications of CTO revascularization according to symptoms, ischaemia, and viability. CTO, chronic total occlusion.

		Asymptomatic			Symptomatic ClassI II			Symptomatic ClassIII–IV		
		Low risk	Interm. risk	High risk	Low risk	Interm. risk	High risk	Low risk	Interm risk	High risk
Single-vessel disease	CTO	I	U	U	U	U	A	U	A	A
	Non-CTO	I	U	A	U	A	A	A	A	A

			No left main involvement		Left main involvement	
			No LAD Low Syntax score	High Syntax score with LAD involvement	Low Syntax score	High Syntax score
Muti vessel disease	CTO	PCI	A	U	U	I
		CABG	A	A	A	A
	Non-CTO	PCI	A	U	A	I
		CABG	A	A	A	A

I	Inappropriate	U	uncertain	A	Appropriate

Figure 3 Suggested workflow from appropriate use criteria document for CTO and non-CTO revascularization in single- and multivessel diseases. CABG, coronary artery bypass graft; CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

performed when technically feasible without the Heart Team discussion) and the Syntax Score (when ≥22 CABG can be performed without the Heart Team discussion in patients at low surgical risk). Obviously, the weight given to the presence of a CTO in the calculation of the SYNTAX score is such that very few patients with multivessel disease and a CTO will qualify for PCI, because a complex LAD CTO will almost be sufficient by itself to reach the surgical threshold of 23 (or 33 if the left main is involved).

Finally, discussing revascularization modalities and risk/benefit ratios in 'patients with CTO', in general, is an oversimplification and decisions should be made based on the overall clinical presentation. Indeed, CTOs can be encountered in vastly diverse clinical scenarios, such as elderly patients, presence of comorbidities, post CABG, and normal or impaired left ventricular ejection fraction (LVEF). These latter conditions should be considered in addition to the operator's experience, in order to indicate the best management strategy for CTO patients.

Chronic total occlusion percutaneous coronary intervention in current European and North American guidelines

The evolution of the approach to CTO treatment in the European Society of Cardiology Guidelines reflects the growing acceptance of this technique in the Stable Angina Guidelines of 2004 and the first PCI Guidelines.[57,58]

Starting with the 2010 revascularization Guidelines[59] and continuing with the Chronic Stable Angina[60] and the most recent Revascularization Guidelines,[17] no specific negative caveats against CTO are reported in the tables of indications for revascularization or guidance of the decision between PCI and surgery. The indication for revascularization in CTO patients, like any CAD patient, can be for symptoms, if the patient remains severely symptomatic under optimal anti-anginal therapy, or prognostic improvement. Also in choosing between bypass surgery and PCI, CTO is not explicitly mentioned, although it figures prominently in the decision since the SYNTAX is such a prominent consideration in determining whether PCI or surgery can be used interchangeably in patients with suitable indications for surgery, and at low/normal risk for surgery. The cut-off of 22 for three-vessel disease without left main involvement, and 33 for patients with left main disease stems from the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial, can be considered a clear bias against CTO recanalization. In lesions with stenosis severity between 50 and 99%, the weight of each segment is multiplied by 2. However, a factor of 5 is used for CTO lesions, so that a proximal LAD (weight 3.50) occlusion alone with CTO criteria of risk-adding points (e.g. absence of stump, bridging collaterals, and calcification) nearly reaches the critical 22 threshold.

In the 2011 ACCF/AHA/SCAI Guideline for PCI report,[61] CTO PCI is examined in the section 'PCI in Specific Anatomic Situations,

along with PCI in SVGs, Bifurcation, Aorto-Ostial and Calcified Lesions'. The committee acknowledges the complexities associated with CTO PCI and assigns CTO PCI a class IIa recommendation: 'PCI of a CTO in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise' (level of evidence: B). Class IIa favours CTO PCI as being useful and effective since it seems that the benefits outweigh the risks, but the evidence is not conclusive and additional studies with focused objectives are needed. The recommendation is based on the level of evidence B, which in general means that there is some conflicting evidence from a single randomized trial or non-randomized studies. It is important to mention that, to date, there is no published randomized trial comparing CTO PCI with CABG, or medical therapy.

It is worthwhile to note that the statement supporting the recommendation considers the different clinical scenarios associated with CTO lesions and emphasizes that CTO PCI should be performed 'in patients with appropriate clinical indications'. However, the remainder of the statement is rather vague, particularly since the definition for 'suitable anatomy' or 'appropriate operator expertise' is not specified and remains evolving concepts. Since the publication of these guidelines, CTO PCI in the USA (as well as around the world) has undergone drastic improvements with success rates consistently above 90% and major complication rates around 2% reported in several expert CTO sites.[62,63]

In Canada, the current guidelines are vague for the management of patients with CTOs. In the latest Canadian Cardiovascular Society Guidelines for the Diagnosis and Management of Stable Ischemic Heart Disease published in 2014, there is not even a single mention about CTOs.[64] It is, however, recognized that 'technical issues about optimal revascularization of distal vessel quality (surgical targets), bifurcations, and chronic total occlusions are evolving and cannot be addressed in this document'.[65] Moreover, in the 2012 Society Guidelines Management of Patients With Refractory Angina: Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines, none of the co-authors were experts in complex CTO PCI. Surprisingly, there are lengthy descriptions of spinal cord stimulation and outdated myocardial laser revascularization, with any mention of CTO PCI as a valuable option for the treatment of these patients.[66] *Table 4* summarizes the current recommendations regarding CTO PCI in both the European and North American guidelines.

Finally, in the absence of special recommendations, the authors do believe that surgical backup is not mandatory for CTO PCI programmes. However, the performance of CTO PCI at facilities without on-site surgery is discouraged unless performed by expert CTO operators at a laboratory that has immediately available all interventional equipment needed for the procedure and the management of potential complications.

How to further increase the evidence that chronic total occlusion percutaneous coronary intervention is beneficial, useful, and effective

Although the recanalization of CTOs can be achieved with a similar success rate as non-CTO lesions by experienced operators, a higher

Table 4 CTO PCI in recent European and North American guidelines

Guidelines	Specific CTO guidelines	Class of recommendation	Level of evidence	Recommendations
European	Yes	IIa	B	• 'Percutaneous recanalization of CTOs should be considered in patients with expected ischaemia reduction in a corresponding myocardial territory and/or angina relief'
		IIb	C	• 'Retrograde recanalization of CTOs may be considered after a failed anterograde approach or as the primary approach in selected patients'.
American	Yes	IIa	B	• 'PCI of a CTO in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise'
Canadian	No	–	–	• 'Revascularization therapy is also indicated to improve symptoms or quality of life and/or to reduce the risk of MI and premature death. There is no controversy regarding the need to explore revascularization in stable ischaemic heart patients with inadequate symptom relief, suboptimal quality of life, or emergence of acute chest pain syndromes while using medical therapy' • 'Revascularization can be considered early when high-risk features are identified in non-invasive test results although even this common practice is under current investigation' • 'The choice between coronary artery bypass grafting and percutaneous coronary intervention can be complicated because the decision must consider comorbidities such as diabetes, extent of atherosclerosis, and many technical issues including but not limited to location of stenosis with respect to side branches and bifurcations, and whether arterial vs. venous conduits are feasible'

CTO, chronic total occlusion; PCI, percutaneous coronary intervention; MI, myocardial infarction.

equipment cost and an increased radiation exposure remain two major limitations to its widespread adoption. This and a lack of randomized studies for this specific lesion subtype are the main reasons why the European and American guidelines classify the indication for CTO PCI as IIa only,[17,61] and might explain the reluctance of many interventional cardiologists to attempt CTO PCI in symptomatic patients. Noteworthy, in the SYNTAX trial, approximately one-third of the CTOs referred for CABG were not surgically revascularized[67] and there is high likelihood of graft occlusion in CTO arteries other than the LAD after 1 year.[68] Thus, it should not be assumed that referral of a patient with a CTO for CABG ensures a better outcome than treatment by an experienced CTO PCI operator.

Despite observational data in favour of CTO PCI from >20 000 patients, the physiological evidence, and the steady increase in PCI success rates in CTOs to a range similar to complex non-occlusive lesions, there is a major need for randomized trials to support the treatment option. At least three major randomized trials are under way. The EURO-CTO trial (NCT01760083), supported by the EuroCTO club, is examining the impact of PCI on the QOL parameters as assessed by standardized questionnaires in patients with a CTO when compared with optimal medical therapy alone within 12 months of treatment. Furthermore, the safety of the interventional approach is being assessed by comparing clinical endpoints at 3 years. Unfortunately, the results of this latter trial will not be available before 2016. Another group from Korea is currently randomizing patients with CTOs and stable angina to PCI vs. medical therapy [DECISION-CTO (NCT01078051)] to assess the impact of the intervention on cardiac mortality and MI during a follow-up of 5 years. The ongoing EXPLORE trial is a randomized clinical trial powered to investigate whether recanalization of a CTO in a non-infarct-related artery after primary PCI for STEMI in 300 patients randomized to either elective PCI of the CTO within 7 days or standard medical treatment. The primary endpoints are LVEF and left ventricular dimensions, as determined by magnetic resonance imaging. Enrolment has been completed and results are anticipated during 2015.

Despite the paucity of randomized trials, one question arises in light of the recent technical advances in CTO revascularization, why should the indication to treat a CTO by an expert operator should be considered any different from the one to treat other non-CTO lesions in stable angina, when symptoms and/or ischaemia are present? We can at least say that there is no evidence to support that a CTO is less relevant with regard to clinical outcomes than for non-occlusive lesions.

Conclusion

Although several observational studies have demonstrated that CTO PCI can improve cardiovascular outcomes and enhance QOL, its prognostic impact remains under debate. As a result, the recommendations for CTO PCI are downgraded in the current guidelines of myocardial revascularization, when compared with non-CTO lesions. Such a downgrade may not be justified based on data and in light of current developments in CTO PCI. In addition to the development of dedicated equipment and the high success rates achieved among different interventionalists' communities, the expected results of randomized trials might hopefully remove remaining doubts about the efficacy and safety of CTO PCI and therefore expand its indications. Rational patients' selection and operator's experience will remain key factors to ensure procedural success and optimal outcomes.

Authors' contribution

A.R.G.: conceived and designed the research. M.B., A.R.G., S.D.T., D.K., C.D.M., B.H.S., S.R., M.Y., O.K., G.S.W., and G.S.: drafted the manuscript. A.R.G., E.S.B., and N.R.: made critical revision of the manuscript for key intellectual content.

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