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Percutaneous coronary interventions of chronic total occlusions; a review of clinical indications, treatment strategy and current practice

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Abstract Chronic total occlusions (CTOs) are commonly encountered in patients undergoing coronary angiography, but percutaneous coronary intervention (PCI) for CTO is currently infrequently performed owing to the perception of limited clinical benefit, high complexity and cost of intervention, and perceived risk of complications. Numerous 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 remains debated. Nevertheless, over the past decade the interest in CTO-PCI has exponentially grown due to important developments in dedicated equipment and techniques, resulting in high success and low complication rates. A number of factors must be taken into consideration in selecting patients for CTO-PCI, including presence of symptoms attributable to the CTO, extent of ischaemia distal to the occlusion, and degree of myocardial viability. In this review, we focus on the impact of CTO revascularization on clinical outcomes and QOL and on appropriate patient selection. Data regarding efficacy and safety of recent advances in PCI-CTO techniques will be discussed. Steps involved in setting up a dedicated CTO program will be outlined and the current CTO landscape in Belgium will be briefly highlighted. The overall aim of this review is to promote a more balanced approach to management of patients with a CTO.

Keywords *Chronic total occlusion – percutaneous coronary interventions – clinical indications.*

INTRODUCTION

A coronary chronic total occlusion (CTO) is defined as an occluded coronary artery with thrombolysis in myocardial infarction (TIMI) flow 0 for >3 months duration[1]. Coronary CTOs are commonly encountered in everyday catheterization laboratory practice, with a prevalence ranging widely from 16-50% in patients with significant coronary artery disease, and a general prevalence of 11-20% in large registries[2-3]. CTO is often referred to as the final frontier for interventional cardiologists, who are frequently confronted with these complex coronary lesions. In a large Canadian multi-centre CTO registry the majority of patients with CTOs were treated medically (64%) or referred for coronary artery bypass grafting (CABG) surgery (26%) whereas only 10% were referred for percutaneous CTO revascularization[2]. The disparity between the high prevalence of CTO and the low rate of invasive treatment accentuates the greater technical difficulty and perceived risk of complications, high cost and resource utilization, the uncertainty regarding which patients benefit from CTO revascularization, and the lack of randomized trials demonstrating clinical benefits. Nevertheless, numerous observational studies support the rationale of CTO revascularization in cases of documented viability and ischaemia in the territory distal to the CTO. Successful CTO recanalization has been related to improved survival, increased exercise tolerance, improvement in

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angina status and left ventricular function, decreased need for CABG and better tolerance of future acute coronary syndromes[4,5]. Success rates of operators using conventional CTO techniques were never greater than 60-70% [5], whilst now high rates of success and low rates of complications are achieved by expert operators, even in complex cases[6].

In the current review we will evaluate the place for CTO PCI with an emphasis on current evidence regarding clinical relevance and rationale. Contemporary percutaneous recanalization techniques will be briefly discussed before considering steps involved in setting up a dedicated CTO program. Current CTO PCI practice in Belgium will be highlighted with emphasis on the recent establishment of the Belgian Working Group on Chronic Total Occlusions (BWG-CTO).

RATIONALE FOR CTO PCI

CTO and clinical outcomes

In the SYNTAX trial a CTO was the most important predictor of incomplete revascularization, which in turn was associated with increased major adverse cardiac events (MACE)[7].

The presence of a CTO in a non-infarct-related artery (non-IRA) in patients undergoing primary PCI for ST-elevation myocardial infarction (STEMI) and in patients presenting with a non-STEMI is associated with worse early and late clinical outcomes[8]. 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[9]. Furthermore, in sub-studies of the TAPAS and HORIZONS-MI trials, the presence of an CTO was associated with incomplete ST-segment resolution, lower myocardial blush grades, and lower post-procedural culprit artery TIMI flow grades[8,9]. Finally, the prevalence of a CTO in a non-IRA was significantly higher in patients with cardiogenic shock on admission and a CTO was found to be an independent predictor of cardiogenic shock in STEMI patients[10]. This is probably due to the fact that after occlusion of an artery donating collaterals to a CTO vessel, the myocardium at risk extends beyond the perfusion area of the culprit artery.

In STEMI patients with cardiogenic shock, multivessel disease with or without a CTO was a predictor of short-term mortality. However, in terms of long-term mortality only the presence of a CTO appeared to be of importance[11]. Whether a CTO is just an indicator of adverse prognosis, or whether additional staged CTO-PCI revascularization after a primary PCI for STEMI improves the clinical outcome remains unclear.

Dispelling some commonly held beliefs

The presence of well-developed collaterals on coronary angiography remains an important reason for some interventional cardiologists to defer CTO treatment. The presence of highly developed coronary collaterals is inversely correlated with degree of myocardial injury[12]and is predictive of residual viability on dobutamine stress echocardiography[13]. Nevertheless, clearly visible collaterals in the absence of residual viability, or the absence of clearly visible collaterals in the presence of viable myocardium are not uncommon findings, and are present in up to 20.7% and 33.3% of cases, respectively[13].

It is important to emphasize that the presence of visible collaterals does not necessarily indicate that ventricular function is normal and that significant ischaemia is absent in the CTO territory. Ventricular function can be preserved but not necessarily so despite the presence of well-developed collaterals[14,15]. Of note, in a recent study by Stuifzand et al. 66 patients with a documented CTO and preserved left ventricular ejection fraction underwent H_20 positron emission tomography (PET) perfusion imaging. The vast majority of these patients (> 90%) showed significantly impaired perfusion, suggesting that perhaps no additional ischaemia testing is mandatory prior to revascularization in this patient population[16].

In a recent study of CTO patients with ischaemic symptoms and/or positive stress test results compatible with myocardial ischaemia, 78% of patients had evidence of resting ischaemia (defined as resting Pd/Pa < 0.80, with Pd = pressure distal to the CTO and Pa = pressure proximal to the CTO) and all had an ischaemic fractional flow reserve (FFR)[17]. Werner et al. showed that only 7% of a population of CTO patients without prior Q-wave myocardial infarction had a normal coronary flow reserve despite angiographically well-developed collaterals and that coronary steal may be present in at least one third of patients[14]. The latter is mainly due to significant donor artery disease but can also occur due to an impaired vasodilatory reserve of the coronary microcirculation in absence of donor artery lesions. Finally, the long-term clinical outcome of 738 CTO patients with angina or documented ischaemia and with well-developed collaterals on angiography treated either with medical therapy (n = 236), or with revascularization (CABG (n = 170) or PCI (n = 332)) was recently evaluated. During a median follow-up duration of 42 months, multivariate analysis revealed a significantly lower incidence of cardiac death (HR: 0.29; 95% CI: 0.15 to 0.58; $P < 0.01$) and major adverse cardiac events (HR: 0.32; 95% CI: 0.21 to 0.49; $P < 0.01$) in the revascularization group compared with the medication group. After propensity score matching, the incidence of cardiac death (HR: 0.27; 95% CI: 0.09 to 0.80; $P = 0.02$) and MACE (HR: 0.44; 95% CI: 0.23 to 0.82; $P = 0.01$) remained significantly lower in the revascularization group than in the medication group[14]. In conclusion, one can see the presence of well-developed collaterals as an argument in favour of revascularization of the CTO rather than an argument against it, provided that there is normal ventricular function, or/and the patient has signs and/or symptoms suggestive of ischaemia[18].

Further data cited as possible argument against CTO revascularization are the negative results from the Open Artery Trial (OAT). However, it is important to clarify that this trial did not include patients with a CTO but rather patients with a recent acute coronary syndrome, and hence the findings do not apply to CTO PCI.

Benefits of CTO-PCI

A major limitation of studies designed to evaluate clinical outcomes after CTO PCI is selection bias, which is inherent to observational interventional studies. To date, no randomized clinical trial has been performed to evaluate the effect of successful CTO-PCI revascularization on clinical outcomes. The majority of available data originates from numerous observational studies and multicentre registries of patients who have an indication for CTO revascularization, where a comparison is made between successful and failed PCI[19,20]. These studies do therefore not include a control group of patients with CTOs being treated with optimal medical therapy alone. Multicentre randomized trials, such as the DECISION-CTO have been launched recently and will provide important data regarding the prognostic impact of CTO revascularization[1].

Relief of symptomatic ischaemia and angina, and improvement of prognosis are the ultimate aims of CTO revascularization. The evidence that CTO PCI is effective in improving outcomes is very strong for several indications:

Improvement in left ventricular function

The myocardium supplied by the CTO may be dysfunctional (akinetic/dyskinetic) either because of previous infarction or chronic ischaemia in viable myocardium. Several studies have shown improvement in left ventricular ejection fraction after successful CTO revascularization[18,20]. In a large meta-analysis of 34 studies performed between 1987 and 2014 in 2,243 patients, successful recanalization of a CTO resulted in an overall improvement of 4.44% absolute ejection fraction points (95% CI: 3.52-5.35, $P = 0.01$) [21]. In addition left ventricular end-diastolic volume (LVEDV) decreased with 6.14 ml/m^2 (95% CI: -9.31 to -2.97; $P < 0.01$) after successful recanalization.

The expected recovery of left ventricular function declines with the extent of non-viable myocardium, which correlates with the extent of infarction[22]. With magnetic resonance imaging (MRI) evaluation, the improvement in LV remodelling and function was related to the transmural extent of infarction (TEI) on pre-treatment MRI with the most pronounced effect seen with TEI $< 75\%$ [23].

Improvement in quality of life (QOL) and angina

The assessment of QOL is an important measure of the utility of revascularization in patients with coronary artery disease. Quality of life assessments according to the Seattle Angina Questionnaire (SAQ) has now been examined in several CTO revascularization studies[24-26]. In two of these studies, SAQ scores in patients with successful versus failed CTO PCI were compared, and significant improvement in physical limitation, angina episodes, and treatment satisfaction was demonstrated in successful versus failed patients[24,25]. One study compared revascularization (either by PCI or CABG) with medical therapy in CTO patients[26]. The medical therapy group had no change in any SAQ domains, whilst patients in the revascularized group showed improved physical limitation, angina frequency, and disease perception domains. Recently, the clinical outcome of 1,305 patients with 1,582 CTO lesions who underwent retrograde CTO revascularization was reported by the EuroCTO club. This revealed a significant improvement in angina and dyspnaea status after a median follow-up period of 24 months in patients successfully revascularized[27].

Reduction of CABG frequency

The advantage of avoiding CABG centres on CTO PCI offering the patient similar clinical improvement without the recognized potential morbidities associated with and recuperative period inherent to CABG. The CREDO-Kyoto registry cohort-2 showed a reduced need for CABG[28]. Of interest, in this study there was no difference in long-term mortality or MI rates in patients with failed CTO PCI who subsequently underwent CABG (11.3%) versus those patients who proceeded straight to CABG (88.7%), suggesting the safety of attempting CTO revascularization prior to CABG.

Improvement in myocardial electrical stability

Several arrhythmogenic factors might increase the incidence of ventricular arrhythmias in patients with

CTOs; firstly, ischaemia resulting from inadequate perfusion of the myocardium can lead to abnormal automaticity of the ventricular myocardial cells, and secondly, re-entry circuits in patients with a previous myocardial infarction and fibrous tissue interspersed with islands of viable tissue[29]. Restoration of antegrade flow by successful CTO PCI could in theory resolve the ischaemia and thereby enhance electrical stability in patients with ventricular arrhythmias. There are currently no data showing that myocardial electrical stability is improved after successful CTO PCI. However, in patients (n = 162) with ischaemic cardiomyopathy who underwent implantation of an implantable defibrillator, the presence of a CTO was associated with higher rates of ventricular arrhythmias requiring ICD therapy[30].

Protection against future cardiac events

As already discussed, CTO patients who develop an ACS have increased short- and long-term mortality rates. In a single-centre observational study, STEMI patients with co-existing CTO who underwent successful staged CTO revascularization had lower cardiac mortality rates and a higher MACE-free interval as compared to patients with failed CTO revascularization during a 2-year follow-up[31]. The recent EXPLORE trial randomly assigned 304 patients, who presented with STEMI and a CTO in a non-culprit vessel, to CTO PCI within 7 days of STEMI or no CTO PCI. MRI was performed at 4 months to determine left ventricular ejection fraction and end-diastolic volume. At 4 months, the mean ejection fraction and end-diastolic volume on MRI were similar in the CTO PCI and the non-CTO PCI arms. On subgroup analysis, CTO PCI appeared to be beneficial in patients with left anterior descending (LAD) CTO, but not among those with right coronary (RCA) or left circumflex (LCx) CTO. However, this study has a number of important weaknesses including: relatively low CTO PCI success rates (72%), CTO PCI being performed within 7 days of STEMI presentation, long enrolment period (7 years), lack of data on viability of the territory supplied by the treated CTO, and the fact that the study was not powered for clinical end points[32].

Improvement in long-term survival

Possible reasons for survival benefit following successful CTO recanalization include decrease in ischaemic burden, with consequent reduction in arrhythmias and improved LV contractility, and avoidance of "double jeopardy" where occlusion of a vessel supplying collaterals to a CTO acutely results in a double infarction. The prognostic impact of successful CTO recanalization remains under debate. Current data on the effect of CTO PCI on survival are suggestive, though not conclusive. The vast majority of recent non-randomized series report a survival benefit with successful revascularization[22,33]. In the largest registry of 13,443 patients, successful PCI of at least 1 CTO was associated with improved survival (hazard ratio [HR]: 0.72; 95% CI: 0.62 to 0.83; $P < 0.001$) during a mean follow-up period of 2.65 years [25]. Furthermore, complete revascularization was associated with improved survival compared with partial revascularization ($P = 0.002$) or failed revascularization ($P < 0.001$). In the recent meta-analysis of 34 studies with 2,243 patients who underwent CTO PCI, successful CTO PCI was associated with significantly reduced mortality rates in comparison with failed CTO PCI[18]. Of note, the target vessel seems to affect the prognostic outcome with a recent series reporting improved long-term survival with successful PCI of CTOs affecting the LAD or LCx, but not the RCA[34]. The majority of the above studies and those summarized in table 1[35-38] compared long-term outcomes in patients with successful PCI versus unsuccessful PCI attempt, and did not evaluate PCI to either medical therapy or CABG. Data from the randomized controlled trials DECISION CTO and EURO-CTO are awaited.

CLINICAL INDICATIONS FOR CTO REVASCULARIZATION

In anticipation of the results of randomized studies, the indications to revascularize CTOs should not differ from the indications to revascularize sub-occlusive lesions.

In the presence of a CTO lesion, decision-making leading to revascularization comprises a three-step evaluation; (1) the evaluation of symptoms, (2) the assessment of ischaemic burden, and (3) the demonstration of viability (figure 1). As discussed previously, CTO recanalization is associated with angina relief, improved physical function and enhanced QOL only in symptomatic patients at baseline. One should consider that patients affected by CTOs sometimes show more atypical symptoms with dyspnoea and exercise intolerance featuring more frequently than angina.

The expected prognostic benefits of CTO revascularization are thought to be due to a significant reduction of ischaemic myocardium, as has been observed in patients with obstructive coronary artery disease in general[39]. Galassi et al. reported a worse cardiovascular outcome in patients with non-revascularized CTO lesions and large perfusion defects when compared with those with normal and almost normal perfusion scans[40].

Table 1 Clinical outcome following CTO-PCI

Authors	Patient (n)	Enrolment period	Stents used (%)	Success rate	Follow-up (years)	Outcomes measured	Outcome rates (successful vs failed)
Jones et al.[34]	836	2003-2010	DES (76%) BMS (21%)	69.6%	3.8	All-cause mortality	4.5% vs 17.2%, $P < 0.001$
George et al.[25]	13,443	2005-2009	DES (82.2%) BMS (13.7%)	70.4%	2.7	All-cause mortality	HR: 0.72;95% CI: 0.62 to 0.80 (favouring successful outcome)
Borgia et al.[24]	302	2003-2009	DES (98.2%)	78%	4	Cardiac death MACE (cardiac death, MI and TVR)	1.3% vs 1.5%, $P = 0.86$ 8% vs 20%, $P = 0.01$
Jolicoeur et al.[36]	346	1999-2008	DES (51.6%) BMS (50.7%)	62%	5.6	MACE (death and cardiac Vascular re-admission)	40.4% vs 45.4%, $P = 0.33$
Mehran et al.[33]	1,791	1998-2007	DES (66%) BMS (34%)	68%	5	All-cause mortality Cardiac mortality Need for CABG	6% vs 8.6%, $P = 0.01$ 3.0% vs 5.8%, $P < 0.01$ 3.2% vs 13.3%, $P < 0.01$
Valentin et al.[20]	486	2003-2006	DES (100%)	71%	2	Cardiac mortality	8.4% vs 12.6%, $P = 0.025$
de Labriolle et al.[37]	172	2003-2005	DES (84%) BMS (9.7%)	73.8%	2	Cardiac morality MACE (MI and TVR)	5.3% vs 4.9%, $P = 0.3$ 22.7% vs 5.3%, $P = 0.2$
Chen et al.[38]	152	2004-2005	DES (95.5%)	86.8%	3	MACE (cardiac death, MI and TVR)	14.4% vs 35%, $P = 0.04$

DES: drug-eluting stent, BMS: bare metal stent, HR: hazard ratio, CI: confidence interval, MI: myocardial infarction, TVR: target vessel revascularization, MACE: major adverse cardiac event.

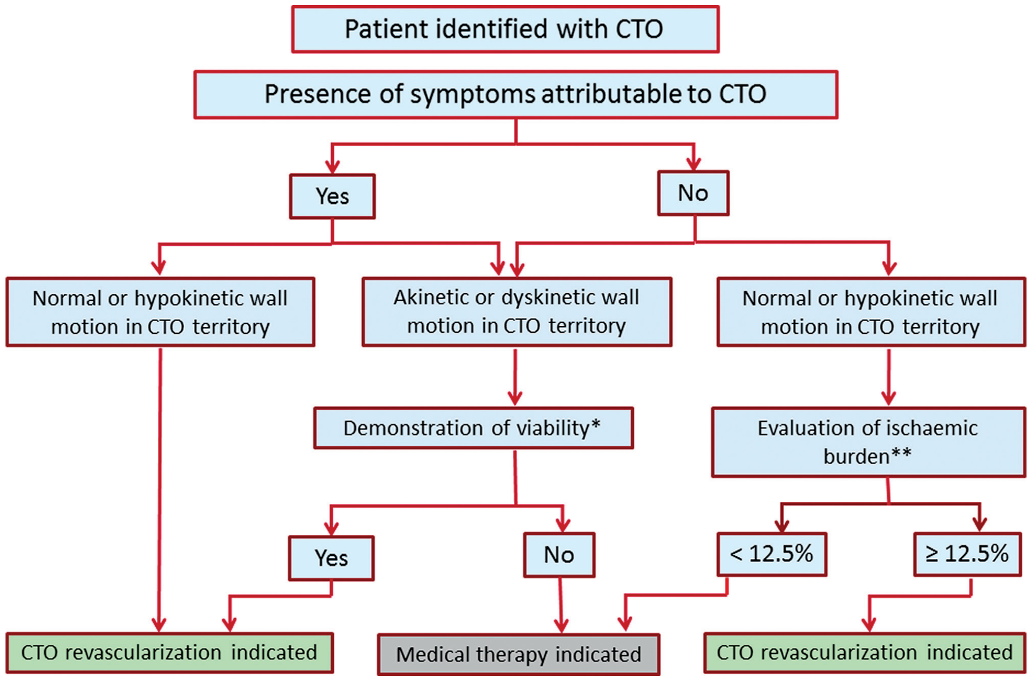

Fig. 1 Algorithm for determining who will benefit from CTO revascularization. *on magnetic resonance imaging (MRI); **on perfusion magnetic resonance imaging (MRI), perfusion myocardial imaging (MPI) or positron emission tomography (PET) perfusion imaging.

In a further study[41], a baseline ischaemic burden of 12.5% was identified as an optimal cut-off to identify patients most likely to have a significant decrease in ischaemic burden post CTO PCI. Conversely, patients with a baseline ischaemic burden of < 6.25% were more likely to have worsening ischaemia post successful CTO PCI, suggesting that treating these patients medically would be more appropriate.

In terms of viability, several studies have shown that in patients with CAD and LV dysfunction but documented viability, long-term survival is better among revascularized patients (by either CABG or PCI) when compared with medically treated patients[22]. MRI is the gold standard to detect pharmacologically induced wall motion changes, precisely assessing myocardial fibrosis, perfusion and viability. Sub-endocardial extent of late gadolinium enhancement smaller than 50% of the wall thickness and reversible perfusion deficits greater than 10-12.5% of the total myocardial mass on perfusion MRI or myocardial perfusion imaging are currently used as gold standard for viability and prognostic relevant ischaemia[42].

The most recent European guidelines on myocardial revascularization give CTO PCI a class IIa recommendation; percutaneous recanalization of CTOs should be considered in patients with expected ischaemia reduction in a corresponding myocardial territory and/or angina relief[43]. Furthermore, there is a IIb recommendation for retrograde recanalization of CTOs; retrograde CTO PCI may be considered after a failed anterograde approach or as a primary approach in selected patients.

If CTO PCI should be performed, can it "technically" be done?

In the majority of cases, the answer is a definite "yes". Significant advances in techniques and equipment have resulted in increasing success rates. Traditionally, intraluminal antegrade techniques resulted in success rates of 60-70% in selected "favourable" cases. The development of antegrade and retrograde dissection and re-entry techniques has increased the success rates to the 80-90% range, even in more complex CTOs, whilst rates of major complications are consistently under 2% [64]. Currently, technical advances are moving at a rapid pace with the expectation that success rates will continue to improve, even for the more challenging coronary anatomies.

CTO RECANALIZATION TECHNIQUES

The optimal approach to CTO-PCI continues to evolve as new and existing CTO-dedicated materials (guidewires, microcatheters, etc.) and techniques are continuously being developed and improved. Some of these techniques apply a subintimal strategy (dissection and re-entry in antegrade or retrograde direction) to revascularize the coronary vessel (figure 2).

Importantly, the initial strategy of an antegrade or retrograde approach depends on the anatomical characteristics of the occluded vessel. In January 2011, several high-volume CTO operators developed a consensus algorithmic approach, which has been named the

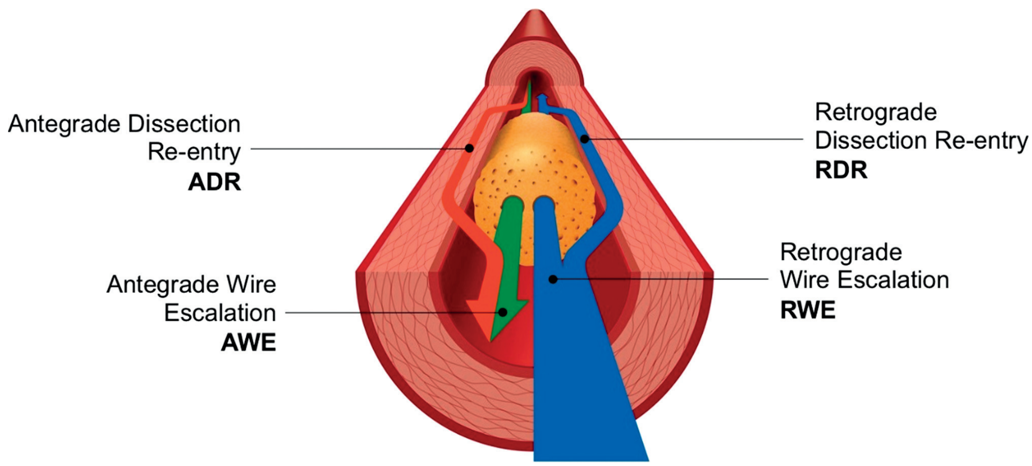

Fig. 2 Overview of the different percutaneous CTO revascularization strategies (With courtesy of James Spratt).

"hybrid" approach to CTO PCI[44] (figure 3). The main principle behind the "hybrid" approach is that operators should be able to alternate between techniques during the same CTO PCI procedure in order to successfully recanalize the CTO. In this algorithm several steps must be followed[44]:

Step 1 – Dual injection: this is of critical importance in CTO PCI. The double catheter injection provides optimal visualization of the CTO segment, as well as the collateral circulation (figure 4). By reduction of the collateral competitive flow, it allows the assessment of both (proximal and distal) caps and the distal vessel beyond the CTO. ***Step 2 – Assessment of CTO characteristics***: four anatomical variables are considered to determine the initial strategy: morphology of the proximal cap, lesion length ($<$ or $\geq$ 20 mm), quality of the distal target and suitability and anticipated ease of crossing of retrograde "interventional" collaterals. *Proximal cap*: is it possible to localize an unambiguous entry point to the CTO lesion by angiography or intravascular ultrasonography (IVUS)? A favourable proximal cap is one that is tapered, as opposed to being blunt, without any bridging collateral or major side branch located at the beginning of the occlusion. *Lesion length*: short CTOs ($<$ 20 mm) are usually best approached with antegrade wiring. A lesion length of $<$ 20 mm has been identified as a predictor of rapid CTO crossing in the Japan CTO Registry (Multicentre CTO Registry in Japan)[45]. Conversely, in

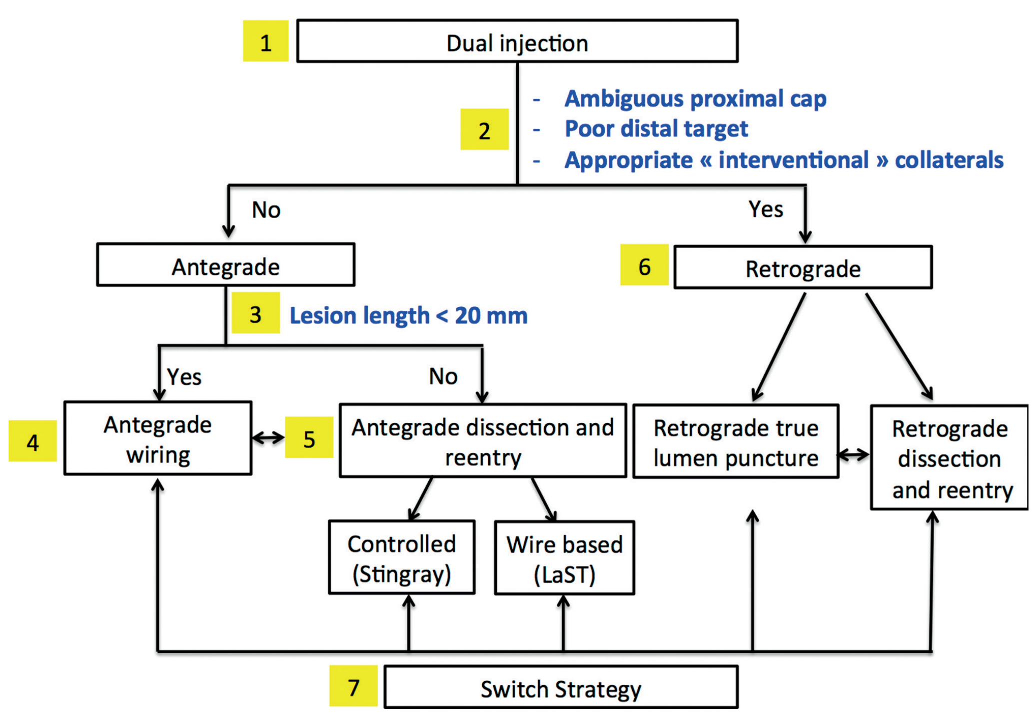

Fig. 3 The "hybrid" algorithm approach to percutaneous CTO revascularization. *LaST*, limited antegrade subintimal tracking (Taken from Brilakis et al. *JACC Cardiovasc Interv* 2012; 5: 367-79).

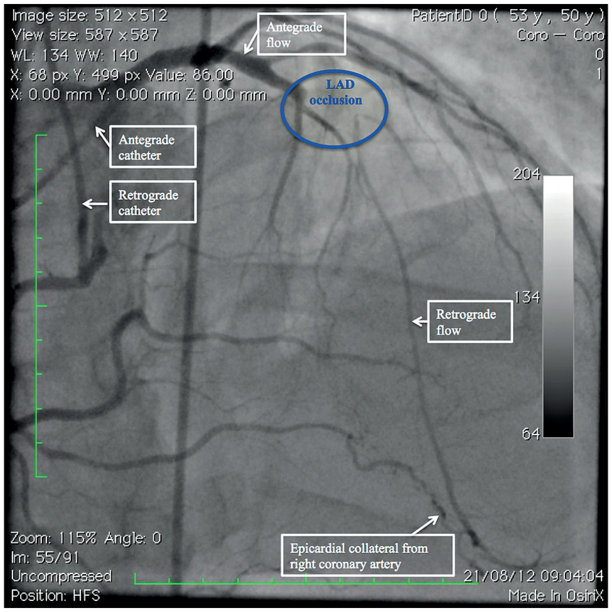

Fig. 4 Example of dual catheter injection. Epicardial collateral from the RCA providing flow retrograde to the location of the proximal left anterior descending (LAD) chronic total occlusion (CTO).

long (≥ 20 mm) CTOs, there is a high probability that wire-base crossing attempts will result in subintimal space wire position. In such cases, a subintimal dissection/re-entry technique is preferred. *Target coronary vessel beyond the distal cap*: this anatomic characteristic refers to the size of the lumen, presence of significant side branches and vessel disease. *Size and suitability of collateral circulation*: collaterals are considered "interventional" if they are not too tortuous, if the entry point/angle into the collateral circulation and subsequently into the distal CTO vessel looks favourable, and preferably if the collateral is not the only source of blood supply from the donor vessel to the CTO vessel (thus avoiding intra-procedural ischaemia). In summary, short lesions (< 20 mm) with clearly identified proximal caps and good distal vessel targets are initially approached with an antegrade wire escalation strategy. Whilst longer and complex lesions with clearly identified proximal caps and distal target favour a primary antegrade dissection re-entry approach. Conversely, long complex lesions with poor distal targets or ambiguous access points may favour an initial retrograde approach.

Step 3 – Recanalization techniques: depending on the analysis of the CTO anatomy the operator will decide upon which technique will be tried first. When entering into failure mode, alternative techniques are proposed in the hybrid algorithm (figure 3).

(I) Antegrade wire escalation: the initial wire to probe the CTO is typically a low-gram-force, polymer-jacket wire, unless the proximal cap is clearly blunt, calcified, or ambiguous. The wire is advanced within an over the wire (OTW) microcatheter, (like the Corsair (Asahi Intecc, Nagoya, Japan), Finecross (Terumo Corporation, Tokyo, Japan) or Turnpike (Vascular Solutions, Minnesota, VS), to support column strength at the tip and avoid buckling of the wire, and to allow for adequate wire-tip shaping. Experienced CTO operators favour a tapered wire (such as Fielder XTA, Asahi Intecc) in the antegrade direction. If the crossing distance is long, uncertain, or tortuous, it is recommended to use a moderately high-gram-force, non-tapered, polymer-jacket wire, such as the Pilot 200 (Abbott vascular, Santa Clara, CA, USA). Polymer-jacket wires might have the disadvantage to quickly exit the true lumen. To be more directional within the CTO body, the Gaia wires (Asahi Intecc) with their dual core technology and micro-cone tip are applied. They provide high penetration force (through harder tissue or fibrous caps) without loss of flexibility. If the lesion distance is short and its course well understood, a stiff, tapered penetration wire (such as Confianza Pro 12, Asahi Intecc) is chosen[44]. The availability of wires with different penetration power allows a step-up and a step-down strategy within the CTO body. If the wires fail to progress, or enter the subintimal space, conversion to dissection re-entry techniques is considered or occasionally parallel wiring technique with or without the use of dual lumen catheters. ***(II) Antegrade dissection and re-entry (ADR):*** in this strategy, a limited coronary dissection is created and a knuckled polymer-jacketed guidewire (such as Fielder XT or Pilot 200) is advanced, often with the help of the CrossBoss catheter (Boston Scientific, Massachusetts, USA). Beyond the body of the occlusion, re-entry into the distal true lumen can be achieved using a stiff polymer-jacketed and/or a stiff tapered guidewire directed or more consistently by using the Stingray system. The Stingray system (Boston Scientific) consists of a balloon that assumes a flat shape when inflated at 3 to 4 atm (wrapping itself around the true lumen like a stingray), and a guidewire with an extreme 0.0025-inch tapered distal tip[46]. The Stingray balloon has two exit ports that are 180° opposed. The Stingray guidewire is advanced through the luminal exit port of the balloon (up or down) until the wire crosses into the distal true lumen. ***(III) Retrograde wiring***: this approach is a major component of a contemporary CTO PCI program and can be used either upfront or after a failed antegrade crossing attempt. Retrograde wire crossing can occur by advancing the retrograde guidewire into the proximal true lumen (retrograde wire escalation, RWE) or by using one of the dissection/re-entry techniques (*retrograde dissection and re-entry (RDR)*. From the latter the reverse CART (controlled antegrade and retrograde tracking) technique is most often applied. In this method, a microcatheter is placed across a collateral vessel from the donor artery and into the CTO segment over a guidewire. An antegrade wire is advanced into the CTO segment alone or in combination with a crossing catheter or a balloon. An angioplasty balloon is approximated over the antegrade wire adjacent to the retrograde microcatheter and inflated to create a connection space (figure 5). A retrograde wire can then be passed into the proximal vessel, and wire externalization can be performed[65]. Conventional stenting techniques are then applied.

Efficacy and safety of current strategies for CTO-PCI

In contemporary practice, data reported by experienced operators indicate that success rates of 80 to 90% can be achieved with a low incidence of complications[47]. A recent meta-analysis of 65 studies including 18,061 patients undergoing CTO PCI reported a low incidence of acute complications. These were death 0.2%; emergency coronary artery bypass grafting 0.1%; stroke <0.01%; MI 2.5%; Q-wave MI 0.2%; coronary perforation 2.9%; tamponade 0.3%; and contrast nephropathy 3.8%[48]. In a further meta-analysis, including more than 4,000 patients, the use of DES in CTO interventions resulted in a very low incidence of MACE (death, myocardial infarction and need for coronary revascularization), and reduced need for target vessel revascularization (TLR) due to restenosis or reocclusion[49].

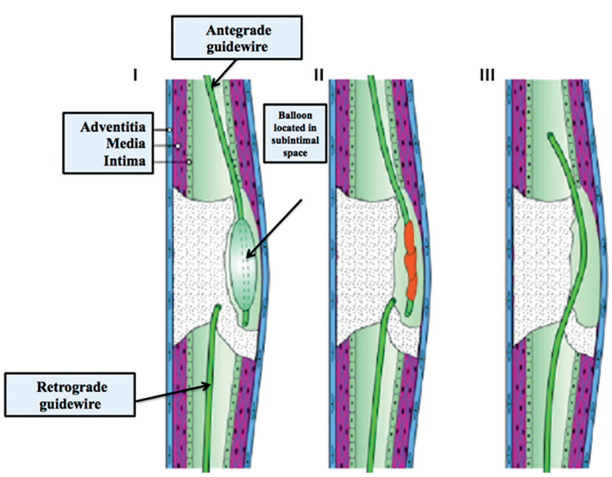

Fig. 5 Retrograde dissection and re-entry technique. An angioplasty balloon is positioned over an antegrade wire in the subintimal space of the CTO segment adjacent to a retrograde wire with microcatheter and inflated to create a connection space (panel I). On deflation of this antegrade angioplasty balloon a retrograde wire can connect with the subintimal space (panel II) before being passed into the proximal "true lumen" (panel III) after which wire externalization can be performed.

SETTING UP A CTO PROGRAM

As already discussed, in selected patients, there is compelling evidence for CTO PCI. However, historically poor CTO PCI success rates had tempered enthusiasm for this.

Recent technical advances and increasing familiarity with these advances and with new equipment, and improved awareness of the potential benefits of recanalizing a CTO has led to increased interest in this field of interventional cardiology. We hope to highlight certain issues particular to CTO PCI that will hopefully allow the establishment of a successful CTO PCI program in your centre. The CTO-PCI program will be "successful" when enough patients are being referred for CTO PCI, good procedural and long-term clinical results are achieved and when the cost efficiency relationship is favourable.

Create a CTO team and framework

Initiating a formal CTO PCI program presents an opportunity for open discussion with colleagues regarding their own aspirations for sub-specialization. We suggest that opportunities for sub-specialization within the interventional field should be distributed within a group or laboratory, and agreement to support one another's subspecialty interests is a constructive approach that fosters individual and collective excellence.

Therefore, select dedicated CTO operators and specific catheterization laboratory personnel with special interest in CTO. Depending on the CTO PCI volume, it makes sense to have at least two dedicated CTO operators as this allows for real-time feedback and adaptation of the procedural plan. It can avoid tunnel vision and operator fatigue. The dedicated CTO nurses can take responsibilities in checking the dedicated CTO material

Table 2 The perfect diagnostic angiogram for a CTO procedure

Optimal visualization
– Proximal cap (consider need for **intravascular ultrasound**)
– Distal cap/target vessel
– Collaterals: right anterior cranial views for septals (customized views for others)
– Calicification, bends (consider need for **computerized tomography**)
Dual injections (except for homocollateralized CTO); at the initial angiogram single injections of both right and left coronary artery in exactly the same angle can be useful
Long loop
No panning
Lower magnification
Optimized image settings: contrast, brightness, frame rate, dose/frame

(table 2 "dedicated CTO toolkit"), procedural planning and patient workflow. They can also have a teaching role towards their nursing colleagues and raise awareness for CTO PCI and complex PCI techniques in general. Create dedicated patient flow charts and protocols for the cardiology ward and the catheterization laboratory. Refrain from performing CTO PCI ad hoc but rather schedule CTO PCI days where you plan preferably two or maximum three CTO cases. This enables adequate case preparation and avoids time pressure. Pre-procedure planning includes access site preparation (in the majority of cases dual access is required), pre-treatment with regard to antiplatelet therapy, renal protection, contrast allergy and sedation. A temporary urinary catheter should be considered. Obtaining informed consent is mandatory. During the procedure the nurse is in charge of monitoring radiation and contrast usage, and checks and adjusts activated clotting time (ACT) every 30 minutes. After the procedure cardiac monitoring and close observation of access sites and general clinical condition are vital. There should be a low threshold for cardiac echocardiography in case of clinical deterioration.

Table 3 CTO tool kit

Sheaths: 45 cm 6-/7-/8-Fr sheath
Guiding catheters: AL 0.75, 90 cm guides, sheathless guides
Spring-based Y-connector: Okay II/Guardian
Dedicated CTO wires: Fielder XTA, XTR, Gaia 1st-2nd-3rd, Pilot 200, Confianza 9, ConfianzaPro 12, Sion, Sion Black, RG3, Stingray wire
Microcatheters:
– Corsair, Finecross, Turnpike Spiral, Turnpike Low Profile, Turnpike Gold /Tornus
– Double lumen microcatheter: Crusade/NHancer RX/Twinpass
– Angled microcatheter: Venture/Supercross 90/120
– Crossboss, Stingray catheter
Low profile and over the wire (OTW) balloons
Child-in-mother catheters: Guideliner 6-8 Fr, Guidezilla 6 Fr
Endovascular Snares: ENsnare 18-30 mm
Complication management toolkit: pericardiocentesis set, coils, covered stents, readily available cardiac ultrasound

Becoming a dedicated CTO operator

Training in CTO-PCI requires a substantial commitment of time and resources by operators and institutions. Participate in CTO PCI courses and meetings, and join online communities (www.ctofundamentals.org). Once acquainted with the different techniques, attend several CTO procedures in a centre with a well-developed CTO program. Get you and your team proctored several times by an experienced CTO operator and build yourself a network with fellow CTO operators.

When embarking on CTO-PCI, first select CTOs with favourable characteristics followed by more difficult lesions according to the recommendations of the European CTO club[1]. Favourable CTO characteristics include a tapered proximal CTO cap, CTO length of < 15 mm, and proximal vessel angulation of < 45°. Only after achieving volumes recommended by the European CTO club (50 simple CTOs) should CTO trainees embark on learning the more difficult techniques and using niche devices in carefully selected cases, preferably with the direct supervision of an experienced operator.

Prepare your procedures thoroughly. Make sure you have a good diagnostic angiogram at your disposal (table 3) and study the images for at least 10-15 minutes. Make a strategic plan, remembering that anatomy dictates strategy, and foresee not just one strategy but also alternative strategies, allowing for quick changes during the procedure (hybrid approach). Discuss complex cases upfront with other CTO-operators. Practice makes perfect thus volume matters. For smaller PCI centres, collaboration with other centres in a CTO network can be a solution to insufficient procedure numbers. An operator could limit himself/herself to the antegrade approach as it still has the potential to achieve reasonable success rates, especially in selected cases like more recent CTOs, shorter lesions in less calcified and more straight vessels (low J-CTO scores)[45]. However, when the case does not progress well, it is recommendable to discontinue the case and refer the patient to a colleague/centre that can offer the full spectrum of CTO treatment. When working with a second CTO operator, sometimes switching places during the procedure can help to avoid operator fatigue. Track your procedural results and clinical outcome in a local and national database. Learn from your failures and reschedule a failed case, if necessary with a proctor. Do not get discouraged, but think about the progress you already made. To maintain expertise, the European CTO club recommends of at least 50 CTO-PCIs per year per operator. Maintaining these volumes requires hospitals and groups to restrict CTO-PCI procedures to approximately 1 CTO operator for every 500 PCIs performed.

Cost efficiency

CTO PCI is costly in terms of materials and time consumption. Additionally, in some countries like Belgium, a special CTO-PCI reimbursement is lacking. In such countries a national registry, reporting good clinical results and outcome can maybe convince authorities to change policy. In general, CTO operators should always strive for optimal results and satisfaction of patients and referring physicians. Provide good physician and patient information (brochures, online information). The return on investment will often be found in increased referral and internal volumes.

There are definitely a number of hurdles to cross when setting up a CTO program However, with appropriate forethought, planning and with support from colleagues and relevant institutional departments, these potential obstacles can be overcome allowing establishment of a successful CTO PCI program.

THE BELGIAN CTO LANDSCAPE

So far no prospective data are collected in Belgium. The data requested by the Belgian government do not address CTO procedures. As a result, currently the number of the CTOs treated annually and the procedural outcome are unknown. Although CTOs are found in about 11-20% of patients referred for angiography, less than 5% will be treated. For Belgium one can estimate that less than 1,200 CTOs are treated yearly, but the number might be even substantially lower, since some operators are reluctant to do so, and others even do not believe in the beneficial benefits for the patient. Also, based on larger registries, about 30% of these CTOs will have favourable characteristics making them treatable with antegrade wiring, the technique most widely used to open CTOs[50]. The last 5 years, a limited number of catheterization laboratories (10-15) started to use more complex techniques like ADR and retrograde approaches. Typically, operators using hybrid techniques, will use AWE in 60-80%, ADR in 20% and retro-techniques in 40% at any stage during the procedure. One can expect that the following 5 years, the Belgian CTO landscape will change, concerning numbers of patients treated, anatomy tackled, techniques used and outcome of procedures. For this reason, it seemed time to collect data on CTO procedures, prospectively to address these questions. The BWG-CTO (Belgian Working Group of CTO) as a task force of the BWGIC has started collecting these data by using an e-platform from the second half of 2016.

CONCLUSIONS

Technical and procedural success rates for CTO PCI have risen steadily over the past 10 years, mainly as a result of increased operator experience, improved materials, the refinement of the anterograde approach and the development of the retrograde approach, but also by dedicated groups of experts focusing on technical development, training and education worldwide.

CTO revascularization should not be avoided on the basis of "historical" poor success rates, unclear patient benefits, adverse outcomes or time and resource use. Neither should CTO recanalization not be attempted because of a lack of requisite knowledge. Where local expertise is not (yet) available, patients should be referred to interventional cardiologists with the required expertise in order to optimize the treatment of these patients suffering from a frequently disabling condition.

CONFLICTS OF INTEREST: none.

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