Current considerations regarding the percutaneous revascularization of chronic total coronary occlusions

Chronic total coronary artery occlusions are commonly encountered, occurring in 15–33% of patients in the angiography suite. Reasons to consider percutaneous coronary revascularization of these lesions include the relief of angina, enhancement of left ventricular ejection fraction and the potential for improved survival. Owing to the complex nature of these lesions, attempts at percutaneous revascularization have traditionally been infrequent (≤12% of encountered cases). Advances in technique and equipment have resulted in improved success rates that now approach 90% at specialized centers. It remains to be seen if these positive results can be achieved by the interventional cardiology community at large.

**KEYWORDS:** angina angioplasty chronic occlusion coronary artery hibernating myocardium stent

Major advances in the drugs, devices and techniques used for percutaneous coronary intervention (PCI) treatment of coronary artery disease have resulted in generally high procedure success rates and low complication rates. Despite these advances, patients with chronic total coronary occlusions (CTOs) remain a vexing problem without a standardized solution or treatment algorithm. This point is illustrated by an examination of the recent Syntax study. Although investigators for this study were very experienced PCI operators, the presence of a CTO remained a major reason for referral to coronary artery bypass surgery (CABG) as demonstrated by a CTO prevalence of 10% in the randomized arm compared with 40% in the nonrandomized arm [1]. This article examines the current status of PCI for CTO.

**Prevalence**

Chronic total coronary occlusions are frequently encountered in the catheterization laboratory, occurring in 15–33% of all patients with coronary artery disease and in up to 50% of patients with multivessel coronary artery disease [2]. The incidence of CTO increases with advancing age. Data from the National Heart Lung and Blood Institute (NHLBI) Registry demonstrates an incidence of 18.2% for patients under 65 years of age rising to 22.8% for patients over 80 years of age [3]. Chronic occlusions are most commonly found in the right coronary artery (>40%) and are least commonly found in the left main coronary [4,5].

**Definition of a CTO**

Traditional criteria utilized to define a CTO include degree of stenosis, the age of occlusion and thrombolysis in myocardial infarction (TIMI) grade blood flow through the lesion. Unfortunately, in the past, the definition of CTO has varied from study to study. The term ‘chronic’ has variously been defined as an occlusion of greater than 2 weeks, 1 month or 3 months duration. The definition of occlusion has varied from a 100% stenosis with TIMI grade 0 blood flow through the lesion to a ‘functional’ occlusion with a near 100% stenosis and TIMI grade 1 blood flow through the lesion. These different definitions certainly describe lesions with very different histopathology and therapeutic responses. It is therefore imperative that when evaluating data and results from the literature, strict attention be paid to the definition of CTO. The American Heart Association consensus document regarding PCI of CTO has recommended that a 100% occlusion of more than 3 months duration be used in the future as the definition of CTO [6]. This definition was also adopted in the consensus document of the EuroCTO Club [7].

**Histopathology**

Chronic total coronary occlusions can arise either from a slow progression of an atherosclerotic stenosis or the gradual organization, fibrosis and calcification of an acute thrombotic lesion (following acute myocardial infarction). The CTO lesion is comprised of intracellular lipids,
extracellular lipids, smooth muscle cells, and extracellular matrix comprised primarily of type I and III collagens [8]. In one study, 64% of CTOs were characterized as fibrocalkic, 11% were primarily lipid laden and 25% were mixed [9]. The histopathologic composition of the CTO appears to be related to its age. Younger lesions contain more lipid and inflammatory cells and older lesions consist of increasing proportions of collagen and calcium. Neovascularization is the pathologic hallmark of a CTO and occurs through large capillary formation, which first occurs in the adventitia and over time involves the intima. Interestingly, little neovascularization is seen in the lumen or media [10].

**Rationale for CTO recanalization**

Relief of symptomatic myocardial ischemia is the most obvious indication for attempting recanalization of a CTO. Other indications include recovery/augmentation of left ventricular function and reducing the occurrence of malignant ventricular arrhythmias in patients with chronically ischemic or hibernating myocardium. There is also some evidence to suggest that successful revascularization of a CTO may benefit survival. When objectively assessing these benefits it is important to note that, to date, all CTO studies have been either multicenter registries or large single-center experiences. There have been no large, multicenter, randomized studies specifically designed to measure comparative clinical outcomes regarding revascularization of CTOs.

Relief of symptoms is an intuitive indication for CTO PCI, and objective data support this. The Total Occlusion Angioplasty Study – Societa Italiano Cardiologica Invasiva (TOAST-GISE) trial demonstrated a significant difference in angina-free survival following successful CTO PCI compared with failed CTO PCI (86 vs 70%; p = 0.008) [11]. Cheng et al. noted a 76% reduction in angina following successful CTO PCI compared with only a 17% reduction in angina for those patients treated medically [12].

Improvement in left ventricular (LV) ejection fraction (LVEF) and regional radial shortening measured by standard contrast ventriculography has been demonstrated following CTO PCI [13]. MRI has been a more helpful tool for assessing the benefit of CTO revascularization in regard to recovery of LV function. One recent report demonstrated improved myocardial blood flow and segmental LV contractility that was sustained to 6 months following successful CTO PCI [14]. A similar study utilizing MRI revealed decreased LV volumes, improved LVEF, and improved segmental LV wall thickness following successful CTO PCI that was sustained to 3 years. This study also correlated the degree of improvement with the amount of viable myocardium subtended by the occlusion [12].

Survival may be significantly impacted by a CTO. The SAVE study demonstrated that persistent occlusion of an infarct-related artery following acute myocardial infarction was associated with a significant relative risk of 1.47 in adjusted 4-year mortality [15]. Similarly, van der Schaaf et al. reported that, in the setting of acute myocardial infarction, multivessel disease was associated with increased mortality with the majority of risk attributed to the presence of a CTO [16]. Analysis of data from the New York State PCI database also demonstrated a higher mortality rate for patients with incomplete revascularization due to untreated CTO compared with a subtotal occlusion [17].

The Mid America Heart Institute reported their experience with CTO revascularization (n = 2007) between 1980 and 1999. Compared with patients with failed CTO PCI, patients with successful recanalization of the CTO had improved cumulative 10-year survival (73.5 vs 65%; p = 0.001) [18]. Survival of the successfully revascularized group was similar to that of a matched non-CTO PCI group. Multivariate analysis demonstrated that failure to successfully recanalize a CTO was an independent predictor of reduced survival. However, in the group of patients with failed CTO PCI, patients who were subsequently referred for CABG had improved survival compared with patients who were medically treated [19]. The 64-center STAR registry (n = 2002) also demonstrated similar clinical outcomes for patients with successful CTO PCI and successful non-CTO PCI at 1 year [20]. Hoye et al. reviewed the experience with consecutive CTO PCI procedures at the Thoraxcenter at Erasmus University Medical Center, The Netherlands, between 1992 and 2002 (n = 874). Patients with a successful procedure had a higher survival rate (93.5 vs 88%; p = 0.02) and survival free of major adverse cardiac events (63.7 vs 41.7%; p < 0.0001) compared with patients with a persistently occluded artery. Benefit was sustained to 5 years. Multivariable analysis confirmed successful PCI as an independent predictor for survival [20]. Another single-center experience (n = 543) also demonstrated improved survival at a mean of 1.7 ± 0.5 years for propensity-matched patients with successful CTO PCI compared with an unsuccessful procedure with a hazard ratio of 4.63 (95% CI: 1.01–12.61; p = 0.04) [21]. An examination of the
Mayo Clinic experience revealed similar findings, but the benefit of successful CTO PCI on 5-year survival was limited to the group with left anterior descending (LAD) occlusion (88.9 vs 80.2%; p < 0.01) [22]. One study reported no benefit with regard to 2-year cardiac mortality or Q wave myocardial infarction for patients with successful CTO PCI compared with those with an unsuccessful attempt (5.3 vs 4.9%; p = not significant [NS]). However, the incidence of coronary perforation in this study (6.7%) was high and may have impacted results [23].

**Considerations on PCI for CTO**

Although commonly encountered, percutaneous revascularization for CTO is attempted in a minority of cases. The NHLBI reported that between 1997 and 1998 PCI was attempted for only 15.6% of encountered CTOs [24]. The number of attempts fell to 5.7% of encountered CTOs in a subsequent NHLBI analysis [25]. A detailed analysis from the National Cardiovascular Data Registry (NCDR) suggests that PCI was attempted in only 13.6% of CTOs between January 2004 and March 2005 [26]. In 2006, the 15 founding centers comprising the EuroCTO Club attempted PCI on only 12% of encountered CTOs [7].

It is notable that despite improvements in equipment and advances in technique over time, it does not appear that attempts at PCI for CTO have increased in frequency. There are many potential barriers to treatment that may include:

- A significant time commitment
- High radiation exposure for the patient and operator
- Large volumes of radiographic contrast (often a contraindication for elderly patients and those with reduced creatinine clearance)
- The frequent need for dual arterial access
- Requirements for specialized equipment
- Lack of an urgent indication
- Significant patient comorbidities
- The need for a viability study
- Cumulative economic disincentives
- Operator experience level

Data from the NCDR has demonstrated that over 90% of the operators in the USA are considered low or intermediate volume. These operators are half as likely to attempt CTO PCI as a high-volume (>200 cases per year) operator [26].

The fact that overall procedural success rates for CTO PCI have not demonstrated widespread improvement may also be a significant reason that these procedures are not more frequently attempted [6,7,27]. Variables positively associated with an attempt at CTO PCI include younger patient age, diabetes, single-vessel disease, unstable symptoms, a positive stress test, an ejection fraction of more than 40%, LAD lesion location, and high annual volume by the operator [7,26,28].

Lesion characteristics may also affect the decision to proceed with CTO PCI. It has been demonstrated that procedure success is inversely related to CTO lesion age. Morphologic characteristics of CTOs associated with procedure failure include a blunt proximal CTO surface (rather than tapered), heavy lesion calcification, long CTO length, presence of an adjacent side-branch and position beyond an acute angle in the vessel [29]. These considerations may contribute to the decision not to attempt CTO PCI.

**New efforts & directions**

While the frequency and success rates for CTO PCI have not changed overall, there have been significant efforts at specialized centers – particularly in Japan – at refining techniques for crossing CTOs. Similarly, the medical device industry remains intrigued by the prospect of providing a solution to this problem and significant resources have been allocated toward developing novel equipment for tackling these procedures.

**Technique**

Advances in technique have included contra-lateral coronary angiography, parallel wire technique, the controlled antegrade and retrograde subintimal tracking (CART) technique, retrograde approaches, use of intravascular ultrasound (IVUS), anchor balloon technique, intracoronary injection of contrast and the ‘knuckle’ technique (Box 1).

**Box 1. Specialized techniques for crossing chronic total coronary artery occlusion.**

- Controlled antegrade and retrograde subintimal tracking/STAR
- Parallel wire
- Anchor balloon
- Intracoronary injection of contrast
- Intravascular ultrasound in proximal side branch
- ‘Knuckle’
- Retrograde
  - Via atrial collaterals
  - Via epicardial collaterals
  - Via septal collaterals
When adequate collaterals are present, contralateral coronary angiography should be strongly considered in all complex CTO cases to aid in visualization of the true distal lumen and help direct wire manipulation [30]. The parallel wire technique is used when the crossing wire is advanced into a dissection plane/false lumen. With the initial wire remaining in place (marking the dissection plane), a second wire is then advanced to attempt crossing directed away from the initial wire and toward the true lumen [31]. CART utilizes a subintimal dissection plane to advance the crossing wire(s) beyond the hard occlusion. The wire is then directed back into the true lumen distally. The false channel is then definitively revascularized with stent placement and becomes the lumen for antegrade blood flow [32]. IVUS has been utilized in a branch vessel proximate to the CTO to provide imaging of the adjacent parent vessel. These images can aid in the determination of the true lumen and help direct wire manipulation/advancement through the occlusion [33]. Use of an anchor balloon inflated proximal to the occlusion may facilitate support (‘back-up’) for wire crossing attempts [34]. The injection of contrast into the fibrous cap of the occlusion through a balloon or microcatheter (intraocclusion injection of contrast technique) has been described as potentially facilitating wire passage through dilatation of microchannels and allowing for decreased contrast utilization [35]. The ‘knuckle’ technique is frequently employed in crossing peripheral CTOs and involves prolapse of the wire proximal to the occlusion and forceful blunt dissection with the aid of a balloon or microcatheter [29].

Retrograde recanalization was pioneered by the Japanese and is a complex technique utilizing contralateral collateral channels for retrograde wire passage through the distal end of the CTO (Figure 1). This method takes advantage of the fact that the distal end of the lesion is sometimes softer than the proximal fibrous ‘cap’ allowing for less difficult wire crossing. Antegrade access to the CTO is simultaneously obtained so that following retrograde crossing of the occlusion, antegrade wire crossing can be achieved to ultimately effect passage of balloons and stents for definitive recanalization of the vessel [36,37]. Several methods of retrograde crossing have been described but it appears that, owing to safety concerns, traversing septal collaterals rather than epicardial collaterals are favored. Once retrograde access is achieved, all of the various techniques for crossing the lesion described above may be employed [38]. Thompson et al. recently described a two-center experience with the adoption of the retrograde approach to CTO that reported improved success with operator volume and suggested that at 125 cases an ‘inflection point’ occurs after which improved success rates can be anticipated. In this study an impressive CTO success rate of over 90% was achieved by retrograde operators [39].

**Equipment**

There have been several improvements in the equipment available for treating CTOs (Box 2) [29,38,40]. Specialized wires have been a major advance. In general there are two categories of these specialized wires. The first category consists of those with a tapered hydrophilic tip. These wires are designed to traverse through CTO microchannels and are generally useful for initial antegrade attempts or retrograde access through a collateral route. Examples of these wires include the Whisper (Cordis Co., NJ, USA), ChoICE PT (Boston Scientific, Natick MA, USA) and Fielder (Asahi Intecc, CA, USA). The second category is comprised of hydrophobic wires with tips of progressive stiffness (6, 9 and 12 g) designed to push through the hard fibrous proximal cap of the lesion. Examples of these include the Miracle (ASAHI Intecc,
CA, USA) and Confienza (ASAHI Intecc, CA, USA). Microcatheters such as the Corsair (ASAHI Intecc, CA, USA) and the Finercross (Terumo, NJ, USA) have been developed that provide support for the wire while crossing the CTO, aid in traversing the CTO once the wire has crossed, and allow for traversing collaterals in the retrograde technique.

Drug-eluting stents have demonstrated benefit with regard to long-term patency following recanalization of CTOs. A recent study revealed an absolute reduction in binary restenosis of 37% with sirolimus-eluting stents compared with bare-metal stents [41–43].

New devices have been specifically designed to help cross coronary and peripheral CTOs and include the Tornus® device (Asahi/Abbott Vascular, CA, USA) that consists of eight stainless steel strands woven in a corkscrew fashion at the distal end of the device. By turning the catheter counterclockwise with slow forward pressures advancement through the occlusion is facilitated and excellent wire support is achieved. The Frontrunner® device (Cordis J & J, NJ, USA), which utilizes a blunt dissection technique to pass through the occlusion; the SafeCross® device (Spectranetics, CO, USA) that uses radiofrequency energy to ablate the fibrous cap and determine catheter location within the lumen; the Crosser® device (FlowCardia Co., CA, USA), which utilizes high frequency ultrasound vibration to disrupt the hard fibrous proximal cap; and the RVT CTO guidewire (ReVascular Therapeutics, CA, USA), which is a 0.014” guidewire with a mechanically active distal tip [44–47]. These devices have been used with acceptable safety and success rates. The CrossBoss™ catheter system (BridgePoint Medical, MN, USA) utilizes bidirectional rotation of a wire integrated with a 3 French support catheter and is currently undergoing clinical evaluation. New imaging modalities have also been employed in assessment of coronary CTOs. Advances in CT angiography have allowed for rapid accumulation of image data (multislice 64, 128 and 256) and accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowed for accurate assessment of rapid accumulation of image data (multislice CT angiography has allowe

### Complications

Percutaneous recanalization of coronary CTOs is technically challenging and, as such, can be associated with complications. Specific coronary concerns include coronary perforation, which occurs with a reported frequency of 2–5%, and ischemia related to injury of existing collaterals [6,7,23,26,38]. The latter is especially pertinent in the retrograde approach [38]. Despite these concerns, the overall coronary complication rate appears to be low. Grantham et al. reported in their matched series of PCI for CTO procedures (n = 2007) the incidence of death (1.3 vs 0.8%; p = NS), Q-wave MI (0.5 vs 0.6%; p = NS), and total major adverse cardiac events (3.8 vs 3.7%; p = NS) was not significantly different from non-CTO PCI [26].

Prolonged procedure duration also results in the potential for serious noncoronary complications. Excessive contrast utilization can result in contrast nephropathy, which is a particular concern for patients with baseline renal insufficiency. Radiation injury (dermatitis) can result from long fluoroscopy times, particularly when the imaging angle is not changed. Some experienced CTO operators have advocated cut-offs for both contrast (300 ml) and procedure duration time (90 min) in order to mitigate these concerns [38].

### Future perspective

Chronic total coronary occlusion remains a commonly encountered problem in catheterization laboratories. When subtending significant amounts of viable myocardium, evidence suggests that CTO revascularization may provide significant clinical benefit for relief of symptoms, improved LV function, and perhaps survival. Although specialized centers have emerged with encouraging results, overall attempts at PCI remain infrequent. This is likely to be due to high procedural complexity and generally low success rates. Innovations in technique and equipment may provide improved results in the future.
Executive summary

Prevalence of chronic total occlusion
- Chronic total occlusion (CTO) occurs in 15–33% of patients undergoing coronary angiography.
- A CTO is found in up to 50% of patients with multivessel coronary disease.

Potential clinical benefit with percutaneous coronary intervention
- Chronic total occlusion recanalization can result in relief of symptoms.
- Recanalization of CTO can result in improved left ventricular systolic function.
- Successful CTO recanalization may result in improved survival.

Frequency of attempted chronic total coronary occlusion percutaneous coronary intervention
- Percutaneous coronary intervention (PCI) is attempted in only 12–16% of chronic total occlusions.
- High-volume operators (>200 PCI per year) are twice as likely to attempt CTO PCI.

Barriers to chronic total coronary occlusion percutaneous coronary intervention
- A significant time commitment is required for CTO PCI.
- Patients with CTO have a high incidence of comorbidities resulting in an increased risk for complications.
- Chronic total occlusion PCI may require significant amounts of radiographic contrast.
- A viability study may be needed for complete patient assessment prior to CTO PCI.
- Procedural complexity may discourage low volume operators.

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Percutaneous revascularization of chronic total coronary occlusions


* Recent manuscript supporting benefit of CTO PCI.


* Recent manuscript supporting benefit of CTO PCI.


** Summary of international CTO experience.


