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Original Studies

Treatment of the Chronic Total Occlusion: A Call to Action for the Interventional Community

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There is substantial evidence that recanalization of a chronic total occlusion is beneficial; nonetheless, it is generally underutilized in clinical practice. We consider the Aesop's fable of the "Fox and the Grapes" as analogous to the current situation in interventional cardiology. The technical challenges in achieving CTO recanalization has led interventionalists, clinical cardiologists, and sometimes even patients to believe that CTO recanalization is not effective, and, therefore, not needed. This perspective reviews available data regarding efficacy and safety of CTO percutaneous coronary intervention (PCI) in the current drug-eluting stent era, discusses areas where more studies are required, and encourages the interventional community to utilize CTO PCI where appropriate based on current evidence.

Key words: chronic total occlusions; percutaneous coronary intervention; coronary artery bypass grafting; myocardial infarction; coronary artery disease

INTRODUCTION

In the Aesop's fable of the fox and the grapes, a fox sees some high-hanging grapes and wishes to eat them. However, the fox is unable to reach the grapes and decides that they are probably sour and not worth eating. The fox has rationalized his lack of success. We are concerned that this same phenomenon has slowed the acceptance of chronic total occlusion (CTO)

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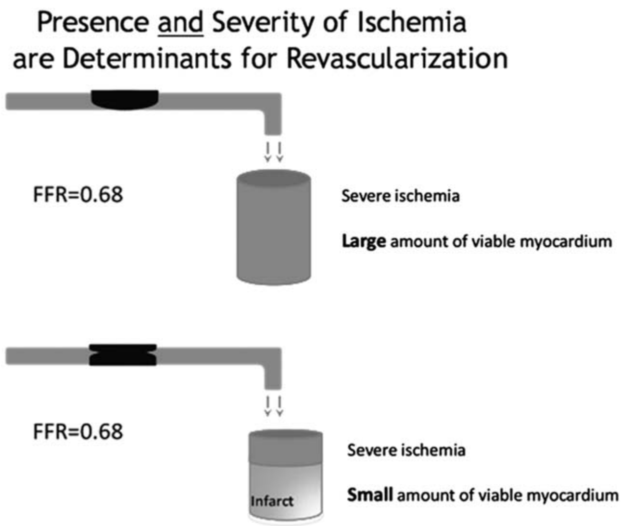

Fig. 1. The role of the severity and extent of ischemia in CTO revascularisation. The decision to revascularize a CTO should be based not only on the severity of myocardial ischemia but also on the extent of viable myocardium.

percutaneous coronary intervention (PCI) as a valuable method to improve outcomes in patients with coronary artery disease (CAD). There may, in fact, be two groups of "foxes." The first is the clinical cardiologist who believes there is insufficient data supporting CTO PCI and champions optimal medical therapy (OMT). In this regard, we concede that the evidence for efficacy is incomplete; nonetheless, available data are sufficient regarding symptomatic benefit and strongly suggestive for prognostic benefit. The second "fox" is the interventionalist who refuses to perform CTO PCI because he/she believes it is futile. Whilst the utility of CTO recanalization should be considered on an individual basis, recanalization might sometimes not be attempted because of lack of requisite expertise. We believe that such interventionalists should either obtain the necessary skills or refer the patient to a CTO interventionalist. In this presentation, we review the value of CTO PCI and the need for the treating cardiologist to consider this approach in a "patient-centered" management strategy.

Prevalence of CTO and PCI Attempt Rates

A CTO, defined as a coronary occlusion with TIMI 0 flow with an estimated occlusion duration of >3 months, has been relatively underrepresented in terms of research because many of these lesions have been considered "untreatable" by PCI.

The prevalence of CTOs in angiographic series is reported to be between 15 and 50%. This variation may be partly attributable to different CTO definitions, study populations, and study designs. Despite this relatively high prevalence, attempt rates have remained low and static. The National Cardiovascular Data Registry reported an attempt rate of 12.4%. Furthermore, operator PCI volume (not CTO PCI volume) was an independent predictor of attempt rate, such that low and intermediate volume operators were half as likely as high volume operators to attempt PCI among eligible patients. An attempt rate of 10% was observed in the Canadian Multicenter CTO Registry [1]. Interestingly, significant differences in attempt rate (1% to 16%) were observed between the three participating centers, suggesting that patients with CTOs are treated according to institutional and operator practice rather than clinical need. The generally low attempt rate is likely attributable to technical complexity, traditionally lower success rate than PCI of non-CTO lesions, perceived higher complication risk, need for specific operator training, and high cost and resource utilization.

Is the CTO a "Benign" Lesion?

One of the underlying myths regarding CTO is that it is "benign" and can be treated conservatively. However, such a statement is not supported by current evidence.

1. ***The Myocardium Subtended by the CTO Is an "Ischemic Zone"***
   Two studies using fractional flow reserve (FFR) and/or coronary flow reserve have evaluated the frequency of ischemia in symptomatic patients referred to angiography [2,3]. Both demonstrated ischemia in the myocardium subtended by the CTO. Interestingly the severity of ischemia as judged by FFR was not related to the size of angiographic collaterals, the territory at risk or previous myocardial infarction (MI). Another study showed that well-developed collaterals do not offer protection against adverse events because of residual distal ischemia, as demonstrated on myocardial perfusion imaging [4]. An increase in collateral flow reserve during pharmacological stress was shown to occur in only 7% of patients while coronary steal occurred in one-third independent of regional left ventricular (LV) function [3].
   Although it is likely that the CTO zone is ischemic, the extent is variable depending upon the amount of previous infarction within the zone and the size of the artery (Fig. 1). Thus, the value of intervention must consider the same factors as non-CTO interventions, namely, the size of ischemic area, the severity of the symptoms, and the adequacy of medical therapy.
2. ***CTO is Associated with Adverse Prognosis***
   Multiple studies have shown that CAD patients with a CTO have worsened prognosis compared with

CAD patients without a CTO. A CTO is an independent predictor of worsened outcome with acute coronary syndrome (ACS), both ST-segment elevation myocardial infarction (STEMI) [5] and NSTEMI [6], rescue PCI [7], and stable CAD [8]. In the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial a CTO was the most important predictor of incomplete revascularization, which, in turn, was associated with increased major adverse cardiovascular events (MACE). A CTO has also been associated with higher incidence of shocks and mortality rate in ischemic cardiomyopathy patients with an implantable cardioverter-defibrillator [9].

In summary, existing data suggest that a CTO is associated with adverse outcomes when other patient and angiographic factors are comparable.

Benefits of CTO PCI

The evidence that CTO PCI is effective in improving outcomes is relatively strong for several indications:

1. ***Improvement in Angina and Quality of Life***
The basis of treatment of ischemic heart disease, including that from a CTO, is optimized medical therapy. When symptom control is inadequate, revascularization is reasonable [10]. In a meta-analysis, Joyal et al. showed that successful recanalization was associated with a significant reduction in residual/recurrent angina in comparison to unsuccessful attempt at reopening the vessel [odds ratio 0.45, 95% CI: 0.30–0.67] [11]. Physical function, dyspnea and quality of life improved to a similar degree following CTO PCI as with non-CTO PCI. This meta-analysis has a number of limitations, primarily that none of the included studies was randomized or controlled, the quality of reporting for the included studies was not assessed, and angina was described with non-validated tools. Nonetheless, an average improvement in these measures of 55% is likely to be significant, keeping in mind that in most angina trials improvement in symptomatology tends to be at most in the 20–30% range. In the FlowCardia Approach to CTO Recanalization (FACTOR) trial, improvements in 1-month angina frequency and quality of life as assessed using the Seattle Angina Questionnaire were similar to those seen after CABG for multivessel disease (MVD) [12]. Such improvement was also noted at 4 years follow-up [13]. This study was also not randomized or controlled, the sample size was small with a significant number of patients being excluded from the study, and anti-anginal medications were underutilized in patients with failed PCI, thus raising the possibility of a placebo effect. Undoubtedly further studies, preferably randomized ones, are needed for conclusive evidence.
2. ***Improved Left Ventricular Function***
The myocardium subtended by a CTO may be dysfunctional, either because of previous infarction or chronic ischemia in viable myocardium. Following successful CTO PCI, improved ventricular function has been documented by cineangiography [14] and magnetic resonance imaging (MRI) [15]. Improvement in LV remodeling and function has been noted at 5 months and 3 years. With MRI evaluation, this improvement was related to the transmural extent of infarction (TEI) on pre-treatment MRI with the most pronounced effect seen with TEI $<25\%$ [16].
3. ***Reduction in CABG Frequency***
By reducing the need for CABG, CTO PCI offers the patient clinical improvement without the recuperative period inherent in CABG. Both the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) registry cohort-2 [17] and the Multinational Chronic Total Occlusion Registry showed a reduced need for CABG [18]. Interestingly, in the latter study, secondary analysis revealed no differences in mortality or MI during long-term follow-up in patients with failed CTO PCI who subsequently underwent CABG (11.3%) versus those who did not (88.7%), suggesting the safety of attempting CTO revascularization prior to CABG since there does not appear to be a mortality "price" to be paid for an unsuccessful attempt.
4. ***Protection against Future Cardiac Events***
CTO patients who develop an ACS exhibit increased mortality risk both in the short- and long-term [19]. In STEMI patients undergoing primary PCI, Yang et al have shown in a single-center observational study that successful staged revascularization of a CTO in the non-infarct related artery (IRA) was associated with lower cardiac mortality and higher MACE-free survival as compared to subjects with failed revascularization during a 2-year follow-up [20]. Ongoing randomized trials (see below) will further assess the effect of staged revascularization of CTO lesions in the non-IRA for STEMI patients treated with primary PCI.

Improvement in Long-term Survival

Current data are suggestive, though not definitive, on the effect of CTO PCI on survival. Table I presents

TABLE I. Outcomes Following CTO-PCI Stratified According to Technical Success

Author	Patients (n)	Enrolment period	Stent used (%)	Success rate	Follow-Up (years)	Outcome measured	Outcome rate, i.e., successful vs. failed	Adjusted HR in successful vs. failed
Chen et al. [21]	152	2004–2005	DES (95.5%)	86.8%	3	MACE (combined cardiac death, MI & TVR)	14.4% vs. 35%, $P = 0.04$	0.077, 95% CI = 0.073–0.15; $P = 0.002$
De Labriolle et al. [22]	172	2003–2005	DES (84%) BMS (9.7%)	73.8%	2	Cardiac mortality MACE (combined MI & TVR)	5.3% vs. 4.9%, $P = 0.3$ 22.7% vs. 5.3%, $P = 0.2$	N/A
Lee et al. [23]	333	2003–2006	DES (100%)	75.4%	3.6	MACE (composite of death, Q-wave MI, or TVR)	9.4% vs. 7.8%, $P = 0.52$	1.03, 95% CI = 0.35–3.03; $P = 0.89$
Valenti et al. [24][a]	486	2003–2006	DES (100%)	71%	2	Cardiac mortality	8.4% vs. 12.6%, $P = 0.025$	0.44; 95% CI = 0.22–0.87: $P = 0.021$
Mehran et al. [19]	1,791	1998–2007	DES (66%)	68%	5	All-cause mortality	6% vs. 8.6%, $P = 0.01$	0.63; 95% CI = 0.40–1.00, $P = 0.05$
			BMS (34%)			Cardiac mortality	3.0% vs. 5.8%, $P < 0.01$	0.40; 95% CI = 0.21–0.75; $P < 0.01$
						CABG	3.2% vs. 13.3%, $P < 0.01$	0.21; 95% CI = 0.13–0.36, $P < 0.01$
Jolicoeur et al. [25]	346	1999–2008	DES (51.6%) BMS (50.7%)	62%	5.6	MACE (composite of death & cardiovascular rehospitalisation)	40.4% vs. 45.4%, $P = 0.33$	0.90, 95% CI = 0.64–1.25, P = NS
Borgia et al. [13]	302	2003–2009	DES (98.2%)	78%	4	Cardiac death	1.3% vs. 1.5%, $P = 0.86$	0.35; 95% CI = .11–1.12; $P = 0.07$
						MACE (combined cardiac death, MI & TVR)	8% vs. 20%, $P = 0.01$	0.30; 95% CI = 0.13–0.68; $P = 0.003$
Niccioli et al. [26]	317	2005–2009	DES (100%)	62%	3	MACE (combined cardiac death, MI & TVR)	9% vs. 32 26%, $P = 0.008$	0.55, 95% CI = 0.24–0.75, $P = 0.02$
Jones et al. [27]	836	2003–2010	DES (76%) **BMS (21%)**	69.6%	3.8	All–cause mortality	4.5% vs. 17.2%, $P < 0.001$	0.28: 95% CI = 0.15–0.52, $P < 0.05$

[a]CTO revascularisation rather than successful PCI was used in the multivariate model.
Abbreviations: BMS = bare metal stent; CABG = coronary artery bypass grafting; CI = confidence interval; DES = drug eluting stent; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; TVR = target vessel revascularization.

outcome of patients undergoing CTO PCI in the drug-eluting stent (DES) era. The vast majority of studies indicate a survival benefit with successful revascularization. These studies compared long-term outcomes in patients with successful PCI vs. unsuccessful attempt. To date there are no randomized trials specifically evaluating PCI to either OMT or CABG. Possible reasons for survival benefit following successful revascularization include decrease in ischemia with consequent reduction in arrhythmias and improved LV contractility or avoidance of "double jeopardy" whereby a vessel supplying collaterals to a CTO acutely occludes resulting in a "double infarct." The lack of advantage in some studies may be explained by case selection, treatment variability, varying CTO definitions, ambiguous end-points, lack of sufficient power due to small study populations or short follow-up time frame, possible unaccounted confounding factors, varying use of DES and bare metal stents, older data (>8 years when devices and techniques were limited) as well as the possibility that there is truly no improvement in outcome. Nonetheless, the vast majority of recent studies conclude that successful CTO PCI is related to survival benefit. In the most recent meta-analysis conducted by Khan et al [28], successful CTO PCI was associated with decreased all-cause mortality [relative risk [RR] = 0.54, 95% CI = 0.45–0.65, $P < 0.001$), lower MACE (RR = 0.70, 95% CI = 0.60–0.83, $P < 0.001$) and reduced needs for subsequent CABG (RR = 0.25, 95% CI = 0.21–0.3), $P < 0.001$).

It is possible that the worse outcome noted in subjects with unsuccessful PCI is partly due to periprocedural complications such as coronary perforation. However, both the relatively low incidence of coronary perforation and ensuing mortality rate in the study conducted by Mehran et al. argues against this hypothesis

[19]. This study demonstrated that successful CTO PCI was associated with reduced cardiac mortality and a trend toward lower all-cause mortality at long-term follow-up. Recently improved survival up to 5 years was demonstrated by Jones et al. in the largest single-center contemporary series [27]. In the largest registry of 13,443 patients, improved survival over 2.65 years has recently been shown [29].

Three important randomized clinical trials are underway to evaluate the clinical efficacy of CTO PCI: EXPLORE (Evaluating XIENCE V and LV function in Percutaneous Coronary Intervention on Occlusions afteR ST-Elevation myocardial infarction-NTR1108), DECISION CTO (DES Implantation versus Optimal Medical Treatment in Patients with CTOs-NCT01078051) and EURO-CTO (A Randomized Multicenter Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions-NCT01760083). The results of these trials are highly anticipated and may clarify further the benefits associated with CTO PCI.

The CTO Technical Issue: If CTO PCI Should Be Performed for Clinical Indications, then Can It Be Done?

The answer is "yes" in the overwhelming majority. Significant advances in techniques and equipment have resulted in increasing success rate. Using antegrade intra-luminal techniques, success in selected cases, i.e. cases with favorable characteristics traditionally has been in the 60–70% range (see Table I). The development of antegrade and retrograde dissection/re-entry techniques has increased the success rate to the 85–90% range [30–32]. Often these cases are, in fact, less highly selected and technically more challenging but can now be performed with requisite expertise and experience. Currently, the technical advances are moving at a rapid pace with the expectation that success rate will continue to improve for ever more challenging coronary anatomy. These considerations emphasize the importance of disseminating the necessary education and training to allow more widespread use of these techniques.

Which Treatment for CTO: OMT, PCI, or CABG?

Many cardiologists favor OMT as they consider the "stable" ischemic heart disease patient with a CTO to be at relatively low risk. However, as noted above, there are a significant number of studies which indicate the opposite. We believe that the CTO patient should be treated similarly to the patient without CTO but with significant CAD, with the possible exception of assuming a somewhat higher long-term risk in the CTO patient group. As such, current guidelines should be applied similarly in a "patient-centered" approach.

Current guidelines indicate that CABG should be considered the treatment of choice for patients with MVD and high CAD complexity as quantified by the SYNTAX score [33,34]. In fact, both European and American guidelines were highly influenced by results of the SYNTAX trial. However, this study might not be truly representative of contemporary CTO PCI. In the SYNTAX CTO post-hoc analysis, complete revascularization was achieved in only 68.1% of CABG patients and 49% of PCI patients. With current equipment, techniques and expertise, one can expect an 80–90% success rate with PCI. The better long-term outcome with CABG in complex CAD in the SYNTAX trial may be due, at least in part, to more complete revascularization with CABG vs. PCI. Thus, it is incumbent in this era that interventionalists be facile with all CTO techniques or be prepared to refer to interventionalists who are able to achieve complete revascularization including CTO.

The "Heart Team" concept has been formally recommended for evaluation of treatment of left main disease [33]. Such a concept is useful for CTO treatment, and the involvement of surgical colleagues is helpful for best decision-making.

Current ACCF appropriate use criteria (AUC) for PCI provides a somewhat different classification for CTO PCI with regards to risk stratification by stress imaging and gives "less appropriate" indication for the symptomatic patient on medical treatment with a CTO as compared to a 99% stenosis or less [10]. While we do appreciate that CTOs represent a specific subset of complex coronary lesions, we believe that they are equally important with regard to patient outcome. Based on recent evidence it is anticipated that AUC revision will remove the differentiation between non-CTO and CTO lesions in treatment strategies.

Adverse Outcomes with PCI: How Big a Price is Paid for the PCI Attempt?

In experienced hands, there is only a slightly higher incidence of peri-procedural and in-hospital complications compared with PCI of non-CTO lesions. The most important complications are summarized in Table II. These include perforation, dissection, thrombosis of the donor artery, and collateral channel damage. Increased procedure duration and contrast use may lead to radiation injury and contrast-induced nephropathy respectively and careful attention to management of these often overlooked areas is essential. As seen in Table II, these complications are quite rare in the

TABLE II. Adverse Periprocedural and In-Hospital Events Following CTO-PCI Attempt in the Overall Patient Cohort

Author	Enrolment period	In-hospital death (%)	Procedural Q wave MI (%)	Procedural non-Q wave MI (%)	Cardiac tamponade (%)	ST (%)	Urgent CABG	Urgent PCI	CIN (%)	Major bleeding (%)	Stroke	Radiation dermatitis
De Labriolle et al. [22]	2003–2005	0	0	–	–	0.6	1.7	1.2	1.2	–	–	–
Valenti et al. [24]	2003–2006	0	0	4	0.58	–	4.11	–	5.23	5.23	–	–
Rathore et al. [35]	2002–2008	0.55	0.66	2.43	0.66	–	0.22	–	–	–	–	–
Borgia et al. [13]	2003–2009	0	0	1.99	0.33	–	–	–	–	0	0.66	–
Morino et al. [36]	2006–2007	0.4	0.2	2.1	0.4	0	0	0.4	1.2	–	0	0
Michael et al. [37]	2006–2011	0.22	0.37	–	–	0.07	–	–	–	–	–	–
Galassi et al. [38]	2008–2011	0.3	0.1	1.2	0.5	0.05	0.1	–	0.9	–	0.05	–

Abbreviations: CABG = coronary artery bypass grafting; CIN = contrast-induced nephropathy; MI = myocardial infarction; PCI = percutaneous coronary intervention; ST = stent thrombosis.

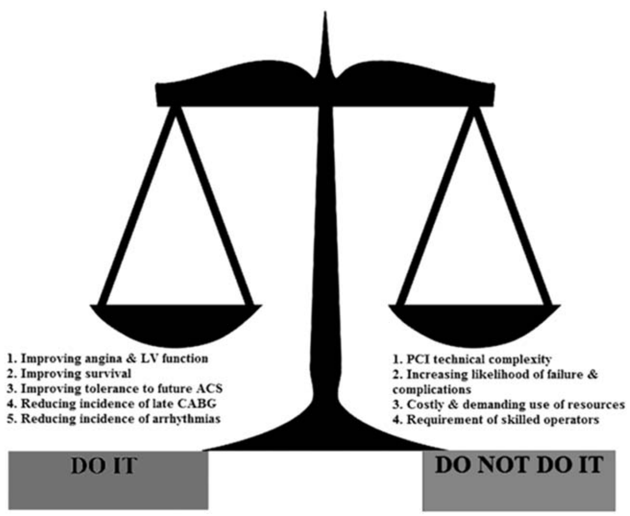

Fig. 2. The CTO PCI balance. With increasing expertise, novel devices and techniques, the balance will shift towards performing CTO PCI and achieving high success rates with low complication rates, resulting in symptomatic and prognostic benefit.

hands of competent operators. In fact, increasing operator experience has led to both high procedural success rate and very low complication rates, as reported by operators of the EuroCTO club [38], the J-CTO registry [36], and Multicenter United States Registry [37]. A low risk for procedural complications was also recently shown in a weighted meta-analysis of 18,061 patients from 65 studies published between 2000 and 2011 with the following pooled estimates of outcomes: death 0.2%, emergent CABG 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% [39].

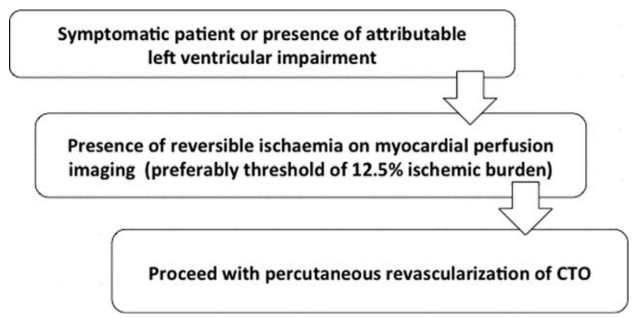

Fig. 3. Algorithm for determining patients who will benefit from CTO PCI attempt.

Success rate was 77%. These results indicate a favorable risk/benefit ratio and support increasing use of this procedure. It should be emphasized that most publications are promulgated by expert operators and "real world" complications may be higher than reported.

Even If CTO PCI Is Safe and Effective, It Must Be Too Expensive!

Costs may be evaluated at various levels, i.e. to the patient, hospital, payers, or society in general. In many cases, resource utilization for a particular CTO case is high with use of multiple wires, microcatheters etc. However, the procedure is likely to be less costly than a CABG. A dedicated CTO program may in fact be profitable to a hospital and similar to non-CTO PCI program [40]. The cost-effectiveness of CTO PCI for stable angina treatment was recently determined in a decision-analytic model. While CTO PCI incurred higher costs relative to OMT, it also resulted in greater quality-adjusted life-years (QALYs), resulting in a cost-effectiveness ratio of US$9505 per QALY [41].

The Current Management Dilemma

There is a growing body of evidence supporting CTO PCI as effective in symptom relief and suggestive for improvement in survival. Until randomized studies are completed, CTO PCI cannot be considered standard of care (Class I) for these indications. There will thus be a period of uncertainty as to how physicians should manage these patients. Guidelines provide direction, but management should be individualized and focused on obtaining the best outcomes for that particular patient. Thus, if CTO PCI is indicated and local expertise is not available, the patient should be referred to an interventionalist with the necessary skills. Ultimately, CTO PCI expertise requires widespread dissemination of education and training to allow patients to be treated appropriately as close as possible to their social supports.

Enthusiasm, commitment and dedication are keys to a successful CTO PCI program (Fig. 2). An algorithm that will assist in identifying patients who will benefit from CTO PCI as compared to OMT alone is outlined in Fig. 3. Patients who will benefit most from revascularization of CTOs are symptomatic subjects with ischemia as determined using MPI [4] as well as CTOs on the left anterior descending or left circumflex artery [42]. Revascularization of CTOs of the right coronary artery should be attempted in subjects undergoing PCI of unprotected left main coronary artery for potential survival benefit [43], and in symptomatic patients despite OMT. Age is not a limiting factor. The Heart Team approach will continue to play an important role in decision-making in complex CAD, including CTOs.

CONCLUSIONS

Our "point of view" paper is intended to highlight that current knowledge and expertise suggest that many chronically occluded coronary vessels are now ready to be opened. While awaiting the results of randomized controlled trials, we strongly recommend that CTO revascularization should not be avoided on the basis of perceived poor success rates, unclear patient benefits, adverse outcomes, time and resource use, or higher expected benefits with CABG (which is challenged by the most recent data). It is now time to offer this approach to symptomatic patients on OMT. Where local expertise is not available, patients should be referred to interventionalists with the required expertise. Undoubtedly, we as an interventional community must work diligently to disseminate and teach the necessary skills to interventionalists to provide optimum care to our patients.

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