Coronary intervention for chronic total occlusion: current indications and future directions

Janarthanan Sathananthan and Vladimír Džavík

Chronic total occlusions (CTOs) are routinely encountered during coronary angiography, but subsequent revascularization rates are low. This has likely been driven by a historical belief that there is minimal clinical benefit and poor success rates with a percutaneous coronary intervention (PCI). However, in the current era, with the development of new techniques and tools, experienced operators can perform CTO-PCI successfully in the majority of patients. The current indications and benefit of CTO-PCI remain a topic of controversy and debate. There is a growing body of predominantly nonrandomized studies reporting both short-term and long-term outcomes of CTO-PCI. Recent and upcoming randomized-controlled trials in this area will also potentially expand indications in both stable and patients with acute coronary syndrome. In this review, we will discuss the current evidence for CTO-PCI and also future directions in this field. *Coron Artery Dis* **28:426–436**
Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Coronary Artery Disease 2017, **28**:426–436

Keywords: chronic total occlusion, coronary artery disease, outcome, percutaneous coronary intervention

Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada

Correspondence to Vladimír Džavík, MD, 6-246 EN, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON, Canada M5G 2C4
Tel: +1 416 340 4800 x6265; fax: +1 416 340 3390;
e-mail: vlad.dzavik@uhn.ca

Introduction

The presence of a chronic total occlusion (CTO), defined as a complete occlusion of a coronary vessel of more than 3 months' duration, is a common finding during routine coronary angiography, with a prevalence between 18 and 52% [1–3]. In recent years, the appropriate management of patients with a CTO has been an important topic of discussion and limited clinical trials. Although a common finding during angiography, the clinical benefit of CTO percutaneous coronary intervention (PCI) continues to be debated, largely driven by a lack of randomized-controlled trial evidence. In addition, the CTO-PCI is complex, costly, and associated with higher complication rates compared with standard PCI [4]. This has led to reluctance to refer these patients for interventions from the wider cardiology community.

The rate of attempted CTO-PCI is low at 10%, with the Canadian multicenter registry showing wide variability in attempt rates of 1–16% across centers. This suggests that patients selected for CTO-PCI are often chosen according to institutional and operator experience rather than clinical need. In certain centers, it is possible that appropriate patients are denied CTO-PCI because of the absence of skills and tools or concern in terms of potential complications. In recent years, CTO-PCI success rates have improved and complication rates have decreased, driven by innovations in both technique and equipment. In experienced CTO centers, success rates of more than 90% can be achieved [5]. Although technical success has improved, the clinical benefits of CTO-PCI have not been resolved. Proponents of CTO-PCI argue that current observational data are sufficient to support the benefit of intervention to improve symptoms and also possibly mortality. To date, there are no randomized-controlled trials comparing CTO-PCI with coronary artery bypass grafting (CABG) or medical therapy. Opponents of CTO-PCI argue that in the absence of rigorous randomized-controlled trials, there is currently insufficient evidence to justify the procedure in this setting.

Historically, there has been a therapeutic nihilism toward CTO-PCI driven by skepticism and misconceptions of the potential benefit. This review will assess the indications for CTO-PCI, particularly which patients benefit the most from intervention, and discuss potential future directions in this field.

Indications

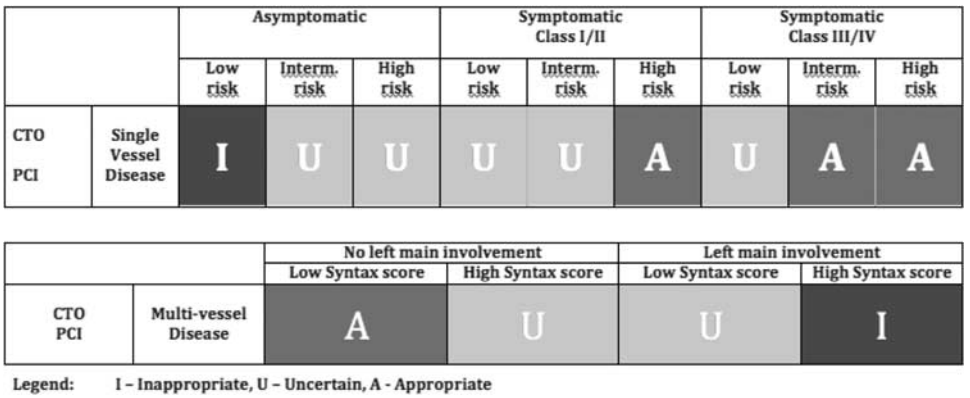
The decision to perform CTO-PCI should be patient focused, with the sole aim of improving clinical outcomes. Patients should not undergo intervention to satisfy operator ego or where outcome improvement is futile.

Currently, there is a low level of accepted evidence for the treatment of CTOs, based predominantly on retrospective observational data. The appropriate use criteria outline recommendations for appropriate revascularization for both CTO and non-CTO lesions. Patients with CTO lesions appropriate for intervention are those who are symptomatic and high risk (Fig. 1) [6]. The European Society of Cardiology guidelines assign CTO-PCI a class IIa indication: reasonable in patients with appropriate clinical indications and performed by operators with appropriate expertise. However, there is ambiguity in the definition of appropriate indications and also what constitutes sufficient

0954-6928 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved. DOI: 10.1097/MCA.0000000000000490

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Fig. 1



Appropriate use criteria for PCI of CTO lesions. A, appropriate; CTO, chronic total occlusions; I, inappropriate; PCI, percutaneous coronary intervention; U, uncertain.

'operator expertise'. The American guidelines have similar recommendations. Both the American and the European guidelines assign a level evidence B, reflecting the presence of conflicting evidence from the randomized and nonrandomized trials [6,7].

The belief that all CTO lesions are benign is likely unsubstantiated, and there are situations where intervention is beneficial. A patient with a CTO lesion requires assessment of symptoms, ischemia, and/or viability before any revascularization [8].

Patient selection

Patients with a CTO lesion and persistent symptoms despite optimized medical therapy should be considered for revascularization. These patients can also present with atypical symptoms such as reduced exercise tolerance and shortness of breath [9]. Assessment of ischemia is also central to patient selection. Patients with CTO lesions and significant ischemia by myocardial scintigraphy are more likely to have adverse cardiac events compared with those with no ischemia [10]. Not all patients with ischemia necessarily require treatment, with Safley *et al.* [11] reporting worse outcomes in patients who had a low ischemic burden before CTO-PCI. In addition, Gerber *et al.* [12] reported a survival difference of CTO-PCI over medical therapy when viability was demonstrated [13].

Overall, patients with persistent symptoms despite optimized medical therapy and asymptomatic patients with a high burden of ischemia or evidence of viability are suitable candidates for CTO revascularization. Patients who do not fulfill any of these criteria should be managed medically. Importantly, all patients should be formally assessed and investigated for suitability before revascularization. Ad-hoc PCI in the absence of a proper work-up is not warranted [6,9]. Although this review focuses on PCI, coronary artery bypass grafting is also a therapeutic option in patients with CTO.

Mortality

There are currently no randomized-controlled trials reporting improved survival with CTO-PCI, but observational studies are suggestive of a possible benefit. Most studies have compared long-term mortality between successful versus unsuccessful attempts at CTO-PCI. Although there is variability in reported outcomes across studies, the majority suggest an association with lower mortality. The heterogeneity across studies reflects differences in patient selection, CTO definition, endpoints, sample size, and technique [14,15]. A recent meta-analysis by Hoebers and colleagues identified 27 studies eligible for a morality endpoint with a total of 11 085 patients with a successful CTO procedure versus 4347 patients with an unsuccessful procedure between 1990 and 2013 (Table 1). There were marked differences in sample size from 44 to 2005 patients. In this study, successful CTO-PCI was associated with a significantly lower mortality compared with failed cases. A subgroup of these studies that had a consistent definition of CTO duration of more than 3 months still showed an association with lower mortality with successful revascularization [14]. The observed difference may be attributable to worse outcomes in patients who have an unsuccessful PCI because of adverse events or because of a possible incremental benefit in the successful PCI group. Although this large meta-analysis is suggestive of benefit, any study reliant on observational data is subject to selection bias, especially one that utilizes comparisons of successful versus unsuccessful procedures, rather than comparisons of PCI versus medical therapy.

The observational data are also not consistent. In a recent large Korean study, 1173 consecutive patients enrolled between 2003 and 2014 were assessed for prognostic

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 Effect on long-term mortality of successful versus unsuccessful chronic total occlusion-percutaneous coronary intervention

References	Design	Study size	Successful PCI (events)	Unsuccessful PCI (events)	Outcome	Odds ratio
Finci *et al.* [16]	Retrospective	200	100 (5)	100 (3)	Equivalent	1.70 (0.40–7.32)
Ivanhoe *et al.* [17]	Retrospective	480	317 (3)	163 (6)	Equivalent	0.25 (0.06–1.01)
Sathe *et al.* [18]	Retrospective	178	116 (3)	62 (4)	Equivalent	0.38 (0.08–1.78)
Angioi *et al.* [19]	Retrospective	201	93 (1)	108 (6)	Equivalent	0.18 (0.02–1.56)
Noguchi *et al.* [20]	Retrospective	226	134 (7)	92 (15)	Favors PCI	0.28 (0.11–0.72)
Suero *et al.* [21]	Retrospective	2005	1491 (395)	514 (180)	Favors PCI	0.67 (0.54–0.83)
Olivari *et al.* [22]	Retrospective	369	286 (3)	83 (3)	Equivalent	0.28 (0.06–1.43)
Hoye *et al.* [23]	Retrospective	871	567 (37)	304 (36)	Favors PCI	0.52 (0.32–0.84)
Arslan *et al.* [24]	Retrospective	232	117 (19)	115 (37)	Favors PCI	0.41 (0.22–0.77)
Drozd *et al.* [25]	Retrospective	429	280 (7)	149 (5)	Equivalent	0.74 (0.23–2.37)
Aziz *et al.* [26]	Retrospective	543	377 (9)	166 (12)	Favors PCI	0.31 (0.13–0.76)
Prasad *et al.* [27]	Retrospective	1262	914 (220)	348 (101)	Equivalent	0.78 (0.59–1.02)
de Labriolle *et al.* [28]	Retrospective	167	127 (7)	40 (2)	Equivalent	1.11 (0.22–5.56)
Valenti *et al.* [29]	Retrospective	486	344 (17)	142 (17)	Favors PCI	0.38 (0.19–0.77)
Chen *et al.* [30]	Retrospective	152	132 (2)	20 (3)	Favors PCI	0.09 (0.01–0.56)
Yi *et al.* [31]	Retrospective	1332	1202 (135)	130(24)	Favors PCI	0.56 (0.35–0.90)
Lee *et al.* [32]	Retrospective	333	251 (8)	82 (4)	Equivalent	0.64 (0.19–2.19)
Mehran *et al.* [33]	Retrospective	1791	1226 (74)	565 (49)	Favors PCI	0.68 (0.46–0.98)
Borgia *et al.* [34]	Retrospective	302	237 (19)	65 (9)	Equivalent	0.54 (0.23–1.26)
Joliceour *et al.* [35]	Retrospective	346	213 (22)	133 (24)	Favors PCI	0.52 (0.28–0.98)
Jones *et al.* [36]	Retrospective	836	582 (26)	254 (44)	Favors PCI	0.22 (0.13–0.37)
Niccoli *et al.* [37]	Retrospective	317	196 (5)	121 (10)	Favors PCI	0.29 (0.10–0.87)
Jaguszewski *et al.* [38]	Retrospective	386	247 (5)	139 (2)	Equivalent	1.42 (0.27–7.39)
Tanaka *et al.* [39]	Retrospective	284	231 (25)	53 (6)	Equivalent	0.95 (0.37–2.45)
Yamamoto *et al.* [40]	Retrospective	1524	1192 (92)	332 (35)	Equivalent	0.71 (0.47–1.07)
Yang *et al.* [41]	Retrospective	136	87 (7)	49 (10)	Favors PCI	0.34 (0.12–0.96)
Jaguszewski *et al.* [42]	Retrospective	1110	734 (47)	376 (31)	Equivalent	0.78 (0.49–1.25)
Lee *et al.* [43]	Retrospective	1173	1004 (59)	169 (10)	Equivalent	1.04 (0.53–2.04)

PCI, percutaneous coronary intervention.

benefit between failed and successful procedures [43]. All successful PCI patients underwent drug-eluting stent (DES) implantation. Successful PCI was not associated with a lower mortality risk compared with failed PCI. In addition, there was no mortality benefit irrespective of the presence or absence of coexisting multivessel disease.

The applicability of observational data to clinical practice is difficult, given the significant heterogeneity across these studies [14]. In addition, most of the observational studies predate contemporary techniques and devices, rendering applicability to the modern era problematic. In the absence of randomized-controlled trials, the current evidence for a mortality benefit is at best suggestive rather than definitive. The results of EuroCTO (Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) and DECISION-CTO (Drug-Eluting Stent Implantation versus Optimal Medical Treatment in Patients with Chronic Total Occlusion) are eagerly awaited [44]. Both studies will assess mortality as part of a composite endpoint (Table 2).

Angina and quality of life

The decision to proceed to revascularization for angina and quality of life is dependent on an assessment of symptoms and ischemia. Patients should also be optimized on medical therapy [9]. There is general consensus of expert opinion and guidelines that CTO-PCI is indicated in those patients who are still symptomatic despite adequate medical therapy.

The Seattle Angina Questionnaire has been used to assess the benefit of CTO-PCI on physical limitation, angina stability, angina frequency, disease perception, and treatment satisfaction [45]. Wijeysundera *et al.* [46] reported improved physical limitation and angina frequency compared with medical therapy. However, this study was nonrandomized and patients in the CTO-PCI group were younger, with less comorbidity than the comparator medical therapy group, reflecting an issue of selection bias. Other studies comparing successful versus failed CTO-PCI have also shown significant improvement in angina episodes, physical limitation, and treatment satisfaction [34,47]. In the TOAST-GISE study, patients who had successful versus failed CTO-PCI were more likely to be angina free (89 vs. 75%) and have a negative exercise tolerance test (73 vs. 47%) at 1 year [22]. The FACTOR (FlowCardia Approach to CTO Recanalization) also showed persistent improvement in angina episodes at the 4-year follow-up [47]. Meta-analysis of the observational data is strongly in favor of patients who have successful CTO-PCI versus those with a failed procedure with respect to residual angina. The utility of these results is limited by the variation in how angina was reported as well as the nonrandomized nature of all the studies (Table 3) [49]. Furthermore, not only were these simply observational, comparing PCI versus medical therapy, they were comparing outcomes of patients with successful versus unsuccessful procedures. It is quite conceivable that an unsuccessful procedure could be in itself a marker of more complex anatomy and therefore a higher risk patient, and could untowardly

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Table 2 Study design and characteristics of the EuroCTO and DECISION-CTO studies

	EuroCTO	DECISION-CTO
Design	Randomized	Randomized
Size	450	1284
Estimated completion date	June 2018	December 2023
Inclusion criteria	- ≥ 18 years - CTO in native artery - Stable angina or ischaemia in a territory supplied by CTO, and viability confirmed by MRI - CTO located in segments 1-3 RCA, 6-7 LAD, 11-12 LCx - Target artery ≥ 2.5 mm	- > 18 years - Patients with angina or silent ischaemia and documented ischaemia. - CTO lesion with reference vessel size of 2.5 mm and located in proximal or mid epicardial coronary artery.
Exclusion criteria	- Myocardial infarction within 1 month - Significant untreated artery in a territory other than CTO vessel. - Patients with multivessel disease and significant non-CTO stenoses where it is deemed unsafe to treat the non-CTO lesion first. - Unsuitable for 12 months dual anti-platelet therapy - Any patient unsuitable for PCI or DES - Pregnancy	- History of bleeding or coagulopathy - Pregnancy - Three vessel CTO - Known hypersensitivity or contraindication to contrast agent. - STEMI requiring primary stenting - Left main disease, in stent restenosis, graft vessels or distal epicardial lesion. - Hematological, hepatic, or renal dysfunction. - Contraindication to anti-platelet therapy. - Patients participating in another trial - Any co-morbid condition with limited life expectancy.
Assigned intervention	PCI of CTO using a Biomatrix drug eluting stent system + optimal medical therapy	PCI of CTO with drug eluting stent (Cypher, Xience, Endeavor, Taxus)
Comparator group	Optimal medical therapy	Optimal medical therapy
Primary outcome	1) Quality of life (Baseline and 12 months) 2) Major cardiovascular events (composite of all-cause death, non fatal myocardial infarction at 3 years)	1) Composite endpoint of all cause death, myocardial infarction, stroke, and any revascularization at 3 years follow-up.

CTO, chronic total occlusions; DES, drug-eluting stents; LAD, left anterior descending artery; LCx, left circumflex; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table 3 Effect of successful versus failed chronic total occlusion-percutaneous coronary intervention on residual angina

References	Design	Study Size	Successful PCI (events)	Unsuccessful PCI (events)	Outcome	Odds ratio
Finci *et al.* [16]	Retrospective	200	100 (43)	100 (74)	Favors PCI	027 (0.15–0.48)
Warren *et al.* [48]	Retrospective	44	26 (3)	18 (17)	Favors PCI	0.20 (0.04–0.95)
Ivanhoe *et al.* [17]	Retrospective	430	286 (90)	144 (53)	Equivalent	0.79 (0.52–1.20)
Angioi *et al.* [19]	Retrospective	190	90 (27)	100 (56)	Favors PCI	0.34 (0.18–0.61)
Olivari *et al.* [22]	Retrospective	308	248 (28)	60 (15)	Favors PCI	0.38 (0.19–0.77)
Drozd *et al.* [25]	Retrospective	429	280 (120)	149 (79)	Favors PCI	0.66 (045–0.99)

PCI, percutaneous coronary intervention.

affect collateral circulation. In addition, as there was suboptimal or no reporting on the use of antianginal therapy, it is unclear whether patients in many of these registries were on optimal medical therapy.

Left ventricular function

The myocardium subtended by a CTO may be functionally normal, dysfunctional but viable, or dysfunctional and nonviable. Observational studies have shown improvements in left ventricular function at 6 months following CTO recanalization. A meta-analysis by Hoebers *et al.* [14] reported that in 34 studies with 2243 patients, there was a significant improvement in left ventricular ejection fraction (LVEF) by 4.44% following CTO-PCI compared with preintervention LVEF. The benefit of revascularization has also been maintained with improved left ventricular remodeling and ejection fraction at the 3-year follow-up. A predictor for long-term improvement in LVEF was related to the extent of transmural infarction on cardiac MRI [50]. Cardiac MRI can be used as a preassessment tool before a planned CTO intervention to help in predicting the degree of benefit that can be anticipated.

Summary: who should have chronic total occlusion-percutaneous coronary intervention

As discussed, CTO-PCI can be performed for different indications, but in the absence of randomized-controlled trials, the strength of the observational evidence is for patients with significant symptoms on optimal medical therapy. Although it is accepted that randomized trials are needed, suitable patients should not be denied therapy as clinicians await further evidence. Carefully selected patients with well-defined indications should still proceed to intervention as part of current practice. In the absence of symptoms, there should be a higher

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

threshold to proceed to PCI in this patient group [51]. In asymptomatic patients, the benefit of intervention on outcomes such as mortality or LVEF is tenuous in the absence of randomized trials and intervention in these patients should be approached with caution.

Chronic total occlusion-percutaneous coronary intervention in ST segment elevation myocardial infarction patients

Although the PRAMI (Randomized Trial of Preventive Angioplasty in Myocardial Infarction), CVLPRIT (Randomized Trial of Complete versus Lesion-only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease), and DANAMI-3 PRIMULTI (Complete Revascularization versus Treatment of the Culprit Lesion only in Patients with ST Segment Elevation Myocardial Infarction and Multivessel Disease: an Open-Label, Randomized-Controlled Trial) studies have suggested the benefit of complete revascularization with the treatment of noninfarct-related lesions in addition to the culprit vessel in ST segment elevation myocardial infarction (STEMI) patients, none were adequately powered and further adequately powered trials are underway [52]. Furthermore, patients with CTOs were excluded from these three trials [53]. A concurrent CTO in a noninfarct vessel is present in ~10% of STEMI patients, and is associated with excess mortality and poor LVEF [54]. Three-year follow-up from HORIZONS-AMI showed that the presence of a CTO in a noninfarct artery was an independent predictor of mortality [55]. The EXPLORE (Evaluating XIENCE V and Left Ventricular Function in PCI on Occlusions after STEMI) trial assessed the benefit of opening a concurrent CTO in a noninfarct-related vessel presenting with STEMI. All patients had staged CTO-PCI within 7 days of STEMI-PCI and in those who underwent a CTO intervention, there was no signal to harm from complications. At the 4-month follow-up, however, there was no change in LVEF and left ventricular end diastolic volume by MRI [56]. There was a suggestion that those with a left anterior descending artery-CTO showed improvement in LVEF, but the numbers were small and further validation from a larger trial is needed [56].

Although the results of the EXPLORE study are disappointing, the results must be considered in the context of the trial's limitations. The core lab-assessed CTO success rate was low at 73% compared with the 90% that can be achieved at experienced CTO centers [57]. Completeness of revascularization is unclear in the study. A follow-up period of 4 months may not be sufficient to elicit myocardial recovery. Regional wall motion changes were also not assessed [58].

Future studies in this area need to identify which patients if any with CTO benefit and the potential role of viability assessment.

Chronic total occlusion-percutaneous coronary intervention as part of complete revascularization

The EXPLORE study assessed the CTO intervention only in STEMI patients with multivessel disease. CTO lesions are also common in patients with multivessel disease, presenting with stable angina or non-STEMI. In the Canadian CTO registry, multivessel disease was present in 75% of patients with CTOs. In patients with multivessel disease, CTO-PCI was only attempted in 22% of cases, reflecting that current practice is to perform PCI in the nonoccluded vessels, leaving the CTO unrevascularized [1].

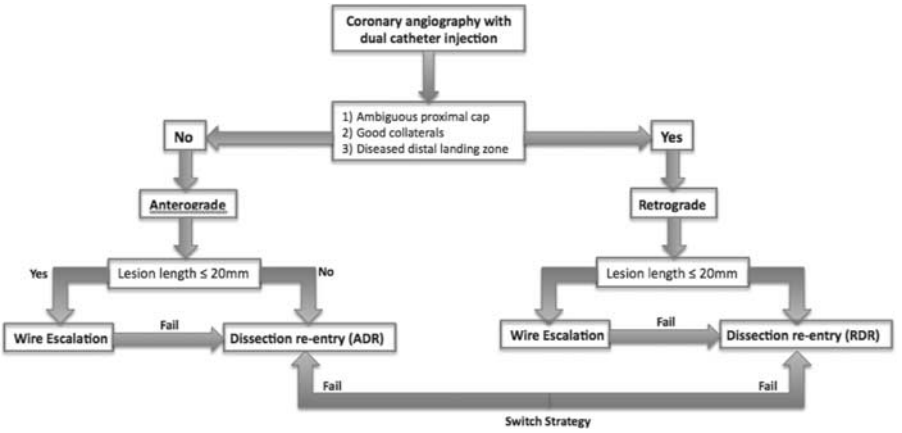
Patients with multivessel disease who have complete revascularization (defined as treatment to the main epicardial arteries) compared with incomplete revascularization have 30% less long-term mortality, a 22% reduction in myocardial infarction, and a 26% reduction in repeat revascularization [59]. Complete revascularization is more frequently achieved with CABG rather than PCI [59]. A major cause of failed complete revascularization in many major trials was because of unsuccessful CTO-PCI. The SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial randomized 1800 patients with multivessel disease to either CABG or PCI [60]. In SYNTAX, CTO prevalence was 23% and successful CTO revascularization was higher in the CABG group than in the PCI group. A CTO was the main reason for not achieving complete revascularization in the PCI arm of SYNTAX. The lower complete revascularization rates in the PCI arm may also have contributed toward the higher rate of major adverse cardiac events compared with CABG [61]. The residual SYNTAX score, which is a score based on the residual coronary disease following PCI, is a marker of completeness of revascularization [62]. A score of more than 8 was associated with increased mortality at 5 years [63]. Registry data from the New York State Percutaneous Intervention Reporting System are also in favor of complete rather than incomplete revascularization [63]. In 22 000 patients, those who had incomplete revascularization because of the presence of a CTO had significantly higher mortality [63]. These data support the importance of complete revascularization, for which the presence of a CTO is a major barrier.

Chronic total occlusion-percutaneous coronary intervention technique in the current era

CTO revascularization has evolved in the current era, introducing new techniques to improve procedural success. Historically, CTO techniques were exclusively antegrade wire escalation, and there was high procedural failure. Novel techniques such as antegrade dissection reentry and retrograde techniques have been integrated into the CTO treatment algorithm [64,65]. This has improved success in specific lesion subsets such as ambiguous proximal cap, poor distal targets, and long

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Fig. 2



Hybrid algorithm for the treatment of chronic total occlusions. ADR, antegrade dissection re-entry; RDR, retrograde dissection re-entry

occlusions. These new techniques have been incorporated into the modern hybrid CTO algorithm (Fig. 2). The hybrid algorithm is based on the principle that patient anatomy dictates PCI strategy. Good angiography is important, usually with dual injections in both coronary arteries, to adequately visualize the proximal segment, the occlusion itself, collaterals, and the distal bed. The three CTO recanalization techniques, antegrade, retrograde, and dissection re-entry, can be alternatively applied or combined as needed.

Antegrade technique

An antegrade technique is the primary strategy for most patients with a CTO. A single-wire technique over a microcatheter is the initial standard approach. A wire escalation technique is then used with increasingly stiffer coronary wires or alternatively a 'step up–step down' approach alternating between stiff and soft coronary wires. The latter approach can be used to overcome an angulated chronic total occlusion. If a single-wire technique fails, a parallel-wire technique can be used by placing a second wire while leaving the first wire in place as a marker [66].

Antegrade dissection/re-entry

The antegrade dissection and re-entry technique involves the intentional use of the subintimal space for crossing CTO lesions and then re-entering the true distal lumen [64]. Tools such as the CrossBoss catheter (Boston Scientific, Natick, Massachusetts, USA) and the Stingray system (Boston Scientific) have eased the procedural challenges of this technique [67]. An antegrade dissection/re-entry technique is used as a last resort as it is associated with a high rate of restenosis and reocclusion [68].

Retrograde technique

An antegrade approach is successful in the majority of patients; however, in those with an ambiguous proximal cap, a poor distal target, or good interventional collaterals, a retrograde technique may be more suitable [69]. In 2005, the introduction of the controlled antegrade retrograde subintimal tracking (CART) technique improved success rates, particularly in challenging lesions. This technique involves intentional wiring of collaterals to allow retrograde wiring and ballooning of the distal cap to facilitate antegrade wiring. This technique has been updated with the reverse-CART technique, in which a balloon is inflated on the antegrade wire to enlarge the subintimal space, allowing the retrograde wire to be advanced into this space. The retrograde wire is then advanced into the antegrade guiding catheter and the wire is then externalized [70].

Summary

Procedural planning is integral to a modern CTO-PCI approach. Ideally, CTO procedures should not be performed ad hoc. Rather, patients should be brought back for a dedicated attempt of the CTO lesion. CTO-PCI should be a standalone procedure and not performed at the same time as non-CTO lesions to minimize complications such as contrast nephropathy and radiation injury. This will allow time to appropriately plan the procedure with careful interrogation of the angiogram, anticipation of required equipment and procedural challenges, and also use of adjunctive imaging tools such as cardiac computed tomography [71].

The use of the hybrid algorithm, in combination with evolution of dedicated CTO devices, has improved CTO success rates to ~90% [57]. Success rates are high even by relatively novice operators [72].

Stent technology in chronic total occlusion-percutaneous coronary intervention

The Total Occlusion Study of Canada (TOSCA) was a randomized trial that established the role of stents in

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

CTO-PCI, showing that use of the heparin-coated Palmaz-Schatz stent was superior to balloon angioplasty alone, with better late patency and less restenosis and target lesion revascularization [73]. However, historical outcomes of CTO-PCI were still hampered by issues of long-term patency particularly in the era of bare metal stents, with rates of restenosis as high as 40% [74]. The development of DESs was a therapeutic advance, their use resulting in significantly less target lesion revascularization, restenosis, and stent reocclusion than the use of bare metal stents (BMS) [75]. DESs are the current standard of care for CTO-PCI. The major adverse cardiac events superiority found with DES was driven predominantly by target lesion revascularization [76]. Early trials evaluated sirolimus-eluting or paclitaxel-eluting stents compared with BMS. In the randomized PRISON-II trial, treatment with sirolimus-eluting stents (SES) significantly reduced restenosis (41–11%) and vessel reocclusion (13–4%) compared with BMS [77]. Treatment with contemporary everolimus-eluting stents (EES) has been shown to be equivalent to SES [78]. The EXPERT CTO (Safety and Effectiveness of EES in Chronic Total Coronary Occlusion Revascularization) assessed the outcomes of 250 consecutive CTO patients in 20 centers, treated with contemporary techniques and EES. Target lesion revascularization at 1 year was 6.3% in these patients with high lesion complexity [79]. The results from these recent studies indicate that with modern techniques and DESs, CTO-PCI can be performed with good long-term durability. These improved results compared with historical outcomes challenge the perception that CTO-PCI is associated with poor long-term outcomes.

Drug-eluting stents with biodegradable polymers

Although modern DES play a central role in modern PCI, some concerns have been raised about late target vessel failure potentially driven by inflammation and hypersensitivity to the presence of a durable polymer [80,81]. To overcome these issues, the novel Osiro stent (Biotronik, Berlin, Germany) was developed, a hybrid thin strut sirolimus-eluting stent with a biodegradable polymer. The PRISON IV (Randomized Multicenter Trials Investigating the Angiographic Outcome of Hybrid Sirolimus-Eluting Stents with Biodegradable Polymer Against Everolimus-Eluting Stents with Durable Polymer in Chronic Total Occlusions) failed to show noninferiority of hybrid SES compared with EES for in-segment late lumen loss and also showed a high rate of binary restenosis in the hybrid SES group [82]. Although the BIOFLOW-II study showed noninferiority of hybrid SES compared with EES in simple lesions, its role in more complex CTO lesions remains uncertain [83].

Bioresorbable scaffolds in chronic total occlusion-percutaneous coronary intervention

Bioresorbable scaffolds (BRS) represent one of the latest innovations in interventional cardiology and provide an alternative treatment choice to DES. BRS allow temporary scaffolding of diseased vessels, subsequently resorbing over time, possibly allowing for restoration of normal vessel vasomotion after the scaffold is completely resorbed [84,85].

Patients with CTO lesions were excluded from all randomized-controlled BRS trials to date, with current BRS experience limited to single-center or registry data [84–87]. The largest registry to date, the BONITO registry, assessed outcomes in 153 patients who underwent CTO-PCI with BRS versus those who were treated with DES. At a median follow-up of 703 days, there was no difference in target vessel failure between BRS and DES, but there was a signal toward a higher rate of ischemia-driven target lesion revascularization in the BRS group [88].

Although these small registry and single-center reports suggest early acceptable outcomes, further long-term randomized-controlled trials are needed. A recent 3-year follow-up from ABSORB II showed an alarmingly higher rate of target vessel myocardial infarction and stent thrombosis using Absorb (Abbott Vascular, Santa Clara, California, USA) compared with Xience (Abbott Vascular) in a patient cohort with relatively low lesion complexity [89]. In light of these findings, current routine use of BRS in CTO-PCI cannot be advocated and highlights the need for further study and validation. Technological advances with thinner strut BRS may play a future role in CTO-PCI.

Novel technologies

New devices and therapies continue to be developed to improve CTO-PCI procedural success.

The TOSCA-5 trial assessed pretreatment of CTO patients with collagenase administered into the proximal fibrous cap, which can potentially soften hard plaque, usually present in CTO lesions. In this small study, patients randomized to the study group were more likely to have successful soft wire crossing, but there was no difference in the overall procedural success by QCA between the groups [90]. The PlasmaWire (RetroVascular Inc, Pleasanton, California, USA) is a new device using a novel wire with radiofrequency energy to aid CTO recanalization. This technology may primarily play a role in penetrating a proximal CTO cap when traditional guidewires have failed. There has been initial experience in seven human cases, but further validation is needed with larger clinical trials [91]. These novel technologies may play a potential future role in CTO-PCI.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Challenges to chronic total occlusion-percutaneous coronary intervention

The current rate of referral and subsequent revascularization of CTO patients is low. Although not every CTO patient warrants intervention, current low revascularization rates of 10% likely reflect that patients who would potentially benefit from intervention are not being referred. As we have established, the course of all CTO patients is not 'benign' and there is likely clinical benefit in carefully selected patients. Therefore, educating clinicians on the importance of the assessment and benefits of CTO-PCI is integral for the field to evolve. However, concurrent development of high-quality clinical trials is essential to hopefully address any doubts in terms of efficacy.

Another main barrier hampering the widespread adoption of CTO-PCI is the complexity of the procedure, higher complication rate, and lower success rate compared with non-CTO-PCI. Recent advances in technique and device technology have improved success rates to 80–90% in specialized centers [92,93]. In addition, the procedure is safer, with an ~1% risk for major complications of death, myocardial infarction, tamponade, and contrast-induced nephropathy [92]. However, outside of centers of excellence with specialized CTO skills, the results have wide variability. Therefore, CTO-PCI should be performed at specialized centers and by operators with the necessary expertise. Training of operators remains a challenge both to the individual and to the institution. The number of CTO cases may be limited and institutional support may be lacking. The European CTO club recommends a minimal annual operator volume of 50 cases, but there is variability across societies on what is deemed to be an adequate annual case load. To concentrate experience, it is also logical that only particular individuals or even particular centers perform CTO intervention rather than all operators or all centers. Data from the USA identified the majority of operators to be low/intermediate-volume operators, with ~75% performing less than 100 PCI cases per year. The median operator volume in 2009 was only 33 [94]. Therefore, when the majority of operators have a relatively low overall annual PCI volume for individual operators to achieve 50 complex CTO cases can be challenging [47]. Training of new operators should include mentorship, proctorship, attendance at meetings, case review, and a consistent minimum case load, all of which are paramount to establishing a successful CTO-PCI program.

Adoption of CTO-PCI can also be limited by cost and resource limitations. CTO intervention in comparison with routine PCI is generally costlier, with a higher demand on resources. Gada *et al.* [95] reported that a CTO-PCI approach was more expensive relative to optimal medical therapy (US$31512 vs. US$27805). However, nonrandomized data have shown that CTO-PCI provided greater quality adjusted life years (2.38 vs. 1.99), yielding acceptable cost-effectiveness [94].

Future direction/summary

The decision to treat patients with CTO should be for patient-driven indications, and importantly, patients should not be denied therapy because of lesion complexity. Current referral rates for CTO-PCI are low and it important to continue further education of clinical cardiologists so that suitable patients are at least considered and assessed for revascularization. Although there is currently a lack of robust evidence in favor of CTO-PCI, it is still likely that a subset of patients will gain some benefit from intervention. This highlights the need for specialized heart teams focusing on high-risk PCI patients to assess these patients. This heart team approach would enable a multidisciplinary assessment, and importantly, management by CTO specialists who have the necessary annual case load and skill set. Evolution in technique and equipment means that in current practice, experienced operators can perform CTO-PCI successfully in most patients.

Finally, for the right patient, and in the right hands, CTO-PCI can be performed safely to improve patient outcomes. However, identifying which patients benefit and validating a prognostic benefit will remain an ongoing challenge for future trials in this area.

Acknowledgements

Conflicts of interest

Dr. Džavík has received speaker honoraria and meeting travel grants from Abbott Vascular. For the remaining author there is no conflict of interest.

References

1 Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, *et al.* Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 2012; **59**:991–997.

2 Jeroudi OM, Alomar ME, Michael TT, Sabbagh A, Patel VG, Mogabgab O, *et al.* Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. *Catheter Cardiovasc Interv* 2014; **84**:637–643.

3 Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, *et al.* Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation* 2005; **112**:2364–2372.

4 El Sabbagh A, Patel VG, Jeroudi OM, Michael TT, Alomar ME, Mogabgab O, *et al.* Angiographic success and procedural complications in patients undergoing retrograde percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 3482 patients from 26 studies. *Int J Cardiol* 2014; **174**:243–248.

5 Galassi AR, Boukhris M, Azzarelli S, Marza F, Tomasello SD. Percutaneous coronary interventions for chronic total occlusions: more benefit for the patient or for the interventionist's ego? *Can J Cardiol* 2015; **31**:974–979.

6 Galassi AR, Brilakis ES, Boukhris M, Tomasello SD, Sianos G, Karmpaliotis D, *et al.* Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. *Eur Heart J* 2016; **37**:2692–2700.

7 Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2009; **53**:530–553.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

8 Boukhris M, Tomasello SD, Galassi AR. Should we give into temptation and attempt all chronic total occlusions? *Interv Cardiol (Lond)* 2014; **6**:399–401.

9 Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, *et al*. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; **34**:2949–3003.

10 Galassi AR, Werner GS, Tomasello SD, Azzarelli S, Capodanno D, Barrano G, *et al*. Prognostic value of exercise myocardial scintigraphy in patients with coronary chronic total occlusions. *J Interv Cardiol* 2010; **23**:139–148.

11 Safley DM, Koshy S, Grantham JA, Bybee KA, House JA, Kennedy KF, Ruthrford BD. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. *Catheter Cardiovasc Interv* 2011; **78**:337–343.

12 Gerber BL, Rousseau MF, Ahn SA, Ahn SA, Ahn SA, Ahn SA, *et al*. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. *J Am Coll Cardiol* 2012; **59**:825–835.

13 Kirschbaum SW, Rossi A, Boersma E, Springeling T, van de Ent M, Krestin GP, *et al*. Combining magnetic resonance viability variables better predicts improvement of myocardial function prior to percutaneous coronary intervention. *Int J Cardiol* 2012; **159**:192–197.

14 Hoebers LP, Claessen BE, Elias J, Dangas GD, Mehran R, Henriques JP. Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. *Int J Cardiol* 2015; **187**:90–96.

15 Khan MF, Wendel CS, Thai HM, Movahed MR. Effects of percutaneous revascularization of chronic total occlusions on clinical outcomes: a meta-analysis comparing successful versus failed percutaneous intervention for chronic total occlusion. *Catheter Cardiovasc Interv* 2013; **82**:95–107.

16 Finci L, Meier B, Favre J, Righetti A, Rutishauser W. Long-term results of successful and failed angioplasty for chronic total coronary arterial occlusion. *Am J Cardiol* 1990; **66**:660–662.

17 Ivanhoe RJ, Weintraub WS, Douglas JS Jr, Lembo NJ, Furman M, Gershony G, *et al*. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Primary success, restenosis, and long-term clinical follow-up. *Circulation* 1992; **85**:106–115.

18 Sathe S, Alt C, Black A, Manolas E, Warren R, Valentine P. Initial and long-term results of percutaneous transluminal balloon angioplasty for chronic total occlusions: an analysis of 184 procedures. *Aust N Z J Med* 1994; **24**:277–281.

19 Angioi M, Danchin N, Juillière Y, Feldmann L, Berder V, Cuillière M, *et al*. Is percutaneous transluminal coronary angioplasty in chronic total coronary occlusion justified? Long term results in a series of 201 patients. *Arch Mal Coeur Vaiss* 1995; **88**:1383–1389.

20 Noguchi T, Miyazaki MS, Morii I, Daikoku S, Goto Y, Nonogi H. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Determinants of primary success and long-term clinical outcome. *Catheter Cardiovasc Interv* 2000; **49**:258–264.

21 Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, *et al*. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. *J Am Coll Cardiol* 2001; **38**:409–414.

22 Olivari Z, Rubartelli P, Piscione F, Ettori F, Fontanelli A, Salemme L, *et al*. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). *J Am Coll Cardiol* 2003; **41**:1672–1678.

23 Hoye A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992–2002. *Eur Heart J* 2005; **26**:2630–2636.

24 Arslan U, Balcioglu AS, Timurkaynak T, Cengel A. The clinical outcomes of percutaneous coronary intervention in chronic total coronary occlusion. *Int Heart J* 2006; **47**:811–819.

25 Drozd J, Wojcik J, Opalinska E, Zapolski T, Widomska-Czekajska T. Percutaneous angioplasty of chronically occluded coronary arteries: long-term clinical follow-up. *Kardiol Pol* 2006; **64**:667–673. discussion 74.

26 Aziz S, Stables RH, Grayson AD, Perry RA, Ramsdale DR. Percutaneous coronary intervention for chronic total occlusions: improved survival for patients with successful revascularization compared to a failed procedure. *Catheter Cardiovasc Interv* 2007; **70**:15–20.

27 Prasad A, Rihal CS, Lennon RJ, Wiste HJ, Singh M, Holmes DR Jr. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: a 25-year experience from the Mayo Clinic. *J Am Coll Cardiol* 2007; **49**:1611–1618.

28 de Labriolle A, Bonello L, Roy P, Lemesle G, Steinberg DH, Xue Z, *et al*. Comparison of safety, efficacy, and outcome of successful versus unsuccessful percutaneous coronary intervention in 'true' chronic total occlusions. *Am J Cardiol* 2008; **102**:1175–1181.

29 Valenti R, Migliorini A, Signorini U, Vergara R, Parodi G, Carrabba N, *et al*. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. *Eur Heart J* 2008; **29**:2336–2342.

30 Chen SL, Ye F, Zhang JJ, Lin S, Zhu ZS, Tian NL, *et al*. Clinical outcomes of percutaneous coronary intervention for chronic total occlusion lesions in remote hospitals without on-site surgical support. *Chin Med J (Engl)* 2009; **122**:2278–2285.

31 Yi XH, Han YL, Li Y, Wang SL, Jing QM, MA YY, *et al*. Long-term clinical outcomes of patients undergoing successful or failed percutaneous coronary intervention for chronic total occlusions of coronary arteries. *Zhonghua Xin Xue Guan Bing Za Zhi* 2009; **37**:773–776.

32 Lee SW, Lee JY, Park DW, Kim YH, Yun SC, Kim WJ, *et al*. Long-term clinical outcomes of successful versus unsuccessful revascularization with drug-eluting stents for true chronic total occlusion. *Catheter Cardiovasc Interv* 2011; **78**:346–353.

33 Mehran R, Claessen BE, Godino C, Dangas GD, Obunai K, Kanwal S, *et al*. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. *JACC Cardiovasc Interv* 2011; **4**:952–961.

34 Borgia F, Viceconte N, Ali O, Stuart-Buttle C, Saraswathyamma A, Parisi R, *et al*. Improved cardiac survival, freedom from MACE and angina-related quality of life after successful percutaneous recanalization of coronary artery chronic total occlusions. *Int J Cardiol* 2012; **161**:31–38.

35 Jolicoeur EM, Sketch MJ, Wojdyla DM, Jayaheri SP, Nosib S, Lokhnygina Y, *et al*. Percutaneous coronary interventions and cardiovascular outcomes for patients with chronic total occlusions. *Catheter Cardiovasc Interv* 2012; **79**:603–612.

36 Jones DA, Weerackody R, Rathod K, Behar J, Gallagher S, Knight CJ, *et al*. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovasc Interv* 2012; **5**:380–388.

37 Niccoli G, De Felice F, Belloni F, Fiorilli R, Cosentino N, Fracassi F, *et al*. Late (3 years) follow-up of successful versus unsuccessful revascularization in chronic total coronary occlusions treated by drug eluting stent. *Am J Cardiol* 2012; **110**:948–953.

38 Jaguszewski M, Targonski R, Fijalkowski M, Masiewicz E, Subaniewicz W, Templin C, *et al*. Recanalization of isolated chronic total occlusions in patients with stable angina. *Int J Cardiol* 2013; **167**:1542–1546.

39 Tanaka Y, Takeshita S, Takahashi S, Matsumi J, Mizuno S, Yamanaka F, *et al*. Comparison of short- and long-term outcomes of percutaneous coronary intervention for chronic total occlusions between patients aged $\geq$ 75 years and those aged <75 years. *Am J Cardiol* 2013; **112**:761–766.

40 Yamamoto E, Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Ono K, *et al*. Long-term outcomes after percutaneous coronary intervention for chronic total occlusion (from the CREDO-Kyoto registry cohort-2). *Am J Cardiol* 2013; **112**:767–774.

41 Yang ZK, Zhang RY, Hu J, Zhang Q, Ding FH, Shen WF. Impact of successful staged revascularization of a chronic total occlusion in the non-infarct-related artery on long-term outcome in patients with acute ST-segment elevation myocardial infarction. *Int J Cardiol* 2013; **165**:76–79.

42 Jaguszewski M, Ciecwierz D, Gilis-Malinowska N, Fijalkowski N, Gilis-Malinowska N, Gilis-Malinowska N, *et al*. Successful versus unsuccessful antegrade recanalization of single chronic coronary occlusion: eight-year experience and outcomes by a propensity score ascertainment. *Catheter Cardiovasc Interv* 2015; **86**:E49–E57.

43 Lee PH, Lee SW, Park HS, Kang SH, Bae BJ, Chang M, *et al*. Successful recanalization of native coronary chronic total occlusion is not associated with improved long-term survival. *JACC Cardiovasc Interv* 2016; **9**:530–538.

44 Brilakis ES, Karmpaliotis D, Werner GS, Spratt JC, Uretsky BF, Luna M, Banerjee S. Developments in coronary chronic total occlusion percutaneous coronary interventions: 2014 state-of-the-art update. *J Invasive Cardiol* 2014; **26**:261–266.

45 Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995; **25**:333–341.

46 Wijeysundera HC, Norris C, Fefer P, Galbraith PD, Knudtson ML, Wolff R, *et al*. Relationship between initial treatment strategy and quality of life in patients with coronary chronic total occlusions. *EuroIntervention* 2014; **9**:1165–1172.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

47 Grantham JA, Jones PG, Cannon L, Spertus JA. Quantifying the early health status benefits of successful chronic total occlusion recanalization: results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) Trial. *Circ Cardiovasc Qual Outcomes* 2010; **3**:284–290.

48 Warren RJ, Black AJ, Valentine PA, Manolas EG, Hunt D. Coronary angioplasty for chronic total occlusion reduces the need for subsequent coronary bypass surgery. *Am Heart J* 1990; **120**:270–274.

49 Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J* 2010; **160**:179–187.

50 Kirschbaum SW, Baks T, van den Ent M, Sianos G, Krestin GP, Serruys PW, *et al*. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. *Am J Cardiol* 2008; **101**:179–185.

51 Brilakis ES, Grantham JA, Rinfret S, Wyman RM, Burke MN, Karmpaliotis D, *et al*. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv* 2012; **5**:367–379.

52 Bainey KR, Welsh RC, Toklu B, Bangalore S. Complete vs culprit-only percutaneous coronary intervention in STEMI with multivessel disease: a meta-analysis and trial sequential analysis of randomized trials. *Can J Cardiol* 2016; **32**:1542–1551.

53 Hassan A, ElGuindy A, Antoniucci D. Culprit lesion-only versus complete revascularization in patients with STEMI: Lessons learned from PRAMI, CvLPRIT, and DANAMI-3 PRIMULTI. *Glob Cardiol Sci Pract* 2015; **2015**:60.

54 van der Schaaf RJ, Timmer JR, Ottervanger JP, Hoorntje JC, de Boer MJ, Suryapranata H, *et al*. Long-term impact of multivessel disease on cause-specific mortality after ST elevation myocardial infarction treated with reperfusion therapy. *Heart* 2006; **92**:1760–1763.

55 Claessen BE, Dangas GD, Weisz G, Witzenbichler B, Guagliumi G, Möckel M, *et al*. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J* 2012; **33**:768–775.

56 Henriques JP, Hoebers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, *et al*. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE Trial. *J Am Coll Cardiol* 2016; **68**:1622–1632.

57 Christopoulos G, Karmpaliotis D, Alaswad K, Yeh RW, Jaffer FA, Wyman RM, *et al*. Application and outcomes of a hybrid approach to chronic total occlusion percutaneous coronary intervention in a contemporary multicenter US registry. *Int J Cardiol* 2015; **198**:222–228.

58 Brilakis ES, Abdullah SM, Banerjee S. Who should undergo chronic total occlusion percutaneous coronary intervention? The EXPLORation continues. *J Am Coll Cardiol* 2016; **68**:1633–1636.

59 Garcia S, Sandoval Y, Roukoz H, Adabag S, Canoniero M, Yannopoulos D, Brilakis ES. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol* 2013; **62**:1421–1431.

60 Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, *et al*. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**:961–972.

61 Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Ståhle E, *et al*. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011; **32**:2125–2134.

62 Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, *et al*. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 2013; **128**:141–151.

63 Hannan EL, Racz M, Holmes DR, King SB 3rd, Walford G, Ambrose JA, *et al*. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 2006; **113**:2406–2412.

64 Colombo A, Mikhail GW, Michev I, Iakovou I, Airoldi F, Chieffo A, *et al*. Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. *Catheter Cardiovasc Interv* 2005; **64**:407–411. discussion 12.

65 Saito S. Different strategies of retrograde approach in coronary angioplasty for chronic total occlusion. *Catheter Cardiovasc Interv* 2008; **71**:8–19.

66 Sianos G, Konstantinidis NV, Di Mario C, Karvounis H. Theory and practical based approach to chronic total occlusions. *BMC Cardiovasc Disord* 2016; **16**:33.

67 Whitlow PL, Burke MN, Lombardi WL, Wyman RM, Moses JW, Brilakis ES, *et al*. Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FAST-CTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. *JACC Cardiovasc Interv* 2012; **5**:393–401.

68 Valenti R, Vergara R, Migliorini A, Parodi G, Carrabba N, Cerisano G, *et al*. Predictors of reocclusion after successful drug-eluting stent-supported percutaneous coronary intervention of chronic total occlusion. *J Am Coll Cardiol* 2013; **61**:545–550.

69 Brilakis ES, Grantham JA, Thompson CA, DeMartini TJ, Parsad A, Sandhu GS, *et al*. The retrograde approach to coronary artery chronic total occlusions: a practical approach. *Catheter Cardiovasc Interv* 2012; **79**:3–19.

70 Joyal D, Thompson CA, Grantham JA, Buller CE, Rinfret S. The retrograde technique for recanalization of chronic total occlusions: a step-by-step approach. *JACC Cardiovasc Interv* 2012; **5**:1–11.

71 Rinfret S, Joyal D, Spratt JC, Buller CE. Chronic total occlusion percutaneous coronary intervention case selection and techniques for the antegrade-only operator. *Catheter Cardiovasc Interv* 2015; **85**:408–415.

72 Vo MN, McCabe JM, Lombardi WL, Ducas J, Ravandi A, Brilakis ES. Adoption of the hybrid CTO approach by a single non-CTO operator: procedural and clinical outcomes. *J Invasive Cardiol* 2015; **27**:139–144.

73 Buller CE, Dzavik V, Carere RG, Mancini GB, Barbeau G, Lazzam C, *et al*. Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of Canada (TOSCA). *Circulation* 1999; **100**:236–242.

74 Rubartelli P, Niccoli L, Verna E, Giachero C, Zimarino M, Fontanelli A, *et al*. Stent implantation versus balloon angioplasty in chronic coronary occlusions: results from the GISSOC trial. Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche. *J Am Coll Cardiol* 1998; **32**:90–96.

75 Colmenarez HJ, Escaned J, Fernández C, Lobo L, Cano S, del Angel JG, *et al*. Efficacy and safety of drug-eluting stents in chronic total coronary occlusion recanalization: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; **55**:1854–1866.

76 Saeed B, Kandzari DE, Agostoni P, Lombardi WL, Rangan BV, Banerjee S, Brilakis ES. Use of drug-eluting stents for chronic total occlusions: a systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2011; **77**:315–332.

77 Suttorp MJ, Laarman GJ, Rahel BM, Kelder JC, Bosschaert MA, Ten Berg JM, *et al*. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation* 2006; **114**:921–928.

78 Moreno R, Garcia E, Teles R, Rumoroso JR, Cyrne Carvalho H, Goicolea FJ, *et al*. Randomized comparison of sirolimus-eluting and everolimus-eluting coronary stents in the treatment of total coronary occlusions: results from the chronic coronary occlusion treated by everolimus-eluting stent randomized trial. *Circ Cardiovasc Interv* 2013; **6**:21–28.

79 Kandzari DE, Kini AS, Karmpaliotis D, Moses JW, Tummala PE, Grantham JA, *et al*. Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization: Results From the EXPERT CTO Multicenter Trial (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions). *JACC Cardiovasc Interv* 2015; **8**:761–769.

80 Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, *et al*. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation* 2009; **120**:391–399.

81 Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motto T, *et al*. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004; **109**:701–705.

82 Teeuwen K, Adriaenssens T, Van den Branden BJ, Henrigues JP, Van der Schaaf RJ, Koolen JJ, *et al*. A randomized multicenter comparison of hybrid sirolimus-eluting stents with bioresorbable polymer versus everolimus-eluting stents with durable polymer in total coronary occlusion: rationale and design of the Primary Stenting of Occluded Native Coronary Arteries IV study. *Trials* 2012; **13**:240.

83 Windecker S, Haude M, Neumann FJ, Stangl K, Witzenbichler B, Slagboom T, *et al*. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW-II trial. *Circ Cardiovasc Interv* 2015; **8**:e001441.

84 Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, *et al*. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. *N Engl J Med* 2015; **373**:1905–1915.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

85 Serruys PW, Chevalier B, Dudek D, Ceguier A, Carrié D, Iniquez A, *et al*. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. *Lancet* 2015; **385**:43–54.
86 Gao R, Yang Y, Han Y, Huo Y, Chen J, Yu B, *et al*. Bioresorbable vascular scaffolds versus metallic stents in patients with coronary artery disease: ABSORB China trial. *J Am Coll Cardiol* 2015; **66**:2298–2309.
87 Kimura T, Kozuma K, Tanabe K, Nakamura S, Yamane M, Muramatsu T, *et al*. A randomized trial evaluating everolimus-eluting Absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan. *Eur Heart J* 2015; **36**:3332–3342.
88 Azzalini L, Giustino G, Ojeda S, Serra A, La Manna A, Ly HQ, *et al*. Procedural and long-term outcomes of bioresorbable scaffolds versus drug-eluting stents in chronic total occlusions: The BONITO Registry (Bioresorbable Scaffolds Versus Drug-Eluting Stents in Chronic Total Occlusions). *Circ Cardiovasc Interv* 2016; **9**:e004284.
89 Serruys PW, Chevalier B, Sotomi Y, Cequier A, Carrié D, Piek JJ, *et al*. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet* 2016; **388**:2479–2491.
90 Buller CE. TOSCA-5: a prospective, randomized trial evaluating collagenase infusion in patients with coronary artery chronic total occlusions. TCT Scientific Sessions; 2016.
91 Tsuchikane E. Initial experience of 'Plasma Wire' for coronary CTOs: results of first in human study. TCTAP 2016; 2016.
92 Hoye A. Management of chronic total occlusion by percutaneous coronary intervention. *Heart* 2012; **98**:822–828.
93 Thompson CA, Jayne JE, Robb JF, Friedman BJ, Kaplan AV, Hettleman BD, *et al*. Retrograde techniques and the impact of operator volume on percutaneous intervention for coronary chronic total occlusions an early U.S. experience. *JACC Cardiovasc Interv* 2009; **2**:834–842.
94 Badheka AO, Patel NJ, Grover P, Singh V, Patel N, Arora S, *et al*. Impact of annual operator and institutional volume on percutaneous coronary intervention outcomes: a 5-year United States experience (2005–2009). *Circulation* 2014; **130**:1392–1406.
95 Gada H, Whitlow PL, Marwick TH. Establishing the cost-effectiveness of percutaneous coronary intervention for chronic total occlusion in stable angina: a decision-analytic model. *Heart* 2012; **98**:1790–1797.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.