Developments in Coronary Chronic Total Occlusion Percutaneous Coronary Interventions: 2014 State-Of-The-Art Update

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ABSTRACT: Percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) is a rapidly developing field. In the present review, we summarize the most important CTO PCI related literature published in 2013.

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Percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) is a rapidly developing field, as evidenced by the publication of two CTO books during 2013: (1) Chronic Total Occlusion: A Guide to Recanalization (R-Waksman and S. Saito, John Wiley & Sons, Oxford); and (2) Manual of Chronic Total Occlusion Interventions: a Step-By-Step Approach (ES Brilakis, Elsevier).

In the present review, we sought to summarize the most important CTO-PCI related literature published in 2013.

Prevalence and indications. Jeroudi et al reviewed 1699 consecutive patients who underwent coronary angiography at a Veterans Affairs hospital and reported that the prevalence of CTO among coronary artery disease (CAD) patients with and without prior coronary artery bypass graft (CABG) surgery was 89% and 31%, respectively,1 higher than reported in a recent large Canadian registry (54% and 18.4%, respectively),2 but similar to other prior studies.3,4

Several studies reported the adverse impact of incomplete revascularization on subsequent clinical outcomes.5,6 In the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial, angiographic complete revascularization was achieved in only 52.8% of the PCI patients. Presence of a total occlusion was the strongest independent predictor of incomplete revascularization after PCI (hazard ratio [HR], 2.70; 95% confidence interval [CI], 1.98-3.67; P<.001).

However, CTO PCI success was only 49.4% in the SYNTAX trial, likely reflecting the limited experience in CTO PCI of many participating centers and the limited availability of CTO crossing techniques (patients were enrolled between 2005 and 2007, before the development of retrograde7,8 and limited antegrade dissection/reentry9,10 techniques).

The lack of randomized-controlled trials comparing CTO PCI with optimal medical therapy led to initiation of two large randomized-controlled clinical trials: the Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO) trial (NCT01078051) and the European Study on the Utilization of Revascularization versus Optimal Medical Therapy for the Treatment of Chronic Total Occlusion (EURO-CTO) trial (NCT01760083). DECISION-CTO is assessing whether, compared to optimal medical therapy, CTO PCI will reduce the composite endpoint of all-cause death, myocardial infarction (MI), stroke, and any revascularization at 3 years after randomization. EURO-CTO is examining the hypothesis that PCI with implantation of the Biosensors biolimus-eluting stent plus optimal medical therapy will be superior to optimal medical therapy alone in improving health status at 12-month follow-up and will be non-inferior with respect to the composite of all-cause death/non-fatal MI at 36-month follow-up in patients with a CTO in an epicardial coronary artery >2.5 mm in diameter and chronic stable angina with evidence of ischemia and viability in the territory subtended by the CTO. Results of these studies are anticipated in 2018.

Pathology of CTOs. Sakakura et al performed an autopsy study of 95 CTO lesions from 82 patients.11 The main findings were that negative remodeling of the CTO body was frequent and its frequency increased with increasing CTO duration.11 Furthermore, microchannels (>200 µm in diameter) were very rare, in contrast to previous pathology studies, which included fewer subjects and often subtotal occlusions. Hence, the current thinking that soft polymer jacketed guidewires, such as the Fielder XT wire by Asahi Intecc, are successful due to passage through microchannels is not corroborated. Another finding that supports the increasing use of the retrograde approach in CTO PCI was the more frequent tapering of the distal cap as compared to the proximal cap (79% vs 50%; P<.001).

Procedural planning. A simple way to assess the lesion-specific difficulty of CTO PCI is using the Multicenter CTO Registry of Japan (J-CTO) score. The score is determined by assigning 1 point to each of 5 variables (previously failed lesion, blunt proximal cap, CTO calcification, severe vessel tortuosity, and occlusion length ≥20 mm), thereby allowing patient classification into 4 groups: easy
Antegrade dissection and reentry. Wilson et al reported 87% technical success (27 of 31 cases) in CTOs due to in-stent restenosis using the CrossBoss catheter (Boston Scientific); the CrossBoss catheter crossed into the distal true lumen in most cases.30 The blunt tip of the CrossBoss catheter can often prevent wire passage outside stent struts, facilitating CTO crossing.

Although the Stingray balloon (Boston Scientific) is considered to require a guide catheter at least 6 Fr in diameter, Wu and Ikari reported for the first time successful CTO PCI through a 5 Fr Ikari left 3.5 transradial guide catheter.31 Takahashi et al reported 2 cases in which an IVUS catheter was inserted into the cardiac vein parallel to the target artery to facilitate antegrade wire crossing (Figure 1).32

Valenti et al reported reocclusion in 16 of 28 patients in whom CTO recanalization was achieved using the Subintimal Tracking and Reentry (STAR) technique.33 Given these poor long-term outcomes, the STAR technique should only be used as a “last resort,” after failure of other techniques and devices to cross the CTO.30

Godino et al reported a case of residual long coronary dissection left unstented after guided STAR in a right coronary artery that had resolved at 2-month follow-up exam, suggesting that sometimes conservative management may be appropriate in areas of coronary dissection, especially if Thrombolysis in Myocardial Infarction (TIMI)-3 flow is present in spite of the dissection and if the dissection persists into distal branches.34

Mogabgab et al reported the short- and long-term outcomes in patients in whom the CrossBoss catheter and Stingray system (Boston Scientific) were used (n = 60) and compared them to patients treated with other techniques (n = 110).35 During a median follow-up of 1.81 years, the CrossBoss/Stingray group had no difference in target lesion revascularization (40.9% vs 29.6%; P = .13) or major adverse clinical events (40.3% vs 35.2%; P = .42) in spite of its use in higher complexity cases.35

Retrograde approach. Several enhancements of the retrograde approach were published in 2013. Mozid et al reported use of a Guideliner catheter to perform reverse controlled antegrade and retrograde tracking and dissection (reverse CART) in a patient in whom the retrograde microcatheter was not long enough to reach the antegrade-guide catheter.36 The Guideliner catheter was advanced through the antegrade guide catheter over the retrograde microcatheter (“capture technique”), allowing wire externalization and successful completion of the case.36 Dai et al performed IVUS-guided reverse CART in 49 patients.37 IVUS identified that initially 61.7% of retrograde wires were located in the intimal space, and 59.5% of antegrade wires were located in subintimal space, leading to excellent technical (95.9%) and procedural success (93.9%).37 Kim et al reported 20 successful retrograde CTO PCI cases in which the rendezvous method was used instead of wire externalization.38 In the rendezvous method, after a retrograde guidewire has successfully crossed into the proximal true lumen, a microcatheter is then advanced into the antegrade guiding catheter over the retrograde guidewire, where it is aligned with an antegrade microcatheter (usually at a point of aortic curvature), followed by insertion of an antegrade guidewire into the retrograde microcatheter and advancement distal to the CTO. Whether the rendezvous methods will gain more popularity, however, remains unclear since wire externalization provides superior support for equipment delivery and can easily be accomplished with contemporary long guidewires, such as the Viper.
Figure 1. (A) Chronic total occlusion of the middle left circumflex artery (LCX) (solid arrow) before transvenous intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI). (B) Final angiography after transvenous IVUS-guided PCI. (C) Angiographic image obtained during transvenous IVUS-guided PCI. The solid arrow indicates a guidewire in the occluded site of the LCX. The dashed arrow indicates an IVUS catheter in the cardiac vein, with (D) corresponding IVUS image. A guidewire can be seen in the center of the occluded site of the LCX (solid arrow). The dashed arrow indicates an IVUS catheter in the cardiac vein. Reproduced with permission from HMP Communications.12

RG3, and R350. Similar to prior reports,90,91 Uehara et al reported retrograde stent delivery through an epicardial collateral after failure of antegrade stent delivery.114 The retrograde approach was used as a bail-out procedure after antegrade crossing failed during primary PCI for ST-segment elevation acute MI, although this should only be performed as a last resort when all other approaches fail.114

Tsuchikane et al reported 84.8% technical success and 83.8% clinical success rates in 801 patients undergoing retrograde CTO PCI between 2009 and 2010 in a Japanese multicenter registry. The use of channel dilators increased in 2010 compared to 2009 (95.3% vs 36%; P<.001), as did the use of the reverse CART technique (41.9 vs 66.5%).114 Finally, Lo et al reported higher incidence of peri-procedural myocardial injury (>3x the upper limit of normal increase in CK-MB levels) in patients treated with the retrograde vs antegrade approach (13.8% vs 6.7%; P=.04).114

Procedural outcomes. A multicenter United States (US) CTO registry of 1361 consecutive native coronary artery CTO PCIs performed at 3 US institutions from January 2006 to November 2011 showed 85.5% and 84.2% technical and procedural success rates, respectively, with a major complication rate of 1.8%.115 The retrograde approach was used in 34% of all procedures and its use increased over time.115

De Felice et al reported that in patients undergoing rescue PCI, presence of a CTO was associated with higher 1-year mortality (HR, 3.4; 95% CI, 1.6-7.1; P=.001).116 Similar findings were reported by Hoebers in ST-segment elevation acute MI patients with and without cardiogenic shock117 and by Gierlotka et al in patients with non-ST segment elevation acute MI.118 Yang et al achieved successful CTO PCI in 64 of 136 patients who had presented with ST-segment acute MI within the past 7-10 days. During 2-year follow-up, cardiac mortality was lower (8.0% vs 20.4%; P=.04) and major adverse event-free survival was higher (78.2% vs 61.2%; P=.04) in patients with successful recanalization vs those with failed recanalization of a CTO in the non-infarct related artery.119

In a single-center experience, Syrseloudis et al reported an increase in attempted CTO lesion complexity over a 10-year period, which may explain the relatively modest improvement in overall procedural success rates, whereas success for each J-CTO score category significantly increased over time.120

Several CTO PCI meta-analyses were published in 2013. Khan et al reported that compared to failed CTO PCI, successful recanalization of a CTO resulted in improved all-cause mortality (relative risk [RR], 0.54; 95% CI, 0.45-0.65; P<.001), lower rates of major adverse cardiac events (RR, 0.70; 95% CI, 0.60-0.83; P<.001) and reduced need for subsequent bypass surgery (RR, 0.25; 95% CI, 0.21-0.30; P<.001).121 Similarly, Pancholy et al reported that successful CTO PCI using a predominantly stent-based strategy was associated with a significant reduction in short- and long-term mortality compared to unsuccessful CTO PCI.122

Godino et al analyzed 1345 consecutive patients who underwent CTO PCI between 1998 and 2008 and found that non-revascularized patients (either because of CTO PCI failure or because CTO PCI was not attempted) had a significantly higher 4-year cardiac mortality (8.5% vs 2.5%; P<.001) and sudden cardiac death (2.7% vs 0.5%; P=.04) compared to revascularized patients.123 The most significant independent predictors of cardiac death were: chronic renal failure (HR, 6.0; 95% CI, 2.66-13.80), low left ventricular ejection fraction (HR, 5.7; 95% CI, 2.84-11.58), and insulin-dependent diabetes mellitus (HR, 4.6; 95% CI, 1.96-10.97).123

“Balloon uncrossable” CTOs. Balloon uncrossable CTOs are lesions that cannot be crossed with a balloon after successful guidewire crossing.29 These lesions are usually approached with a combination of lesion modification techniques (such as use of microcatheters and multiple balloons) and increased guide support (such as use of anchoring techniques and use of guide catheter extensions). Four 2013 publications provided novel insights in this area. Hu et al described the “wire-cutting” technique, in which 2 guidewires (A and B) are inserted into the distal true lumen, followed
by advancing a balloon over guidewire A to the site of the occlusion abutting the proximal cap. The balloon is then inflated, pressing guidewire B between the balloon and the proximal cap, followed by rapid withdrawal of guidewire B, which "cuts" the proximal cap, facilitating balloon crossing. The weakness of this technique is the need to pass 2 wires into the distal true lumen. Michael et al described the "subintimal distal anchor" technique, in which a second coronary guidewire is advanced through the subintimal space distal to the occlusion site with a balloon subsequently inflated to "anchor" the guidewire that has crossed into the distal true lumen, thus facilitating balloon crossing on the initial wire. Kovacic et al reported that use of the Guideliner guidewire catheter extension (Vascular Solutions) was successful in 24 of 28 (85.7%) balloon uncrossable CTO cases. Finally, Fernandez et al reported successful crossing in 13 of 16 (81%) balloon uncrossable CTOs using excimer laser, without any significant complications; in some cases, procedural success was achieved with rotational atherectomy following laser application.

**Stents in CTO PCI.** In the Chronic Coronary Occlusion Treated by Everolimus-Eluting Stent (CIBELES) trial, 207 patients (79.7% of whom had CTO duration >3 months) were randomized to sirolimus-eluting stent (SES) or everolimus-eluting stent (EES). Follow-up coronary angiography performed at 9 months showed similar late loss with SES and EES (0.29 ± 0.60 vs 0.13 ± 0.69 mm, respectively; P = .01 for non-inferiority) and similar clinical outcomes at 12 months, with a trend for lower stent thrombosis risk in the EES group (3% vs 0%; P = .08).

Wöhler and Werner compared 48 patients undergoing CTO PCI with bare-metal stents followed by inflation of a paclitaxel-coated balloon to 48 matched historical treatment with a paclitaxel-eluting stent. Patients treated with BMS and drug-eluting balloons had numerically higher but statistically similar loss and binary restenosis and similarly low rates of target vessel revascularization and stent thrombosis. Hence, the BMS and drug-eluting balloon combination does not appear to be an attractive CTO treatment option.

Valenti et al reviewed the outcomes of 802 consecutive patients who underwent successful CTO PCI at a single center between 2003 and 2010. The angiographic follow-up rate was 82%. Reocclusion rate was 7.5%, whereas binary restenosis (>50%) or reocclusion rate was 20%. EESs were associated with a significantly lower reocclusion rate vs other drug-eluting stents (3.0% vs 10.1%; P = .001). As described above, a successful STAR technique was associated with a 57% reocclusion rate. By multivariable analysis, the subintimal tracking and re-entry technique (OR, 29.5; P = .001) and EESs (OR, 0.22; P = .001) were independently related to the risk of reocclusion.

A systematic review of DES implantation in CTOs suggested that second-generation DESs provide improved deliverability and enhanced efficacy and safety; while bioabsorbable stents are likely to become the next major advancement in the field. La Manna et al reported the first case of multiple everolimus-eluting bioresorbable vascular scaffolds (BVS; Absorb, Abbott Vascular) implantation in the right coronary artery, which he named "full polymer jacket." Possible advantages may include restoration of vessel vasomotion, while minimizing the risk for very late stent thrombosis. Yet, questions remain about the impact of BVS scaffolds in longer stented segments, particularly where subintimal tracking techniques have been employed.

Optical coherence tomography may be useful in limiting the stent length by determining whether a dissection or coronary lesion is present distal to the CTO segment.

**Challenging subgroups.** Patients with prior CABG who undergo CTO PCI have lower success rates compared to patients without prior CABG. Among 1363 patients in a multicenter CTO registry, 37% had prior CABG and those patients were older, had more comorbidities, were treated more frequently with the retrograde approach (46.7% vs 27.1%; P = .001), and had lower technical success rates (79.7% vs 88.3%; P = .02), but similar major complication rates (2.1% vs. 1.5%, P = .39) compared to patients without prior CABG. Sakakura et al reported that CTOs in CABG patients are characterized by severe calcification and moderate negative remodeling, helping to explain in part the lower CTO PCI success rates in these patients, which may also be influenced by surgically induced distortion of anatomy. Although PCI of saphenous vein graft (SVG) CTOs has received a class III recommendation in the American College of Cardiology/American Heart Association PCI guidelines because of high restenosis rates, Garg et al reported a 79% technical success rate in 28 SVG CTO lesions, with significant improvement in angina among successful cases and similar incidence of adverse events during long-term follow-up. Hence, although PCI of a native vessel is preferable to SVG PCI, SVG CTO PCI could be considered in highly selected patients where revascularization to the ischemic territory is appropriate and the native CTO is technically difficult to recanalize. In some cases, a diseased SVG can act as a retrograde conduit for performing native coronary artery CTO PCI.

**Complications of CTO PCI.** Patel et al performed a weighted meta-analysis of 65 studies with 18,061 patients and 18,941 target CTO vessels. Pooled estimates of outcomes were as follows: angiographic success 77% (95% CI, 74.3%-79.6%); death 0.2% (95% CI, 0.1%-0.3%); emergent CABG surgery 0.1% (95% CI, 0.0%-0.2%); stroke <0.01% (95% CI, 0.0%-0.1%); MI 2.5% (95% CI, 1.9%-3.0%); Q-wave MI 0.2% (95% CI, 0.1%-0.3%); coronary perforation 2.9% (95% CI, 2.2%-3.6%); tamponade 0.3% (95% CI, 0.2%-0.5%); and contrast nephropathy 3.8% (95% CI, 2.4%-5.3%). Compared with successful procedures, unsuccessful procedures had higher rates of death (0.42% vs 1.54%; P = .001), perforation (3.85% vs 17.03%; P = .001), and tamponade (0% vs 1.65%; P < .001). The risk for complications...
decreased, whereas procedural success increased over time (Figure 2). However, a shortcoming of this meta-analysis is the fact that radiation risks and contrast-induced nephropathy were not closely monitored in many of the included reports.

Excessive radiation exposure remains a potential concern for CTO PCI, as for all medical procedures involving radiation exposure. Godino et al estimated that after CTO PCI, the lifetime attributable risk (LAR) of lung and bone marrow cancer was up to 18/100,000 persons exposed and up to 3.5/100,000 persons exposed, respectively.70 While measures to reduce patient and operator exposure should be employed, it is worth considering that such estimates of increased cancer risk are based on linear approximations of historical exposure and as such are impossible to validate.

Lo et al performed systematic cardiac biomarker measurement after CTO PCI and reported that the incidence of peri-procedural myocardial injury was higher in patients treated with a primarily retrograde approach compared to an antegrade approach (13.8% vs 6.7%; $P=0.04$).44 Bhattacharyya et al reported formation of a ventricular septal hematoma after retrograde crossing attempts through septal collaterals,71 which was treated conservatively and had almost completely resolved by 10 months post procedure.72 Aggarwal et al described left atrial hematoma formation due to perforation of an epicardial collateral from the circumflex to the right posterior descending artery during retrograde CTO PCI.72 The hematoma extended into the pleural space causing a pleural effusion; impeded filling of the left atrium resulting in “functional” mitral stenosis and compressed the right inferior pulmonary vein, resulting in localized pulmonary edema. A chest tube was placed, which stabilized the patient; this was followed by gradual resolution of the hematoma without surgical intervention, although in similar cases emergent cardiac surgery or CT-guided aspiration may often be required to restore antegrade blood flow. Bagur et al reported use of contrast echocardiography in 4 cases of coronary perforation without overt signs of cardiac tamponade to confirm or exclude active bleeding into the pericardial space when not otherwise visible by conventional imaging measures.73 Patel et al reported a case of inadvertent stent deployment into the subintimal space, without subsequent luminal reentry, leading to ST-segment elevation and no distal outflow.74 A polymer-jacketed guidewire was used to reenter the distal branches of the right coronary artery, restoring antegrade flow and resulting in resolution of ST-segment changes.

Other. Karmpaliotis et al reported their experience initiating a CTO PCI program. After implementation of quality and performance guidelines, CTO PCI was performed with high success (85.6%) and low complication rates.75 Although procedural and total cost per patient were significantly higher among the CTO cohort, the overall contribution margin was similar with non-CTO PCI ($5173±12,052 vs $5730±8958; P=0.58$).75 Guo performed virtual histology IVUS in 50 CTO lesions after guidewire crossing and found fibroatheroma in 84% of lesions, suggesting that most CTO lesions develop from acute coronary syndrome and thrombosis and the minority from atherosclerosis progression.76 Sobajima et al reported that repeated supra therapy improved myocardial perfusion in patients with coronary CTOs.77 Choi performed magnetic resonance imaging in 170 consecutive patients with coronary CTO, showing evidence of prior MI by late gadolinium enhancement in 86%, a much higher proportion that previously recognized, with only 25% of patients showing Q-waves on their electrocardiogram.78

In summary, several developments in CTO PCI appeared during 2013, enhancing our ability to understand and optimally treat these challenging lesions.

References

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