Expert Review of Medical Devices

ISSN: 1743-4440 (Print) 1745-2422 (Online) Journal homepage: https://www.tandfonline.com/loi/ierd20

Current approaches for treatment of coronary chronic occlusions

Giulia Iannaccone, Paola Scarparo, Jeroen Wilschut, Joost Daemen, Wijnand Den Dekker, Peter De Jaegere, Felix Zijlstra, Nicolas M. Van Mieghem & Roberto Diletti

To cite this article: Giulia Iannaccone, Paola Scarparo, Jeroen Wilschut, Joost Daemen, Wijnand Den Dekker, Peter De Jaegere, Felix Zijlstra, Nicolas M. Van Mieghem & Roberto Diletti (2019) Current approaches for treatment of coronary chronic occlusions, Expert Review of Medical Devices, 16:11, 941-954, DOI: 10.1080/17434440.2019.1676729

To link to this article: https://doi.org/10.1080/17434440.2019.1676729

Accepted author version posted online: 09 Oct 2019.
Published online: 21 Oct 2019.

EXPERT REVIEW OF MEDICAL DEVICES
2019, VOL. 16, NO. 11, 941–954
https://doi.org/10.1080/17434440.2019.1676729

REVIEW

OPEN ACCESS Check for updates

Current approaches for treatment of coronary chronic occlusions

Giulia Iannaccone, Paola Scarparo, Jeroen Wilschut, Joost Daemen, Wijnand Den Dekker, Peter De Jaegere, Felix Zijlstra, Nicolas M. Van Mieghem and Roberto Diletti

Department of Interventional Cardiology, Thoraxcenter, Erasmus University Medical Centre, Rotterdam, The Netherlands

ABSTRACT

Introduction: Coronary chronic total occlusions (CTO) represent a challenging subset in interventional cardiology.

Areas covered: During the last decade, improvements in materials, techniques, and meticulous pre-procedural lesion assessment have increased the success rate in CTO lesions. Several scores have been developed to address overall lesion evaluation and help select the most appropriate treatment strategy. In addition, specific algorithms such as the hybrid algorithm have been introduced to provide a framework for CTO operators and a rapid management of the various challenging aspects of the procedure. The hybrid approach requires operator's ability to switch from one treatment strategy to another when the first one appears to be unsuccessful. Adequate training and operators' experience remain crucial to improve the likelihood of success.

Expert opinion: The aim of this review is to provide insights and guidance for operators on current approaches for treatment of CTO and complication management.

ARTICLE HISTORY
Received 7 July 2018
Accepted 2 October 2019

KEYWORDS
Chronic total occlusions; current approaches; complications management; hybrid algorithm; percutaneous coronary interventions

1. Introduction

Chronic total occlusions (CTOs) are coronary segments occluded for more than three months with TIMI grade flow 0 [1]. CTO remains one of the most challenging subsets for the interventional community and a constant effort has been made to develop dedicated tools and to improve techniques [2,3]. Such continuous research translated into a high success rate in experienced centers with a relevant reduction in the occurrence of complications [4,5].

However, the optimal selection of patients and indication for such procedures remain a subject of debate. Observational data reported clinical benefit and improvement in quality of life (QOL) associated with CTO treatment [6–9]. In addition a recent meta-analysis showed improved survival in patient with a successfully treated CTO, due to better left ventricular function and remodeling [10].

On the other hand, two long awaited randomized trials the EUROCTO trial and the DECISION-CTO trial reported an improvement in angina frequency with a benefit in terms of QOL in patients with CTO percutaneous coronary intervention (PCI) as compared with optimal medical therapy (OMT) alone, but no improvements in terms of overall mortality.

The latest European guidelines on myocardial revascularization [11]** give a class IIa (Level of evidence B) recommendation for CTO PCI, in particular in patients with expected ischemia reduction in a corresponding myocardial territory and/or angina relief, and suitable anatomy when performed by operators with appropriate expertise. A retrograde approach via collateral vessels is regarded as offering additional possibility of success after failure of antegrade crossing and especially for right coronary artery and left anterior descending (LAD) artery occlusions (Class IIb, Level of evidence C). In addition, expert consensus documents have been produced on appropriateness of CTO PCI to guide physicians in the decision making process while selecting patients [12]**.

Once the patient has been properly evaluated and accepted for CTO PCI, operators may face a complex intervention requiring the knowledge of several techniques and a large armamentarium of dedicated materials to maximize the chances of success. As underlined in the EuroCTO consensus document of 2012, the 'right operator choice' is of utmost importance, since experience and competence are directly related to procedure success. Moreover, the art of 'knowing when to stop' should characterize CTO-PCI operators, as they are required to be able to recognize the moment to abandon the attempt of revascularization before major complications occur [1].

With the present review, we aim at providing guidance and insights on current technical approaches and strategies for treatment of coronary CTOs and the management of possible complications.

2. The patient with a coronary chronic total occlusion

CTOs are observed in up to one third of patients undergoing a non-emergent coronary angiography, while in patients admitted for acute myocardial infarction (MI), CTO in a non-infarct related artery (IRA) is reported in 10–15% [13–16]. Patients with CTOs often presented an impaired left ventricular function, prior MI, coronary artery bypass grafting (CABG),

CONTACT Roberto Diletti r.diletti@erasmusmc.nl Interventional Cardiology, Thoraxcenter, Erasmus MC, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands

Article highlights

- Percutaneous revascularization of CTOs should be considered in patients with angina resistant to optimal medical therapy or with a large area of documented ischemia in the territory of the occluded vessel.
- Operator experience strongly influences success rates.
- The art of "knowing when to stop" is the key issue to avoid major complications.
- Adequately powered, well designed, randomized trials are needed to elucidate further benefit from CTO PCI.

and a high rate of comorbidity, such as diabetes mellitus and chronic kidney disease [13,14,17]. The presence of a CTO could also increase the incidence of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest and in patients with a CTO in IRA [18–20].

The real prevalence of CTOs among the general population remains difficult to assess, given the presence of well-developed collaterals that can mitigate symptoms [21].

3. Appropriateness of percutaneous revascularization

Patients with coronary CTOs could be potentially treated with OMT, or revascularization performed with either PCI or CABG. Patients with a CTO and single vessel disease could benefit in an early stage from OMT, as PCI never showed a reduction in the risk of cardiac death and major adverse cardiovascular events (MACE) in patients with low APPROACH and SYNTAX scores [22,23]. Moreover, in elderly patients (≥75 years) and in those suffering from diabetes the advantages of CTO PCI are less evident [24,25].

On the other hand, successful CTO treatment (surgical or percutaneously) was observed to improve disease perception, angina frequency, and physical limitation compared with those patients treated medically [26]. In particular, in patients with multivessel disease, complete revascularization has been identified as a key factor to improve clinical outcomes and patient's QOL [27,28]. A sub-analysis of the of SYNTAX trial showed that complete revascularization significantly decreased the incidence of revascularization, MI, death and overall MACE. The same study revealed that CTO was the most important independent predictor of incomplete revascularization in patients with multivessel disease treated with PCI [29] but not with CABG [30].

Appropriate Use Criteria (AUC), elaborated in 2009 and updated in 2012, guide the process of decision-making among the Heart Team in different clinical scenarios, including presence of CTOs. In this case, symptom severity in maximal medical treatment, ischemic burden, and viability demonstration are discriminating factors. An expert consensus document reported in 2016 the indications on appropriateness of CTO revascularization according to symptoms, ischemia, and viability. In summary, the presence of symptoms is considered the first factor to be evaluated. In symptomatic patients with normal wall motion or hypokinesia in the CTO territory, revascularization is suggested. In symptomatic patients with akinesia or dyskinesia in the CTO territory, CTO treatment could be considered after viability demonstration. In asymptomatic patients the decision should be, in general, guided mostly by the demonstration of viability and ischemia. In particular an ischemic burden ≥10% should suggest an invasive strategy [12]. Surgical revascularization should be considered in patients with multiple CTOs and without contraindications for surgery [27].

4. Morphological characteristics of CTO

CTOs consist of a proximal cap, often fibro-calcific, a body, and a distal cap. The body frequently contains some degree of neovascularization, dense fibrous tissue, atheroma, calcified tissue, and focal lymphocyte infiltrate [31]. This type of lesions could involve a long coronary segment with a large plaque burden [32]. A study conducted by Guo et al. using intravascular ultrasounds virtual histology (IVUS-VH) to evaluate CTO lesion characteristics, revealed the presence of two relatively different CTO plaque types: one presenting a large amount of necrotic core, possibly deriving from ruptured plaques associated with previous acute coronary syndromes, and the other one characterized by a little or absent necrotic core, compatible with slowly evolving plaques.

These findings suggest two possible mechanisms for CTO formation, chronic occlusions could be the consequence of either an acute coronary syndrome leading to an acute or subacute coronary occlusion that later stabilizes or they could derive from the slow progression of a large stable atherosclerotic lesion to a total occlusion [33].

Such observation and the CTO composition could have an impact on the PCI procedure as the presence of moderate/severe calcification, in particular, is associated with a higher use of the retrograde approach, lower success rates, and higher incidence of complication [34]. Intra-plaque calcium levels often reflect a long duration occlusion, while recent lesions often present lower amount of calcium and higher quantity of cholesterol and foam cells. Age-related changes in plaque composition from lipid-rich to fibrocalcific might be associated with lower success rate [35].

5. Evaluation and scoring of the CTO lesion

A comprehensive lesion evaluation represents a first step for an appropriate treatment strategy. Morphology of the proximal cap, length of the occlusion, distal target vessel, presence of interventional collaterals, calcification, and tortuosity are all relevant parameters to consider when planning a CTO intervention.

Bilateral diagnostic coronary angiography is crucial for CTO lesion evaluation and in selected cases Computed Tomography for pre-procedural lesion assessment could be helpful [36].

Several scores have been developed with the aim of guiding interventionalists in the choice of the best initial percutaneous approach on the basis of lesion characteristics (Table 1).

One of the most used scores is the J-CTO score, developed from the Japanese Multicentre CTO Registry. Its primary objective is to predict successful guidewire crossing through a CTO within 30 minutes. The J-CTO score takes into consideration five parameters to assess procedure complexity: (1) tapered or blunt proximal cap, (2) occlusion length ≥20 mm, (3) bending

Table 1. CTO scores.

Specific CTO score	*N*	Variables: Clinical	Variables: Angiographic	Variables: CCTA	Predicted variables
J-CTO score (2011)	5		- Entry shape - Lesion length >20 mm - Reentry lesion - Bending >45° - Calcification		Guidewire crossing within 30 min
CL score (2015)	6	- Previous MI - Previous CABG	- Severe calcified lesion - Lesion length >20 mm - Blunt stump - Non-LAD CTO location		Successful antegrade first attempt
CT-RECTOR (2015)	6	- Second attempt - Duration of CTO		- Multiple occlusion - Blunt stump - Severe Calcification - Bending >45°	Guidewire crossing within 30 min
Liu et al.	3	- Age - LVEF - Baseline SCr			Contrast induced nephropathy
PROGRESS CTO score (2016)	4		- Proximal cap ambiguity - Absence of interventional collaterals - Moderate/severe tortuosity - Circumflex CTO		Successful hybrid approach
ORA score (2016)	3	- Age	- Collateral filling - Ostial location		Technical failure by both antegrade and/or retrograde approach
B-CTO score (2017)	6	- Age - Gender	- RCA-CTO - Bending >45° - Lesion length >20 mm - Blunt stump		Successful CTO recanalization
Antegrade CTO score (2017)	6		- Bridging collaterals - Absence of stump - Presence of calcification - Presence of bending - Presence of near side branch - Absence of retrograde filling		Successful antegrade approach
KCCT score (2017)		- Duration of occlusion		- Occlusion length >15 mm - Proximal blunt entry - Proximal side branch - Reattempt - Bending - Severe calcification - Whole luminal calcification	Guidewire crossing <30 min
RECHARGE score (2017)	6	- Previous bypass graft on CTO vessel	- Blunt stump - Calcification - Tortuosity ≥45° - Lesion length 20 mm - Diseased distal landing zone		Prediction of the outcome of CTO coronary angioplasty
CASTLE score (2019)	6	- Previous CABG - Age	- Stump (blunt or invisible) - Tortuosity (severe or unseen) - Length of occlusion (≥20 mm) - Extent of calcification		Prediction of the outcome of CTO coronary angioplasty

CTO: Chronic Total Occlusion; CCTA: Coronary Computed Tomography Angiography; MI: Myocardial Infarction; CABG: Coronary Artery By-pass Graft; LAD: Left Anterior Descendant; LVEF: Left Ventricular Ejection Fraction; SCr: Serum Creatinine; RCA: Right Coronary Artery.

≥45°, (4) presence of calcifications, and (5) prior failed attempt. Lesions are then classified as 'easy, intermediate, difficult, and very difficult' [37]*. Different studies proved the validity of J-CTO score in predicting success rates of CTO PCI, especially in case of low J-CTO score [38,39].

The PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) score was developed to predict technical success of CTO PCI performed using the hybrid approach and it performed similarly to the J-CTO score in estimating technical success. The PROGRESS CTO score considers absence of collaterals, ambiguous cap, involvement of the circumflex artery, and moderate/severe tortuosity as predictors of unsuccessful CTO PCI [40].

The CL score (Clinical and Lesion–related score) has been recently developed as a model predicting procedural success, taking into account both clinical and angiographic characteristics [41]. Such approach could improve accuracy when compared with other scores based only on lesion characteristics [42]. Recent comparison of J-CTO, PROGRESS, and CL scores showed that although the difference in technical success between the minimum and maximum CL score strata is the highest, these scores perform similarly in predicting technical success of CTO PCI, especially when antegrade wire escalation (AWE) is performed [43].

The EuroCTO CASTLE score was recently developed to predict technical success when performing CTO PCI. Six variables (history of CABG, age, stump anatomy, tortuosity degree, length of occlusion, and extent of calcification) were found to be associated with unsuccessful procedure [44]. The EuroCTO CASTLE score was comparable to the J-CTO score in predicting CTO PCI outcomes, and for complex procedures it provided a superior discriminatory capacity [45].

Considering that CTO PCI often requires a relatively high dose of contrast, Liu et al. developed a score specific for estimating the risk of contrast-induced nephropathy in patients undergoing CTO PCI [46]. Four additional scores still pending validation have been proposed the ORA (Ostial location, Rentrop grade, Age), the B-CTO (Busan single-center registry), the Antegrade CTO, and the RECHARGE (Registry of Crossboss and Hybrid Procedures in France, the Netherlands, Belgium, and United Kingdom) scores [47–50].

Two scores have been developed using Coronary Computer Tomography Angiography (CTA), which have the advantage of being a noninvasive assessment of CTO lesions and provide a bilateral image of the coronary anatomy. Furthermore, CTA can reveal specific morphologic properties, such as excessive bending and calcium extension, which can be useful parameters for wire escalation. The CT-RECTOR score (Computed Tomography Registry of Chronic Total Occlusion Revascularization score) and the KCCT score (Korean Multicentre CTO CT Registry score) were observed to be effective in the prediction of procedural duration [51,52].

Although, operator's skills and experience are keys for the success of the CTO intervention the above-mentioned scores represent useful tools to evaluate the CTO lesions and can guide the interventional strategy, in particular when considering the modality of AWE or the decision to immediately start with a retrograde approach [53].

The above mentioned scores have been developed from a relatively modest number of patients, except for the recent EuroCTO CASTLE score validated from 20,000 patients of the EuroCTO registry. The widely adopted J-CTO score was derived from a cohort of 465 patients treated exclusively with the antegrade approach between 2006 and 2007 with a successful guidewire crossing within 30 minutes achieved in 48% of the cases. Moreover, across the different registries there was a great variance regarding the adopted recanalization techniques, CTO PCI success rates, operator skills, and case complexity making these scores poorly attractive for a more generalized adoption.

These scores provide a quantitative evaluation of procedural difficulty and the likelihood of recanalization success and thus facilitate procedural planning. The novel EuroCTO CASTLE scoring system combining additional demographic and anatomical factors might improve the prediction of procedural outcome.

6. Antegrade and retrograde approaches

Before initiating a CTO PCI, lesion visualization with dual injection is advisable in almost every case to ensure optimal lesion assessment and since the lack of bilateral angiography is a predictor of CTO PCI failure [54]. In selected cases and especially in absence of relevant contralateral collateral and well-formed ipsilateral ones a single injection and even retrograde ipsilateral intervention strategy could be considered [55].

6.1. Antegrade approach

AWE is the most frequently performed technique, although it is unlikely to be associated with a high success rate in complex cases (J-CTO ≥ 1) [39,56]. Guidewires with different characteristics (Hydrophilic/non-hydrophilic, polymer jacket, tapered, etc.) and different penetration power (Tip Load/Tip Area) are used to cross the lesion and could be alternated following a step-up/step-down scheme [1,37,57]. As a general rule, CTO lesions with tapered proximal cap and a high probability of having micro-channels could be approached initially with soft hydrophilic taper wires that could navigate the micro-channels and exit in the distal true lumen. Although novel guide wires with a high maneuverability, optimal torque response, and conic tip to improve penetrability like the GAIA family of wires, profoundly improved the AWE technique, for more complicated lesions Karatasakis et al. demonstrated that usually a large number of different guidewires is needed to improve AWE success rate [58] and Maeremans et al. proposed an algorithm to improve Antegrade Wire Technique success rate, focusing on a guidewire alternating sequence [59].

To safely perform AWE technique, the operator should have adequate experience in managing sub-intimal wire tracking and should be able to promptly recognize wire exit from the vessel structure. While misdirected even high tip-load guidewires could be associated with minor perforations, it is extremely dangerous to advance a microcatheter or balloon over a guidewire that has not been confirmed to be in the vessel architecture, resulting in large vessel perforations and tamponade.

In addition, changing the high tip load guidewires for a safer one, once the lesion has been crossed, is necessary to avoid distal vessel complications [60]. In case of guidewire entry into the subintimal space, it is possible to perform the parallel wire technique. This technique consists of leaving the first guidewire, in order to mark the dissection, and then a second, usually with higher tip load is introduced to advance in a different path. Although the recent introduction of new types of guidewires has substantially improved the technique, it can result in a time-consuming effort requiring specific skills and experience [61]. Microcatheters are also of utmost utility when performing different types of CTO-PCI techniques. Principal microcatheter functions include guidewire exchange, support and good positioning, contrast injection, and lumen dilatation if needed. Moreover, double lumen microcatheters allow the negotiation of collaterals and to preserve the whole anatomy of occluded vessel with side branches in large parts of the procedures [62].

Antegrade Dissection and reentry (ADR) technique consisting of advancing in a dissection, and reentering the true lumen distally could be preferred to the parallel wire technique and could be very useful in case of an ambiguous proximal cap and long lesion length provided the presence of a distal vessel suitable for a reentry technique. ADR can be wire-based or device based. Wire-based approaches include STAR (Sub-intimal TrAcking and reentry), contrast injection guided STAR, mini-STAR, and LAST (Limited Antegrade Subintimal Tracking) techniques.

The STAR technique was proposed by Colombo et al. in 2005 for the antegrade treatment of CTOs following the example of an approach already in use for chronic occlusions of peripheral vessels. The STAR technique consists of using a knuckle-wire to create a dissection, from which the true lumen is eventually reentered [63]. The knuckle-wire is a safe and effective technique when appropriate wires are used (soft polymer jacketed); however, there is a high likelihood of creating a large sub-intimal hematoma, which makes reentry difficult because of true lumen compression. Furthermore, the reentry location is often unpredictable and side branches are at risk of occlusion [64].

Carlino et al. modified the STAR technique by introducing an over the wire (OTW) balloon or microcatheter mediated contrast injection in order to better visualize the reentry site [65]. Galassi et al. further improved the STAR technique proposing the mini-STAR technique, which consists of creating a dissection using very soft guidewires (principally Fielder family) followed by entering the subintimal space with a microcatheter, attempting to reduce the subintimal hematoma and minimizing reentry related complications [66]. Long-term follow-up of patients who underwent mini-STAR showed an acceptable rate of MACE and target lesion restenosis (TLR) [67].

The LAST technique, elaborated by Thompson and Lombardi, requires a knuckle wire to create a dissection, and then a polymer-jacketed wire or a non-jacketed stiff wire to redirect toward the distal true lumen [68].

Overall, wire-based ADR has been associated with higher restenosis rate, compared with standard PCI, probably in association with the unpredictability of the reentry site, often translating into long stented segment in the subintimal space. Such data emphasized the need for more controllable reentry techniques [69].

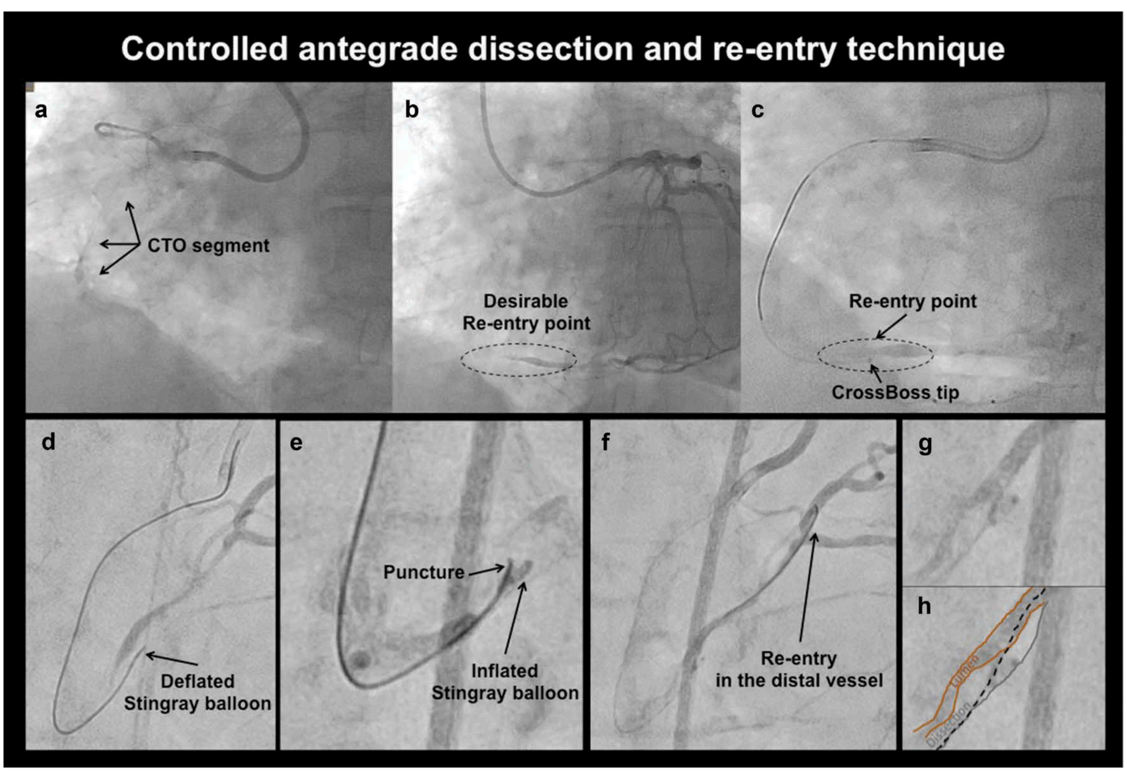

Figure 1. Controlled antegrade dissection and reentry technique. Long CTO of the right coronary artery with a clearly identifiable reentry point at initial angiograms (panels a and b). Despite heavily calcification, the CrossBoss catheter advanced in the subintimal space, rapidly reached the desired reentry point (panel c) and exchanged with a stingrey balloon (panel d), which was inflated facilitating the puncture toward the true lumen performed with the stingray wire (panel e). After fenestration of the subintimal space the reentry can be performed with a standard hydrophilic wire (panel f, g, and h).

Device based ADR is performed using dedicated devices, such as the CrossBoss catheter and Stingray balloon (Figure 1). The principal advantage of the Crossboss/Stingray combination is a subintimal tracking and a subsequent controlled reentry. The CrossBoss is a microcatheter characterized by an atraumatic rounded tip, this catheter must be advanced using rapid rotation, with or without guide-wire, facilitating proximal cap crossing, either passing through the lesion, and exiting into the true lumen or entering the subintimal space. The CrossBoss catheter given the atraumatic tip is designed to remain in the structure of the vessel with a very low risk of perforation. Such complication could occur in the case that the microcatheter enters a small side-branch, but this issue could be corrected retracting the microcatheter and re-directing it with a high tip-load wire.

The Stingray reentry System includes a flat balloon with two wire exit ports, one for each side, and another one located at the tip. The balloon is advanced into the subintimal space up to the desired site of reentry, where it is inflated at low pressure (4 atm). The Stingray balloon given its flat morphology (2.5 mm wide and 10 mm long) is self-orienting with one side port facing toward the true lumen and the other toward the vessel wall unless a very large hematoma is created. It is always advisable to minimize the subintimal hematoma aspirating blood with the STRAW (Subintimal TRAnscatheter Withdrawal) technique [70]. Then, the Stingray wire characterized by a 28° tip angle and a 0.18 mm needle located at the tip for lumen reentry is introduced in the Stingray flat balloon and inserted into one of the side exit ports in order to puncture the intima enabling reentry in the true lumen. After the puncture has been performed the reentry can be done with either the Stingray wire itself ('stick-and-drive') or with another guidewire ('stick-and-swap') usually a hydrophilic wire like the Pilot 200 [71]. This last is a safer method especially if also the hydrophilic wire is later exchanged for a workhorse wire before stenting. The FAST-CTOs trial showed that this system is useful in case of standard technique failure, possibly increasing success rates, without exposing patients to higher complication rates [72]. The Stingray reentry balloon has been designed to work in conjunction with the Crossboss catheter; however, it could be effectively used also in subintimal spaces created with a wire [73].

In case of ambiguous proximal cap or impenetrable lesion, the BASE (Balloon Assisted Subintimal Entry) technique should be considered as an option. This approach consists in entering the subintimal space proximally to the proximal cap using the aid of a slightly oversize balloon to create limited dissection. Once the guidewire is passed through the lesion, it is possible to proceed with a standard anterior dissection and reentry [74]. The side-BASE technique is an evolution of the above-mentioned one and it results useful in case of the presence of a side branch located in proximity of a CTO lesion in a major vessel characterized by an ambiguous or impenetrable proximal cap. The first step is to create a proximal tear in the vessel using a balloon and placing a microcatheter in the proximal vessel using a second guidewire. After that, a second balloon is partially inflated into the side branch in order to deflect and anchor the wire to the microcatheter, so that the wire can be pushed beyond the inflated balloon and pass the proximal cap, usually within the subintimal space. As described for the BASE technique, the procedure could be concluded with anterior dissection and reentry technique [75].

6.2. Retrograde approach

Retrograde approaches include true-to-true lumen crossing and dissection and reentry techniques.

The retrograde approach has been proposed in 2005 by Katoh et al. with the aim of treating CTOs with ambiguous proximal cap and diffusely diseased vessel [76]. To perform a retrograde approach it is possible to use a connection between the distal segment of the occluded vessel and another coronary artery. This connection can be a septal, an epicardial collateral, or a coronary bypass graft. Septal collaterals should always be preferred to epicardials due to their intramuscular course reducing the risk of complications.

Commonly used wires for septal crossing are soft hydrophilic wires like the SION wire (soft tip 0.7 gf), with a dual-core technology improving tip control and the full tip hydrophilic coating (Slip Coat® technology). The SION Blue wire (softer tip 0.5 gf) with also a dual-core technology has a hydrophobic tip coating (15 mm) which on one hand improves safety but on the other makes small and tortuous septal crossing more challenging. The SION Black is the polymer-jacket version of the SION family (0.8 gf tip load) with the highest tip load but good flexibility which make this wire a good option for small channels and vessels although the likelihood of wire exit is slightly higher compared with other non-polymer-jacked SION wires [62].

Despite being in some cases visually appealing, epicardial collaterals are associated with a higher risk of rupture leading to cardiac tamponade, especially when tortuous and small in diameter [77]. Therefore, retrograde treatment of CTOs using epicardial collaterals should be preferably performed only by experienced CTO operators. Nevertheless, novel devices, specifically designed for epicardial channel crossing, have been recently developed, including low profile microcatheters (ASAHI Caravel, Turnpike LP, etc.) and dedicated guidewires like the ASAHI SUOH 03 characterized by an extremely soft pre shaped tip with a tip load of only 0.3 gf, allowing a gentle crossing of very tortuous epicardial collaterals [78].

Retrograde wires should always be followed by a microcatheter when located at the distal segment of a CTO to increase support and allow safe wire exchange. At that point the procedure could be finalized with retrograde wire escalation (RWE) or retrograde dissection and reentry (RDR).

RWE is similar to AWE; however, the distal cap is often less calcified compared with the proximal one. Just as in AWE, the use of a microcatheter support is pivotal in guidewire control and advancement. After the guidewire has entered the true lumen proximally to the CTO, the retrograde wire must enter the antegrade guiding catheter followed by the microcatheter. This manoeuver could be facilitated by a mother-and-child guide catheter extension. Entrapping the retrograde wire inside the antegrade guiding catheter (or the mother-and-child guide catheter extension) could highly enhance the support for the final advancement of the retrograde microcatheter. The guidewire can be then exchanged with an externalization wire and the PCI can be finalized [79]. In case of unfavorable anatomy alternative techniques should be considered. The tip-in technique consists in the advancement of an antegrade microcatheter followed by the insertion of the retrograde guide-wire in the tip of the antegrade microcatheter that can be further advanced up to the distal cap finalizing the procedure antegradely [80].

The success of RWE can sometimes be improved by the 'kissing wire technique' that requires the penetration of the lesion both from the distal and the proximal cap. The technique can aid to detect the vessel course more accurately, with the antegrade wire acting as a marker.

The retrograde dissection and reentry techniques are performed mainly with Controlled Antegrade and Retrograde Subintimal Tracking (CART) and reverse CART (R-CART) [81] technique. The CART and R-CART techniques involve the creation of a retrograde and antegrade subintimal space, typically by using knuckle wires.

The R-CART is the more frequently adopted technique and is performed as follows: the antegrade and retrograde knuckle wires should overlap each other in the subintimal space, the antegrade knuckle is then replaced by a workhorse wire and a balloon is placed in the subintimal space. The antegrade balloon should be inflated to connect the antegrade and retrograde subintimal spaces. When deflating the balloon, the retrograde wire, backed up by the microcatheter, is steered toward the balloon entering the proximal true lumen (Figure 2).

A slight retraction of the deflating balloon toward the proximal vessel can facilitate the advancement of the retrograde wire by creating a vacuum effect. This critical step involving proximal reentry is defined as the 'Deflate, Retract, and Advance into the Fenestration Technique' (DRAFT) proposed by Carlino et al. [82].

In the classic CART technique, CTO PCI is finalized using the antegrade wire, with a retrograde balloon positioned in the retrograde subintimal space to facilitate navigation [83]. Such technique has been almost completely replaced in clinical practice by the R-CART technique.

In case of balloon uncrossable or balloon undilatable lesions rotational atherectomy can be considered to facilitate catheter and guidewire crossing [84,85].

The retrograde is more commonly performed using the collateral connections between the distal segment of the occluded artery and a contralateral coronary vessel.

However, an alternative approach for retrograde CTO interventions, particularly useful in case of lack of contralateral collaterals connections, is the crossing of ipsilateral collateral channels (ILCs). A retrospective Multicenter Registry including 126 patients showed technical and procedural success rates of 87% and 82% when either septal or epicardial ILCs were used to reach retrogradely the CTO lesion [86].

6.3. Hybrid approach

The recent introduction of the Hybrid Algorithm has been a relevant novelty in the strategic approach to the treatment of CTO lesions, combining conventional wire escalation to more complex dissection and reentry techniques with use of dedicated equipment. The algorithm has its flexibility and fast shift from one approach to another its major strength [57]. The four major techniques are AWE, Antegrade Dissection and reentry (ADR), RWE, and RDR. Strategical planning is based on lesion evaluation with dual injection angiography, allowing an optimal visualization of the proximal cap but also of potential interventional collaterals, and the distal vessel. Such evaluation is guiding the decision on initial antegrade or retrograde approach. Lesion length is then assessed to consider the wire escalation or directly a dissection reentry technique. A non-ambiguous proximal cap and limited lesion length (<20 mm) usually favors' an AWE approach. If lesion length is inferior to 20 mm an AWE can be performed with good chances of success in a limited amount of time. Antegrade dissection and reentry can be considered when AWE is not successful, there is a suitable landing zone, and unavailability of any retrograde options.

The presence of an ambiguous proximal cap and a poorly defined distal landing zone (i.e. diffusely disease distal vessel, distal cap at a bifurcation site, etc.), often drives the choice toward a direct retrograde approach (Figure 3).

Rapid change from one strategy to another in case of failure is a key point of the Hybrid approach, but implies for the CTO operator to be familiar with all possible techniques to be able to choose the one with the highest probability of success and to be ready to change it quickly in case of failure [57,87]*. Hybrid Approach efficiency has been recognized from both European and American Registries. The RECHARGE (REgistry of Crossboss and Hybrid procedures in FrAnce, the NetheRlands,

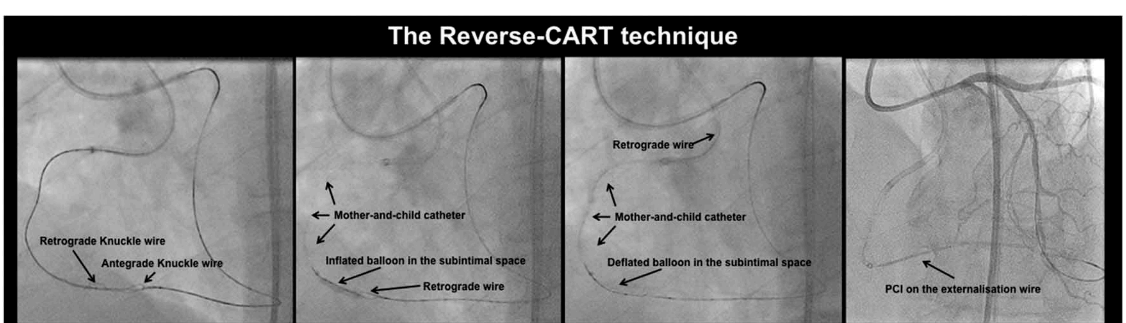

Figure 2. Reverse CART technique. The antegrade and retrograde knuckle wires are advanced in two dissection plans (panel A). A mother-and-child catheter and a balloon are advanced in the antegrade dissection and the balloon is inflated in the subintimal space to connect it with the retrograde subintimal space (panel B). The retrograde wire is advanced up to the guiding catheter to be exchanged with an externalization wire (panel C). the finalization of the PCI is performed on the externalization wire.

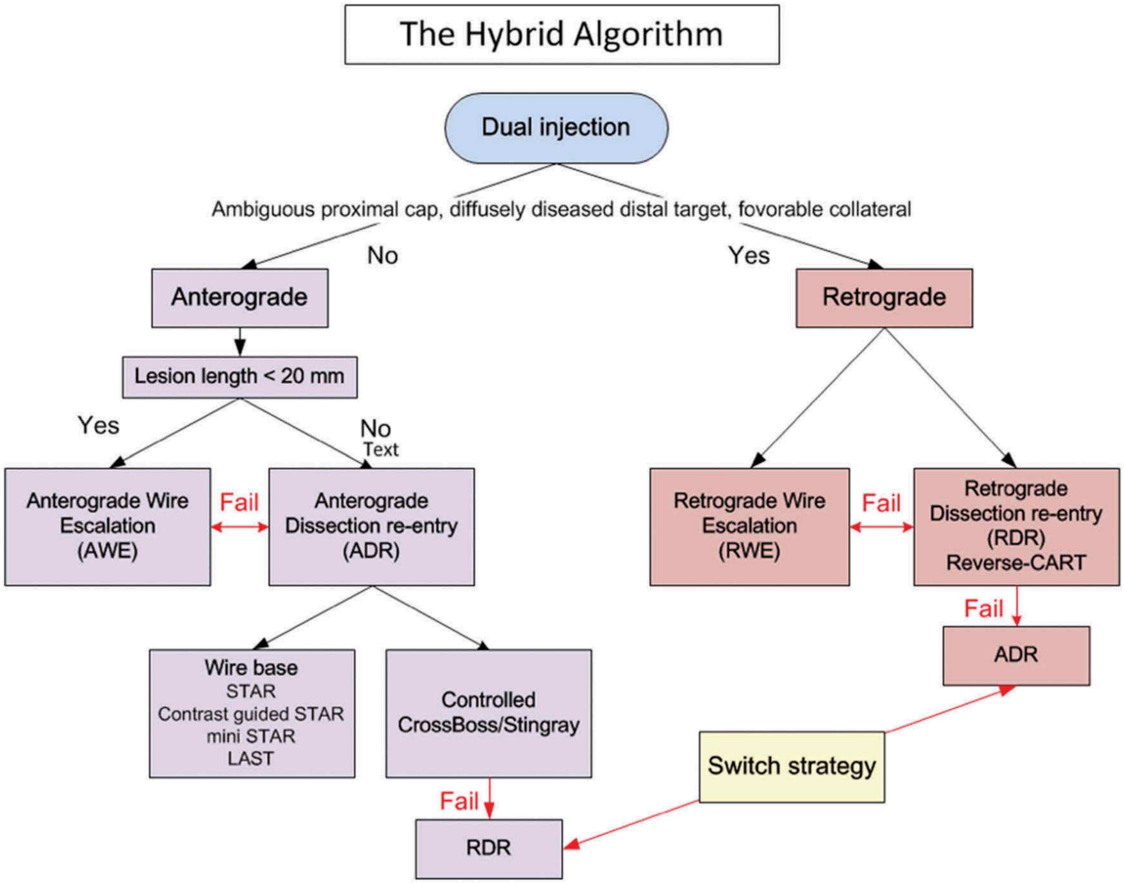

Figure 3. Hybrid approach. The hybrid approach is based on accurate lesion evaluation to guide initial strategy followed by rapid switch to another in case of failure.

BelGium, and UnitEd Kingdom) revealed success rates up to 86% and major in-hospital complication occurrence set to 2.6% [88]. Likewise, a US multicenter registry showed technical success in 91% of cases and major procedural complications in 1.7% of performed CTO PCI [89].

7. Complications management

CTO procedure has been classically regarded as a procedure with a higher rate of complications compared to PCI in non-chronically occluded vessels [90].

Recent advancements in techniques and materials have drastically reduced the occurrence of complications. However, operators should be prepared to face and properly treat them.

In general PCI-related complications could be: (1) coronary artery related, including coronary perforation, coronary thrombosis and occlusion, and equipment loss or entrapment; (2) cardiac non-coronary, such as ventricular arrhythmias, cardiac tamponade, and periprocedural MI; and (3) non-cardiac, among which vascular access complications, systemic embolization, allergic reactions, contrast-induced nephropathy, and radiation-induced injury. The management of such complications should be part of the technical background of every interventional cardiologist.

Specific complications of CTO interventions particularly when adopting a retrograde strategy are (1) donor vessel damage or thrombosis, and (2) collateral perforations [60].

A simple measure to prevent donor vessel complications is to avoid deep ostial intubation of the guiding catheter especially when retracting equipment from collaterals.

The presence of a microcatheter in a donor vessel with intermediate stenosis could impair the blood flow possibly causing ischemia and an unstable hemodynamic condition. Therefore, the status of the donor vessel should be carefully evaluated before adopting a retrograde strategy.

Finally, materials located in the donor vessel for a prolonged time could prompt the occurrence of thrombosis. Regular activated clotting time (ACT) controls should be performed with a target ACT of >350 s.

Collateral perforation could be a challenging complication especially after the chronically occluded vessel has been treated as the collaterals receive blood from the donor vessel and from the treated CTO artery. In this situation, simple balloon occlusion of one of the two arteries will not stop the bleeding. Therefore, Microcoils embolization should be immediately considered [91] or as alternatives autologous fat embolization. Recently, autologous fat embolization has gained in popularity, as this technique has no costs, is safe, and relatively easy to perform [92]. Another possibility is to inject a mixture of thrombin and contrast into the perforated vessel, using a microcatheter to avoid thrombin entry in a coronary vessel other than the intended [93].

As a general safety measure, a wire should be maintained in the collaterals used for retrograde approach up to the end of the procedure and an angiographic control should be performed before removing it. In case of vessel damage/perforation the presence of the wire will allow a fast treatment of the collateral.

8. Short and long term results of CTO-PCI

Recent improvements in CTO PCI techniques and materials have increased success rates and reduced complication occurrence, reducing the gap with non CTO PCI [4,21]. Since the introduction of the Hybrid Approach, both American and European registries showed procedural success rates reaching 90% in high volume and experienced centers, with low rates of in-hospital major adverse events and procedural complications [88,89]. The OPEN-CTO registry revealed in-hospital and 1-month mortality rates 0,9% and 1,3%, respectively, with perforation occurring in 4,8% of cases [17]. Long-term benefits from CTO PCI in terms of QOL in symptomatic patients have been reported in the FACTOR trial and other studies. Werner and Jang showed that in asymptomatic patients, cardiac function improvements post-CTO PCI are relevant [9]. CTO treatment could also increase reverse remodeling and decrease the risk of ventricular arrhythmias, even in older patients [6,7,9,18,94]. The CREDO-Kyoto registry demonstrated that successful CTO-PCIs are associated with less need for subsequent CABG with respect to unsuccessful ones, while no difference was highlighted in terms of 3-year mortality [95]. Other studies, instead, revealed an improved long-term survival in patients undergoing successful CTO PCI [10,96], in particular when a CTO in the LAD artery was treated [97,98].

Recently, the results of two long awaited randomized trials have been made available, namely the DECISION CTO trial and the EuroCTO trial.

The DECISION CTO trial is a prospective, open-label, randomized trial carried out in 19 centers in Korea, India, Taiwan, and Thailand. Patients eligible for PCI were randomized to receive either PCI or medical therapy in case of CTO-lesions with the option for PCI of significant non-CTO lesions. The study included patients with a coronary chronic total occlusion with TIMI flow 0 of at least 3 months of duration located in a proximal to mid epicardial vessel with a reference diameter >2.5 mm, either causing silent ischemia, stable angina, or acute coronary syndrome. Major exclusion criteria were CTOs located in distal vessels, in venous grafts, in-stent restenosis, left main segment involvement, severe comorbidities, and left ventricular ejection fraction (LVEF) <30% [99]*. The primary composite endpoint was the incidence of death from any cause, repeat revascularization, stroke, periprocedural, or spontaneous MI at 5-year follow-up. As a result, no statistically significant difference was detected between the two groups (PCI + CTO 22.3% vs. PCI + OMT 29.3% after 5 years, $p = 0.11$), thus suggesting the non-superiority of additional CTO PCI compared with OMT alone.

However, this trial had several limitations, the study was prematurely terminated due to slow enrollment, out of the planned sample size of 1284 patients only 834 were included. Periprocedural MI an event possible only in the PCI arm was included in the primary combined endpoint, a significant cross-over was observed, namely 18% from the OMT arm to the PCI arm. Finally, overall mortality in the PCI arm was lower than in the OMT arm (3.0% vs. 4.4% at 3 years follow-up, and 4.5% vs. 7.9% at 5 years follow-up), with a reduction of 50% in the particular case of cardiac death at the 3rd year (1.9% vs. 3.6%) [100].

Similar to the DECISION CTO trial, the EuroCTO trial did not reach the planned number of enrolled patients, namely 600 patients for the efficacy endpoint of QOL and 1200 for the primary safety endpoint of MACE [101]*. A total of 396 patients were enrolled, 259 underwent CTO PCI and 127 treated only with OMT. At 12-month follow-up, CTO PCI demonstrated to be effective in improving the QOL, reducing the recurrence of angina, as assessed by the Seattle Angina Questionnaire (SAQ) health status survey. The incidence of MACE resulted similar in the two groups.

9. Conclusions

Treatment of CTO lesions has obtained high success rates in the last decade and a low incidence of complications when performed by experienced operators. Such results were obtained with a continuous improvement of techniques and dedicated materials. Recent studies suggest that CTO treatment could improve patients' QOL, while a real advantage in terms of mortality has not been demonstrated in randomized trials but only in registries. Appropriate patient selection and operator skills following dedicated trainings for CTOs treatment remain crucial.

10. Expert opinion

Chronic total occlusion has been classically regarded as a challenging subset in the field of PCIs, burdened by high complexity, low success rates, and increased procedural risk compared to non-CTO interventions.

However, in the last decade the development of dedicated tools and techniques has enlarged the therapeutic options for patients with CTO especially in centers with dedicated CTO operators and CTO programs.

Cost management, logistical organization and appropriate operator training with high yearly CTO case volume are keys to success when organizing a CTO program.

Contemporary optimal CTO percutaneous treatment appears to be limited to centers with the capability to organize and sustain such effort.

In addition, CTO treatment has been put into question as recent trials failed to show a clear improvement in clinical event rates despite an advantage in terms of QOL and symptoms.

Given this background, advanced CTO PCI still remains a niche treatment performed by a limited number of experts and the majority of interventional cardiologists are not familiar with the numerous techniques related to such procedures.

Therefore, the present review aims at providing a basic knowledge of the materials and strategies to apply during CTO percutaneous interventions. Such knowledge represents the essential background for every CTO operator. Practical guidance by experts and constant up to date techniques and knowledge of materials could further facilitate the learning progression.

At the moment two things appear to be the major limitations to a large widespread adoption of CTO complex interventions in the clinical practice: (1) the absence of solid data elucidating the impact on clinical events and mortality of CTO successful treatment in viable myocardial segments; (2) the absence of programs for a specific training of CTO dedicated operators.

In particular, the need for a well-designed large randomized trial focused on appropriate indications for CTO interventions and evaluating the impact of successful CTO revascularization is extremely needed to clarify the role and appropriateness of these complex and expensive procedures. Unfortunately, such a study has not been planned yet and does not appear to be easy to perform, given multiple reasons comprising, the limited number of patients presenting with CTO, the limited number of large volume CTO expert centers, and the large number of patients probably needed to carry out such clinical research.

On the other hand, angina relief and improved QOL in patients with CTO have been better investigated and represent at the moment the major reasons to perform CTO PCI.

Specific training programs for CTO percutaneous treatment could enhance the general understanding and adoption of the complex techniques often needed during CTO procedures. Such training should not be limited to congresses or live – cases symposia but operators should be practically guided during CTO procedures through an increasing level of case complexity to gradually acquire knowledge, skills, and confidence, additionally familiarizing themselves with the most appropriate case-by-case complication management.

Finally, particularly interesting are the technological advancements in terms of materials and tools for CTO treatment.

New guidewires such as the GAIA family provide an improved operability when entering severe calcifications, with an increased strength against the fracture, better linear torque response, and maintaining the flexibility of the tip. In addition GAIA Next (XTRAND coil) has the same basic structure of the current Gaia, with an innovative structure of the rope coil that consist of seven wires, and each wire is braided in seven thinner wires. Three different tip loads are available (2.0 – 4.0 – 6.0 gf) for different lesion properties.

The recent low profile dual lumen micro-catheters (FineDuo, Sasuke) provide support and easy access to tortuous coronary anatomies, or acute angulated lesions, and stronger penetration force in complex procedures requiring greater force transmission, compared to a conventional microcatheter.

The development of dedicated polymer jacket and hydrophilic coating knuckle wire, such as the new Gladius Mongo and Gladius Mongo ES (ASAHI) could be associated with enhanced performance given the increased lubrication, trackability and torque transmission.

During the last years we have witnessed to an increased use of IVUS-guidance in PCI of CTO lesions. IVUS provides information on the vessel size, calcium distribution, precise location of the guidewires within the architecture of the artery, and could be critical for proximal cap identification in case of ambiguity, potentially reducing perforation risk. After stenting, IVUS allows evaluation of device expansion, apposition, and edge dissection, leading to procedural optimization. The use of IVUS guidance has been reported to improve clinical outcomes in large 'all comers' PCI populations and it could be reasonably speculated that in highly complex procedures like CTO the additional value of IVUS guidance could be even more evident [102,103].

In the last years, the development of clinical robotic systems from the first Navicath to the most advanced CorPath GRX System (Corindus Vascular Robotics) allowed performance of remote coronary artery interventions. The PRECISE (Percutaneous Robotically-Enhanced Coronary Intervention) study evaluated simple lesions that needed treatment with a single stent showing technical and procedural success rates of 98.8% and 97.6%, respectively, in addition to a 95.2% radiation dose reduction for the operators [104]. In 2015, the CORA-PCI Study demonstrated the safety and feasibility of performing robotically assisted PCI in a cohort of patients with complex coronary anatomy and significant comorbidities, including CTO [105]. Moreover, the REMOTE-PCI study introduced the concept of PCI performed robotically by an operator not physically located in the cathlab [106]. However, robotically assisted PCI remains a poorly explored field and at the current state of the art operator experience and skills remain key in complex CTO procedures.

10.1. Five-year view

Coronary interventions for CTO lesions emerged in the last years from high risk procedures burdened by low success and high complication rates to a relatively safe and effective treatment option. Major advancements in strategies and dedicated tools have been instrumental in this evolution.

The development of CTO dedicated materials comprising a large number of innovative guidewires and microcatheters has changed the CTO PCI landscape. The traditional wire escalation has been profoundly changed by the new preshaped high torque response wires, whilst failure of wire base reentry can be overcome using tools for controlled reentry. The recent introduction of ultra-low tip-weight wires has yielded positive feedback on the crossing of epicardial channels, possibly increasing safety when using this, high-risk option for a retrograde approach. In addition, the introduction of the hybrid approach added efficiency to complex CTO procedures.

Despite all these technical improvements, the future challenges for this ultraspecialistic field in interventional cardiology remain clarification of the clinical implication of a successful CTO PCI and dissemination of the CTO PCI techniques.

In particular, although an improvement in QOL has been shown after treatment of patients with ischemia/viability in the territory of the chronically occluded vessel, an appropriate evaluation of the prognostic impact of such procedure remains a major issue and large appropriately powered and well-designed randomized trials are highly needed.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. Sianos G, Werner GS, Galassi AR, et al. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. EuroIntervention. 2012;8:139–145.
2. Tomasello SD, Giudice P, Attisano T, et al. The innovation of composite core dual coil coronary guide-wire technology: a didactic coronary chronic total occlusion revascularization case report. J Saudi Heart Assoc. 2014;26:222–225.
3. Karatasakis A, Danek BA, Karmpaliotis D, et al. Approach to CTO intervention: overview of techniques. Curr Treat Options Cardiovasc Med. 2017;19:1.
4. Christopoulos G, Menon R, Karmpaliotis D, et al. The efficacy and safety of the “hybrid” approach to coronary. J Invasive Cardiolog. 2014;26:427–432.
5. Galassi AR, Boukhris M, Tomasello SD, et al. Incidence, treatment, and in-hospital outcome of bifurcation lesions in patients undergoing percutaneous coronary interventions for chronic total occlusions. Coron Art Dis. 2015;26:142–149.
6. Jang WJ, Yang JH, Choi SH, et al. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. JACC Cardiovasc Interv. 2015;8:271–279.
7. Werner GS, Surber R, Ferrari M, et al. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. Eur Heart J. 2006;27:2406–2412.
8. Safley DM, Grantham JA, Hatch J, et al. Quality of life benefits of percutaneous coronary intervention for chronic occlusions. Catheter Cardiovasc Interv. 2014;84:629–634.
9. Grantham JA, Jones PG, Cannon L, et al. 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.
10. Hoebers LP, Claessen BE, Elias J, et al. 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.
11. Neumann FJS-UM, Ahlsson A, Alfonso F, et al. ESC scientific document group. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019;40:87–165.

•• **Current ESC/EACTS guidelines on myocardial revascularization recommends CTO-PCI in class IIa (level of evidence B) in symptomatic patients despite the medical therapy or with documented ischemia.**

12. Galassi AR, Brilakis ES, Boukhris M, et al. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. Eur Heart J. 2016;37:2692–2700.

•• **Overview on indication and appropriateness of CTO-PCI focusing on clinical outcome and quality of life.**

13. Fefer P, Knudtson M, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian multicenter chronic total occlusions registry. J Am Coll Cardiol. 2012;59:991–997.
14. Christofferson RD, Lehmann KG, Martin GV, et al. Effect of chronic total coronary occlusion on treatment strategy. Am J Cardiol. 2005;95:1088–1091.
15. Claessen BE, van der Schaaf RJ, Verouden NJ, et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. JACC. 2009;2:1128–1134.
16. Claessen BE, Dangas G, Weisz G, 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.
17. Sapontis J, Marso SP, Cohen DJ, et al. The outcomes, patient health status, and efficiency in chronic total occlusion hybrid procedures registry: rationale and design. Coron Artery Dis. 2017;28:110–119.
18. Yap SC, Sakhi R, Theuns DA, et al. Increased risk of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with chronic total coronary occlusion. Heart Rhythm. 2018;15:124–129.
19. Nombela-Franco L, Iannaccone M, Anguera I, et al. Impact of chronic total coronary occlusion on recurrence of ventricular arrhythmias in ischemic secondary prevention implantable cardioverter-defibrillator recipients (VACTO secondary study): insights from coronary angiogram and electrogram analysis. JACC Cardiovasc Interv. 2017;10:879–888.
20. Di Marco A, Anguera I, Teruel L, et al. Chronic total occlusion of an infarct-related artery: a new predictor of ventricular arrhythmias in primary prevention implantable cardioverter defibrillator patients. Europace. 2017;19:267–274.
21. Galassi AR, Boukhris M, Azzarelli S, et al. 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.
22. Hwang JW, Yang J, Choi SH, et al. Optimal medical therapy may be a better initial strategy in patients with chronic total occlusion of a single coronary artery. Int J Cardiol. 2016;210:56–62.
23. Yang JH, Kim B, Jang WJ, et al. Optimal medical therapy vs. percutaneous coronary intervention for patients with coronary chronic total occlusion - a propensity-matched analysis. Circ J. 2016;80:211–217.
24. Lee SH, Yang JH, Choi SH, et al. Long-term clinical outcomes of medical therapy for coronary chronic total occlusions in elderly patients (≥75 years). Circ J. 2015;79:1780–1786.
25. Choi KH, Yang J, Song YB, et al. Long-term clinical outcomes of patients with coronary chronic total occlusion treated with percutaneous coronary intervention versus medical therapy according to presence of diabetes mellitus. EuroIntervention. 2017;13:970–977.
26. Wijeysundera HC, Norris C, Fefer P, et al. Relationship between initial treatment strategy and quality of life in patients with coronary chronic total occlusions. EuroIntervention. 2014;9:1165–1172.
27. Kim BS, Yang JH, Jang WJ, et al. Clinical outcomes of multiple chronic total occlusions in coronary arteries according to three therapeutic strategies: bypass surgery, percutaneous intervention and medication. Int J Card. 2015;197:2–7.
28. Shuvy M, Qiu F, Chee-A-Tow A, et al. Management of chronic total coronary occlusion in stable ischemic heart disease by percutaneous coronary intervention versus coronary artery bypass grafting versus medical therapy. Am J Cardiol. 2017;120:759–764.
29. Farooq V, Serruys PW, Garcia-Garcia HM, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy between percutaneous coronary intervention with taxus and cardiac surgery) trial. J Am Coll Cardiol. 2013;61:282–294.
30. Head SJ, Mack MJ, Holmes DR, et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3–year SYNTAX data. Eur J Cardiothorac Surg. 2012;41:535–541.
31. KatsuragawaM, Fujiwara H, Miyamae M, et al. Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: comparison of tapering and abrupt types of occlusion

and short and long occluded segments. J Am Coll Cardiol. 1993;21:604–611.

32. Park YH, Kim YK, Seo DJ, et al. Analysis of plaque composition in coronary chronic total occlusion lesion using virtual histology-intravascular ultrasound. Korean Circ J. 2016;46:33–40.
33. Guo J, Maehara A, Mintz GS, Ashida K, et al. A virtual histology intravascular ultrasound analysis of coronary chronic total occlusions. Catheter Cardiovasc Interv. 2013;81:464–470.
34. Karacsonyi J, Karmpaliotis D, Alaswad K, et al. Impact of calcium on chronic total occlusion percutaneous coronary interventions. Am J Cardiol. 2017;120:40–46.
35. Srivatsa SS, Edwards WD, Boos CM, et al. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. J Am Coll Cardiol. 1997;29:955–63.
36. Hoe J. CT coronary angiography of chronic total occlusions of the coronary arteries: how to recognize and evaluate and usefulness for planning percutaneous coronary interventions. Int J Cardiovasc Imaging. 2009;25Suppl1:43–54.
37. Morino Y, Abe M, Morimoto T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes. The J-CTO (Multicenter CTO registry in Japan) score as a difficulty grading and time assessment tool. JACC Cardiovasc Interventions. 2011;4:213–221.
    - **Multicentre, prospective, non-randomized study which showed that the J-CTO (CTO Registry in Japan) score can predict the probability of successful guidewire crossing within 30 minutes.**
38. Tanaka H, Morino Y, Abe M, et al. Impact of J-CTO score on procedural outcome and target lesion revascularisation after percutaneous coronary intervention for chronic total occlusion: a substudy of the J-CTO registry (Multicentre CTO registry in Japan). EuroIntervention. 2016;11:981–988.
39. Christopoulos G, Wyman RM, Alaswad K, et al. Clinical utility of the japan-chronic total occlusion score in coronary chronic total occlusion interventions: results from a multicenter registry. Circ Cardiovasc Interv. 2015;8:002171.
40. Christopoulos G, Kandzari D, Yeh RW, et al. Development and validation of a novel scoring system for predicting technical success of chronic total occlusion percutaneous coronary interventions: the PROGRESS CTO (Prospective global registry for the study of chronic total occlusion intervention) score. JACC Cardiovasc Interv. 2016;9:1–9.
41. Alessandrino G, Chevalier B, Lefèvre T, et al. A clinical and angiographic scoring system to predict the probability of successful first-attempt percutaneous coronary intervention in patients with total chronic coronary occlusion. JACC Cardiovasc Interventions. 2015;8:1540–1548.
42. Guelker JE, Bansemir L, Ott R, et al. Validity of the J-CTO score and the CL-score for predicting successful CTO recanalization. Int J Cardiol. 2017;230:228–231.
43. Karatasakis A, Danek BA, Karmpaliotis D, et al. Comparison of various scores for predicting success of chronic total occlusion percutaneous coronary intervention. Int J Cardiol. 2016;224:50–56.
44. Szijgyarto Z, Rampat R, Werner GS, et al. Validation of a chronic total coronary occlusion intervention procedural success score from the 20,000-patient EuroCTO registry: the EuroCTO (CASTLE) score. JACC Cardiovasc Interv. 2019;12:335–342.
45. Kalogeropoulos AS, Alsanjari O, Keeble TR, et al. Comparison of the novel EuroCTO (CASTLE) score with the J-CTO score for predicting technical success of chronic total occlusions percutaneous revascularization. EuroIntervention. 2019. pii:EIJ-D-19-00352. doi: 10.4244/EIJ-D-19-00352. [Epub ahead of print].
46. Liu Y, Liu YH, Chen JY, et al. A simple pre-procedural risk score for contrast-induced nephropathy among patients with chronic total occlusion undergoing percutaneous coronary intervention. Int J Cardiol. 2015;180:69–71.
47. Alfredo R, Galassi MB, Azzarelli S, et al. Percutaneous coronary revascularization for chronic total occlusions: a novel predictive score of technical failure using advanced technologies. JACC Cardiovasc Interv. 2016;9:911–922.
48. Jin C, Kim MH, Kim SJ, et al. Predicting successful recanalization in patients with native coronary chronic total occlusion: the Busan CTO score. Cardiology. 2017;137:83–91.
49. Namazi MH, Serati A, Vakili H, et al. A novel risk score in predicting failure or success for antegrade approach to percutaneous coronary intervention of chronic total occlusion: antegrade CTO score. Int J Angiol. 2017;26:89–94.
50. Maeremans J, Spratt JC, Knaapen P, et al. Towards a contemporary, comprehensive scoring system for determining technical outcomes of hybrid percutaneous chronic total occlusion treatment: the RECHARGE score. Catheter Cardiovasc Interv. 2017;91:192–202.
51. Opolski MP, Achenbach S, Schuhbäck A, et al. Coronary computed tomographic prediction rule for time-efficient guidewire crossing through chronic total occlusion: insights from the CT-RECTOR multicenter registry (Computed tomography registry of chronic total occlusion revascularization). JACC Cardiovasc Interv. 2015;8:257–267.
52. Yu CW, Lee HJ, Suh J, et al. Coronary computed tomography angiography predicts guidewire crossing and success of percutaneous intervention for chronic total occlusion: korean multicenter CTO CT registry score as a tool for assessing difficulty in chronic total occlusion percutaneous. Circ Cardiovasc Imaging. 2017;10.
53. Lembo NJ, Hatem R, Karmpaliotis D. Predictive scores of success in CTO PCI: there is no substitute for operator experience and skill. JACC Cardiovasc Interv. 2017;10:1099–1101.
54. Singh M, Bell MR, Berger PB, et al. Utility of bilateral coronary injections during complex coronary angioplasty. J Invasive Cardiol. 1999;11:70–74.
55. Mashayekhi K, Behnes M, Akin I, et al. Novel retrograde approach for percutaneous treatment of chronic total occlusions of the right coronary artery using ipsilateral collateral connections: a European centre experience. EuroIntervention. 2016;11:e1231–6.
56. Reinfret S, Joyal D, Spratt JC, et al. Chronic total occlusions percutaneous coronary intervention case selection and tecniques for the antegrade-only operator. Catheter Cardiovasc Interv. 2014;85:408–415.
57. Brilakis ES, Grantham A, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC Cardiovasc Interventions. 2012;5:367–379.
    - **The authors proposed an "hybrid" procedural algorithm that permit to switch between different interventional strategies to increase the success rate, improve the efficacy and minimize complications.**
58. Karatasakis A, Tarar M, Karmpaliotis D, et al. Guidewire and microcatheter utilization patterns during antegrade wire escalation in chronic total occlusion percutaneous coronary intervention: insights from a contemporary multicenter registry. Catheter Cardiovasc Interv. 2017;89:E90–8.
59. Maeremans J, Knaapen P, Stuijfzand WJ, et al. Antegrade wire escalation for chronic total occlusions in coronary arteries: simple algorithms as a key to success. J Cardiovasc Med (Hagerstown). 2016;17:680–686.
60. Brilakis ES, Karmpaliotis D, Patel V, et al. Complications of chronic total occlusion angioplasty. Interv Cardiol Clin. 2012;1:373–389.
61. Mitsudo K, Yamashita T, Asakura Y, et al. Recanalization strategy for chronic total occlusions with tapered and stiff-tip guidewire. The results of CTO new techniQUE for STandard procedure (CONQUEST) trial. J Invasive Cardiol. 2008;20:571–577.
62. Mishra S. Language of CTO interventions – focus on hardware. Indian Heart J. 2016;68:450–463.
63. Colombo A, Mikhail GW, Michev I, et al. Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. Catheter Cardiovasc Interv. 2005;64:407–411.
64. Valenti R, Vergara R, Migliorini A, 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.
65. Carlino M, Godino C, Latib A, et al. Subintimal tracking and re-entry technique with contrast guidance: a safer approach. Catheter Cardiovasc Interv. 2008;72:790–796.

66. Galassi AR, Tomasello S, Costanzo L, et al. Mini-STAR as bail-out strategy for percutaneous coronary intervention of chronic total occlusion. Catheter Cardiovasc Interv. 2012;79:30–40.
67. Galassi AR, Boukhris M, Tomasello SD, et al. Long-term clinical and angiographic outcomes of the mini-STAR technique as a bailout strategy for percutaneous coronary intervention of chronic total occlusion. Can J Cardiol. 2014;30:1400–1406.
68. Lombardi WL. Retrograde PCI: what will they think of next? J Invasive Cardiol. 2009;21:543.
69. Wilson W, Spratt JC. Advances in procedural techniques–antegrade. Curr Cardiol Rev. 2014;10:127–144.
70. Smith EJ, Di Mario C, Spratt JC, et al. Subintimal TRAnscatheter Withdrawal (STRAW) of hematomas compressing the distal true lumen: a novel technique to facilitate distal reentry during recanalization of chronic total occlusion (CTO). J Invasive Cardiol. 2015;27: E1–4.
71. Werner GS, Schofer J, Sievert H, et al. Multicentre experience with the BridgePoint devices to facilitate recanalization of chronic total coronary occlusions through controlled subintimal re-entry. EuroIntervention. 2011;8:23–29.
72. Whitlow PL, Burke MN, Lombardi WL, 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.
73. Azzalini L, Dautov R, Brilakis ES, et al. Procedural and longer-term outcomes of wire- versus device-based antegrade dissection and re-entry techniques for the percutaneous revascularization of coronary chronic total occlusions. Int J Cardiol. 2017;231:78–83.
74. Vo MN, Karmpaliotis D, Brilakis ES. "Move the cap" technique for ambiguous or impenetrable proximal cap of coronary total occlusion. Catheter Cardiovasc Interv. 2016;87:742–748.
75. Roy J, Hill J, Spratt JC. The "side-BASE technique": combined side branch anchor balloon and balloon assisted sub-intimal entry to resolve ambiguous proximal cap chronic total occlusions. Catheter Cardiovasc Interv. 2017;92:E15–9.
76. Surmely JF, Tsuchikane E, Katoh O, et al. New concept for CTO recanalization using controlled antegrade and retrograde subintimal tracking: the CART technique. J Invasive Cardiol. 2006;18:334–338.
77. Khand A, Patel B, Palmer N, et al. Retrograde wiring of collateral channels of the heart in chronic total occlusions: a systematic review and meta-analysis of safety, feasibility, and incremental value in achieving revascularization. Angiology. 2015;66:925–932.
78. Tsuyoshi I, Masahiko O, Munehisa M, et al. A novel, modified reverse controlled antegrade and retrograde subintimal tracking technique for bypassing the calcified proximal cap of coronary total occlusion. Case Rep Cardiol. 2017;2017:3850646.
79. Azzalini L, Candilio L, Carlino M, et al. Intracoronary snaring of the retrograde guidewire: how to overcome extreme takeoff angles in chronic total occlusion percutaneous coronary intervention. Catheter Cardiovasc Interv. 2017;91:464–469.
80. Mashayekhi K, Valuckiene Z, Neuser H, et al. Wire externalisation techniques for retrograde percutaneous coronary interventions of chronic total occlusions. EuroIntervention. 2017;13:e1489–e1490.
81. Hsu JT, Tamai H, Kyo E, et al. Traditional antegrade approach versus combined antegrade and retrograde approach in the percutaneous treatment of coronary chronic total occlusion. Catheter Cardiovasc Interv. 2009;74:555–563.
82. Carlino M, Azzalini L, Colombo A. A novel maneuver to facilitate retrograde wire externalization during retrograde chronic total occlusion percutaneous coronary intervention. Catheter Cardiovasc Interv. 2017;89:E7–12.
83. Rathore S, Katoh O, Tuschikane E, et al. A novel modification of the retrograde approach for the recanalization of chronic total occlusion of the coronary arteries intravascular ultrasound-guided reverse controlled antegrade and retrograde tracking. JACC Cardiovasc Interv. 2010;3:155–164.
84. Tiroch K, Cannon L, Reisman M, et al. High-frequency vibration for the recanalization of guidewire refractory chronic total coronary occlusions. Catheter Cardiovasc Inter. 2008;72:771–780.
85. Sandoval Y, Brilakis ES. The role of rotational atherectomy in contemporary chronic total occlusion percutaneous coronary intervention. Catheter Cardiovasc Interv. 2017;89:829–831.
86. Azzalini L, Agostoni P, Benincasa S, et al. Retrograde chronic total occlusion percutaneous coronary intervention through ipsilateral collateral channels: a multicenter registry. JACC Cardiovasc Interv. 2017;10:1489–1497.
87. Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC Cardiovasc Interv. 2012;5:367–379.
88. Maeremans JWS, Knaapen P, Spratt JC, et al. The hybrid algorithm for treating chronic total occlusions in Europe: the RECHARGE registry. J Am Coll Cardiol. 2016;68:1958–1970.
89. Christopoulos GKD, Alaswad K, RW Y, 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.
90. Riley RF, Sapontis J, Kirtane AJ, et al. Prevalence, predictors, and health status implications of periprocedural complications during coronary chronic total occlusion angioplasty. EuroIntervention. 2018;14:e1199–e1206.
91. Gaxiola E, Browne KF. Coronary artery perforation repair using microcoil embolization. Cathet Cardiovasc Diagn. 1998;43:474–476.
92. Shemisa K, Karatasakis A, Brilakis ES. Management of guidewire-induced distal coronary perforation using autologous fat particles versus coil embolization. Catheter Cardiovasc Interv. 2017;89:253–258.
93. Kotsia AP, Brilakis ES, Karmpaliotis D. Thrombin injection for sealing epicardial collateral perforation during chronic total sealing epicardial collateral perforation during chronic total. J Invasive Cardiol. 2016;26:E124–6.
94. Guelker JE, Rock T, Ott R, et al. Acute outcome of chronic total occlusion (CTO) recanalizsation in the elderly. Med J Malaysia. 2017;72:236–240.
95. Yamamoto E, Natsuaki M, Morimoto T, et al. Investigators. C-KPCRC-. 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.
96. Hoye A, van Domburg R, Sonnenschein K, et al. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience. Eur Heart J. 2005;26:2630–2636.
97. Safley DM, House JA, Marso SP, et al. Improvement in survival following successful percutaneous coronary intervention of coronary chronic total occlusions: variability by target vessel. JACC Cardiovasc Interv. 2008;1:295–302.
98. Claessen BE, Dangas GD, Godino C, et al. Impact of target vessel on long-term survival after percutaneous coronary intervention for chronic total occlusions. Catheter Cardiovasc Interv. 2013;82:76–82.
99. Lee SW, Lee PH, Ahn JM, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. Circulation. 2019;139:1674–1683.
   - **RCT comparing CTO PCI and optimal medical therapy showing similar effectiveness in terms of mortality of any cause, non-fatal myocardial infarction and any revascularization. Despite some limitation of the study it provides several considerations.**
100. Juan Luis Gutiérrez-Chico YL. DECISION-CTO: A "negative" clinical trial? Really? Cardiol J. 2017;24:231–3.
101. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. Eur Heart J. 2018;39:2484–2493.
   - **Randomized controlled trial showing CTO PCI to be superior to medical therapy for angina relief and quality of life.**
102. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. J Am Coll Cardiol. 2018;72:3126–3137.
103. Cho S, Shin DH, Kim JS, et al. Rationale and design: impact of intravascular ultrasound guidance on long-term clinical outcomes

of everolimus-eluting stents in long coronary lesions. Contemp Clin Trials. 2015;40:90–94.
104. Weisz G, Metzger DC, Caputo RP, et al. Safety and feasibility of robotic percutaneous coronary intervention: PRECISE (Percutaneous robotically-enhanced coronary intervention) study. J Am Coll Cardiol. 2013;61:1596–1600.
105. Mahmud E, Naghi J, Ang L, et al. Demonstration of the safety and feasibility of robotically assisted percutaneous coronary intervention in complex coronary lesions: results of the CORA-PCI Study (Complex robotically assisted percutaneous coronary intervention). JACC Cardiovasc Interv. 2017;10:1320–1327.
106. Madder RD, VanOosterhout SM, Jacoby ME, et al. Percutaneous coronary intervention using a combination of robotics and telecommunications by an operator in a separate physical location from the patient: an early exploration into the feasibility of telestenting (the REMOTE-PCI study). EuroIntervention. 2017;12:1569–1576.