Heart, Lung and Circulation (2024) **33**, 764–772
1443-9506/24/$36.00
https://doi.org/10.1016/j.hlc.2024.01.031

REVIEW

Chronic Total Occlusions: A State-of-the-Art Review

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Received 30 July 2023; received in revised form 18 January 2024; accepted 22 January 2024; online published-ahead-of-print 1 April 2024

The percutaneous management of chronic total occlusions (CTO) is a well-established sub-specialty of Interventional Cardiology, requiring specialist equipment, training, and techniques. The heterogeneity of approaches in CTO has led to the generation of multiple algorithms to guide operators in their management. The evidence base for management of CTOs has suffered from inconsistent descriptive and quantitative terminology in defining the nature of lesions and techniques utilised, as well as seemingly contradictory data about improvement in ventricular function, symptoms of angina, and mortality from large-scale registries and randomised controlled trials. Through this review, we explore the history of CTO management and its supporting evidence in detail, with an outline of limitations of CTO-percutaneous coronary intervention and a look at the future of this growing field within cardiology.

Keywords Chronic total occlusion • CTO • Percutaneous coronary intervention • PCI

Introduction

Significant progress has been made in recent years in the percutaneous management of chronic total occlusions (CTO). Once thought to be of minimal clinical importance—and perhaps best managed medically—increasing evidence suggests that in the correct patient population, successful percutaneous coronary intervention (PCI) to a CTO may result in a significant reduction in symptom burden and functional ischaemia [1]. Additionally, with increased operator experience, dedicated training programs, the wider release of specialised equipment, and the development of novel lesion-crossing strategies, the rate of procedural success has become considerably higher [2,3]. However, even with the increasing success rates and improvements in patient quality of life, CTO–PCI does not have universal uptake across all countries with the majority of data and techniques coming from three main regions—North America, Europe, and Asia [4–9].

Background

Commonly ascribed attributes of a CTO include an estimated chronicity of greater than 3 months, heavy atherosclerotic burden, and occlusive (or near-occlusive) disease with complete interruption of anterograde arterial filling and thrombolysis in myocardial infarction (TIMI) grade 0 flow beyond the lesion, or TIMI 1 flow in functional CTOs [10,11]. The prevalence of CTOs is potentially under-appreciated. Domestically, a relative lack of country-specific data makes direct comparison challenging [12,13]. However, with an ageing population, the assumption can be made that higher complexity lesions such as CTOs will increase in frequency [14].

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Historically, CTOs were managed medically with anti-platelet agents, and statin and anti-anginal therapy [15]. Despite their ingenuity with non-specialised equipment, the early CTO operators found themselves faced with high rates of vessel re-occlusion and complications [16]. With the advent of drug-eluting stents, more adventurous proceduralists began to open lesions previously considered 'untreatable' in the era of bare metal stents. Much of the early data supporting percutaneous management of CTOs was authored in Japan, with the Japanese leading the way with techniques, equipment, outcomes, and success rates [4]. The creation of retrograde and dissection and re-entry techniques improved success rates, and over time fewer complications were experienced [17]. However, these skills were challenging to teach, and even more so to master. Operators were aware of this difficulty and as CTO–PCI expanded across the world, experts collaborated to simplify the procedure with the creation of scoring systems such as the Japanese-CTO (J-CTO) score, as outlined in Table 1, helping risk-stratify lesions from very difficult to more achievable [4].

The publication of the J-CTO score allowed bolder Interventionalists to venture into CTO management, with the use of an objective tool for CTO assessment, potentially allowing lower-volume operators to select less challenging lesions and thus increasing attempts plus improving success rates [15,18,19]. The system of categorising the angiographic characteristics of CTO seen in the J-CTO scoring system was the beginning of the development of what is now known as the "CTO–PCI Algorithm," which is a way to tackle CTO lesions based on angiographic characteristics. Over time the community developed various algorithms designed to guide operators and provide a strategic approach, improve outcomes, and allow easier teaching [20–22]. This systematic approach to CTO–PCI led to an explosion in new techniques, equipment, and self-minted "CTO operators" who focused on opening chronically occluded arteries successfully, efficiently, and with low complication rates [23].

Table 1 Variables of the Japanese-CTO score.

Variable	Points Attributed	Notes
Stump Morphology	Tapered=0 Blunt=1	A stump must not be tapered to be awarded 1 point
Calcification	Absent=0 Present=1	The point is awarded for *any* degree of calcification within the lesion
Tortuosity	$<45°=0$ $>45°=1$	This only applies to tortuosity within the CTO segment, *not elsewhere* in the vessel
Occlusion Length	<20 mm=0 >20 mm=1	Preferentially determined via dual injection
Number of Attempts	First=0 Subsequent=1	There is no specification about the level of experience of the initial operator.
Scoring (add points for each variable): Category of Difficulty: Easy=0; Intermediate=1; Difficult=2; Very Difficult ≥3		

Adapted from Morino et al. [4].
Abbreviation: CTO, chronic total occlusion.

The History of Algorithmic Management of CTOs

Initial uptake in CTO–PCI procedures in the early 2000s was low [18,21]—often attributed to procedural complexity, suboptimal outcomes, and higher-than-standard rates of complication [5,24], but equally due to a lack of dedicated CTO tools and limited number of CTO operators who could teach CTO–PCI. To improve CTO–PCI uptake and success rates, several groups aimed to standardise patient selection and techniques. Taking inspiration from algorithms designed to help operators choose the ideal procedural strategy for severe aortic stenosis—such as those borne out of the original PARTNER trials [25]—various groups devised instructional algorithms aimed at improving outcomes, procedural efficiency, and guiding lower-volume operators in their management of CTOs.

The 'hybrid' approach, first described by Brilakis et al. [20], became the starting point of the algorithmic trend in CTO management [26]. The hybrid approach gave operators an algorithm to not only devise their initial strategy but also several suggestions for altering their approach based on the level of intra-procedural success [26]. This algorithm helped to further uptake of CTO–PCI, improve success rates and quality-of-life outcomes, reduce procedural complications, and increase reproducibility [27].

However, the hybrid approach was not universally adopted. The Asia Pacific CTO (AP-CTO) Club crafted their own, slightly different algorithm to guide low-to-medium volume operators in 2017 [22]. Novel features of the AP-CTO algorithm include prompts for intravascular imaging, earlier use of CrossBoss catheters, suggestions for in-stent CTO, and when to terminate the procedure. Follow-up data from two years later demonstrated procedural success was improved, with a higher mean J-CTO score (2.9±1.2), and main mode of failure being inability to re-wire the true lumen [6]. Similarly, the Euro-CTO Club devised their own algorithm focusing on the length of CTO as an important variable and incorporating optical coherence tomography [21]. Shortly thereafter, Chinese CTO [28] and J-CTO [29] algorithms were also published.

The proliferation and integration of regional-based algorithms established the importance of this form of CTO–PCI, but the plethora of methods led to confusion. A group of over 125 authors from 50 countries attempted to establish a Global CTO Crossing Algorithm [30]. The purpose of this tool was to generate uniformity in approach across centres, and to assist operators in describing and assessing lesions and determining strategies for managing CTO lesions [30]. The core tenets of the document are that dual angiography is essential, that CTO proximal cap morphology, length, composition, and distal vessel quality must be assessed in the planning stage, and, lastly, that in the presence of ambiguity of the proximal cap, a retrograde approach be utilised [30]. Similar to the AP-CTO algorithm, strategies are suggested for failure with advice on when to abandon. The authors also highlighted the need for proctorship [30]. This single algorithm, outlined in the Figure, is now commonly used as the single teaching algorithm for new CTO–PCI operators.

Evolving Evidence

The techniques and success rates of CTO–PCI have come a long way. However, the question is often asked—is there evidence to support this complex class of intervention? The first form of evidence supportive of CTO–PCI came from registry data, and this remains the mainstay. The number of randomised controlled trials (RCTs) involving CTO–PCI is vastly outnumbered by retrospective data pools and registries. The Interventional community has long expressed a hunger for an RCT to support the more routine opening of CTO lesions. To coordinate and run a prospective RCT in this field requires significant funding, time to delineate primary and secondary outcomes, and a sufficient volume of patients to achieve statistical significance [31]. The heterogeneous nature of both CTO lesions (e.g., comparison of a left main CTO with a side branch) and the patient substrate opens such research to a broad range of confounding factors [8]. Many patients nominated for CTO–PCI have failed prior medical therapy, with more medical comorbidities and factors precluding surgical revascularisation [32], which make this cohort more prone to adverse events and thus more challenging to definitively establish benefits [33].

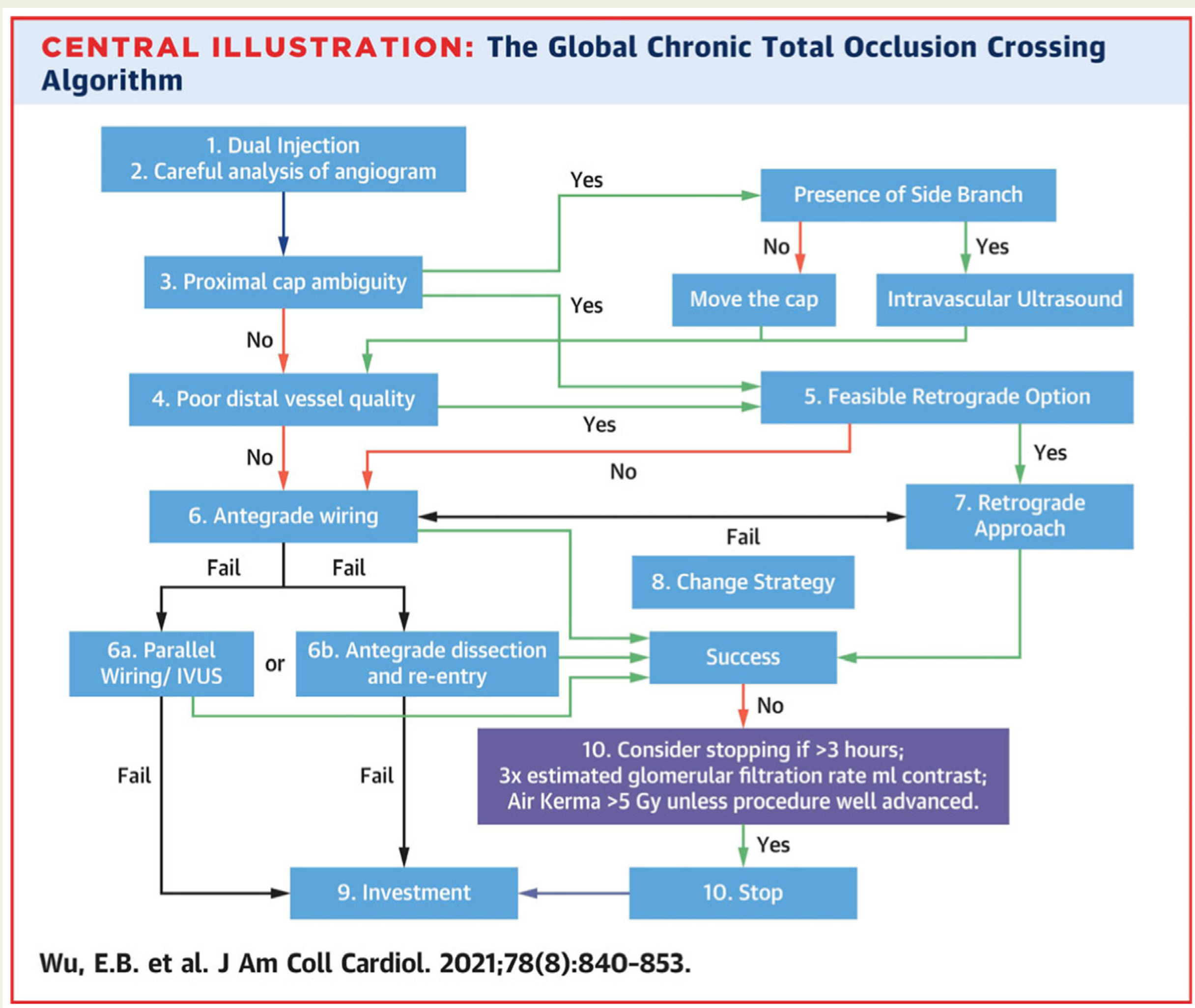

Figure The global chronic total occlusion crossing algorithm. Source: Wu et al. [30].

Reflecting upon the literature paints a mixed picture of results. Despite clear evidence that CTO–PCI reduces symptom burden beyond what is achievable with maximal medical therapy [32,34,35], a signal towards improved left ventricular function [19,36], and possibly even a late mortality benefit [1], large-scale RCTs have thus far failed to demonstrate improved short-term mortality benefit [34], with a harm signal towards some patients who experienced complications of their procedure [3]. Of note, many trials did not differentiate dedicated CTO operators from the more general Interventional pool of staff, potentially diluting their results [31,37].

Hence, registry data is key to understanding the role of CTO–PCI in modern intervention. There are now many large-scale registries active in Europe, North America, and Asia, which show promising rates of technical success with fewer complications than prior studies [5,6,9,21]. The inherent weaknesses of retrospective data are well-established, particularly selection bias—where operators include easier cases while excluding difficult cases. Despite this, registries allow for robust, population-level information to be gathered, and their results can be combined with the data obtained from landmark RCTs to guide operators to make evidence-based decisions tailored to their individual patients. Table 2 outlines key features of the seminal publications in the field of CTO management.

As seen in Table 2, there are many high-quality papers in the field of CTO—with a relative dearth of RCTs. Starting in 2011 with the seminal J-CTO paper, with a technical success rate of 70% [4], subsequent authors report higher rates of successful PCI with an increasing number of cases classed as CTO in registry data from North America, Europe, and the Asia Pacific [5,9,21,38]. Christakopoulos et al. [33] performed a weighted meta-analysis of 28,486 patients in 2015 who had successful vs unsuccessful CTO–PCI. He found that compared with failed procedures, successful CTO–PCI is associated with a lower risk of death, stroke, and coronary artery bypass grafting (CABG) with less recurrent angina. These findings were confirmed by Hoebers et al. [39], who also performed a meta-analysis including 15,459 patients who underwent CTO–PCI which also revealed an improvement in survival and in left ventricular ejection fraction (LVEF) in those who had successful CTO–PCI. However, the interventional community sought robust RCT data to confirm what the registries suggested.

Contrary to registry data, landmark RCTs such as EXPLORE found no difference in LVEF between no PCI and CTO–PCI (with a small improvement in LVEF in those with left anterior descending artery CTO) [34]. DECISION-CTO found no improvement in major adverse cardiovascular and cerebrovascular events (MACCEs) and a small harm signal with bleeding events in the CTO–PCI arm [31]. EURO-CTO, which investigated symptom relief rather than MACCE, found improvement in angina, dyspnoea, and effort tolerance. More recently REVASC, a smaller, German study using cardiac magnetic resonance imaging markers found no improvement in segmental wall thickness in the revascularised territory, but a reduction in rate of MACCE [40].

Ultimately, and despite conflicting registry data, the conclusion from the above RCTs was that CTO–PCI was unlikely to affect prognosis except in the most severe cases with an extensive area of ischaemia, and should be reserved for symptom alleviation [3,5,34,35]. This correlates with current scientific guidelines, which recommend CTO–PCI in patients who have failed optimal medical therapy or who have a large area of ischaemia in the territory of the occluded vessel [41]. Thus, not only should symptoms be used to determine the need for revascularisation, but non-invasive imaging can be used to help identify large areas of ischaemia, along with identifying hibernating and non-hibernating myocardium [42].

Further complexities are added when considering two other common situations. CTOs do not appear commonly in isolation, but rather in multivessel disease, and secondly, how should a CTO be treated in the context of an acute coronary syndrome (ACS)? These situations are highly patient-specific yet existing evidence demonstrates complete revascularisation, including CTO–PCI, leads to improvements in survival. Ahn et al. [43] performed a patient-level pooled analysis of the SYNTAX, PRE-COMBAT and BEST trials, comparing stenting to CABG surgery according to completeness of revascularisation. Their conclusions were complete PCI revascularisation (including CTO) had similar long-term survival rate to those seen in CABG, and those who had incomplete revascularisation had a higher rate of death from any cause (adjusted hazard ratio 1.43; 95% confidence interval 1.03–2.00). In relation to ACS, registry data indicates favourable outcomes in those who have CTO–PCI performed within the first 30 days after infarction [44]. Conversely, the CREDO-Kyoto acute myocardial infarction (AMI) registry showed no benefit at 5 years in those who had CTO–PCI after ACS [45]. CTO experts are familiar with conflicting data, but on balance it appears to favour complete revascularisation. Despite initial debate on the importance of revascularisation in ACS, the preponderance of data (CvLPRIT, DANAMI-3-PRIMULTI, and COMPARE-ACUTE) shows the benefit of complete revascularisation of ACS patients [46–50]. Timing of said revascularisation remains vital, as CULPRIT-SHOCK showed performing CTO–PCI during shock in ACS could also cause harm [51]. Once again, most data looking directly at CTO–PCI and ACS is from registries or extrapolated from RCT subset analyses, with no RCT focussed primarily on CTO–PCI. This area still lacks dedicated RCTs, but there may be enough evidence in the complete revascularisation setting to warrant CTO–PCI on a case-by-case basis.

Ongoing RCTs may provide our best look yet at the positive effect of CTO–PCI. ISCHEMIA-CTO is a subset analysis of patients from within the famous ISCHEMIA study. Formal reports are not yet published, as there is ongoing analysis, however preliminary "late-breaker" data suggests a

Table 2 Summary of evidence in CTO management.

Study & Author	Year	Region	Type	Cohort Size	Primary Outcome	Secondary Outcomes	Results	Notes
J-CTO *Morino et al*	2011	Japan	Multi-centre [12], non-randomised, prospective registry	465	Procedural success	N/A	Overall success=70.4% Success <30 min=41.4%	The study from which the J-CTO score was derived, predicting procedural success in <30 min
PROGRESS CTO [8] *Christopoulos et al*	2016	USA	Opt-in, multi-centre [7] registry	762	Technical success	N/A	Technical success=92.9%	Mean J-CTO=2.5±1.2 in successful Mean J-CTO=3.3±1.0 in failed
EXPLORE [34] *Henriques et al*	2016	Europe, Canada	RCT: CTO-PCI vs no CTO-PCI	304	LVEF LVEDV	Infarct size Regional myocardial function	Success rate=73% LVEF did not differ between groups No difference in adverse events	Sub-group analysis demonstrated LAD CTO did see some improvement in LVEF
DECISION-CTO [35] *Lee et al*	2016	Asia (Korea, India, Indonesia, Thailand, Taiwan)	Open-label, multi-centre [19] RCT with 4-year follow-up	834	Composite death, MI, stroke, or revascularisation (inc. PCI and surgical)	Bleeding, stent thrombosis, quality of life	No statistical difference in 1° outcome Higher bleeding in PCI group	Large crossover from no PCI to CTO–PCI Three complications - stroke, tamponade, intra-coronary thrombus
SCAAR [9] *Ramuåddal et al*	2016	Sweden	Observational, multi-centre registry	6,442	Mortality	Technical success, symptomatic burden	Higher mortality in CTO group (HR 1.41) Success=54.2%	Registry began in 1999 - techniques have significantly improved
RECHARGE [38] *Maeremans et al*	2016	Europe (UK, France, Belgium, Netherlands)	Multi-centre [17] registry	1,177	Technical success	Procedural safety, MACCE, breakdown of techniques used	Success=86% Low incidence of MACCE (= 2.6%)	Required CTO operators to have a minimum level of experience Used hybrid algorithm
AP-CTO [6] *Harding et al*	2016	Asia Pacific	Multi-centre [8] registry	485	Technical or procedural success	N/A	Technical success=93.8%; procedural=89.9%	Main mode of failure was in attempting antegrade-only PCI
OPEN-CTO [5] *Sapontis et al*	2017	USA	Observational, single-arm, multi-centre [12] registry	1,000	Technical success	Mortality, symptomatic burden	Technical success=86%; in-hospital mortality 0.9; 1-month mortality 1.3%, anginal improvement	Hybrid approach examined
EURO-CTO [32] *Wener et al*	2018	Europe	Prospective, multi-centre, open-label, RCT	396	Symptom burden	Technical success, physical limitation	Angina, physical limitation, dyspnoea class were improved	All non-CTO lesions treated in advance Technical success=86.6%

Table 2. **(continued).**

Study & Author	Year	Region	Type	Cohort Size	Primary Outcome	Secondary Outcomes	Results	Notes
REVASC [39] *Mashayeki et al*	2018	Europe (Germany)	Prospective, single-centre, open-label RCT	205	Δ in segmental wall thickening in CTO territory	Improvement of RWMA, indices of LV function, MACCE	No benefit for primary or secondary endpoints Reduced major adverse coronary event rates	Suggest CTO-PCI gives benefit over no CTO-PCI with reduced rates of coronary events at 12 months
CASTLE *Szijgyarto et al*	2019	Europe	Multi-centre [55] registry	14,882	Technical success	Validation of CASTLE score	Technical success=84.2% Retrograde subset success=67.3%	Demonstrated CASTLE score could be used to supplement J-CTO score for predicting success
Korean Registry [7] *Rha et al*	2020	Korea	Open-label, multi-centre [26] registry	3,271	Technical success	MACCE, revascularisation	Technical success=81.6%	Most frequent were RCA
ISCHEMIA-CTO *Author not finalised* NCT #03563417	2024	USA, Europe	Prospective, multicentre, open-label RCT (Sub-study of ISCHEMIA)	1,470 (subset of 5,179)	Time to death/ AMI	MACCE, time to death/AMI, quality of life/symptoms, hospitalisation for cardiac cause	–	Results pending as trial proceeds

Abbreviations: CTO, chronic total occlusion; J-CTO, Japanese CTO; N/A, not available; RCT, randomised controlled trial; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; MI, myocardial infarction; SCAAR, Swedish Coronary Angiography and Angioplasty Registry; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; RWMA, regional wall motion abnormality; LV, left ventricular; AMI, acute myocardial infarction.

significant reduction of angina and improved quality of life in the CTO–PCI cohort. The NOrdic-Baltic Randomised Registry Study for Evaluation of PCI in Chronic Total Coronary Occlusion (NOBLE-CTO; NCT03392415) is an RCT looking at optimal therapy with and without CTO–PCI, examining hard outcomes.

Despite the numerous registries throughout Asia, Europe, and the United States, there are still countries where CTO–PCI is not as widely adopted. Domestically, there is currently no national registry for collecting Australian CTO data. The majority of datasets exist only at the state level (e.g., the Victorian Cardiology Outcomes Registry), and the data points in this impressive body of work do not include CTO-specific nomenclature or collection. Subset data is also available from some registries, such as the Melbourne Interventional Group.

Limitations of PCI in CTO Management

CTO management is not without its limitations, which are particularly relevant in the Australian context and contribute to reduced uptake in our hospitals. These procedures tend to be significantly longer [3], with diversion of Cardiac Cath Lab resources away from shorter cases, having downstream effects on the flow of patients through the hospital. The majority of Australian research in the area of CTO is approaching 5 years of age [13,52,53]. Perhaps exacerbating the situation, Australia has very few dedicated, complex intervention programs (e.g., Complex High-risk Indicated Patients), with even large, tertiary centres employing few dedicated CTO operators. Without growing this subspecialty training program, the Australian evidence base will continue to stagnate. Historically, many centres have described a higher-than-standard complication rate, with lower overall success rates (defined as residual stenosis >10% or failure to restore TIMI 3 flow) when compared with standard PCI [24].

An economic argument is often made to limit Cath Lab time dedicated to CTOs, with the suggestion that their percutaneous approach to management is not cost-effective. On the contrary, several studies have demonstrated that in the correctly identified patient cohort, CTO–PCI is cost-effective and improves patients' quality-of-life metrics [54–56]. However, where complications arise, higher hospital costs may occur with a subsequent increase in length of stay, which occurs in approximately 14% of cases [55]. In some countries, including Australia, the percutaneous management of CTOs currently attracts the same financial reimbursement (measured by Weighted Inlier Equivalent Separation funding) as standard PCI [57]. This provides even less incentive for operators to perform CTO–PCI, which may be a longer, far more complicated procedure compared with standard PCI, potentially pushing patients towards medical therapy or PCI of non-CTO lesions.

Pleasingly, newer registry data would suggest that the rates of complications are falling as success rates rise [3]. With a stronger training program for CTO operators—performing more regular CTO–PCI—these negative consequences could be further minimised, which will be essential as their incidence continues to rise [37]. As CTOs become more frequently identified, referral pathways must become solidified to ensure non-CTO operators have a clear process for ensuring their patients are reviewed by the correct interventionalists.

The Near Future of CTOs

By its very nature, the percutaneous management of a CTO is complex. With the incidence of CTO lesions increasing and our ageing population in Australia [14], it is apparent there will be an increased need for CTO operators, as patients with residual angina who are non-surgical candidates will require assistance. This would necessitate dedicated training programs and proctoring, which has been objectively shown to improve outcomes (particularly in lesions with a J-CTO score of ≥2) [58]. Not only are the skills required for percutaneous CTO management significantly more extensive than basic PCI, but there is also a range of specialised equipment already in circulation that one must become familiar with and have the ability to use as the situation requires. Moving forward, techniques will no doubt evolve using both the pre-existing tools at our disposal, as well as developing further specialised devices.

Conclusion

CTOs represent an oft-neglected frontier within Interventional Cardiology. CTO–PCI remains an invaluable tool in reducing anginal symptom burden. As CTO lesion incidence rises and their percutaneous management becomes more commonplace, it would be ideal to see the evidence base become more robust. With RCTs demonstrating mixed results and having several design issues at their core, collaborative data registries—in both a national and international forum—will become essential. Locally, the development of CTO–PCI registries, research and dedicated training programs will allow Australia to collaborate and compare more directly with CTO operators in Europe, North America, Asia, and on the global stage.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No conflict of interest for commercial products. AI and AI-assisted technologies have not been used in the writing process.

Conflict of Interest

Dr Dautov received proctoring and lecturing fees from Boston Scientific and Bio-Excel Pty Ltd. The remaining authors have no conflicts of interest to disclose.

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