Chronic Total Occlusion Coronary Intervention: In Search of a Definitive Benefit

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ABSTRACT: Percutaneous coronary intervention (PCI) of chronic coronary total occlusion is the latest frontier in percutaneous intervention. There are vast improvements in the initial success and safety of the procedure as well as a better understanding of appropriateness and benefits. Advances in technology and skill allow for increased utilization of PCI in cases of chronic coronary total occlusion, with benefits regarding symptoms and quality of life. Percutaneous coronary intervention for chronic coronary total occlusion can correct ischemia and achieve complete revascularization while avoiding traditional coronary bypass grafting, although survival benefits remain unclear.

BACKGROUND

The field of coronary interventions has advanced tremendously in the last 2 decades and is particularly evident with regard to chronic total occlusion (CTO) percutaneous coronary intervention (PCI). There are vast improvements in the procedure's safety and initial success as well as a better understanding of its benefits and patient suitability. Even so, many doubts and questions remain as to the benefits of CTO PCI. It has been described that the procedure offers symptomatic benefits and improves quality of life, but this is based more on observational studies rather than on randomized clinical trials.[1] CTO PCI is considered by most to be a long, expensive, technically difficult procedure with low success and high complication rates. Also, CTO is perceived as a benign and stable lesion since it does not progress or cause a heart attack. If there are adequate collateral arteries, what is the need for revascularization?

Coronary CTO is defined as a totally occluded coronary artery with TIMI (Thrombolysis in Myocardial Infarction) 0 flow for at least 3 months.[2] It is reported to occur in 15% to 23% of patients who undergo coronary angiograms and is the most common feature leading to coronary bypass surgery as a treatment recommendation for revascularization.[3,4] The Bypass Angioplasty Revascularization Investigation (BARI) registry suggested that CTO was a powerful predictor of referral for coronary artery bypass graft (CABG) and treatment with medical therapy. When a CTO was present in the BARI trial, 10% received PCI, 40% received CABG, and 50% received medical therapy. When a CTO was not present, the numbers shifted to 35% PCI, 30% CABG, and 35% medical therapy.[5] Interestingly, there are many times during surgery that CTO arteries are not amenable for bypass (e.g., too small or diseased arteries). For example, in the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) CTO substudy, only 68% of those sent to surgery actually underwent CABG, leading to 49.6% overall complete revascularization in the CTO subset.[6]

In the past, PCI for a CTO had low success rates of about 50%, which meant that CABG was the gold standard in terms of complete revascularization. Patients with a failed CTO PCI had higher rates of CABG at 2 years compared to patients with successful procedures ($P < .001$). After adjustment, successful CTO PCI remained associated with a lower risk for CABG surgery (HR 0.14; 95% CI, 0.08-0.24; $P < .01$).[7] Novel PCI techniques have helped to overcome this barrier by improving PCI success rates to > 85% at some centers.[8,9]

TECHNIQUES

The significant improvement in coronary CTO PCI success rates is due to a variety of reasons, with the most important being technological advances. Wire designs with higher crossing power lead to higher success rates. Polymer-jacketed wires are used in most cases, including the most successfully crossed cases.[10] Crossing catheters are designed to advance in intimal and subintimal spaces, allowing for subsequent exchange to support wires and, eventually, low-profile balloons.

There are primarily four techniques for CTO PCI, including (1) antegrade wire escalation, (2) antegrade dissection and reentry (ADR), (3) retrograde wire escalation, and (4) retrograde dissection and reentry. The typical ADR technique uses the Stingray LP (Boston Scientific) wire and balloon. This allows the wire to reenter in the luminal space after having traversed beyond the CTO segment in the subintimal space. If the antegrade techniques are unsuccessful, retrograde wire crossing using septal or epicardial "interventional" collaterals can be used (Figure 1). Skilled operators can yield

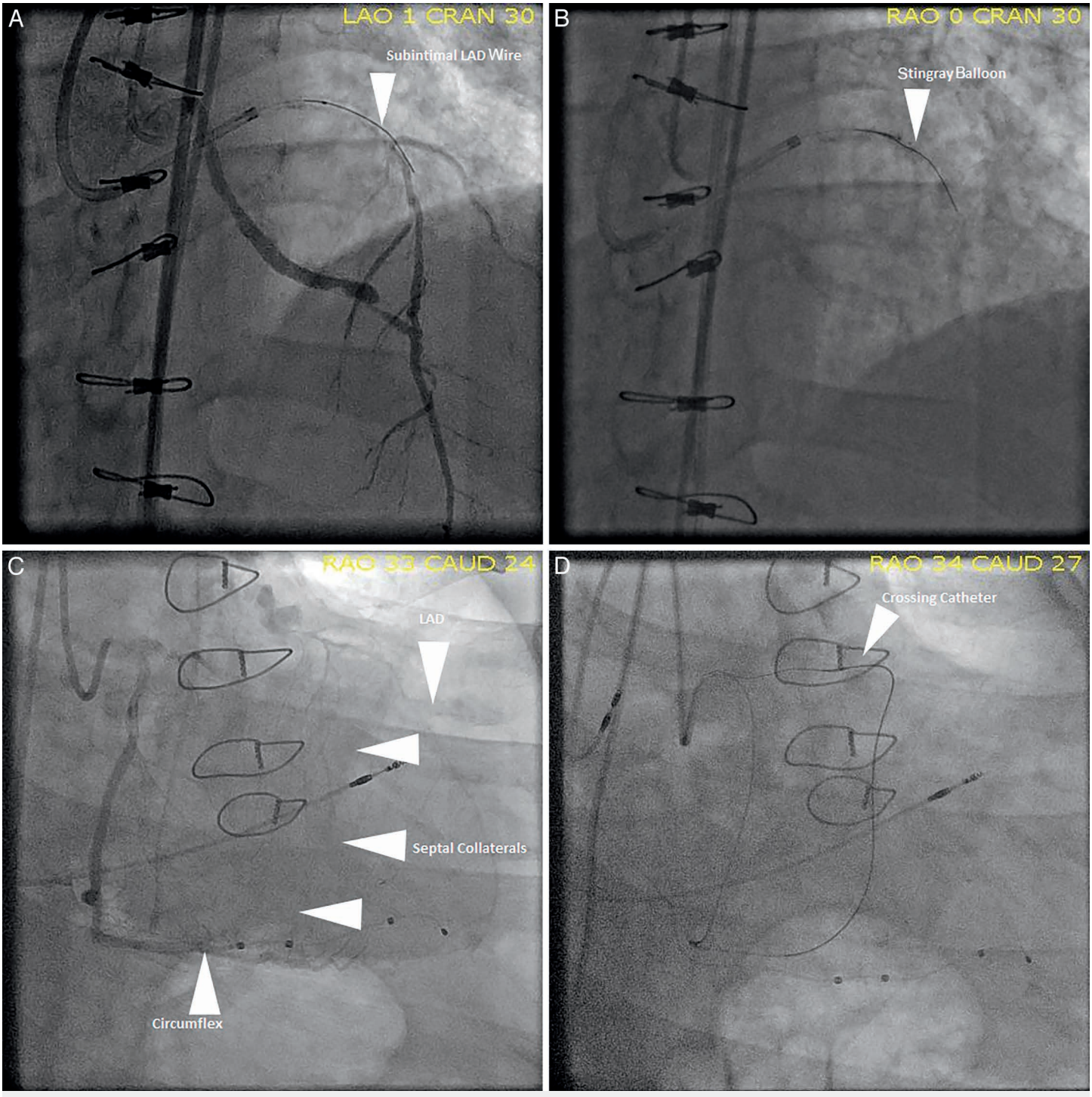

Figure 1.
(A, B) Antegrade wire reentry technique using a Stingray (Boston Scientific) balloon in mid LAD (left anterior descending). (C, D) Retrograde wire escalation technique using septal collaterals from circumflex to LAD.

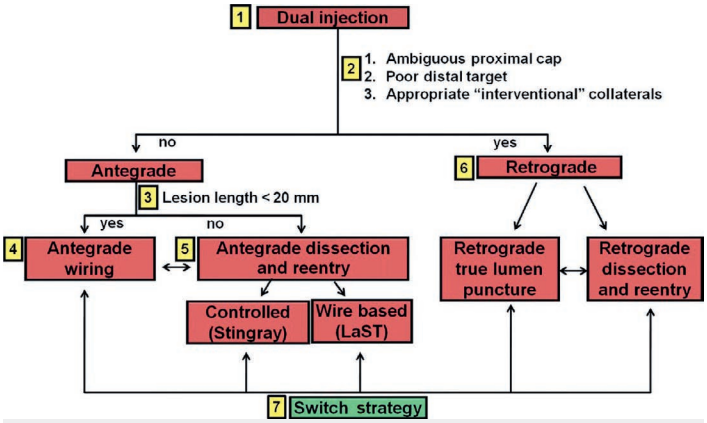

Figure 2.
Hybrid algorithm for chronic total occlusion percutaneous coronary intervention. Reprinted with permission.[11]

high crossing rates with dissection reentry via the retrograde approach, often using a hybrid CTO crossing algorithm for guidance (Figure 2).[11]

Success rates depend not only on operator experience but also on anatomical features. Length, calcification, tortuosity, and an ambiguous cap are features that will affect initial success rates. The PROGRESS CTO registry (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) has shown high success rates of 91% and low major complication rates of 1.7% for CTO interventions performed at high-volume centers with skilled operators.[12]

As shown by the OPEN CTO investigators, a successful CTO program requires skill and knowledge of all four techniques (Table 1).[8] Early complication rates are slightly higher than those of routine PCI, regardless of which technique is used, but can be properly identified and managed by experienced sites. The OPEN CTO registry is a comprehensive, core-lab adjudicated, single-arm, multicenter registry of 1,000 consecutive patients who underwent CTO PCI with the hybrid approach. The technical success was 86%, in-hospital and 1-month mortality were 0.9% and 1.3%, respectively, and 48 patients (4.8%) had perforations requiring treatment. Periprocedural myocardial infarction (MI) was observed in 26 patients (2.6%) and in-hospital repeat PCI occurred in one (0.1%). Seven patients overall (0.7%) were referred for emergent surgery, and no in-hospital strokes were identified. Acute kidney injury was identified in eight patients (0.8%), and there were three (0.3%) major bleeding events that required treatment.

The durability of second-generation drug-eluting stents has made CTO PCI a viable alternative to CABG, especially compared to saphenous vein graft bypass. The EXPERT CTO trial used everolimus-eluting stents for CTO PCI in 250 patients.[13] At 1 year, clinically driven target lesion revascularization was seen in 6.3% of patients, and cardiac death occurred in 1.9%. Definite subacute stent thrombosis (ST) was identified in two patients (0.9%), with no definite events observed after 30 days. Late probable ST was identified in one patient (0.5%).

SYMPTOMATIC BENEFIT

Determining which individuals are clinically appropriate and will benefit from CTO PCI requires more research. However, there are several well-established clinical benefits. Improved Seattle Angina Questionnaire (SAQ) angina frequency score and quality of life score have been well recognized after CTO interventions.[14] This improvement has been confirmed in many registries, capturing a clinically relevant end point that compels patients to seek a cardiologist in the first place–to control or avoid altogether their disabling symptoms. Sometimes patients attribute their fatigue and dyspnea to old age or poor fitness, but after revascularization, they recognize how much of their limitation was caused by the occluded artery. In the OPEN CTO registry,[8] mean ± SEM SAQ quality of life scores improved from 49.4 ± 0.9 to 75.0 ± 0.7 ($P < .01$), mean Rose Dyspnea Scale scores improved (decreased) from 2.0 ± 0.1 to 1.1 ± 0.1 ($P < .01$), and physician health questionnaire scores for depression improved (decreased) from 6.2 ± 0.2 to 3.5 ± 0.1 ($P < .01$) at 1 month. After adjusting for baseline differences, the mean group difference between successful and unsuccessful CTO PCI in SAQ quality of life was 10.8 (95% CI, 6.3-15.3; $P < .001$).

IMAGING GUIDANCE

Imaging studies are playing a pivotal role in guiding CTO PCI. Information regarding wall motion, ischemia, and viability is

	AWE (%)	ADR (%)	RWE (%)	RDR (%)
First strategy	54.7	13.9	13.3	18.1
Second strategy	11.7	44	20.6	23.7
Successful strategy	40.8	24.3	10.3	24.6

Table 1.
First, second, and successful strategies employed during hybrid chronic total occlusion (CTO) percutaneous coronary intervention (PCI). ADR: antegrade dissection and reentry; AWE: antegrade wire escalation; RDR: retrograde dissection and reentry; RWE: retrograde wire escalation[8]

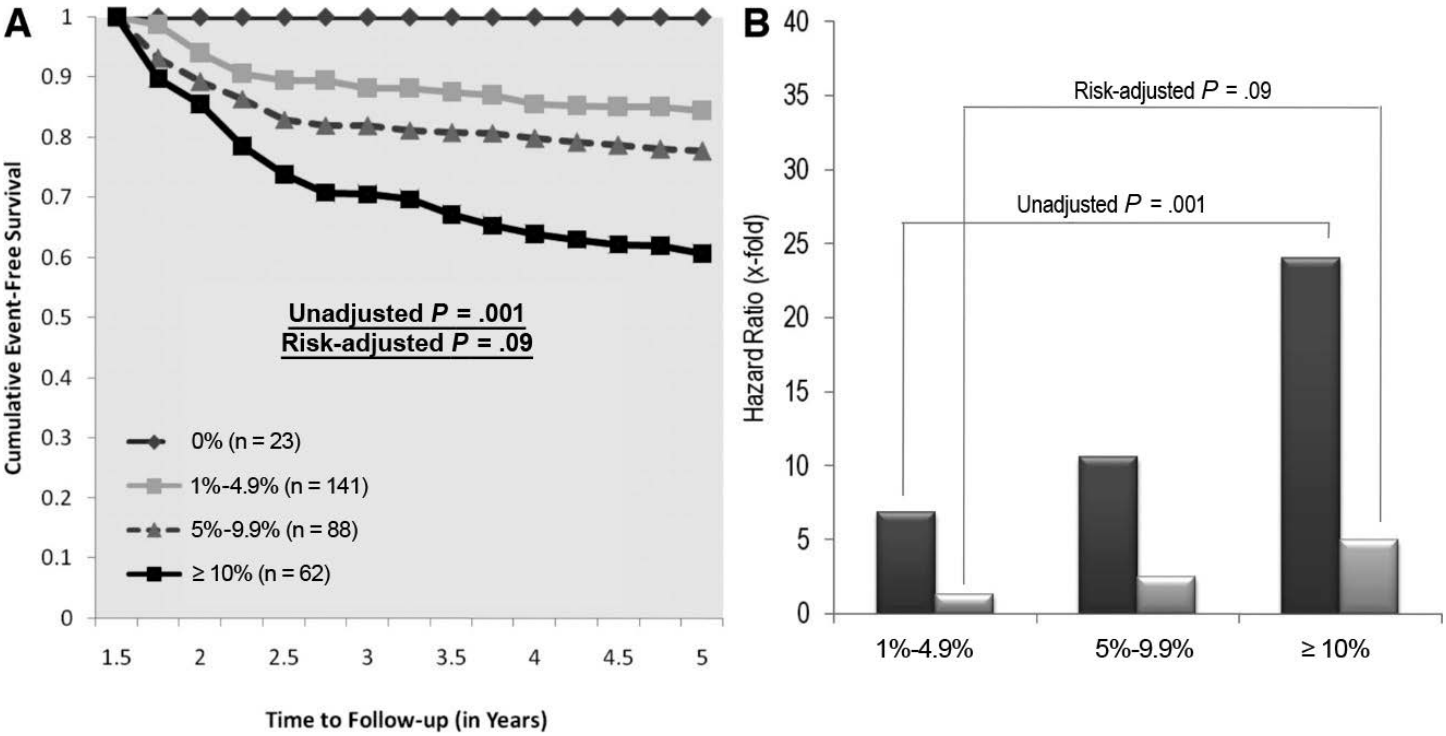

Figure 3.
(A) Kaplan–Meier survival for patients by residual ischemia, including 0%, 1% to 4.9%, 5% to 9.9%, and ≥ 10% ischemic myocardium, respectively, after 6 to 18 months of combined percutaneous coronary intervention and optimal medical therapy or optimal medical therapy alone. Reprinted with permission.[15]

priceless in clinical decision making since symptoms are often nonspecific. There is also a growing use of coronary computed tomography angiography for better visualization of the arterial wall, occluded segment, and its course.

Image-guided PCI is especially relevant given that a large proportion of patients with CTOs are treated with medical therapy alone. The COURAGE trial demonstrated that optimal medical therapy (OMT) is inferior to combined OMT and PCI in reducing ischemic burden, anginal class, and reliance on nitrate therapy. In a nuclear substudy, it was shown that a higher proportion of left ventricular (LV) ischemia on stress testing was associated with higher rates of death and MI. Thus, while symptoms may be controlled by medical therapy, evidence is in favor of CTO PCI in asymptomatic patients with residual ischemic burden > 10% for the benefit of survival (Figure 3).[15]

Although it is thought that retrograde collateralization provides adequate blood flow to reduce ischemia, Sachdeva et al. reported that the patients with successfully wired CTOs all had physiologically significant ischemia as assessed by fractional flow reserve (FFR), irrespective of the angiographic appearance of collaterals.[16] In other words, no CTOs are adequately collateralized to correct ischemia. Since FFR of an infarcted bed will be negative, it is critically important to assess viability in myocardium subtended by a CTO, especially among asymptomatic patients.

Bucciarelli-Ducci et al. explored the possible use of cardiac magnetic resonance imaging for guiding CTO PCI.[17] In their study, 32 patients were selected for recanalization based on the presence of significant inducible perfusion deficit and myocardial viability within the CTO region. There was a low incidence of symptoms since the majority of patients had limited or no angina (Canadian Cardiovascular Society classes I and II; n = 26; 81%) and New York Heart Association functional classes I and II (n = 21; 66%). After PCI, myocardial perfusion reserve (MPR) in the CTO region improved significantly to 2.3 ± 0.9 ($P = .02$) versus baseline, with complete or near-complete resolution of CTO-related perfusion defect in 90% of patients. Remote territory MPR was unchanged after PCI (2.5 ± 1.2; P = NS vs baseline). Three months after CTO PCI, LV ejection fraction had increased from 63 ± 13% to 67 ± 12% ($P < .0001$) and end-systolic volume decreased from 65 ± 38 mL to 56 ± 38 mL ($P < .001$). Despite minimal postprocedural infarction from distal embolization and side branch occlusion in 8 of 32 patients (25%), the total SAQ score improved from a median

of 54 (range 45-74) at baseline to 89 (range 77-98) after CTO recanalization ($P < .0001$).

SURVIVAL BENEFIT

Presence of CTO and Mortality

In the setting of acute ST-elevation myocardial infarction (STEMI), the presence of a CTO is an independent predictor of mortality. Van der Schaff et al.[18] showed mortality rates in patients with single-vessel disease, multivessel disease (MVD), and a CTO to be 8%, 16%, and 35%, respectively. Although MVD was an independent predictor of mortality, this was not the case when CTO was included in the model. Chronic total occlusion was a strong and independent predictor for 1-year mortality in patients with STEMI treated with PCI (Figure 4).

Batalle et al.[19] showed that CTO is an independent predictor of mortality in patients presenting with cardiogenic shock. Mortality was substantially high in patients with one CTO and exceedingly higher in those with more than one. The prevalence of one or more than one CTO in a non–infarct-related artery was 23% and 5%, respectively, among patients with shock compared with 6% and 0.5% in patients without shock ($P < .001$). Thirty-day mortality was 100% in shock patients with more than one CTO, 65.6% with one CTO, and 40.2% in patients without CTO ($P < .001$).

The association between CTO lesions and increased mortality still leaves important questions as to whether or not CTO revascularization alters that risk. Estimates of potential survival benefits with CTO PCI are limited by the available data, which consists mainly of observational series and registries (Table 2).

CTO PCI and Survival Benefit

The Veterans Affairs Clinical Assessment Reporting and Tracking program examined outcomes in 2,394 consecutive veterans who underwent elective CTO PCI from 2007 to 2013.[7] Cumulative 2-year survival curves demonstrated slightly higher unadjusted survival among patients with successful versus failed elective CTO PCIs ($P = .05$). After adjustment for differences in baseline characteristics, successful CTO PCI remained an independent predictor of 2-year survival (HR 0.67; 95% CI, 0.47-0.95; $P = .02$) (Figure 5).

A few randomized controlled trials have attempted to assess outcomes of CTO PCI in patients with stable disease. Unlike registries that are focused and driven by experienced CTO PCI operators, randomized controlled trials are limited by excessive scrutiny, less-symptomatic patients (in general), limited funding, and slow enrollment. The recently presented DECISION CTO trial, which tested OMT with or without stenting for CTO, had to stop enrolling after 834 patients due to slow enrollment; it also suffered from high crossover rates of almost 20%.[20] The study concluded that OMT is noninferior to CTO PCI with respect to the primary composite end point of death, MI, stroke, or any revascularization at 3 years. In addition, quality of life indices were comparable between the two groups.

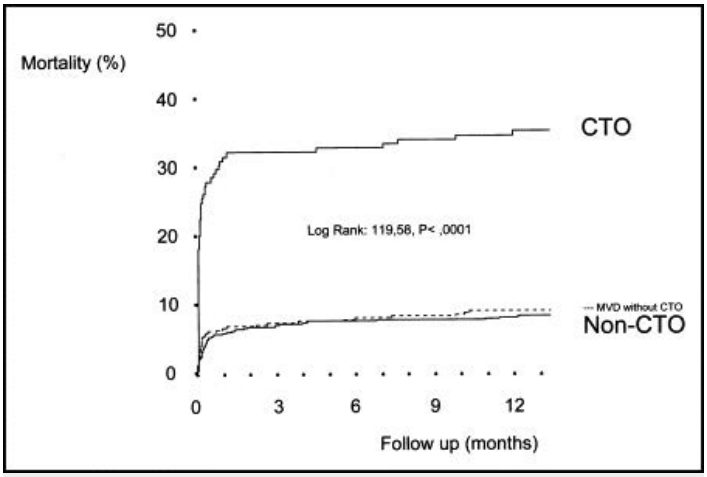

Figure 4.
Mortality in 1,417 patients with STEMI treated with primary percutaneous coronary intervention (*log-rank test for CTO vs no CTO). Reprinted with permission.[18] MVD: multivessel disease; CTO: chronic total occlusion

The EUROCTO trial included 407 patients with a CTO from 26 participating centers and randomized them 2:1 to PCI or OMT.[21] The rate of major adverse cardiac and cerebrovascular events at 12 months was similar between both arms (PCI 5.2% vs OMT 6.7%; $P = .52$), although there was significant improvement in angina frequency with CTO PCI over OMT ($P = .009$). The trial was terminated early with only 40% of the planned enrollment.

CLINICAL DECISION MAKING

The American College of Cardiology/American Heart Association guideline for coronary intervention provides a class IIa rating for CTO PCI, stating that "PCI of a chronic total occlusion in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise" (Level of Evidence B).[22] Before proceeding with revascularization, however, it is important to fully understand the burden of symptoms and risk attributable to CTO as well as the possible benefits of OMT.

The challenge of incomplete revascularization remains in patients with multivessel coronary artery disease who undergo PCI. This is due to variety of factors. Operators treating patients

REGISTRY/TRIAL	DATE(S)	OBJECTIVE	N
BARI[5]	1990-2000	Comparison of cardiac mortality and MI rates in patients with multivessel disease randomized to CABG or PTCA	8,004 (single center)
SYNTAX[6]	2005-2008 (primary)-2012 (final)	Post-hoc comparison of 4-year clinical outcomes of PCI and CABG patients with and without angiographic CR	• Randomized: 1,800 • PCI: 903 • CABG: 897
PROGRESS CTO[12]	2012-2015	Assess procedures and outcomes of CTO PCIs performed using a hybrid approach	1,036 (11 centers)
OPEN CTO[8]	2013-2017	Describe the 1-month success rate, risks, and patient-reported benefits of CTO PCI using the hybrid approach	1,000 (multicenter)
EXPERT CTO[13]	2011-2014	Assess procedural and clinical outcomes of CTO PCI using EES	250 (20 centers)
COURAGE[15] (randomized clinical substudy)	1999-2004	Nuclear substudy: Compared the effectiveness of PCI + OMT to OMT alone to reduce ischemic burden as evaluated by MPS	314 (sub-sample of patients from COURAGE trial who had stable CAD with ≥70% stenosis and MPS ischemia)
VA CART[7]	2007-2013	Evaluate incidence success of elective CTO PCI, including complications and long-term outcomes	2,394 (70 Veterans Affairs sites)
DECISION CTO[20] (randomized controlled trial)	2010-2016	Test OMT with or without stenting for CTO	834 (stopped due to slow enrollment, high crossover rates)
EuroCTO[21] (randomized controlled trial)	2012-2015	Compare outcomes of patients randomized to PCI or OMT	407 (26 centers); terminated early with 40% of planned enrollment

CTO: chronic total occlusion; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; CR: complete revascularization; ICR: incomplete revascularization; MI: myocardial infarction; SAQ: Seattle Angina Questionnaire; EES: everolimus-eluting stents; MACE: major adverse cardiac events; MACCE: major adverse cardiac and cerebrovascular events; OMT: optimal medical therapy; MPS: myocardial perfusion single photon emission computed tomography
BARI: Bypass Angioplasty Revascularization Investigation registry; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; PROGRESS CTO: Prospective Global Registry for the Study of Chronic Total Occlusion Intervention registry; OPEN CTO: Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures; EXPERT CTO: Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions; COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation nuclear substudy; VA CART: Veterans Affairs Clinical Assessment Reporting and Tracking program; DECISION CTO: Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion

Table 2.
Major registries and clinical trials for chronic total occlusion.

RESULTS	CONCLUSIONS
• 52% of patients presenting for catheterization with significant coronary artery disease had CTO • Referrals when patient presented with CTO: 10% PCI, 40% CABG, 50% medical therapy • Without CTO: 35% PCI, 30% CABG, 35% medical therapy	• Peripheral vascular disease is a strong predictor of CTO • CTO is a strong predictor of CABG/medical therapy over PCI
• 68% of CTO patients sent to surgery underwent CABG, leading to 49.6% CR • CR in 53.8% PCI patients, 66.9% CABG patients • ICR associated with higher frequency of 4-year mortality, all-cause revascularization, stent thrombosis (in PCI), and MACCE • Presence of CTO was the strongest independent predictor of ICR after PCI	• ICR associated with worse long-term clinical outcomes, regardless of whether a patient had a CTO
• Dual injection was most common technique (71%) • 91% technical success, 1.7% major complications • 58% initial crossing strategy successful, 39% used > 1 approach • Approaches used, total: 71% antegrade wire escalation 26% antegrade dissection/re-entry 42% retrograde	• CTO PCIs using a hybrid approach had high success and low complication rates
• 86% technical success • In-hospital mortality 0.9%, 1-month mortality 1.3% • 4.8% patients had perforations requiring treatment • Major complications: 2.6% periprocedural MI 0.1% in-hospital repeat PCI 0.7% referred for emergent surgery 0% in-hospital strokes 0.8% acute kidney injury 0.3% major bleeding Patients with successful CTO PCI reported 10.8-point increase in SAQ quality of life compared to those with unsuccessful PTO	• CTO PCI had high technical success but higher rates of major complications than seen in non-CTO PCI • Still need to clarify the benefits and risks of CTO PCI so that patients can participate in informed decision-making
• 96.4% procedural success (guidewire recanalization, no in-hospital MACE) 97.9% success with antegrade-only methods 86.2% success with retrograde/combined methods • EES treatment associated with fewer adverse events compared with prior CTO drug-eluting stent trials • 6.3% target lesion revascularization • 0.9% definite stent thrombosis, 0.5% possible late stent thrombosis; no definite events after 30 days	• Favorable procedural success and late-term clinical outcomes support CTO PCI in a patient population with high lesion complexity
• 33% patients treated with PCI+OMT had significant ischemia reduction with PCI+OMT; 19% for OMT alone • Greater reduction in ischemic burden for PCI+OMT • Ischemia reduction associated with lower unadjusted risk for death or MI	• OMT inferior to combined OMT and PCI in reducing ischemic burden, anginal class, and reliance on nitrate therapy • Favors CTO PCI in asymptomatic patients with residual ischemic burden > 10% for the benefit of survival
• 79.7% procedural success • Odds of success increased in successive years • Successful CTO PCI had lower adjusted mortality risk and CABG surgery at 2 years compared with unsuccessful PCI (no significant difference in risk of hospitalization for MI)	• After adjustment for differences in baseline characteristics, successful CTO PCI remained an independent predictor of 2-year survival
• Primary endpoint = MACE at 3 yr 20.6% for CTO PCI + OMT 19.6% for OMT alone Noninferiority $P = 0.008$	• OMT alone is noninferior to CTO PCI with respect to the primary composite end point of death, MI, stroke, or any revascularization at 3 years • Quality of life indices were comparable between the two groups
• Significant improvement in angina frequency with CTO PCI over OMT ($P = 0.009$) • Greater improvements in Canadian Cardiovascular Society angina scores with PCI over OMT ($P < 0.001$) • MACCE at 12 months was similar between the PCI and OMT arms (5.2% vs 6.7%; $P = 0.52$)	• In patients with CTO lesions: CTO PCI + OMT vs OMT alone associated with a significant improvement in primary endpoint of quality of life as measured by SAQ score and no difference in secondary endpoint of MACCE

Table 2. Extended

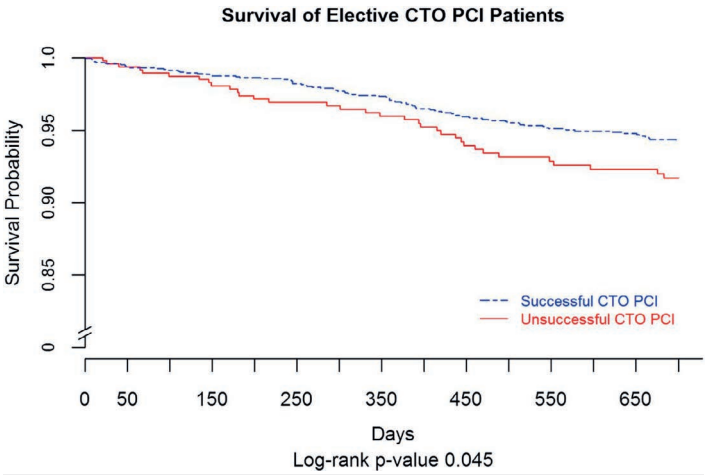

Figure 5.
Kaplan-Meier estimates of survival rates in patients with successful chronic total occlusion (CTO) percutaneous coronary intervention (PCI) (blue) versus unsuccessful CTO PCI (red). Reprinted with permission.[7]

with CTOs often revascularize coronary vessels that were not supplying areas of ischemia detected on stress imaging.[23] Although non-CTO PCI may potentially augment collateral flow to the CTO territory, it may be insufficient in alleviating ischemia and anginal symptoms due to the CTO. Resistance to treating the CTO lesion may reflect operator perceptions about the higher risks associated with CTO PCI, a lack of skills and equipment for technically more complex procedures, and the greater investment of time and resources required for successful treatment.

There is also the issue of bias, in which some believe an occluded epicardial coronary vessel is not as worthy of PCI as is a vessel with severe stenosis. One can argue that neither lesion anatomy has been associated with mortality reduction except maybe lesions in the left main or proximal left anterior descending arteries. Interestingly, during CABG, a CTO is expected to be bypassed with the hope of achieving complete revascularization. If CTO PCI revascularization is not a priority, why do we insist on bypassing a CTO segment with adequate collaterals during bypass surgery?

Assessing symptoms is another consideration in clinical decision making because, more often than not, the only symptoms reported by the patient are fatigue and/or shortness of breath but not chest pain. Patients also tend to adapt to those limitations and learn to live with them, often unknowingly, similar to living with a bad knee or back. Cardiologists are trained to pursue life-saving procedures, and anything less—such as improved quality of life or symptoms—is deemed unworthy, especially in research settings. Therefore, selecting the right patient who will benefit from CTO PCI is extremely important. A smart, detailed assessment of symptoms is essential in patients with an active lifestyle and good life expectancy. Imaging studies should be used to determine how the CTO impacts ischemia and myocardial viability. Furthermore, patient education with regard to risks, benefits, and options is vital.

Selecting the right CTO PCI operator is just as vital, as inadequate techniques often lead to higher failure and lower success rates. The institution has an obligation to provide CTO patients with a highly skilled operator who has expertise in all types of CTO PCI techniques. Various registry outcomes with high CTO volume operators have suggested procedural success rates greater than 80% as a benchmark.

SUMMARY

Chronic total occlusion PCI is the latest frontier in the evolution of percutaneous revascularization. The last decade has seen tremendous growth in terms of operator skill and device technology. Barriers to widespread adoption of CTO PCI may include biases that influence operator and clinician decision-making. CTO PCI has often been equated to a box of chocolates, where, in the words of Forrest Gump, "you never know what you're gonna get." One thing is for certain: when successful, CTO PCI allows for complete revascularization while avoiding CABG. Technical success rates at experienced centers exceed 85%, and it clearly benefits patients by alleviating symptoms and improving quality of life. There is significant evidence of improvement in LV function and reduction of ischemia. Despite strong arguments, however, convincing proof of survival benefit remains elusive.

KEY POINTS

- Technical success of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has improved with experienced operators to > 80%.
- Fractional flow reserve confirms persistent ischemia in CTO segments despite collaterals that appear adequate.
- The presence of CTO in a noninfarct artery during a myocardial infarction is associated with high mortality.
- Chronic total occlusion PCI is shown to improve symptoms, reduce ischemia, and improve left ventricular function.
- Convincing proof of survival benefit from CTO PCI remains elusive.

Conflict of Interest Disclosure:
Dr. Shah serves in an advisory role for Abbott Vascular, Boston Scientific, Medtronic, and AstraZeneca.

Keywords:
chronic total occlusion, percutaneous coronary intervention, complete revascularization, angina, CAD, interventional cardiology, ischemia, ischemic heart disease

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