



Current Evidence and Rationale of Percutaneous Therapy for Chronic Total Coronary Occlusions

**Udit B. Bhatnagar, MD, Anup Shrestha, MD,
Marian Petrasko, MD, Tomasz P. Stys, MD, and
Adam T. Stys, MD**

Abstract: The prevalence of chronic total occlusion (CTO) lesions in coronary arteries is notably high in patients with significant coronary artery disease. However, only a relatively small fraction of observed CTOs classically go for revascularization. Recent advances in techniques and equipment has greatly improved the success rates of CTO revascularization while reducing complications. There has also been an increasing body of evidence regarding clinical benefit of CTO revascularization. However, until recently majority of the evidence was observational and based on data from large multicenter registries. Recent randomized studies have reported on clinical benefits of CTO revascularization particularly with relief of angina. However, there is heterogeneity of results among different studies and the magnitude of benefit is not consistently seen in all studies. This article reviews the existing literature on the current evidence regarding clinical benefits and other rationale for CTO revascularization. (Curr Probl Cardiol 2019;44:100412.)

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Introduction

The last few decades have seen tremendous growth in the expertise and revascularization techniques of coronary chronic total occlusions (CTOs). These are classically defined as significantly occlusive lesions in the coronary arteries characterized by absent distal flow TIMI grade 0 and typically present for >3 months.¹

The prevalence of CTO lesions among patients with significant CAD ranges from 18% to 35%.²⁻⁴ However, CTOs have been classically quite complex to treat percutaneously and pose a significant management dilemma. Previously, they have been preferentially treated with medical management or undergo surgery. However, expertise of percutaneous coronary intervention (PCI) of CTOs has been increasing and there has been a growing body of evidence regarding the benefits/risks of these procedures.

Patients with CTOs have more complex risk stratification with increased incidence of multivessel disease, diabetes mellitus, and extensive coronary calcification. Only a relatively small fraction of CTOs encountered on angiography undergo an attempt for revascularization. However, with progressive improvement in techniques and instruments, the technical success of these procedures has increased, approaching up to 90% in the last few years.⁵

This review attempts to summarize the current evidence and recent advances in the field of CTO revascularization.

CTO: Disease Burden and Revascularization

CTO are defined as significant atherosclerotic coronary lesions with either completely absent distal flow (TIMI grade 0 flow) or minimal distal contrast penetration (TIMI grade 1—so called “functional” total occlusions).¹ These are mainly composed of dense fibrous and atheromatous tissue with variable amount of calcification. Recent reports show the prevalence of CTOs to be in up to 35% of patients with significant CAD.⁴ In patients presenting with ST elevation myocardial infarction (STEMI), the incidence of CTOs is around 13%, and the presence of CTOs has been shown to have a significant effect on both short-term and long-term mortality and attenuation of LVEF improvement in these patients.⁶ Despite this, reports suggest that only about 10%-30% of patients with CTO undergo attempt at PCI.⁴ With growing expertise and technical advancements, procedural success rates >85% have been consistently reported in several ‘real world’ registries.⁷ Recent years have revealed increasing data including randomized trials studying effects of

revascularization of CTO lesions. We explore the current evidence regarding clinical benefits from this procedure.

CTO Revascularization—Clinical Endpoints

Relief of Angina

Symptomatic relief has been one of the main goals of CTO revascularization and one of the most common reasons for referral. Despite this, there are surprisingly few randomized trials comparing the difference in symptoms/quality of life with CTO revascularization vs medical therapy. EURO-CTO (Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) was the first randomized trial to study the effect of CTO revascularization on quality of life as a primary outcome.⁸ A total of 396 patients were randomized to either PCI or Optimal Medical Therapy (OMT) in a 2:1 ratio (CTO PCI—259 vs OMT—137). At 12 months follow-up, there was significant improvement in quality of life as assessed by the SAQ score. Secondary outcome of major cardiovascular events was comparable between PCI vs OMT groups (5.2% vs 6.7% $P = 0.52$).

Another ongoing trial—DECISION CTO (Drug-Eluting Stent Implantation vs Optimal Medical Treatment in Patients with CTO) looked at the cardiovascular outcomes of ‘routine’ CTO-PCI vs medical therapy among patients with at least 1 CTO. Outcomes were revealed in March 2017 at the American College of Cardiology meeting, however, full results are not published yet as of November 2018.⁹ Due to slow enrolment, 834 patients were included in the trial in contrast to the assumed sample size of 1284 patients. Although symptomatic relief was not the primary endpoint, there were no significant differences in quality of life metrics at 1 year, including SAQ score and EQ-5D visual analogue scale. However, in this study, randomization was completed prior to any revascularization attempts. As a result, about 70% of patients in the OMT arm of received PCI, which may account for the improved SAQ scores in the OMT group. In an OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in CTO), a multicenter, prospective, observational registry of CTO patients undergoing PCI with 1000 consecutive patients showed significant symptomatic relief with improved SAQ quality of life scores (49.4 ± 0.9 - 75.0 ± 0.7 , $P < 0.01$) and decreased dyspnea and depression scores (PHQ-8).^{7,10}

Another observational study, FACTOR trial, by Grantham et al compared outcomes in patients with successful vs unsuccessful CTO revascularization and showed that successful procedures were associated with

substantial improvement in patient's angina frequency, physical limitation, and quality of life early after the procedure. The benefits were greatest in those with preprocedural angina. There was a nonsignificant trend toward increased 30-day MACE rates in the unsuccessful group as compared with the successful group (16% vs 6%, $P = 0.06$).

Overall, the data seems to suggest merit for revascularization of CTOs as a strategy to significantly improve symptoms and quality of life. Appropriate patient selection with significant symptomatology/clinical ischemia may be appropriate to obtain substantial benefit.

Improvement in Left Ventricular Systolic Function

Patients with CTO are commonly associated with reduced ejection fraction. Several observational reports have studied the effect of CTO PCI on left ventricular function (LVEF).¹¹⁻¹⁴ However, the overall benefit appears modest as suggested by a recent meta-analysis of 34 observational studies with 2243 patients, who underwent successful CTO PCI, showed an improvement in LVEF by 4.44% (95% confidence interval [CI]: 3.52-5.35, $P < 0.01$) compared to baseline and a reduction in left ventricular end diastolic volume by 6.14mL/m².¹⁵ This improvement of LVEF was also associated with a reduction in mortality after successful vs failed CTO. The overall beneficial effect on LVEF disappeared upon reocclusion of the successfully treated CTO. A retrospective study by Y Adachi et al studied determinants of improvement in ejection fraction and found that revascularization including CTO to be predominant determinant of LVEF improvement (odds ratio 5.43, 95% CI 1.06-27.74, $P = 0.04$).¹⁶

One of the most important randomized studies on effect of CTO PCI on LVEF was with the EXPLORE Trial (Evaluating Xience and LVEF in PCI on Occlusions After ST-Elevation Myocardial Infraction).¹⁷ This randomized trial studied patients presenting with STEMI to evaluate whether there was a benefit of early PCI of concurrent CTO arteries after primary revascularization. Although a small scale study with about 150 patients in each arm, there was no difference in left ventricular systolic function detected at 4 months after STEMI in patients undergoing CTO PCI of a noninfarct-related artery vs OMT (44.1% \pm 12.2% vs 44.8% \pm 11.9% respectively; $P = 0.60$). However, in a subgroup analysis based on location of CTO, revascularization of CTO lesion in the left anterior descending artery (LAD) was associated with an increase in systolic function compared to the non-PCI arm (LVEF 47.5% \pm 12.3% vs 40.4% \pm 11.9%; $P = 0.02$). Therefore, there seems to be a signal towards stronger benefit of revascularization of CTO lesions in the LAD especially in a setting of systolic dysfunction.

Furthermore, in a setting of reduced LV systolic function and coronary CTO, several studies point towards the role of viability evaluation prior to revascularization attempt.^{16,18,19} A sub-study from the EXPLORE population, used CMR to further evaluate functional status and viability.²⁰ In this study, CTO PCI improved regional systolic function in the affected coronary artery territory and this effect was most pronounced in dysfunctional but viable segments.

Major Cardiovascular Events

As previously mentioned, DECISION CTO is currently the largest randomized trial studying major cardiovascular outcomes as a primary outcome.⁹ At 3 years, OMT was noninferior to PCI in decreasing Major Cardiovascular Endpoints (MACE)—a composite of all-cause mortality, Myocardial Infarction (MI), stroke, and repeat revascularization (19% of OMT vs 21.4% of PCI).

However, several observational studies have suggested long-term survival benefit with CTO PCI. A large analysis of 13,443 patients from UK database showed that successful CTO PCI was associated with improved long-term survival (hazard ratio [HR] 0.72, $P < 0.001$).²¹ In a meta-analysis by Hoebbers et al, 27 studies were included and patients with successful CTO revascularization (11,085 patients) were compared to unsuccessful CTO PCI (4347 patients).¹⁵ Successful CTO PCI was associated with reduced mortality in comparison to failed CTO PCI (odds ratio: 0.52, 95% CI: 0.43-0.62, $P < 0.01$). From the Italian CTO registry, Tomasello et al reported that medical therapy was associated with a higher MACE rate (7.6% vs 1.7%, $P < 0.01$), cardiac death (4.4% vs 1.5%; $P < 0.01$), acute myocardial infarction (2.9% vs 1.1%; $P = 0.03$), and rehospitalization (4.4% vs 2.3%; $P = 0.04$), compared with CTO PCI.²²

Jang et al in their study with a median follow-up of 42 months, found that patients who underwent coronary revascularization (with PCI or Coronary artery bypass graft (CABG); $n = 502$) had a lower incidence of cardiac death (HR, 0.29; 95% CI, 0.15-0.58; $P < 0.01$) and MACE (HR, 0.32; 95% CI, 0.21-0.49; $P < 0.01$), even after propensity matching (cardiac death: HR, 0.27; 95% CI, 0.09-0.80; $P = 0.02$; and MACE: HR, 0.44; 95% CI, 0.23-0.82; $P = 0.01$).²³

Ventricular Arrhythmias

Presence of CTO has been previously linked to higher incidence of ventricular arrhythmias and appropriate implantable cardiac defibrillator

therapies.²⁴⁻²⁷ A meta-analysis of studies looking at arrhythmic endpoints in patients with ischemic heart disease showed the presence of CTO increased the risk of ventricular tachycardia/fibrillation by a factor of 1.68 (95% CI: 1.02-2.78; $P < 0.05$; $I^2 = 91\%$).²⁸ This study also showed a 1.5 fold increase in all-cause mortality in patients with unrevascularized CTO compared to successful revascularization (95% CI: 0.96-2.43; $I^2 = 76\%$), however this did not reach statistical significance. Although there is not enough data about effectiveness of CTO revascularization in reducing ventricular tachyarrhythmias—studies have demonstrated improvement of ventricular repolarization after PCI.²⁹

Other Quality of Life Metrics

Studies have also looked at other quality of life metrics including walking distance, angina frequency, and depression. In a study by Rosello et al, which followed 47 patients after CTO revascularization—there was improvement in 6 minute walk time (417 ± 126 minutes- 463 ± 103 minutes, $P = 0.002$) and decreased angina frequency (39% vs 8%; $P < 0.001$) and the improvement was more pronounced in patients with a higher ischemic burden as measured by stress CMR.³⁰ More objective measures obtained by cardiopulmonary testing were evaluated in a study by Abdullah et al—where CTO PCI was associated with a significant improvement in peak oxygen uptake from 17.7 ± 4.3 mL/kg/min to 19.1 ± 4.0 mL/kg/min ($P = 0.02$) and plasma BNP decreased from 143 ± 138 pg/mL to 102 ± 123 pg/mL ($P = 0.01$).³¹ Significant reduction in depression rates were seen in patients after successful CTO PCI intervention in a study by Bruckel et al 40.0% vs 11.1%; $P = 0.01$).³²

Effect of CTO Revascularization Based on Location

It has been previously discussed that location of coronary CTO could have an impact on clinical benefit of revascularization. Patients presenting with acute coronary syndrome EXPLORÉ trial as mentioned before, showed a statistically significant improvement in LVEF after revascularization of CTO of LAD compared to non-LAD CTO lesions.¹⁷ A study by Ahn et al, compared CTO revascularization vs medical therapy and further stratified them by location of the lesions—one group with proximal to mid LAD CTO and the second group with CTO at other locations.³³ With a median follow-up of 46 months, revascularization of CTO LAD was associated with lower rates of cardiac death compared to OMT. However with non-LAD CTO lesions—no difference was observed among the PCI vs OMT groups.

Conclusion

There has been increasing evidence seen regarding the clinical effects of CTO revascularization recently. Currently available evidence seems to suggest significant benefit of CTO PCI on relief from symptomatic angina and ischemia which remains the main indication for revascularization of these lesions. Other studies suggest additional benefits as described above including improvement in left ventricular systolic function and possibly a survival benefit. Patient and lesion characteristics, location, and viability of affected myocardium are important variables to consider prior to consideration of revascularization. More definitive data from ongoing trials are awaited which would help us understand disease pathophysiology and treatment effect and help in patient selection to maximize benefit to risk ratio.

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Chronic total coronary occlusion is highly prevalent in patients with significant coronary artery disease. The prevalence of chronic total occlusion (CTO) lesions in coronary arteries is notably high in patients with significant coronary artery disease. Advances in techniques and equipment have improved the success rates and clinical benefits of CTO revascularization while reducing complications.

Several perspectives can be taken from these interesting manuscripts.

First, the single center experience demonstrated that a careful attempt at antegrade intraluminal CTO PCI of intermediate to difficult lesions is viable in highly selected patients a hospital without on-site cardiac surgery. The authors demonstrate that it was safe and with a reasonable success.

Second, there are several points that need to be present in order to achieve success with few complications. These are, a well-equipped PCI facility with well-trained interventional cardiologists and staffs, careful selection of elective cases and lesions, and a formalized agreement and structured transfer protocol with a facility with cardiothoracic surgery and open communication with the cardiac surgeons will result in a favorable outcome of a CTO PCI even when performed in a facility with no surgery back up.

The review of the clinical benefits of CTO revascularization is very comprehensive and has several points to draw attention to:

First, available evidence suggests significant benefit of CTO PCI on relief from symptomatic angina and ischemia.

Second, other studies suggest that CTO revascularization have additional benefits such as improvement in left ventricular systolic function and possibly a survival benefit.

Third, patient and lesion characteristics, location and viability of affected myocardium are important variables to consider prior to consideration of revascularization.

Finally, more definitive data from ongoing trials will help us to understand the disease pathophysiology and treatment effect and it help in patient selection in order to maximize benefit to risk ratio.

I want to thank the authors for these two excellent manuscripts and I hope the readers of the Journal will find a very helpful guide of the different clinical aspects of chronic total coronary occlusion its pathophysiology and management.
