

Impact of CTO Angioplasty on Long-Term Clinical Outcomes

More data are needed to demonstrate the benefit of PCI for CTO.

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Percutaneous coronary intervention (PCI) for a chronic total occlusion (CTO) remains a major challenge in interventional cardiology, despite the notable advances of novel technologies and procedural techniques, including the use of drug-eluting stents (DES).

CTO is defined as an estimated >3-month-old obstruction of a native coronary artery without any luminal continuity and thrombolysis in myocardial infarction (TIMI) grade 0 flow.¹ CTOs occur frequently, with registry studies reporting an incidence of 30% to 50% in patients with significant coronary artery disease undergoing coronary angiography,² meaning that most patients with multivessel coronary disease who arrive in a catheterization lab have at least one CTO. Therefore, assessing the risk and management of these patients includes a more effective strategy of revascularization in multivessel coronary disease. CTO PCI accounts for <10% of all PCI, and the presence of CTO represents the main reason for referring patients to coronary surgery.

The rationale for percutaneous CTO revascularization is the improvement in survival rates and quality of life, as demonstrated by some retrospective studies. Despite this strong rationale, there is no evidence based on randomized trials that successful CTO revascularization increases the chance for survival, whereas large registry studies have produced conflicting results. The potential benefits

of CTO percutaneous revascularization include improvement in left ventricular function in patients with viable myocardium, prevention or attenuation of ventricular remodeling, increased tolerance to future coronary occlusion events, decrease in electrical instability and subsequent fatal arrhythmic events, reduced need for coronary surgery, and significant reductions in angina burden after CTO PCI.

The negative effect of CTO on survival has been shown in patients who experienced an acute MI treated by primary PCI. Untreated CTO was associated with a threefold increase in mortality at 1 year.³ A recent analysis from the New York State Survey showed that incomplete coronary revascularization involving a CTO lesion in patients treated by PCI led to higher mortality at 3 years of follow-up, as compared to complete revascularization.⁴ In the current era, improvements in long-term vessel patency with DES may increase the survival advantage in patients with successful CTO revascularization.

LONG-TERM OUTCOME IN LARGE REGISTRIES

Current knowledge of the long-term prognostic impact of CTO PCI is derived from the outcomes from a few large registries in the last decade (Table 1). We must consider that the robustness of the results of these

TABLE 1. LONG-TERM MORTALITY ACCORDING TO CTO PCI RESULTS IN LARGE REGISTRIES

Registry	PCI Success N (%)	PCI Failure N (%)	Follow-Up (y)	Mortality		
				PCI Success (%)	PCI Failure (%)	P Value
Suero et al (2001)	1,491 (74%)	514 (24%)	10	26.6	35	.001
British Columbia Registry (TCT 2003)	1,118 (77%)	340 (23%)	7	10	19	.001
TOAST-GISE (2003)	289 (77%)	87 (23%)	1	0.35*	3.61*	.037
Thoraxcenter Registry (2005)	567 (65%)	304 (35%)	5	6.5	12	.02
Aziz et al (2007)	377 (69%)	166 (31%)	1.7	2.5	7.3	.002
Mayo-Clinic Registry (2007)	914 (72.5%)	348 (27.5%)	2	5	5	NS
Milano-New York Registry (2008)	910 (67%)	452 (33%)	3	8.7	3.6	.012
Valenti et al (2008)	344 (71%)	142 (29%)	2	8.4*	12.6*	.025
*Cardiac mortality. CTO, chronic total occlusion; PCI, percutaneous coronary intervention.						

studies are hampered by the relatively low PCI success rate, despite the selection of favorable characteristics of CTO lesions, the very high rate of restenosis or reocclusion in the balloon angioplasty or bare-metal stent (BMS) era, the lack of routine angiographic follow-up assessing the patency of the CTO vessel, and the inclusion of patients with occlusions less than 3 months in duration. The reported procedural success rate ranges from 50% to 70%, and is confounded by variability in operator technique and experience, definition of CTO, and case selection. Nevertheless, among the longitudinal studies of patients undergoing attempted CTO revascularization, a common finding has been a temporal trend toward improvements in both technical and procedural success consonant with the introduction of advanced guidewire and device technologies. Recent data from several registries suggest that the use of DES in CTO, as with all other lesion subsets, is effective in further decreasing restenosis and the need for revascularization when compared with BMS. Thus, the maintained vessel patency of the treated vessel may improve the prognostic impact of these patients.

The first large registry, from the Mid America Heart Institute of Kansas City, was reported by Suero et al in 2001.⁵ In a consecutive series of 2,007 patients undergoing intended PCI of a nonacute coronary occlusion at a single center over a 20-year period from 1980 to 1999, procedural success was achieved in 72.3% of cases. A CTO was defined as any vessel occlusion with TIMI grade 0 or 1 flow that was not related to MI within the previous 7 days. Due to the early period during which the registry took place, stents were only used in 7% of the cases. Compared with patients in whom the procedure was successful, the in-hospital occurrence of major adverse cardiac events was significantly higher among patients with procedural failure (3.2% vs 5.4%; $P=.023$). Long-term survival over 10 years among patients with successful recanalization of a CTO was similar to a matched cohort of patients undergoing successful revascularization of a nonocclusive lesion and was significantly greater when compared with patients having CTO revascularization failure (10-year survival was 73.5% with CTO success vs 65.1% with CTO failure; $P=.001$). In a multivariable analysis, CTO failure and the presence of multivessel disease,

advanced age, diabetes, impaired left ventricular function, unstable angina, and renal failure were independently predictive of reduced survival.⁵

The clinical benefit of successful CTO PCI has been demonstrated by the British Columbia Cardiac registry,⁶ in which attempted revascularization of nonacute lesions accounted for more than 15% of all PCI procedures. Among the 1,458 patients with a CTO, over a 7-year follow-up period, successful PCI was associated with clinically significant avoidance of subsequent surgical revascularization ($P<.001$) and death ($P<.001$). CTO PCI success was related to a 56% relative reduction in late mortality (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.30–0.64).

The prospective multicenter TOAST-GISE (Total Occlusion Angioplasty Study–Società Italiana di Cardiologia Invasiva) study included 376 patients with CTO (defined as more than 1 month in duration).⁷ The technical success rate was 77%, and BMS were used in 90% of cases. No difference in overall mortality was found at 1-year follow-up, but cardiac mortality was higher in the CTO PCI failure group as compared to the CTO PCI success group (3.61% vs 0.35%; $P=.037$). The absolute number of events was very small (six deaths, including cardiac deaths), reflecting the bias selection of non–high-risk patients favorable to a PCI attempt. A successful CTO PCI was also associated with a reduced 12-month incidence of cardiac death or MI (1.1% vs 7.2%; $P=.005$), a reduced need for coronary artery bypass surgery (2.5% vs 15.7%; $P=.0001$), and greater freedom from angina (88.7% vs 75%; $P=.008$).

Hoye et al reported the results of 874 patients who underwent CTO PCI at the Thoraxcenter in Rotterdam over a 10-year period from 1992 to 2002.⁸ All patients with CTOs older than 1 month were considered. The PCI success rate was 65.1%. BMS were used in 81% of cases. At 5 years of follow-up, the study demonstrated survival benefit after successful CTO PCI as compared to unsuccessful CTO revascularization (93.5% vs 88%; $P=.02$). Subgroup analysis showed that the survival advantage was limited to patients with multivessel coronary disease (92.5% vs 86.3%; $P=.02$), whereas patients with single-vessel disease had a similar survival rate at 5 years (97.3% vs 99% for CTO PCI success and the CTO PCI failure group, respectively; $P=.3$). More than half of the patients with failed CTO PCI underwent bypass surgery in the follow-up period, whereas the coronary surgery rate in the PCI success group was lower (survival free from coronary surgery was 87.4% in patients with successful PCI and was 61.5% in patients with failed PCI; $P<.0001$). Successful revascularization was an independent predictor of both survival and major adverse cardiac events.

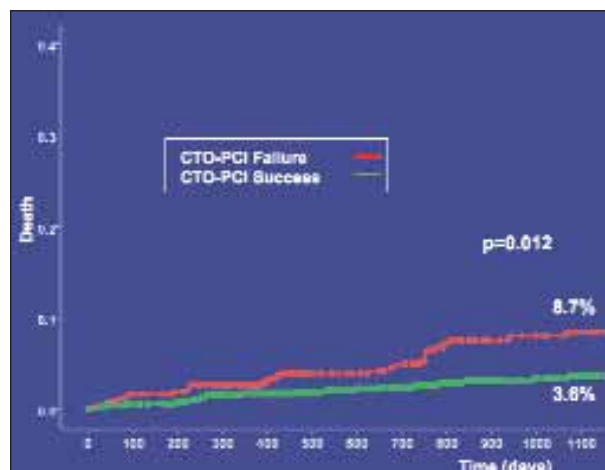


Figure 1. Survival rates according to the CTO-PCI result in the Milan-New York CTO registry (Adapted from Obunai K. The Milan-New York CTO registry. Presented at: Transcatheter Therapeutics annual scientific symposium; October 13, 2008; Washington, DC.¹¹).

Aziz et al reported the outcome of 543 patients with CTO lasting more than 3 months who were treated by PCI at the Cardiothoracic Centre in Liverpool from 2000 to 2004, representing 9.4% of all PCI over the study period.⁹ The mean follow-up was 1.7 years, and the technical success rate was 69.4%. Coronary stents were used in 97.7% of all successfully treated CTO lesions, and DES were used in 17.3%. The mortality rate was 2.5% in the CTO success patients and 7.3% in the CTO failure patients ($P=.002$). Coronary surgery was more frequently performed in patients with CTO failure compared with CTO success (21.7% vs 3.2%; $P<.001$). An unexpected, more evident benefit was found in patients with single-vessel disease and CTO; the mortality rate was 0.8% in single-vessel CTO PCI success and 6.1% in single-vessel CTO PCI failure ($P=.003$). Multivariate analysis showed CTO PCI failure to be an independent predictor of death in the propensity-matched cohort to adjust for the differences in case mix (HR, 4.95; 95% CI, 1.03–23.89; $P=.049$).

The 25-year experience (1979 to 2005) from the Mayo Clinic revealed that 1,262 patients who required PCI for a CTO accounted for a very low rate of the total PCI procedures.¹⁰ Procedural success improved from 51% in the early period to 73% in a more recent period. In this study, technical failure of CTO PCI was not associated with increased 10-year mortality. Patients with CTO PCI success did appear to have a slightly greater chance of survival after 6 years of follow-up, but no immediate or midterm survival advantage was observed. Technical failure was not an independent predictor of mortality by

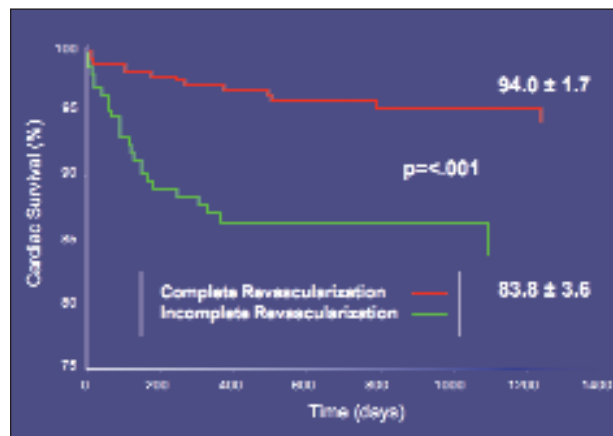


Figure 2. Cardiac survival according to complete or incomplete revascularization in patients with at least one CTO in the CTO Florence registry. (Adapted from Valenti R, Migliorini A, Signorini U, et al. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. *Eur Heart J*. 2008;29:2336-2442.¹⁴)

multivariable analysis. The investigators explained that survival did correlate with left ventricular dysfunction and patient attributes associated with greater atherosclerotic burden, supporting the hypothesis that technical failure may only be a marker of disease severity.

In October 2008, the outcome of the Milan-New York registry was presented at the Transcatheter Cardiovascular Therapeutics meeting in Washington, DC.¹¹ This registry assessed 1,362 patients with CTO older than 3 months who were treated with PCI from 2000 to 2007. The procedural success of PCI was 66.8%. DES were used in 61% of cases (more than 80% in the last 4 years), BMS were used in 30%, and balloon angioplasty was used in 9%. At 3 years of follow-up, mortality was lower in patients with CTO PCI success as compared to patients with CTO PCI failure (3.6% vs 8.7%; $P=.012$) (Figure 1), as was the need for coronary surgery (2.4% vs 11%; $P<.001$). The most benefit in reducing mortality was evident in patients with successful recanalization of a left anterior descending artery (LAD) CTO as compared to unsuccessful LAD PCI (4.7% vs 15%; $P=.018$) and non-LAD CTO PCI success or failure (3.6% vs 6%). This observation is consistent with two other reports from the Florence CTO registry and the Mid America Heart Institute registry.^{12,13}

The Florence PCI registry assessed the prognostic effect of successful PCI in 486 patients with at least one CTO, yielding a total of 527 CTOs treated between 2003 and 2006.¹⁴ The clinical median follow-up was 2 years, with scheduled angiographic follow-up at 6 to 9 months. PCI

was successful in 344 patients (71%) and was unsuccessful in the remaining 142. PCI was also successful in 361 (68%) lesions. All patients with successful PCI received DES. Patients with PCI failure were significantly older than PCI success patients (69.8 y vs 67.4 y; $P=.036$) and had a higher incidence of previous coronary surgery (18% vs 8%; $P=.002$). Multivessel PCI was common in both the PCI success group and in the PCI failure group (71% vs 62%). The cardiac survival rate was significantly higher in the PCI success group than in the PCI failure group (91.6% vs 87.4%; $P=.025$). Cardiac survival rates were also higher in patients with multivessel disease and PCI success than in those with PCI failure (91.4% vs 86.6%; $P=.021$) and were higher in patients with complete revascularization as compared to incomplete revascularization (94% vs 83.8%; $P<.001$) (Figure 2). Coronary surgery was more frequent in the CTO PCI failure group than in the CTO PCI success group (9.1% vs 2%; $P<.001$). Angiographic follow-up showed that successfully treated CTO patients had an 88% patency rate with an 11.2% rate of binary restenosis. The independent predictors of cardiac mortality were age, impaired left ventricular ejection fraction, CTO vessel, and the completeness of revascularization (HR for complete revascularization, 0.44; 95% CI, 0.22–0.87; $P=.021$). Although the mechanisms of improved survival in patients with CTO PCI success cannot be ascertained and was beyond the scope of the study, the number of survivors with successful CTO PCI who had left ventricular ejection fractions at 6 months was significantly increased when compared with the baseline values (46.5 ± 11.3 vs $42.2\pm 12.1\%$; $P=.001$).

The study assessed the prognostic impact of not only successful PCI for a CTO, but more widely, of a strategy for a complete revascularization in patients with single- or multivessel disease and at least one CTO. From this study, the completeness of revascularization emerges as an adjunctive independent predictor of survival, confirming the results of large surgical and PCI retrospective registries in patients with multivessel disease in the current era.^{4,15}

CONCLUSION

Data from randomized trials are needed to show the benefit of PCI for CTO and the completeness of coronary revascularization in patients with multivessel disease and CTO. In the meantime, it seems reasonable to adopt a complete revascularization strategy in patients with multivessel disease and at least one CTO.

Conversely, there is uncertainty regarding the potential benefit of routine late PCI for subacute MI on left ventricular remodeling and clinical outcome. This issue has long been a matter of debate. It is easy to predict that the debate will not end after the negative results of the Occluded

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Artery Trial study, which did not show any benefit of PCI as compared to medical therapy.¹⁶ However, a recent meta-analysis of 10 randomized studies (the Occluded Artery Trial included) comparing PCI with medical therapy in subacute MI showed a strong benefit of PCI in terms of improved survival rates.¹⁷ ■

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