

Percutaneous Coronary Intervention for Chronic Total Occlusions: Improved Survival for Patients with Successful Revascularization Compared to a Failed Procedure

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Background: There are limited data on the impact of successful chronic total occlusion (CTO) revascularization by percutaneous coronary intervention (PCI) on survival. We performed a retrospective study comparing the survival between patients with a successful and a failed CTO revascularization by PCI. **Methods:** Between January 1, 2000 and June 30, 2004, 543 of 5803 (9.4%) patients underwent PCI for a CTO at our center. A CTO was defined as an occlusion of the artery present for at least 3 months with Thrombolysis in Myocardial Infarction flow grade 0 or 1. Patient records were linked to a national database to monitor all deaths during follow up. Propensity matching was used to balance out case mix differences. **Results:** Technical success for CTO was 377 of 543 (69.4%). In-hospital mortality was 0.3% and 1.2% for the CTO success and CTO failure patients, respectively. During a mean (SD) follow up of 1.7 (0.5) years, the mortality rate was 2.5% in the CTO success patients and 7.3% in the CTO failure patients. The crude hazard ratio for death with CTO failure was 3.92 (95% confidence intervals 1.56–10.07; $P = 0.004$). The rates of coronary artery bypass were 3.2% vs. 21.7% ($P < 0.001$) for the CTO success and CTO failure patients, respectively. Our propensity matched 157 CTO success to CTO failure patients and the associated hazard ratio for death with CTO failure was 4.63 (95% confidence interval 1.01–12.61; $P = 0.049$). Multivariate analysis showed that CTO failure was an independent predictor of death. **Conclusion:** Patients with a successful revascularization of a CTO by PCI have an increased survival rate compared to patients with a failed CTO procedure. © 2007 Wiley-Liss, Inc.

Key words: chronic total occlusion; angioplasty; stents

INTRODUCTION

Approximately 30% of all coronary angiograms performed in patients with coronary artery disease will show a chronic total occlusion (CTO) [1]. Percutaneous coronary intervention (PCI) of CTOs accounts for 10–20% of all PCI activity. Successful revascularization of a CTO remains one of the most difficult challenges for interventional cardiologists. The presence of a CTO is one of the commonest reasons for referral for coronary artery bypass grafting (CABG) and many CTO lesions are left untreated due to the uncertainty regarding procedural success and long-term benefit [2].

Studies of balloon angioplasty in patients with CTOs have shown that successful revascularization is associated with an improved long-term survival [3]. Randomized clinical trials in patients with CTOs have reported a reduction in the rates of restenosis and reocclusion

with coronary stenting compared to balloon angioplasty [4–9]. The aim of the present study was to evaluate the survival of patients with successful and unsuccessful CTO revascularization after PCI with coronary stent deployment.

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METHODS

Patient Population and Study Design

We performed a retrospective observational study in patients who underwent PCI for at least one CTO lesion between January 1, 2000 and June 30, 2004. A CTO was defined as an obstruction of a native coronary artery with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1. The duration of the occlusion had to be >3 months. This was calculated from the time of the last diagnostic coronary angiography; otherwise CTO duration was estimated from history of acute chest pain or previous acute myocardial infarction (AMI). Patients with stent occlusions or with >1 CTO PCI attempts were excluded.

The local cardiac catheter database system was used to identify all cases. Baseline demographics, procedural data, and in-hospital events were recorded as routine in the clinical database system. Each patient record was subsequently validated by a Clinical Audit Officer to add missing details, clarify any discrepancies between the patients' records and the database, and to ensure all in-hospital complications were recorded. A designated Consultant Cardiologist adjudicated all complications that constituted a major adverse cardiac event (MACE).

Outcome Measures

The main outcome measure was medium-term all cause mortality. This was recorded by linking all patient records to the National Strategic Tracing Service (NSTS), which records all deaths in the United Kingdom. To establish vital status, patients were matched to the NSTS based on patient name, National Health Service number, date of birth, gender, and postcode. The patient's general practitioners or referring physicians were contacted directly to ascertain the exact cause of death where necessary.

We also recorded in-hospital MACE rate. This comprised of all cause mortality, non-fatal AMI, and repeat revascularization by either PCI or coronary artery bypass surgery (CABG). Routine enzyme screening was performed with the measurement of creatine kinase-MB level 12–18 hr post procedure. The diagnosis of AMI required an elevation of creatine kinase-MB fraction to twice the upper limit of normal.

Target vessel revascularization (TVR) was defined as repeat intervention driven by any lesion located in a coronary artery previously treated by PCI.

Technical success was defined as <30% residual stenosis, TIMI 3 flow, and no residual dissection. Procedural success was defined as technical success without death, emergency CABG surgery, or myocardial infarction.

Procedural Technique

All procedures were performed via the femoral or radial route. Intravenous heparin was given at the start of the procedure to maintain an activated clotting time of 220–300 s. The choice of guide wires, balloons, and stents was left to the discretion of the operators. All patients received aspirin and clopidogrel according to local practice.

Statistical Methods

Continuous variables are shown as median with 25th and 75th percentiles, and comparisons between CTO success and failure were made with Wilcoxon rank-sum tests. Categorical variables are shown as a percentage and comparisons between CTO success and failure were made with χ^2 tests. Deaths occurring over time for CTO success and failure patients were described using Kaplan–Meier survival curves. To adjust for differences in case-mix, we performed a propensity-matched cohort analysis. To do this, logistic regression was used to develop a propensity score for CTO success group membership [10]. The propensity score included all the variables listed in Table I. The C statistic, which is equivalent to the receiver-operating characteristic curve, for the propensity model was 0.86 [11]. CTO success patients were matched with CTO failure patients who had an identical 5-digit propensity score. If this could not be done, we then proceeded to a 4-, 3-, 2-, or 1-digit match. We also performed a forward stepwise Cox proportional hazards analysis to identify risk factors for death in the propensity-matched patients. All variables listed in Table I were offered to the Cox proportional hazards analysis as potential risk factors. In all cases, a *P* value < 0.05 was considered significant. All statistical analysis was performed retrospectively with SAS for Windows Version 8.2 (SAS Institute, Cary, NC).

RESULTS

Patient and Procedural Characteristics

Over the study period, 5,803 consecutive patients underwent PCI at the Cardiothoracic Centre, Liverpool. 543/5,803 (9.4%) of these patients had a PCI procedure that included the treatment of at least one CTO lesion. The total number of CTO lesions attempted were 572, with 394 CTO lesions with TIMI 0 flow and 178 CTO lesions with TIMI 1 flow.

Technical success for CTO PCI was achieved in 377 of 543 (69.4%) patients representing 400 CTO lesions. In patients where >1 CTO lesion was attempted, technical success was defined as the successful treatment of all attempted CTO lesions. Treatment of CTO and

TABLE I. Patient and Disease Characteristics

| | CTO success (n = 377) | CTO failure (n = 166) | P value |
|-----------------------------|--------------------------|--------------------------|---------|
| Age (years) | 58.8 (52–67) | 58.8 (52–65.4) | 0.92 |
| Female (%) | 24.1 | 18.7 | 0.16 |
| Family history | | | |
| of CHD (%) | 59.4 | 50 | 0.041 |
| Diabetes (%) | 13.5 | 9 | 0.14 |
| Renal dysfunction (%) | 0.3 | 1.8 | 0.053 |
| PVD (%) | 2.4 | 7.2 | 0.007 |
| Hypertension (%) | 48.3 | 57.2 | 0.054 |
| Hypercholesterolaemia (%) | 90.5 | 87.9 | 0.38 |
| Ex smoker (%) | 49.1 | 48.2 | 0.85 |
| Current smoker (%) | 18.3 | 21.1 | 0.45 |
| Previous MI (%) | 58.1 | 57.8 | 0.96 |
| Previous CABG (%) | 3.7 | 6.6 | 0.14 |
| Previous PCI (%) | 3.2 | 5.4 | 0.21 |
| NYHA class ≥ 3 (%) | 12.2 | 15.7 | 0.27 |
| Cerebrovascular disease (%) | 5.6 | 9.6 | 0.083 |
| Extent of disease | | | |
| 1-vessel (%) | 50.4 | 40.4 | 0.006* |
| 2-vessel (%) | 39.8 | 42.7 | |
| 3-vessel (%) | 9.8 | 16.9 | |
| Ejection fraction (%) | 53.1 | 52.7 | 0.85 |
| Indication | | | |
| Stable angina (%) | 88.1 | 80.7 | 0.018* |
| Unstable angina (%) | 8.5 | 13.3 | |
| Acute MI (%) | 3.4 | 6.0 | |
| CTO length >20 mm (%) | 64.9 | 31.9 | <0.001 |
| CTO duration (days) | 122 (104–165) | 144 (115–185) | <0.001 |

CTO, chronic total occlusion; CHD, coronary heart disease; PVD, peripheral vascular disease; renal dysfunction (serum creatinine >200 $\mu\text{mol/L}$); MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary interventions; NYHA, New York Heart Association. Continuous variables are shown as a median with 25th and 75th percentiles; test of significance = Wilcoxon rank sum test. Categorical variables are shown as a percentage; test of significance = Chi-square test (* indicates test for trend).

non-CTO lesions was frequently performed at the same procedure. In patients with successful CTO PCI, additional non-CTO lesions were treated in 52.5% (198/377) of cases. In patients with multivessel disease and unsuccessful CTO PCI, 73.1% (38/52) had additional non-CTO lesions treated at the same procedure. Coronary stents were used in 97.7% (391/400) of all successfully treated CTO lesions. Drug-eluting stents (DES) were used in 17.3% (69/400) of all CTO treated lesions.

Patient characteristics of CTO success and CTO failure patients are shown in Table I. Multivessel coronary disease and peripheral vessel disease were more common in patients with CTO failure compared to CTO success. An unstable presentation and longer CTO duration were associated with a higher rate of CTO failure. A trend towards greater CTO success was seen for lesions located in the LAD compared to the RCA and LCx (Table II).

TABLE II. Target Vessel of CTO Lesion

| Vessel | CTO success (n = 400 lesions) | CTO failure (n = 170 lesions) | P value |
|-----------|----------------------------------|----------------------------------|---------|
| LAD n (%) | 175 (43.8) | 58 (34.1) | 0.083 |
| Cx n (%) | 69 (17.2) | 38 (22.4) | |
| RCA n (%) | 156 (39.0) | 74 (43.5) | |

LAD, left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery ($P = 0.083$ by chi-squared).

TABLE III. In-Hospital Outcomes

| | CTO success (n = 377) | CTO failure (n = 166) | P value |
|------------------------------|--------------------------|--------------------------|---------|
| Mortality (%) | 0.3 | 1.2 | 0.17 |
| Myocardial infarction (%) | 6.4 | 4.8 | 0.48 |
| Emergency CABG (%) | 0 | 0 | – |
| Cerebrovascular accident (%) | 0.5 | 1.2 | 0.40 |

CTO, chronic total occlusion; CABG, coronary artery bypass grafting. Categorical variables are shown as a percentage; test of significance = Chi-square test.

In-Hospital Events

In-hospital outcomes are shown in Table III. In-hospital mortality was slightly higher in the CTO failure vs. CTO success patients although this did not reach statistical significance. There were no documented in-hospital Q-wave AMIs. The rates of post procedural non-Q wave MI were similar between the two groups. No patients required emergency in patient CABG.

Medium-Term Follow-up

Patients were followed up for a maximum of 2-years with a mean (SD) follow-up of 1.7 (0.5) years. During this period 19 deaths were recorded, of which only 2 were non-cardiac. Both of these deaths were due to malignancy and occurred in the CTO success group. Figure 1 shows the observed mortality curves for both CTO success and CTO failure patients. The crude hazard ratio for death with CTO failure was 3.92 (95% confidence intervals 1.56–10.07; $P = 0.004$). Death for CTO success patients at 2-years was 2.5% compared to 7.3% in CTO failure patients. In patients with single vessel disease, unsuccessful CTO PCI was associated with increased medium-term mortality. A similar trend was seen in patients with multivessel disease although this did not reach statistical significance (Table IV).

CABG was more frequently performed in patients with CTO failure compared with CTO success, 21.7% vs. 3.2% ($P < 0.001$), respectively. Patients with single vessel disease and CTO failure had a CABG rate of 29.8% (34/114) compared with 3.8% (2/52) for patients with CTO failure and multivessel disease. One

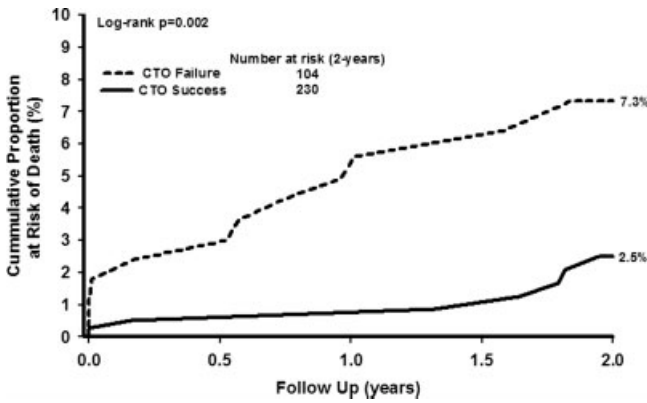


Fig. 1. Mortality curves for CTO success and CTO failure patients in the unmatched groups.

TABLE IV. Follow-up Mortality in Patients with Single-Vessel and Multivessel Disease

| | Mortality n (%) | | P value |
|---------------|-----------------------|-----------------------|---------|
| | CTO Success (n = 247) | CTO failure (n = 114) | |
| Single vessel | 2 (0.8) | 7 (6.1) | 0.003 |
| Multi vessel | 5 (3.8) | 5 (4.6) | 0.12 |

death was observed at 1.6 years after follow-up in patients with CTO failure and subsequent CABG. Clinically driven repeat PCI for TVR of CTO lesion was 6.4% during follow-up.

We were able to successfully match 157 CTO success patients to 157 unique CTO failure patients. The patient and disease characteristics of the propensity-matched patients are shown in Table V.

The observed survival curves for both CTO success and CTO failure patients in the propensity-matched cohort are shown in Fig. 2. The associated hazard ratio for death with CTO failure was 4.63 (95% confidence intervals 1.01–12.61, $P = 0.049$). Death for CTO success patients at 2-years was 2.0% compared to 5.8% in CTO failure patients. Multivariate analysis showed that CTO failure was an independent predictor of death, hazard ratio 4.95 (95% confidence intervals 1.03–23.89, $P = 0.046$, Table VI).

DISCUSSION

The principal findings of this retrospective observational study are that successful revascularization of CTOs by PCI and coronary stenting is associated with an improved survival and reduced need for CABG compared to patients with a failed CTO procedure.

Two previous studies have examined the impact of CTO PCI with stent implantation on long term survival. The prospective multicenter TOAST-GISE (Total Occlusion Angioplasty Study-Società Italiana di Cardi-

TABLE V. Patient and Disease Characteristics (Propensity-Matched Cohort)

| | CTO success (n = 157) | CTO failure (n = 157) | P value |
|-----------------------------|-----------------------|-----------------------|---------|
| Age (years) | 58.1 (50–67.2) | 58.7 (52–65.6) | 0.46 |
| Female (%) | 14.6 | 19.7 | 0.23 |
| Family history of CHD (%) | 54.1 | 51 | 0.57 |
| Diabetes (%) | 7 | 9.6 | 0.41 |
| Renal dysfunction (%) | 0.6 | 1.3 | 0.56 |
| PVD (%) | 3.2 | 5.7 | 0.27 |
| Hypertension (%) | 51 | 57.3 | 0.26 |
| Hypercholesterolaemia (%) | 88.5 | 89.2 | 0.86 |
| Ex smoker (%) | 49.7 | 49 | 0.91 |
| Current smoker (%) | 22.3 | 20.4 | 0.68 |
| Previous MI (%) | 58.6 | 56.7 | 0.73 |
| Previous CABG (%) | 5.7 | 5.7 | >0.99 |
| Previous PCI (%) | 3.8 | 4.5 | 0.78 |
| NYHA class ≥ 3 (%) | 13.4 | 12.7 | 0.87 |
| Cerebrovascular disease (%) | 7.6 | 9.6 | 0.54 |
| Extent of disease | | | |
| 1-vessel (%) | 43.9 | 42.7 | >0.99* |
| 2-vessel (%) | 40.2 | 42.6 | |
| 3-vessel (%) | 15.9 | 14.7 | |
| Ejection fraction (%) | 52.3 | 53.6 | 0.15 |
| Indication | | | |
| Stable angina (%) | 84.1 | 84.1 | 0.91* |
| Unstable angina (%) | 11.5 | 12.1 | |
| Acute MI (%) | 4.5 | 3.8 | |
| CTO length >20 mm (%) | 56.7 | 46.5 | 0.071 |
| CTO duration (days) | 138 (110–177) | 140 (112–180) | 0.65 |

CTO, chronic total occlusion; CHD, coronary heart disease; PVD, peripheral vascular disease; renal dysfunction (serum creatinine >200 $\mu\text{mol/L}$); MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary interventions; NYHA, New York Heart Association. Continuous variables are shown as a median with 25th and 75th percentiles; test of significance = Wilcoxon rank sum test. Categorical variables are shown as a percentage; test of significance = Chi-square test (* indicates test for trend).

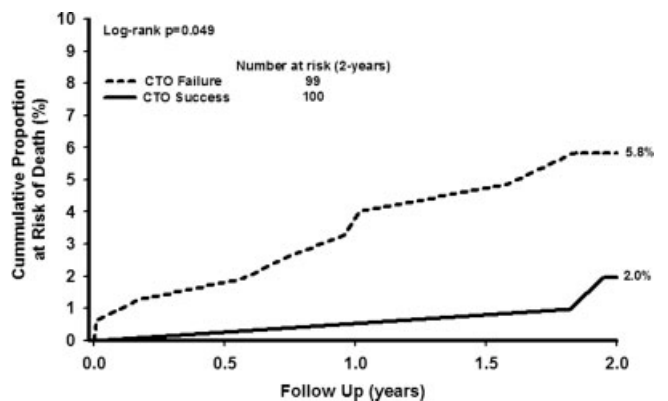


Fig. 2. Mortality curves for CTO success and CTO failure patients in the propensity matched groups.

ologia Invasiva) study included 376 patients with CTOs (defined as >30 days of duration) [12]. The technical success rate was 77% compared with 69% in our report and stents were used in 90% of all cases.

TABLE VI. Predictors of Mortality Propensity-Matched Cohort

| | Hazard Ratio ^a | 95% Confidence Interval | <i>P</i> value |
|------------------------|---------------------------|-------------------------|----------------|
| Age ^b | 1.14 | 1.06–1.22 | <0.001 |
| Ejection fraction <50% | 4.87 | 1.22–19.53 | 0.025 |
| Diabetes | 4.61 | 1.13–18.86 | 0.034 |
| CTO failure | 4.95 | 1.03–23.89 | <0.046 |

CTO, chronic total occlusion.

^aAdjusted for the propensity score (Hazard Ratio = 0.38; *P* = 0.71).

^bFor each additional *unit*.

The higher technical success rate reported in this study may be related to the definition of a CTO. This was defined as >30 days occlusion compared with >3 months as in our study. During a follow-up period of 12 months, fewer cardiac deaths were observed in patients with a successful CTO PCI compared to those with a failed procedure (0.35% vs. 3.61%, *P* = 0.037). The absolute number of events was small with only 6 deaths comprising of 4 cardiac deaths observed during the study period. No difference was found in all cause mortality between the two groups. In the present study, we have reported all cause mortality and cardiac mortality over a mean follow up period of 1.7 years. A significant survival advantage was seen in patients with a successful vs. unsuccessful CTO procedure, which was still evident although less marked with propensity matching.

Hoye et al. published the results of 874 patients who underwent CTO PCI at the Thoraxcenter over a 10-year period [13]. Technical success rate was 65.1% with stents used in 81.0% of cases. At 5 years follow up, survival was significantly higher in patients with successful vs. unsuccessful CTO revascularization by PCI. Subgroup analysis showed that the survival advantage was limited to patients with multivessel disease. Patients with single vessel CTO disease had similar survival at 5 years, 97.3% for CTO success vs. 99% for CTO failure patients (*P* = 0.3). These results are in contrast to our study. We showed that patients with single vessel disease had a survival advantage with successful CTO revascularization by PCI. These findings may be explained by the use of CABG in patients with unsuccessful PCI. Approximately half of the patients with single vessel disease and failed CTO PCI at the Thoraxcenter underwent CABG or repeat PCI. In our study the use of CABG in similar patients was 29.8%. Further studies are required to compare optimal medical therapy with revascularization in these patients.

We have shown that patients with CTO failure are nearly 7 times more likely to require CABG during follow-up. The majority of CABG cases were in patients with CTO failure and single vessel disease.

Only 3.8% of patients with multivessel disease and CTO failure underwent CABG. Non-CTO lesion PCI was performed in 73% of these cases. Previous studies have shown that the presence of a CTO is an independent predictor of incomplete revascularization in patients undergoing multivessel PCI [14]. Factors that may influence the use of PCI over CABG in patients with CTO and multivessel disease include patient comorbidity, patient preference, CTO vessel supplying area of previous myocardial infarction, and poor distal vessels in CTO territory. In our study testing for myocardial viability was not routinely performed. Studies have shown that magnetic resonance imaging can be used to detect viability and predict improvement in left ventricular function following CTO revascularization by PCI [15]. More accurate assessment of viability may result in improved patient selection.

We have also shown that CTO failure is more likely when PCI is performed for unstable angina or acute MI. Revascularization in these patients is often focused on treatment of the culprit vessel. Additional PCI of CTO lesions may be limited due to patient instability, long procedure duration, and lack of importance attributed to CTO. The propensity matched analysis corrected for any differences in presentation between the two groups.

The results of our study concur with the two previously mentioned studies that multivessel disease is more common in patients with CTO failure [12,13]. This would influence long-term survival in unmatched groups. Patients with multivessel disease have more advanced coronary disease and increased CTO duration is a predictor of PCI failure [16].

Several possible mechanisms may explain the improved survival in patients with a successful CTO revascularization. These include increase in left ventricular ejection fraction [17,18], better tolerance of future ischemic episodes, and reduced predisposition to arrhythmias. Inability to cross the occlusion with a guidewire is the main factor that prevents successful revascularization of CTO by PCI. The use of stiffer guidewires specifically designed for CTOs has been documented with improved procedural success rates [19]. Newer technologies with steerable dissecting and ablating devices may further enhance the use of PCI for more resistant CTO lesions [20].

Even with the use of bare metal stents, the long-term outcomes are suboptimal. In the TOSCA trial (Total Occlusion Study of Canada), restenosis occurred in 55% and reocclusion in 11% of patients following stent deployment [4]. Reocclusion was associated with increased mortality over a follow-up period of 3 years. DES have been shown to significantly reduce the incidence of restenosis and reocclusion compared with

bare metal stents in CTO lesions [21]. DES were used in only 17% of cases due to limited availability during the early study period. Improvements in long-term vessel patency with DES may increase the survival advantage seen in patients with CTO success compared with CTO failure.

LIMITATIONS

The present study compared survival in patients referred for CTO PCI. We have no information regarding the survival of patients with CTOs that are managed medically or referred directly for CABG. The reasons for improvement in survival have not been investigated. The Cox proportional hazards model is limited by the small number of outcomes observed in our study.

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