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ORIGINAL ARTICLE

Both surgical and percutaneous revascularization improve prognosis in patients with a coronary chronic total occlusion (CTO) irrespective of collateral robustness

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Abstract

The impact of surgical or percutaneous coronary revascularization on prognosis in patients with a chronic total occlusion (CTO) remains uncertain. Particularly, whether revascularization of those with robust coronary collaterals improves prognosis is unknown. The objective of this study was to determine the predictors and prognostic impact of revascularization of a CTO, and to determine the clinical impact of robust coronary collaterals. Patients with a CTO diagnosed on coronary angiography between Jul 2010 and Dec 2019 were included in this study. Management strategy of the CTO was defined as percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or medical management. The degree of collateral robustness was determined by the Rentrop grading classification. Demographic, angiographic and clinical outcomes were recorded. A total of 954 patients were included in the study, of which 186 (19.5%) patients underwent CTO PCI, 296 (31.0%) patients underwent CABG and 472 (49.5%) patients underwent medical management of the CTO. 166 patients (17.4%) had Rentrop grade zero or one collaterals, 577 (60.5%) patients had Rentrop grade two and 211 (22.1%) had Rentrop grade three collaterals. The independent predictors of medical management of the CTO were older age, greater stenosis in the donor vessel, an emergent indication for angiography, a non-LAD CTO and female sex. The degree of collateral robustness was not associated with long-term mortality, while patients who were revascularized either through CABG or PCI had a significantly lower mortality compared to medical management alone ($p < 0.0001$). In patients with a CTO, the presence of robust collaterals is not associated with prognosis, while both surgical and percutaneous revascularization is associated with improved prognosis. Further research into the optimal revascularization strategy for a CTO is required.

Keywords Coronary collaterals · Chronic total occlusion · CTO · Mortality · Revascularization · Coronary artery bypass grafting · Percutaneous coronary intervention

Introduction

A chronic total occlusion (CTO) is defined as complete, or near-complete occlusion of an epicardial coronary artery vessel, present for at least 3 months [1], angiographically appreciated via opacification of the distal vessel via the collateral circulation. The prevalence of a CTO identified during coronary angiography is between 18 and 52% [2, 3], with 6.6% of patients presenting with an ST elevation myocardial infarction (STEMI) having a concurrent CTO in a non-infarct-related artery [4]. Observational data have suggested that both surgical and percutaneous revascularization of a CTO are associated with improved quality of life and similar clinical outcomes [5, 6].

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The presence of well-developed collaterals is often described as "benign" and an indication to avoid revascularization [7], due to an apparent sufficient perfusion of the territory subtended by the CTO. However, there is substantial evidence that the territory of myocardium subtended by a CTO is in a constant state of ischemia, irrespective of the degree of collateral formation [8, 9]. In addition, among patients with ischemic cardiomyopathy receiving an implantable cardioverter-defibrillator for secondary prevention of sudden cardiac death, presence of CTO had been shown to confer a higher risk of ventricular arrhythmia recurrence and mortality [10]. We have previously shown that in patients undergoing CTO percutaneous coronary intervention (PCI), the presence of well-matured collaterals is not associated with an improvement in prognosis [11, 12].

Whether the degree of collateral development, irrespective of management strategy affects prognosis, remains uncertain. We sought to determine the predictors of and impacts of either surgical or percutaneous revascularization on patient outcomes. We also sought to determine prognostic implications of variation in collateral grade in patients with a CTO.

Methods

We reviewed all patients undergoing clinically indicated diagnostic coronary angiography at our tertiary center from July 2010 to Dec 2019. We identified patients who had a reported CTO through a commercially available reporting system (McKesson, Irving TX, USA). Patients who had a functioning coronary artery bypass graft (CABG) to either the CTO or the donor vessel were excluded from the analysis to allow characterization of native collaterals alone. Patients presenting with ST elevation myocardial infarction (STEMI), whereby acute recruitment of robust collaterals is associated with improved prognosis [13, 14], were also excluded.

Procedural characteristics, in-hospital course along with left ventricular function, and biochemical results were reviewed using electronic medical records. Mortality and last medical contact were determined through medical record-linking systems. Left ventricular function was assessed by transthoracic echocardiography or if not performed, then based on ventriculography at the time of diagnostic angiography. The presence and degree of collaterals were graded according to the Rentrop classification [15], where grade zero is no filling of any collateral channel, grade one is filling of the side branches of the infarct related artery, grade two is partial filling of the epicardial vessel of the infarct related artery, grade three is complete filling of the epicardial vessel (Fig. 1). The collateral connection grade (CC) [16] which is based on the size of the collaterals, was also assessed, whereby grade zero is no continuous connection between donor and recipient artery, grade one is continuous, threadlike connections (diameter $\leq$ 0.3 mm) and grade two continuous, small, side-branch-like size of the collaterals throughout its course (diameter $\geq$ 0.4 mm). The donor vessel was defined as the epicardial coronary artery from which the predominant collaterals arose.

Patients presenting with unstable angina, non-ST elevation myocardial infarction, ventricular arrhythmia or cardiac arrest not fulfilling criteria for STEMI were defined as emergent indications for angiography. Those presenting with stable symptoms included angina or angina equivalent symptoms were defined as non-emergent indications. All angiograms were performed for clinically indicated symptoms. Left ventricular impairment was defined as left

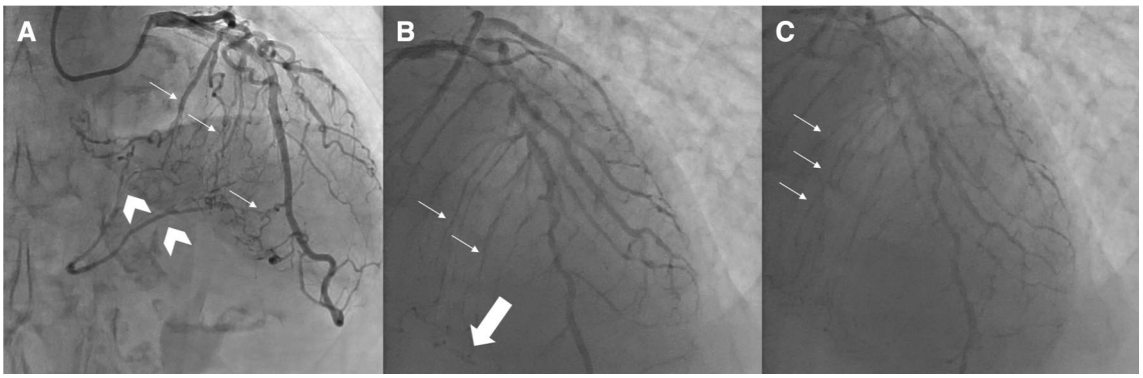

Fig. 1 Rentrop grading of a chronic total occlusion (CTO) of the right coronary artery (RCA). Three cases of a chronic total occlusion (CTO) of the right coronary artery (RCA). **a** Rentrop grade three collaterals—contrast injection of the left main stem (LMS) results in contrast opacification of the right coronary artery (RCA) via septal collaterals (thin white arrows) resulting in complete filling of the occluded RCA and its branches (Chevron). **b** Rentrop grade two—contrast injection of the LMS resulting in contrast opacification of septal collaterals (thin white arrows) resulting in partial filling of the occluded RCA (thick arrow). **c** Rentrop grade one—contrast injection of the LMS results in filling of the side branch of the RCA, the septal artery (arrows) but no opacification of the occluded RCA

ventricular ejection fraction (LVEF) ≤ 50%, while valvular heart disease was defined as moderate or severe mitral or aortic valve disease, either stenosis or regurgitation, as determined on echocardiography. Management of the CTO was defined as the "as-treated" population, whereby patients who had failed CTO PCI were stratified by subsequent management—CABG or medical management. Patients who had PCI performed to a non-CTO vessel were defined as medical management of the CTO. Project approval by the local human ethics committee was obtained prior to data analysis (NSLHD 2020/ETH00525).

Statistical analysis

Categorical variables were reported as %, whilst continuous variables were presented as means ± standard deviation (normally distributed data) or as medians and interquartile ranges, (data not normally distributed). Comparisons between groups were performed using Pearson's chi square test for all categorical variables. Continuous variables were firstly assessed by the Shapiro–Wilk test to ascertain normality of distribution, after which, a one-way analysis of variance (ANOVA) test was used for normally distributed data, and the Kruskal–Wallis ANOVA test was used for continuous data not distributed normally. Multivariable logistic regression analyses were performed to determine variables associated with medical management of the CTO. The multivariable model was built by forward linear regression, with entry and exit criteria set at the $p < 0.10$. Cox regression analysis was performed to determine the independent predictors of mortality with entry set at $p < 0.05$ and removal at $p > 0.1$ from the model, built by forward linear regression. All tests were two sided, and a $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS (version 24, IBM, New York, New York).

Results

Over the study period, 954 patients were identified with a CTO on diagnostic angiography. The mean age was 70.2 ± 12.3 with 18.4% females and 491 patients (51.5%) having an emergent indication for coronary angiography. The CTO vessel was the left anterior descending artery (LAD) in 225 (23.6%) patients, the left circumflex artery (LCx) in 199 (20.9%) and the right coronary artery (RCA) in 530 (55.6%) patients. Two hundred and twenty one (23.1%) patients were planned to have PCI performed, of which 186 (84.2%) procedures were successful. Of those with failed CTO PCI, 30 were managed medically, with five patients undergoing CABG. Consequently, the as-treated management of patients presenting with a CTO was CTO PCI in 186 (19.5%) patients, CABG in 296 (31.0%) and medical management of the CTO in 472 (49.5%) patients.

Patients who underwent medical management of the CTO were older (73.0 vs 68.5 vs 67.0 years, $p < 0.0001$), had a lower body mass index (BMI) (26.7 vs 27.4 vs 27.4 kg/m^2, $p < 0.05$) and more likely to be females (22.9 vs 15.6 vs 13.2%, $p < 0.01$) as compared to those who underwent PCI or CABG, respectively. Patients who were medically managed were less likely to be on aspirin (93.9 vs 88.3 vs 90.5%, $p < 0.01$) or a statin (77.8 vs 88.3 vs 90.1%, $p < 0.0001$) but more likely to be a on a nitrate (23.7 vs 18.4 vs 13.8%, $p < 0.01$) and angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker two (ARB) (66.0 vs 63.7 vs 56.9%, $p < 0.05$) compared to those who underwent PCI or CABG, respectively. Patients with an LAD CTO were less likely to have medical management compared to those with an LCx or RCA CTO (40.0 vs 50.8 vs 53.0%, $p < 0.05$). The demographic and angiographic predictors of differing management strategies are shown in Table 1. Patients undergoing CTO PCI were less likely to have LV impairment (33.7 vs 50.7 vs 47.8%, $p < 0.001$) or an emergent indication of angiography (25.8 vs 58.1 vs 57.4%, $p < 0.0001$) but higher LVEF (60 vs 50 vs 55%, $p < 0.0001$) compared to those undergoing CABG and medical management, respectively. Patients undergoing CABG were more likely to have concurrent valvular heart disease (20.6 vs 6.1 vs 11.9%, $p < 0.001$) and higher degree of stenosis in the donor vessel (70 vs 30 vs 50%, $p < 0.0001$) compared to those undergoing CTO PCI and medical management, respectively.

Variables included in the multivariate regression model to determine independent predictors of medical management of the CTO were: age, BMI, CTO vessel, degree of collaterals (as assessed by the Rentrop classification and CCS), diabetes mellitus, hypercholesterolemia, hypertension, indication for angiography, left ventricular impairment percent stenosis in the donor vessel, presence of multiple CTOs, sex, smoking history, and valvular heart disease. The independent predictors of medical management of a CTO were age (OR 1.5 per 10 years of age, 95% CI 1.3–1.8, $p < 0.0001$), stenosis in the donor vessel (OR 0.8 per 10%, 95% CI 0.8–0.9, $p < 0.0001$), emergent indication for angiography (OR 1.8, 95% CI 1.3–2.5, $p < 0.0001$), a non-LAD CTO (OR 1.8, 95% CI 1.2–2.6, $p < 0.01$) and female sex (OR 1.5, 95% CI 1.01–2.2, $p < 0.05$).

Mean clinical follow-up was 872.2 days for those who underwent CTO PCI, 849.5 days for those who underwent CABG and 928.8 days for those who underwent medical management ($p = 0.76$). Subsequent cox-regression analysis was performed to identify the independent predictors of mortality in patients with a CTO, which were left ventricular impairment (HR 2.4, 95% CI 1.6–3.6, $p < 0.0001$), age (HR 1.7 per 10 years 95% CO 1.4–2.1), medical management of the CTO (HR 1.8, 95% CI 1.2–2.7, $p < 0.01$),

Table 1 Demographic and angiographic characteristics of patients with a CTO

	PCI–CTO $n=186$	CABG $n=296$	Medical management $n=472$	p value
Age (years)	68.5 ± 12.0	67.0 ± 11.8	73.0 ± 12.2	< 0.0001
BMI (kg/m^2)	27.4 (24.5–31.4)	27.4 (24.7–30.2)	26.7 (23.6–30.4)	< 0.05
Female sex (*n*)	29 (15.6%)	39 (13.2%)	108 (22.9%)	< 0.01
Previous AMI (*n*)	57 (31.1%)	83 (29.4%)	170 (37.4%)	0.06
Medications (*n*)				
Aspirin	168 (93.9%)	256 (90.5%)	370 (82.8%)	< 0.01
P2Y12 inhibitor	152 (84.9%)	95 (33.6%)	290 (64.9%)	< 0.0001
Beta blocker	113 (63.1%)	221 (78.1%)	302 (67.6%)	< 0.01
ACE-I|ARB	114 (63.7%)	161 (56.9%)	295 (66.0%)	< 0.05
Nitrate	33 (18.4%)	39 (13.8%)	106 (23.7%)	< 0.01
Statin	158 (88.3%)	255 (90.1%)	348 (77.8%)	< 0.0001
Risk factors (*n*)				
Hypertension	145 (79.2%)	252 (86.0%)	396 (85.2%)	0.11
Hypercholesterolemia	144 (79.1%)	246 (84.2%)	374 (81.1%)	0.34
Smoking history				0.48
Never	91 (49.7%)	143 (53.1%)	200 (46.6%)	
Ex-smoker	69 (37.7%)	89 (33.1%)	162 (37.8%)	
Current	23 (12.6%)	37 (13.7%)	67 (15.6%)	
Diabetes mellitus	57 (31.0%)	114 (40.1%)	160 (35.1%)	0.12
Multiple CTOs (*n*)	14 (7.5%)	76 (34.5%)	84 (17.8%)	< 0.0001
CTO vessel (*n*)				< 0.05
LAD	58 (25.8%)	77 (34.2%)	90 (40.0%)	
LCx	37 (18.6%)	61 (30.6%)	101 (50.8%)	
RCA	91 (17.2%)	158 (29.8%)	281 (53.0%)	
Rentrop				0.08
0/1	25 (13.4%)	52 (17.6%)	89 (18.8%)	
2	107 (57.5%)	187 (63.2%)	283 (60.0%)	
3	54 (29.0%)	57 (19.3%)	100 (21.2%)	
CCS				0.08
0	8 (4.3%)	21 (7.1%)	32 (6.8%)	
1	35 (18.8%)	66 (22.3%)	128 (27.1%)	
2	143 (76.9%)	209 (70.6%)	312 (66.1%)	
LV impairment (*n*)	57 (33.7%)	150 (50.7%)	216 (47.8%)	< 0.001
Valvular heart disease (*n*)	9 (6.1%)	50 (20.6%)	47 (11.9%)	< 0.001
Emergent indication (*n*)	48 (25.8%)	172 (58.1%)	271 (57.4%)	< 0.0001
LVEF (%)	60 (45–60)	50 (40–60)	55 (40–60)	< 0.0001
Stenosis of donor vessel (%)	30 (20–50)	70 (50–80)	50 (30–70)	< 0.0001

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *AMI* acute myocardial infarction, *BMI* body mass index, *CCS* collateral connection score, *CTO* chronic total occlusion, *Kg* kilogram, *LAD* left anterior descending artery, *LCx* left circumflex artery, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *m* meter, *RCA* right coronary artery, *yrs* years

diabetes mellitus (HR 1.8 95% CI 1.3–2.7, $p < 0.01$) and current smokers (HR 1.9, 95% CI 1.1–3.5, $p < 0.05$) [Table 2]. There was no difference in survival between patients with differing degrees of collateral recruitment (mean survival = 7.3 vs 8.7 vs 7.7 years, $p = 0.53$ for Rentrop zero or one, two and three, respectively) in all patients, or in those patients who underwent medical management only (Fig. 2).

Discussion

In a large cohort of patients undergoing coronary angiography diagnosed with a CTO, the independent predictors of medical management, as compared to revascularization are older age, lower degree of stenosis in a donor vessel, emergent indication for angiography, the LCx or RCA as the CTO vessel and female sex. Prior studies have suggested that

Table 2 Cox regression analysis of independent predictors of mortality

	Hazard ratio	95% confidence interval	*p* value
LV impairment	2.4	1.6–3.6	< 0.0001
Age (per 10 years)	1.7	1.4–2.1	< 0.0001
Medical management of CTO	1.8	1.2–2.7	< 0.01
Diabetes mellitus	1.8	1.3–2.7	< 0.01
Current smoker	1.9	1.1–3.5	< 0.05

CTO chronic total occlusion, *LV* left ventricular

older patients with a CTO have more complex anatomical disease, and have consequently been less frequently revascularized [17] despite the evidence of comparable outcomes with successful revascularization as compared to younger patients [18]. A lower degree of stenosis in a donor vessel is likely reflective of single vessel disease, which is more likely to be managed medically. While the applicability of physiological assessment of the donor vessel in the setting of a CTO remains uncertain [19], it may still play a role in determining the need for more comprehensive revascularization.

The finding of a CTO in patients with emergent indication for coronary angiography likely reflects either a concurrent CTO along with a culprit vessel, or a cause of demand ischemia. Despite the evidence that a concurrent CTO in the setting of an acute coronary syndrome have poorer prognosis [20], and specifically revascularization of the CTO improved outcomes [21], revascularization rates remain low accounting for less than 5% of total PCI volume [22].

Patients with an LAD CTO were more likely to undergo revascularization as compared to those with an RCA or LCx CTO. Previous studies have differed with respect to trends of management of LAD CTO with one study finding higher rates of PCI, while another found no difference in management strategy in patients with an LAD CTO [3]. This is despite observational evidence suggesting that LAD CTO revascularization is associated with a reduction in mortality [23, 24], although this was not observed in our study. The prevalence of LAD CTO was 23.6%, which is similar to the previously published data [5]; however, it is possible that the lack of prognostic benefit seen with LAD revascularisation seen in this study is due to insufficient power in the study. Females were less likely to have their CTO revascularized compared with men. There is significant evidence that

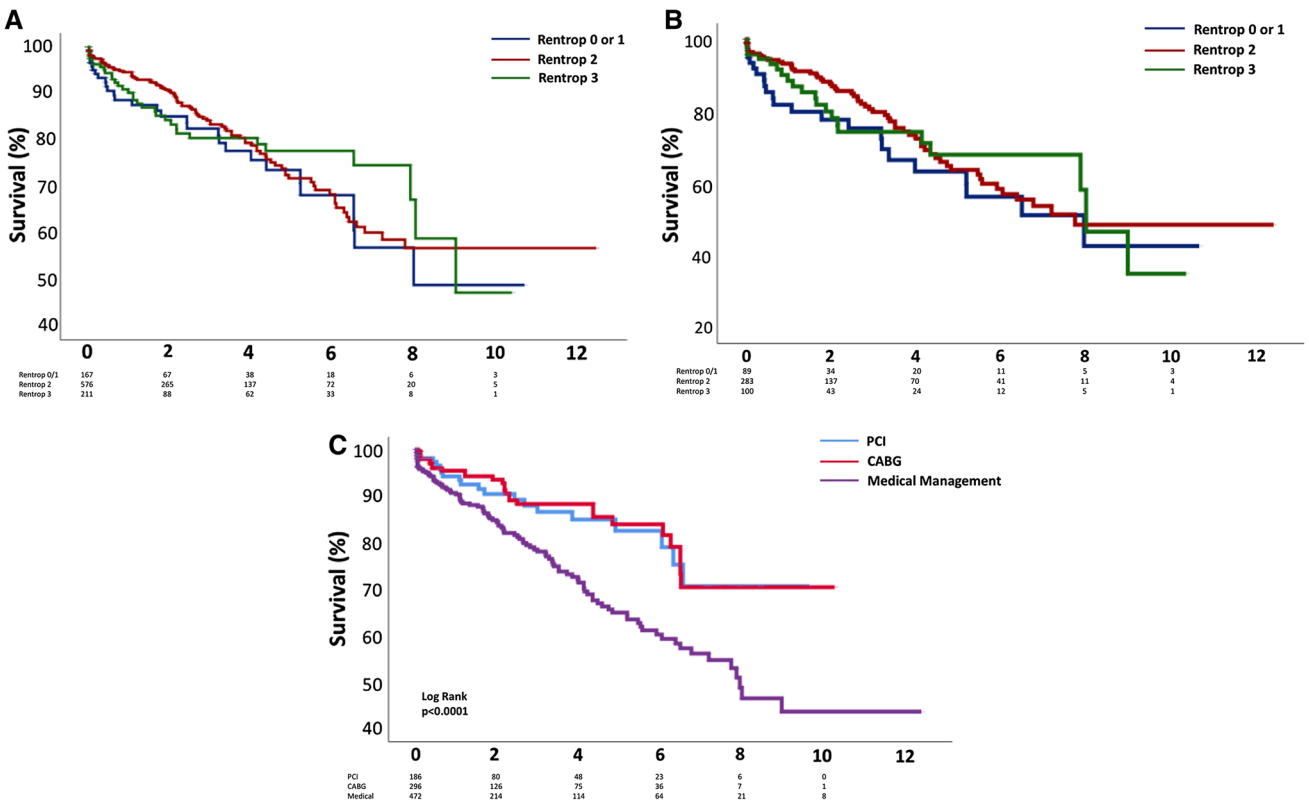

Fig. 2 Kaplan Meier survival curves for patients with a CTO. **a** survival curves for all patients with a CTO stratified by Rentrop grade, showing no difference in survival. **b** survival curves for patients undergoing medical management for a CTO, stratified by Rentrop grade showing no difference in survival. **c** survival curves for all patients with a CTO stratified by management, showing significantly higher mortality in those managed medically compared to those managed with PCI or CABG

women are less likely to be adequately managed or offered invasive treatment for coronary artery disease [25], resulting in poorer outcomes. In a previous study, women were less likely to undergo CABG for their CTO; however, rates of CTO PCI were similar [26]. Further studies aimed at identifying the underlying reasons for this disparity are required as is further physician education.

Whilst the degree or coronary collateralisation is often cited as a reason to avoid revascularization, we found no difference in mortality in patients with robust coronary collaterals compared to those with poor coronary collaterals. Similarly, we found no difference in patients who were medically managed with respect to mortality and degree of collateralization. Previous studies in the setting of acute coronary syndrome suggest that acute collateral recruitment is constant and reproducible [27], and reduce the degree of myocardial necrosis and left ventricular impairment and improve outcomes [13, 14]. However, in the setting of a CTO, there does not appear to be a similar improvement in prognosis with more robust collaterals [13, 14].

Coronary collaterals, which mature in response to a combination of shear stress, inflammation, redox state, gene expression as well as hypoxia [28, 29], are a natural bypass mechanism and, whilst they may alleviate symptoms, they appear to be insufficient to affect prognosis. Instead revascularization, either through PCI or CABG, was associated with a reduction in mortality as compared to medical therapy, with those not revascularized having an almost twofold higher risk of mortality. Despite these findings as well as the previously documented association between a CTO and higher mortality [3], greater recurrence of ventricular arrhythmia [30] and ongoing anginal symptoms, data from randomized trials [31–33] failed to show any significant prognostic improvement with CTO PCI, and consequently, the current role of CTO PCI remains to improve symptoms and quality of life [34]. Previous studies [35] have suggested a prognostic benefit with revascularisation, as was seen in the present study. A significant reduction in myocardial ischemia as would be expected following CTO revascularization is associated with a reduction in cardiovascular events [36], which may explain this finding. Furthermore, a reduction in ventricular arrhythmias following CTO revascularisation has been observed [30], suggesting another explanation for the reduction in mortality in CTO revascularization. Although the lack of benefit of CTO PCI on prognosis in randomized trials may reflect issues with study design and appropriate power of the randomized trials, further evidence is required to determine the precise role for CTO revascularization.

The evidence base for revascularization through CABG for CTO is also controversial. Observational data [37] suggest that use of the left internal mammary artery to bypass the LAD is associated with high revascularization success, low major adverse events, with 100% patency rate at 1 year [38]. Conversely, patency rates of saphenous vein grafts (SVG) to a CTO are significantly lower than when grafted to a non-CTO vessel, with a 1-year patency rate of 23% [38]. Whilst we did not classify revascularization based on whether total arterial revascularization or SVGs were used, it appears that revascularization of the CTO, rather than just a donor vessel or bystander vessel, is associated with improved prognosis.

Limitations

This is a single-center retrospective observational, non-randomized study, which has inherent limitations, particularly with respect to case selection. However, given results included multivariate regression analyses, this provides some degree of independent associations, whilst the center is a regional and district CTO referral center, therefore providing expert management options. Furthermore, with respect to the CABG group, whether complete revascularization was achieved was not determined, and consequently, the CTO may have remained non-revascularized. All patients did not have viability assessment performed prior to revascularisation and decision making was based on clinician discretion, which may have affected results. However, there is controversy with respect to whether viability assessment is required, with studies in stable disease finding no association between viability assessment and prognosis [39], while CTO revascularization in apparent 'non-viable' myocardium resulted in improvements in quality of life, left ventricular function and frequency of angina [40]. Therefore, whilst the lack of viability assessment may introduce a degree of bias to the study, nevertheless, the overall results are hypothesis generating, and with increasing use of adjunctive imaging technology [41] as well as newer revascularization strategies to improve success and stent longevity, further research is needed to determine whether CTO revascularization corresponds with meaningful clinical benefit, even in those with robust coronary collaterals. Furthermore, the current study had a mean follow-up of up to 929 days. Future studies should include longer-term follow-up to determine whether the observed survival advantage persist over time.

Conclusions

In patients diagnosed with a CTO, older age, greater stenosis in the donor vessel, an emergent indication for angiography, non-LAD CTOs and female sex are independent predictors of non-revascularization. Both surgical and percutaneous revascularization were independently associated with a reduction in mortality. Whilst often cited as a reason to avoid

revascularization, due to perceived adequate myocardial perfusion, patients with robust collaterals do not have better prognosis compared to those with poorer angiographically determined collaterals, irrespective of management strategies. Further investigation should continue to determine which subset of patients with a CTO derive prognostic benefit from revascularization through either modality.

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Declarations

Conflicts of interest UKA has received an unconditional research grant from Heart Research Australia. RB has received an unconditional future leaders fellowship from the Heart Foundation.

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