Long-Term Outcomes in Patients With Chronic Total Occlusion

Daniel A. Gold, MD[a], Pratik B. Sandesara, MD[a], Vardhmaan Jain, MD[a], Matthew E. Gold, MD[a], Nishant Vatsa, MD[a], Shivang R. Desai, MD[a], Malika Elhage Hassan, MD[a], Chenyang Yuan[b], Yi-An Ko, PhD[b], Kiran Ejaz, MD[a], Zain Alvi, BS[a], Wissam A. Jaber, MD[a], William J. Nicholson, MD[a], and Arshed A. Quyyumi, MD[a,*]

Although a chronic total occlusion (CTO) in the setting of an acute coronary syndrome is associated with greater risk, the prognosis of patients with a CTO and stable coronary artery disease (CAD) remains unknown. This study aimed to investigate adverse event rates in patients with stable CAD with and without a CTO. In 3,597 patients with stable CAD (>50% coronary luminal stenosis) who underwent cardiac catheterization, all-cause mortality, cardiovascular mortality, and the composite major adverse cardiac event (MACE) rates for cardiovascular death, myocardial infarction, and heart failure hospitalization were evaluated. Cox proportional hazards and Fine and Gray subdistribution hazard models were used to compare event-free survival in patient subsets after adjustment for covariates. Event rates were higher in patients with CTOs than in those without CTOs after adjusting for demographic and clinical characteristics (cardiovascular death hazard ratio [HR] 1.29, 95% confidence interval [CI] 1.05 to 1.57, p = 0.012). Patients with CTO revascularization had lower event rates than those of patients without CTO revascularization (cardiovascular death HR 0.43, CI 0.26 to 0.70, p = 0.001). Those with nonrevascularized CTOs were at particularly great risk when compared with those without CTO (cardiovascular death HR 1.52, CI 1.25 to 1.84, p <0.001). Moreover, those with revascularized CTOs had similar event rates to those of patients with CAD without CTOs. Patients with CTO have higher rates of adverse cardiovascular events than those of patients with significant CAD without CTO. This risk is greatest in patients with nonrevascularized CTO. **© 2024 Published by Elsevier Inc. (Am J Cardiol 2024;214:59−65)**

Keywords: chronic total occlusion, obstructive CAD, revascularization

Chronic total occlusion (CTO) of the coronary arteries is a management conundrum in contemporary interventional cardiology practice. CTOs are encountered in 15% to 30% of patients who undergo diagnostic coronary angiography.[1,2] Despite its high prevalence, percutaneous coronary intervention (PCI) for CTO is attempted in <10% and bypass surgery in <25% of cases owing to technical difficulties and uncertainties regarding its prognostic efficacy.[1,2] The 2021 American College of Cardiology/American Heart Association PCI guidelines provide a class IIb/level of evidence B recommendation for CTO PCI in patients with refractory angina after PCI of non-CTO lesions.[3] Although a CTO in the setting of an acute coronary syndrome is associated with greater risk than in patients without CTOs,[4−11] the prognosis of patients with CTOs in nonacute settings remains to be established. One study reported a greater all-cause mortality in stable patients with a CTO than in those with coronary artery disease (CAD) with ≥1 vessel with >50% stenosis, but the study excluded patients with a history of coronary artery bypass graft surgery (CABG) and did not investigate cardiovascular event rates.[12]

In this report, we investigated the long-term adverse cardiovascular outcome rates in stable patients with CTO compared with those with significant CAD without a CTO, with the hypothesis that patients with CTO will have higher adverse events rates.

Methods

Patients were enrolled in the Emory Cardiovascular Biobank (NCT00378924), a prospective cohort of patients referred for clinically indicated cardiac catheterization at 3 Emory healthcare sites in Atlanta, Georgia between May 2004 and July 2022.[13] Exclusion criteria included (1) history of cardiac transplantation and (2) presentation with acute coronary syndrome. Significant CAD was defined as CAD ≥50% in any major coronary artery. CTO was defined as 100% luminal diameter stenosis with absence of anterograde flow on angiography of known or assumed 3-month duration.[14] CTO with a history of CABG was defined as a

[a]Emory Clinical Cardiovascular Research Institute, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; and [b]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, Georgia. Manuscript received September 19, 2023; revised manuscript received and accepted December 24, 2023.

Dr. Quyyumi is supported by National Institutes of Health (Bethesda, Maryland) grants P01HL154996-01A1, R33HL138657-05, U54AG062334-01, P30DK111024-07S2, R61HL154116-01, R01HL109413-07, R01HL166004-01.

See page 64 for Declaration of Competing Interest.

*Corresponding author: Tel: 404-712-2741.

E-mail address: aquyyum@emory.edu (A.A. Quyyumi).

0002-9149/© 2024 Published by Elsevier Inc.
https://doi.org/10.1016/j.amjcard.2023.12.052

Table 1
Baseline characteristics

Variable	No CTO	CTO	*P* Value
N	2675	922	
Age (IQR)	66.4 (58.9, 73.9)	65.4 (57.6, 72.7)	**0.008**
Male	1870 (70.0%)	705 (76.5%)	**0.001**
Black	483 (18.1%)	169 (18.3%)	0.85
Hypertension	2213 (83.3%)	763 (83.5%)	0.93
Dyslipidemia	2093 (78.8%)	735 (80.2%)	0.35
Diabetes	1043 (39.2%)	364 (39.8%)	0.76
Smoking history	1768 (66.1%)	616 (66.8%)	0.69
BMI (IQR)	28.7 (25.6, 32.9)	28.9 (25.6, 32.7)	0.85
Ejection Fraction (%) (SD)	53.3 (12.0)	49.5 (13.1)	**<0.001**
History of MI	696 (26.3%)	338 (37.1%)	**<0.001**
Chronic Kidney Disease	388 (14.5%)	139 (15.1%)	0.67
History of HF	885 (33.1%)	333 (36.1%)	**0.093**
Revascularization at enrolment	1436 (53.7%)	468 (50.8%)	0.13
Disease Severity*			
1-Vessel Disease	959 (55.7%)	175 (32.9%)	
2-Vessel Disease	505 (29.3%)	191 (35.9%)	**<0.001**
3-Vessel Disease	257 (14.9%)	166 (31.2%)	
Medications			
ACEi/ARB	1643 (61.4%)	570 (61.8%)	0.83
Beta Blocker	1968 (73.6%)	691 (74.9%)	0.41
Statin	2164 (80.9%)	779 (84.5%)	**0.015**
Outcomes			
All-Cause Mortality	744 (27.8%)	286 (31.0%)	**0.063**
CV Death	398 (14.9%)	163 (17.7%)	0.23
MI	230 (8.6%)	99 (10.7%)	**0.052**
HF Hospitalization	182 (10.6%)	72 (13.5%)	**0.059**
MACE	651 (24.3%)	254 (27.5%)	**0.052**

Values are median or n (%). The no CTO group had significant CAD defined as having ≥ 50% stenosis in at least one coronary artery, without CTO. MACE was defined as CV death, MI or HF hospitalization.

* Patients without a history of CABG.

ACEi/ARB = angiotensin converting enzyme inhibitors/angiotensin-receptor blocker; BMI = body mass index; CAD = coronary artery disease; CTO = chronic total occlusion; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; IQR = interquartile range; MACE = major adverse cardiac events; MI = myocardial infarction; SD = standard deviation.

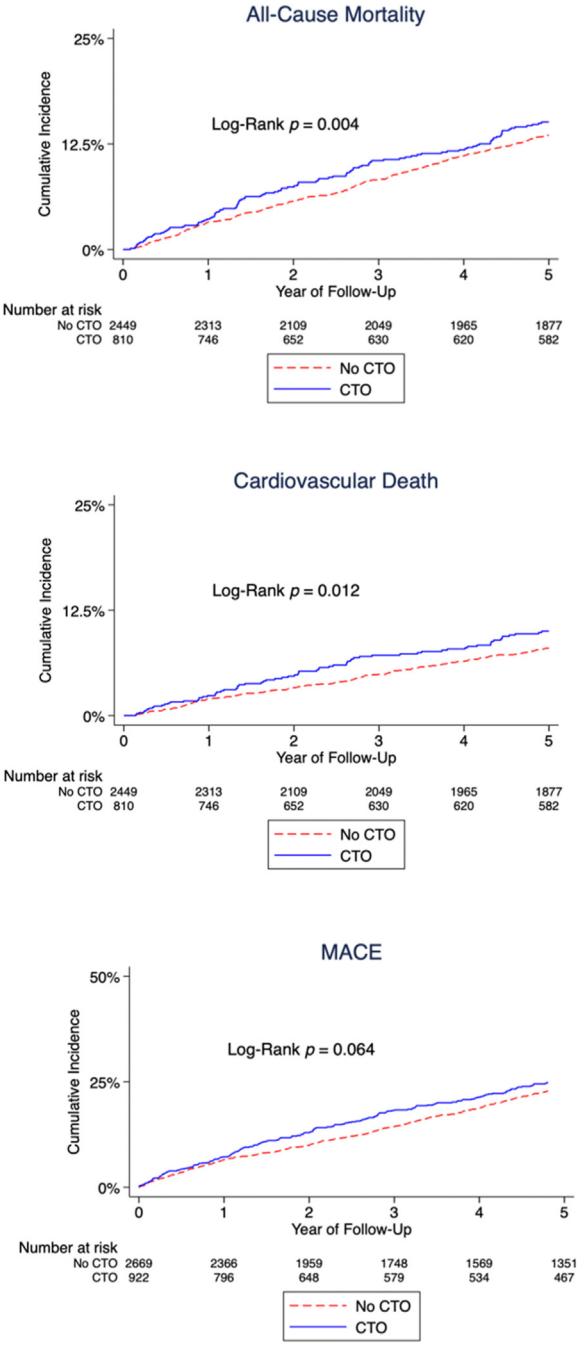

Figure 1. Cumulative incidence of adverse events in patients with and without CTO. Unadjusted cumulative incidence function was used to visualize differences in survival outcomes in patients with CTO (n = 922) and significant CAD without CTO (n = 2,675), coupled with log-rank tests. CTO was associated with higher event rates of all-cause mortality, cardiovascular death, and a MACE, defined as a composite of cardiovascular death/MI/HF hospitalization. The no-CTO group had significant CAD, defined as ≥50% stenosis in ≥1 coronary artery.

CTO of the native vessel and the graft supplying the territory. Three-vessel or left main disease was defined as patients with ≥50% stenosis in the left anterior descending artery, right coronary artery, and left circumflex artery, or in the left main artery.

Demographic and clinical data obtained from questionnaires and medical records included age, gender, race, history of hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or treatment with antihypertensive medications), dyslipidemia (total cholesterol ≥200 mg/100 ml, low-density lipoprotein >130 mg/100 ml, high-density lipoprotein <40 mg/100 ml or treatment with lipid-lowering medications), diabetes mellitus (hemoglobin A_{1c} >6.5 or treatment with insulin or oral antidiabetic medications), current or history of smoking, body mass index, estimated glomerular filtration rate (eGFR), history of chronic kidney disease, left ventricular ejection fraction (LVEF) (measured by most recent transthoracic echocardiography or ventriculography), history of myocardial infarction (MI), history of heart failure (HF), use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β blockers, or statins as previously described.[15] The study was approved by the institutional review board at Emory University, Atlanta, Georgia. All subjects provided written informed consent.

Table 2
Risk of adverse events in patients with compared to without CTO

Model	All-Cause Mortality HR (CI)	P Value	CV Death HR (CI)	*P* Value	MACE HR (CI)	*P* Value
1	1.22 (1.07 − 1.40)	**0.004**	1.26 (1.05 − 1.52)	**0.012**	1.15 (0.99 −1.33)	**0.064**
2	1.23 (1.07 − 1.40)	**0.004**	1.29 (1.08 − 1.56)	**0.006**	1.17 (1.01 − 1.35)	**0.036**
3	1.27 (1.09 − 1.47)	**0.002**	1.31 (1.07 − 1.60)	**0.008**	1.12 (0.96 − 1.31)	0.16
4*	1.24 (1.01 − 1.53)	**0.042**	1.30 (0.97 − 1.74)	**0.075**	1.21 (0.98 − 1.49)	**0.073**
5	1.25 (1.08 − 1.45)	**0.003**	1.29 (1.05 − 1.57)	**0.013**	1.11 (0.95 − 1.30)	0.20

Multivariate cox proportional hazard ratio was analyzed for all-cause mortality and multivariate Fine and Gray proportional hazards regression analysis for CV death and MACE of significant CAD compared to CTO with the CTO group as the reference group. Significant CAD was defined as having ≥ 50% stenosis in at least one coronary artery. MACE was defined as CV death/MI/HF hospitalization.

Model 1 unadjusted.

Model 2 adjusted for demographic covariates [age, sex, race (black vs. non-black)].

Model 3 adjusted for model 2 + clinical covariates [BMI, history of smoking, history of heart failure, hypertension, diabetes, dyslipidemia, chronic kidney disease, history of MI].

Model 4 adjusted for model 3 + disease severity [1, 2 or 3 vessel disease].

Model 5 adjusted for model 3 + any revascularization at study enrollment.

BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CI = 95% confidence interval; CTO = chronic total occlusion; CV = cardiovascular; HF = heart failure hospitalization; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction.

* (Patients without a history of CABG).

Patients were revascularized as clinically indicated. Revascularization was defined as PCI that decreased the stenosis grade by ≥50% and restored to Thrombolysis in Myocardial Infarction flow grade 2 or 3 flow, or CABG within 90 days of enrollment. CTO revascularization was defined as PCI or CABG that bypassed the CTO lesion. Non-CTO revascularization was defined as revascularization that did not include the CTO (PCI of non-CTO lesions only or CABG that did not bypass the CTO). Patients with CTO who received non-CTO revascularization only were included in the nonrevascularized CTO group.

Patients were observed for a median period of 5.1 interquartile range (IQR) (2.1 to 6.5) years for determination of all-cause mortality, cardiovascular death, MI, HF hospitalization, and major adverse cardiac events (MACEs). MACE was defined as cardiovascular death/MI/HF hospitalization. Follow-up data were collected by personnel blinded to the clinical data through telephone interview, chart review, and query of the Social Security Death Index and State records, as previously described.[15] Two independent cardiologists adjudicated the cause of death. Cardiovascular death was defined as death attributable to an ischemic cardiovascular cause (i.e., fatal MI, stroke, or peripheral arterial disease) or sudden death because of presumed cardiovascular cause in patients at great risk. Medical records were accessed to validate all self-reported events.

Patient characteristics were summarized using medians and IQR, or frequency counts and percentages, as appropriate. Baseline differences among patients were assessed using Mann-Whitney *U* tests for continuous variables and the chi-square test for categorical variables. The cumulative incidence function was used to visualize differences in survival outcomes across groups coupled with log-rank tests. Cox proportional hazards models were used to examine the association between groups and time to all-cause mortality after adjustment for covariates. Fine and Gray subdistribution hazard models were used for time to cardiovascular death and major adverse outcomes (MACE) of cardiovascular death/MI/HF hospitalizations, with noncardiovascular deaths treated as competing events. Covariates considered included baseline demographics (age, gender, race [Black vs non-Black]), clinical characteristics (body mass index,

Table 3
Risk of adverse events in patients with CTO revascularization compared to those without CTO revascularization

Model	All-Cause Mortality HR(CI)	*P* Value	CV Death HR (CI)	*P* Value	MACE HR (CI)	*P* Value
1	0.54 (0.39 − 0.73)	**<0.001**	0.40 (0.25 − 0.63)	**<0.001**	0.47 (0.33 − 0.66)	**<0.001**
2	0.54 (0.39 − 0.73)	**<0.001**	0.41 (0.26 − 0.65)	**<0.001**	0.49 (0.34 − 0.69)	**<0.001**
3	0.48 (0.34 − 0.69)	**<0.001**	0.43 (0.26 − 0.70)	**0.001**	0.56 (0.39 − 0.81)	**0.002**

Multivariate cox proportional hazard ratio was analyzed for all-cause mortality and multivariate Fine and Gray proportional hazards regression analysis was analyzed for CV death and MACE of revascularized CTO compared to non-revascularized CTO, with the non-revascularized CTO group as the reference group. CTO revascularization was defined as PCI or CABG that bypassed the CTO. MACE was defined as CV death/MI/HF hospitalization.

Model 1 unadjusted.

Model 2 adjusted for demographic covariates [age, sex, race (black vs. non-black)].

Model 3 adjusted for model 2 + clinical covariates [BMI, history of smoking, history of heart failure, hypertension, diabetes, dyslipidemia, chronic kidney disease, history of MI].

BMI = body mass index; CABG = coronary artery bypass graft surgery; CI = 95% confidence interval; CTO = chronic total occlusion; CV = cardiovascular; HF = heart failure hospitalization; HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; PCI = percutaneous coronary intervention.

current or history of smoking, hypertension, diabetes, dyslipidemia, chronic kidney disease, history of MI, history of HF), disease severity (1-, 2-, or 3-vessel disease), and any revascularization at enrollment. The disease severity adjustment was used for patients without a history of CABG only. All analyses were performed using Stata/BE 17.0 (StataCorp, College Station, Texas) software and R 4.2.0. p Values <0.05 were considered statistically significant.

Results

Of the 3,597 patients enrolled, the median age was 60.7 IQR (51.7 to 68.9) years, 71.7% were male, and 18.1% were Black. Of the total population, 922 (25.6%) had a CTO, and 2,675 (74.4%) had significant CAD ≥50% without CTO. The CTO group was younger and had lower LVEF. A greater proportion of the CTO group was male and had a history of MI. In patients without a history of CABG, the severity of CAD was greater in patients with a CTO than in those without a CTO (Table 1).

During a median 5.1 IQR (2.1 to 6.5) year follow-up period, there were 1,030 deaths (28.6%), 561 cardiovascular deaths (15.6%), 329 nonfatal MIs (9.1%), and 254 HF hospitalizations (7.1%) (Table 1). Unadjusted all-cause mortality, cardiovascular mortality, and MACE rates were higher in the patients with CTO than in those with significant CAD without CTO (Figure 1, Table 2, model 1). The hazard ratios remained unchanged even after adjustment for demographic variables (age, gender, race [Black vs non-Black]) and clinical characteristics (body mass index, current or history of smoking, hypertension, diabetes, dyslipidemia, chronic kidney disease, history of MI, history of HF) (Table 2, model 3). After adjustment for disease severity in the subset without a history of CABG, adverse event rates remained higher in those with a CTO with cardiovascular mortality risk of 29% (confidence interval [CI] 5 to 57, p = 0.013) higher than in those without a CTO. Even after adjustment for revascularization, all-cause and cardiovascular mortality rates were higher in those with a CTO (Table 2, model 5). These results did not differ between groups with and without a history of CABG (interaction term p value = 0.90).

Of the overall cohort, 1,436 patients (53.7%) with significant CAD without CTO and 475 patients (51.5%) with CTO underwent revascularization at enrollment (Table 1). In those without CTO, patients who received revascularization were younger, had a higher eGFR, less HF, less history of MI, and greater disease severity. Baseline characteristics of patients with CTO and revascularization status are shown in Supplementary Table 1. Of the patients with CTO, 254 patients (27.5%) underwent CTO revascularization (66.9% PCI and 33.1% CABG); 221 (24.0%) had non-CTO vessel revascularization only, and 447 (48.5%) received medical management only. Patients with only non-CTO vessel revascularization were included in the non-CTO revascularization group. Patients with CTO revascularization were younger and more frequently male, had a higher eGFR, and had less disease severity than those without CTO revascularization (Supplementary Table 1). Unadjusted event rates for all-cause mortality, cardiovascular death, and MACE were lower in patients who underwent CTO

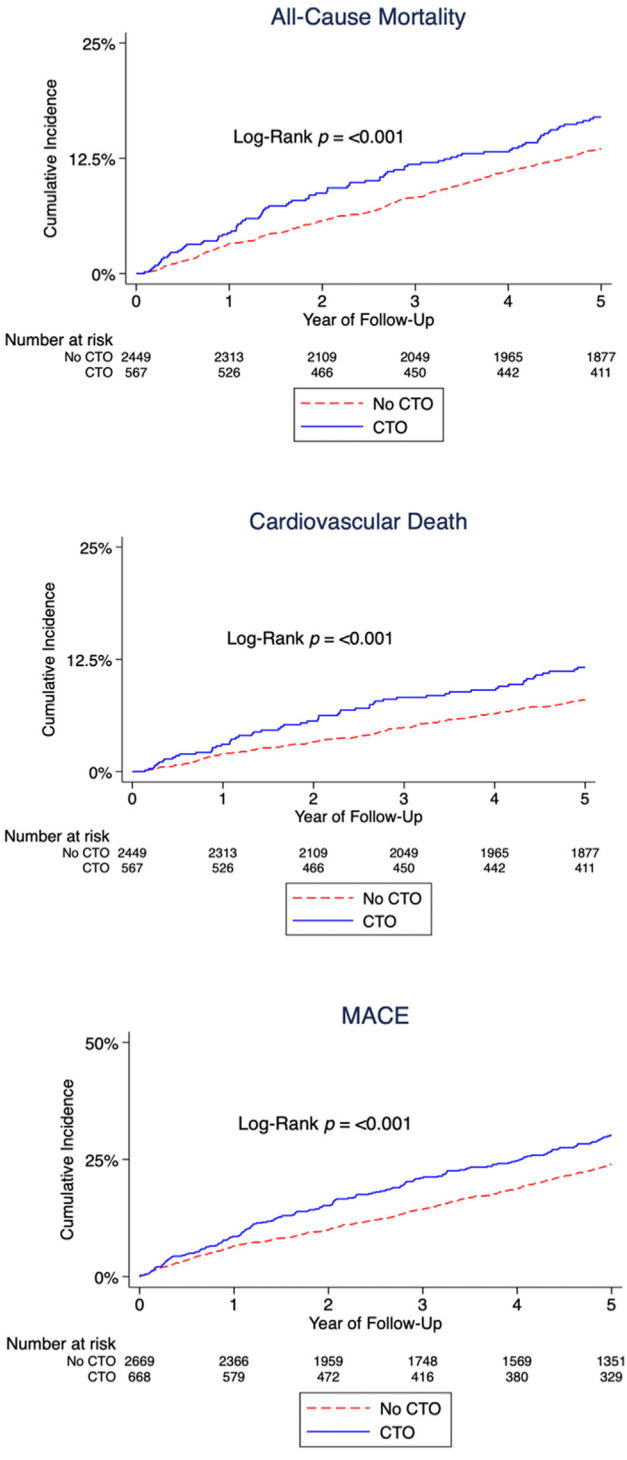

Figure 2. Cumulative incidence of adverse events in patients without CTO and nonrevascularized CTO. Unadjusted cumulative incidence function was used to visualize differences in survival outcomes in patients with CTO who did not receive CTO revascularization (n = 668) and significant CAD without CTO (n = 2,675), coupled with log-rank tests. Nonrevascularized CTO was associated with higher event rates of all-cause mortality, cardiovascular death, and a MACE, defined as cardiovascular death/MI/HF hospitalization. The no-CTO group had significant CAD, defined as ≥50% stenosis in ≥1 coronary artery. Revascularization was defined as percutaneous intervention or CABG that bypassed the CTO.

Table 4
Risk of adverse events in patients with non-revascularized CTO compared to those with CAD without a CTO

Model	All-Cause Mortality HR (CI)	P Value	CV Death HR (CI)	*P* Value	MACE HR (CI)	*P* Value
1	1.41 (1.22 − 1.63)	**<0.001**	1.52 (1.25 − 1.84)	**<0.001**	1.35 (1.16 −1.58)	**<0.001**
2	1.40 (1.21 − 1.62)	**<0.001**	1.53 (1.26 − 1.86)	**<0.001**	1.36 (1.16 − 1.59)	**<0.001**
3	1.45 (1.24 − 1.70)	**<0.001**	1.50 (1.21 − 1.86)	**<0.001**	1.24 (1.05 − 1.48)	**0.012**
4*	1.37 (1.09 − 1.71)	**0.006**	1.38 (1.01 − 1.89)	**0.042**	1.31 (1.04 − 1.64)	**0.022**

Multivariate cox proportional hazard ratio was analyzed for all-cause mortality and multivariate Fine and Gray proportional hazards regression analysis for CV death and MACE of significant CAD compared to non-revascularized CTO with the non-revascularized CTO group as the reference group. Significant CAD was defined as having ≥ 50% stenosis in at least one coronary artery. MACE was defined as CV death/MI/HF hospitalization.

Model 1 unadjusted.

Model 2 adjusted for demographic covariates [age, sex, race (black vs. non-black)].

Model 3 adjusted for model 2 + clinical covariates [BMI, history of smoking, history of heart failure, hypertension, diabetes, dyslipidemia, chronic kidney disease, history of MI].

Model 4 adjusted for model 3 + disease severity [1, 2 or 3 vessel disease].

BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CI = 95% confidence interval; CTO = chronic total occlusion; CV = cardiovascular; HF = heart failure hospitalization; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction.

* (Patients without a history of CABG).

revascularization at enrollment than in patients who did not, and remained significantly lower after adjusting for demographic and clinical covariates (Table 3).

Incident adverse event rates in patients with nonrevascularized and revascularized CTO were compared with those in patients with significant CAD without a CTO. Unadjusted all-cause mortality, cardiovascular death, and MACE rates were substantially higher in the patients with nonrevascularized CTO than in those with significant CAD without a CTO, and remained higher after adjusting for demographics and clinical characteristics (hazard ratio 1.50, CI 1.21 to 1.86, p <0.001) (Figure 2, Table 4, models 1 to 3). After further adjusting for disease severity in those without a history of CABG, the event rates remained significantly higher (Table 4, model 4). In contrast, patients who received CTO revascularization had lower adverse event rates than did those with significant CAD, without a CTO (Table 5, models 1 to 3), and similar event rates after further adjusting for disease severity (Table 5, model 4).

Discussion

Our data show that patients with CTO had higher rates of adverse cardiovascular events than did those with significant CAD without CTO even after adjustment for demographics, clinical characteristics, and disease severity. Those with nonrevascularized CTO were at greatest risk, whereas those in whom the CTO was revascularized had similar risk to that of patients with significant CAD without CTO.

Previous studies have shown that CTOs are associated with greater mortality in patients with ischemic cardiomyopathy[16] and in those presenting with acute coronary syndrome.[4−11] To date, only 1 study has investigated long-term outcomes in patients with CTO without acute coronary syndrome and found that the presence of a CTO was associated with a 19% greater risk of all-cause mortality during a 3-year follow-up period than in those with significant CAD without CTOs.[12] Our data are consistent with these findings and specifically investigate cardiovascular morbidities including cardiovascular death, MI, and HF hospitalizations. Our data also included patients with a CTO and a history of CABG, which, to the best of our knowledge, has not been previously investigated.

The high-risk nature of a CTO may be due to the persistently ischemic state that increases risk of arrhythmic events from hypoperfusion[17] and progression of ischemic cardiomyopathy.[18] These patients also may have a poor tolerance for additional ischemic events because there is limited collateral supply and a simultaneous acute and chronic coronary occlusion in separate territories. Thus, acute occlusion of the donor vessel in the presence of a CTO jeopardizes a much larger area of myocardium than it does in patients without CTO.

We show that the risk of cardiovascular events in patients with CTO is substantially greater in the patients who did not receive CTO revascularization. In the patients who had their CTO revascularized, their long-term risk of adverse events was similar to that of patients with significant CAD without a CTO, possibly owing to revascularization removing the risk of CTO. Alternatively, patients with successful revascularization may have been a smaller-risk cohort than those who did not receive CTO revascularization. Understanding the high-risk nature of CTOs is important given their management is still a subject of controversy. Those with CTO revascularization had lower event rates than did patients who did not undergo CTO revascularization. This is consistent with observational studies that have indicated reduction in mortality with CTO revascularization compared with that in patients without CTO revascularization.[19−22] However, the Drug-Eluting Stent Implantation versus Optimal Medical Treatment in Patients with Chronic Total Occlusion (Decision-CTO) trial found no significant difference in the incidence of composite end point of death, MI, stroke, and target vessel revascularization between patients randomly allocated to CTO revascularization and those treated medically.[23] This trial was limited owing to a high crossover rate and slow patient recruitment that may have obscured a potential benefit of CTO revascularization because there was a failure to reach final sample size and therefore low power to show improvement in the mortality end point. Additionally, A Randomized Multicentre Trial to Evaluate the Utilization of

Table 5
Risk of adverse events in patients with revascularized CTO compared to those with CAD without a CTO

Model	All-Cause Mortality HR (CI)	P Value	CV Death HR (CI)	*P* Value	MACE HR (CI)	*P* Value
1	0.74 (0.55 − 0.99)	**0.041**	0.59 (0.38 − 0.91)	**0.018**	0.61 (0.44 −0.85)	**0.003**
2	0.76 (0.57 − 1.02)	**0.064**	0.64 (0.41 − 0.99)	**0.045**	0.65 (0.47 − 0.91)	**0.011**
3	0.73 (0.53 − 1.02)	**0.068**	0.71 (0.44 − 1.14)	0.16	0.72 (0.51 − 1.02)	**0.065**
4*	0.88 (0.57 − 1.37)	0.58	1.05 (0.59 − 1.88)	0.87	0.94 (0.63 − 1.41)	0.78

Multivariate cox proportional hazard ratio was analyzed for all-cause mortality and multivariate Fine and Gray proportional hazards regression analysis for CV death and MACE of significant CAD compared to revascularized CTO with the revascularized CTO group as the reference group. Significant CAD was defined as having ≥ 50% stenosis in at least one coronary artery. MACE was defined as CV death/MI/HF hospitalization.

Model 1 unadjusted.

Model 2 adjusted for demographic covariates [age, sex, race (black vs. non-black)].

Model 3 adjusted for model 2 + clinical covariates [BMI, history of smoking, history of heart failure, hypertension, diabetes, dyslipidemia, chronic kidney disease, history of MI].

Model 4 adjusted for model 3 + disease severity [1, 2 or 3 vessel disease] *(Patients without a history of CABG).

BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CI = 95% confidence interval; CTO = chronic total occlusion; CV = cardiovascular; HF = heart failure hospitalization; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction.

Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions (EURO CTO) trial found that CTO PCI improves health status assessed by the Seattle angina questionnaire but had no difference in major adverse events compared with medical management alone.[24] This trial, however, was limited by slow patient recruitment and very low event rates, likely due to selection bias from excluding patients with severe symptoms. Because the high-risk nature of CTO is established, it is important to identify the best management for these patients and determine which patients may benefit from revascularization.

Our study has several strengths. We enrolled patients of both genders and races, and patients with a range of LVEF, reflecting a population typical of those who undergo cardiac catheterization. However, revascularization was not randomized and was performed for clinical reasons. There were differences in the clinical characteristics between patients who did and those who did not undergo revascularization. To address this, we adjusted for differences in the clinical variables in all our analyses. However, additional confounders such as severity and complexity of lesions may affect the differences observed. Moreover, our results may not apply to all patients with CTO given these patients underwent clinically indicated coronary angiography.

Patients with CTO had higher rates of cardiovascular events than those of patients with significant CAD without CTO. Patients with nonrevascularized, but not those with revascularized CTO, were at particularly great risk when compared with patients with significant CAD without CTO.

Declaration of competing interest

Dr. Quyyumi serves on the editorial board of the *American Journal of Cardiology.*

CRediT authorship contribution statement

Daniel A. Gold: Conceptualization, Formal analysis, Investigation, Writing − original draft. **Pratik B. Sandesara:** Conceptualization, Investigation, Methodology, Supervision, Writing − review & editing. **Vardhmaan Jain:** Formal analysis, Investigation. **Matthew E. Gold:** Conceptualization, Investigation, Writing − review & editing. **Nishant Vatsa:** Conceptualization, Investigation, Writing − review & editing. **Shivang R. Desai:** Conceptualization, Writing − review & editing. **Malika Elhage Hassan:** Writing − review & editing. **Chenyang Yuan:** Formal analysis. **Yi-An Ko:** Formal analysis. **Kiran Ejaz:** Data curation, Writing − review & editing. **Zain Alvi:** Data curation. **Wissam A. Jaber:** Data curation, Investigation, Writing − review & editing. **William J. Nicholson:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing − review & editing. **Arshed A. Quyyumi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing − original draft, Writing − review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.12.052.

1. Serruys PW, Ono M, Garg S, Hara H, Kawashima H, Pompilio G, Andreini D, Holmes DR, Onuma Y, King SB. Percutaneous coronary revascularization: JACC historical breakthroughs in perspective. *J Am Coll Cardiol* 2021;78:384–407.
2. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA, Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 2012;59:991–997.
3. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, Fremes SE, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS, Nnacheta LC, Rao SV, Sellke FW, Sharma G, Yong CM, Zwischenberger BA. 2021 ACC/AHS/SCAI Guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e18–e114.
4. Watanabe H, Morimoto T, Shiomi H, Kawaji T, Furukawa Y, Nakagawa Y, Ando K, Kadota K, Kimura T, CREDO-Kyoto AMI Investigators. Chronic total occlusion in non-infarct-related artery is associated with increased short-and long-term mortality in patients with ST-segment elevation acute myocardial infarction complicated by cardiogenic shock (from the CREDO-Kyoto AMI registry). *Catheter Cardiovasc Interv* 2018;92:455–463.
5. Claessen BE, Dangas GD, Weisz G, Witzenbichler B, Guagliumi G, Möckel M, Brener SJ, Xu K, Henriques JP, Mehran R, Stone GW.

Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J* 2012;33:768–775.
6. Claessen BE, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjauw KD, Kikkert WJ, Vis MM, Baan J, Koch KT, de Winter RJ, Tijssen JG, Piek JJ, Henriques JP. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 2009;2:1128–1134.
7. Lexis CP, van der Horst IC, Rahel BM, Lexis MA, Kampinga MA, Gu YL, de Smet BJ, Zijlstra F. Impact of chronic total occlusions on markers of reperfusion, infarct size, and long-term mortality: a substudy from the TAPAS-trial. *Catheter Cardiovasc Interv* 2011;77:484–491.
8. O'Connor SA, Garot P, Sanguineti F, Hoebers LP, Unterseeh T, Benamer H, Chevalier B, Hovasse T, Morice MC, Lefèvre T, Louvard Y. Meta-analysis of the impact on mortality of noninfarct-related artery coronary chronic total occlusion in patients presenting with ST-segment elevation myocardial infarction. *Am J Cardiol* 2015;116:8–14.
9. Tajstra M, Gasior M, Gierlotka M, Pres D, Hawranek M, Trzeciak P, Lekston A, Polonski L, Zembala M. Comparison of five-year outcomes of patients with and without chronic total occlusion of noninfarct coronary artery after primary coronary intervention for ST-segment elevation acute myocardial infarction. *Am J Cardiol* 2012;109:208–213.
10. Saad M, Fuernau G, Desch S, Eitel I, de Waha S, Pöss J, Ouarrak T, Schneider S, Zeymer U, Thiele H. Prognostic impact of non-culprit chronic total occlusions in infarct-related cardiogenic shock: results of the randomised IABP-SHOCK II trial. *EuroIntervention* 2018;14:e306–e313.
11. Gierlotka M, Tajstra M, Gąsior M, Hawranek M, Osadnik T, Wilczek K, Olszowski D, Dyrbuś K, Poloński L. Impact of chronic total occlusion artery on 12-month mortality in patients with non-ST-segment elevation myocardial infarction treated by percutaneous coronary intervention (from the PL-ACS Registry). *Int J Cardiol* 2013;168:250–254.
12. Råmunddal T, Hoebers LP, Henriques JP, Dworeck C, Angerås O, Odenstedt J, Ioanes D, Olivecrona G, Harnek J, Jensen U, Aasa M, Albertsson P, Wedel H, Omerovic E. Prognostic impact of chronic total occlusions: a report from SCAAR (Swedish coronary angiography and angioplasty registry). *JACC Cardiovasc Interv* 2016;9:1535–1544.
13. Nishiyama S, Iwase T, Nishi Y, Ishiwata S, Komiyama N, Yanagishita Y, Nakanishi S, Seki A. Long-term outcome in triple-vessel coronary artery disease in medically treated Japanese patients. *Jpn Heart J* 1998;39:67–77.
14. Mehran R, Claessen BE, Godino C, Dangas GD, Obunai K, Kanwal S, Carlino M, Henriques JPS, Di Mario C, Kim Y, Park S, Stone GW, Leon MB, Moses JW, Colombo A. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. *JACC Cardiovasc Interv* 2011;4:952–961.
15. Ko YA, Hayek S, Sandesara P, Samman Tahhan A, Quyyumi A. Cohort profile: the Emory cardiovascular biobank (EmCAB). *BMJ Open* 2017;7:e018753.
16. Tajstra M, Pyka Ł, Gorol J, Pres D, Gierlotka M, Gadula-Gacek E, Kurek A, Wasiak M, Hawranek M, Zembala MO, Lekston A, Poloński L, Bryniarski L, Gąsior M. Impact of chronic total occlusion of the coronary artery on long-term prognosis in patients with ischemic systolic heart failure: insights from the COMMIT-HF registry. *JACC Cardiovasc Interv* 2016;9:1790–1797.
17. Nombela-Franco L, Mitroi CD, Fernández-Lozano I, García-Touchard A, Toquero J, Castro-Urda V, Fernández-Diaz JA, Perez-Pereira E, Beltrán-Correas P, Segovia J, Werner GS, Javier G, Luis AP. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). *Circ Arrhythm Electrophysiol* 2012;5:147–154.
18. Liao R, Li Z, Wang Q, Lin H, Sun H. Revascularization of chronic total occlusion coronary artery and cardiac regeneration. *Front Cardiovasc Med* 2022;9:940808.
19. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J* 2010;160:179–187.
20. Megaly M, Saad M, Tajti P, Burke MN, Chavez I, Gössl M, Lips D, Mooney M, Poulose A, Sorajja P, Traverse J, Wang Y, Kohl LP, Bradley SM, Brilakis ES. Meta-analysis of the impact of successful chronic total occlusion percutaneous coronary intervention on left ventricular systolic function and reverse remodeling. *J Interv Cardiol* 2018;31:562–571.
21. Tomasello SD, Boukhris M, Giubilato S, Marzà F, Garbo R, Contegiacomo G, Marzocchi A, Niccoli G, Gagnor A, Varbella F, Desideri A, Rubartelli P, Cioppa A, Baralis G, Galassi AR. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. *Eur Heart J* 2015;36:3189–3198.
22. Christakopoulos GE, Christopoulos G, Carlino M, Jeroudi OM, Roesle M, Rangan BV, Abdullah S, Grodin J, Kumbhani DJ, Vo M, Luna M, Alaswad K, Karmpaliotis D, Rinfret S, Garcia S, Banerjee S, Brilakis ES. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *Am J Cardiol* 2015;115:1367–1375.
23. Lee SW, Lee PH, Ahn JM, Park DW, Yun SC, Han S, Kang H, Kang SJ, Kim YH, Lee CW, Park SW, Hur SH, Rha SW, Her SH, Choi SW, Lee BK, Lee NH, Lee JY, Cheong SS, Kim MH, Ahn YK, Lim SW, Lee SG, Hiremath S, Santoso T, Udayachalerm W, Cheng JJ, Cohen DJ, Muramatsu T, Tsuchikane E, Asakura Y, Park SJ. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. *Circulation* 2019;139:1674–1683.
24. Werner GS, Martin-Yuste V, Hildick-Smith DD, Boudou N, Sianos G, Gelev V, Rumoroso JR, Erglis A, Christiansen EH, Escaned J, di Mario C, Hovasse T, Teruel L, Bufe A, Lauer B, Bogaerts K, Goicolea J, Spratt JC, Gershlick AH, Galassi AR, Louvard Y. EUROCTO Trial Investigators. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J* 2018;39:2484–2493.