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ORIGINAL RESEARCH

Predictors of Adverse Events Among Chronic Total Occlusion Patients Undergoing Successful Percutaneous Coronary Intervention and Medical Therapy

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Objective: Limited data are available on the predictors of major adverse cardiac events (MACE) after a successful coronary chronic total occlusion (CTO) percutaneous coronary intervention (PCI) and medical therapy. This study aimed to identify predictors of MACE in CTO patients undergoing successful recanalization and medical therapy.

Methods: A total of 2015 patients with CTOs were enrolled. About 718 patients underwent successful CTO recanalization, and 1297 patients received medical therapy. The primary outcome was the frequency of MACE, defined as a composite of cardiac death, myocardial infarction, and target-vessel revascularization. Multivariate models were used to determine predictors of MACE.

Results: In successful CTO recanalization group, MACE occurred in 123 (17.1%) patients. In multivariate analysis, heart failure (hazard ratio [HR] 1.77, 95% confidence interval [CI]: 1.04–3.04, $p = 0.036$) was identified as independent predictors for MACE in successful CTO recanalization. Additionally, in medical therapy group, the significant predictors of MACE were male gender (HR 1.53, 95% CI: 1.13–2.05, $p = 0.005$), diabetes mellitus (HR 1.39, 95% CI: 1.11–1.74, $p = 0.003$), heart failure (HR 1.44, 95% CI: 1.10–1.87, $p = 0.007$), J-CTO score (HR 1.17, 95% CI: 1.07–1.28, $p = 0.001$) and multivessel disease (HR 2.20, 95% CI: 1.42–3.39, $p < 0.001$).

Conclusion: Heart failure was predictor for composite cardiovascular events in patients with CTO after successful recanalization. Male gender, diabetes mellitus, heart failure, J-CTO score and multivessel disease were predictors of MACE in CTO patients with medical therapy.

Keywords: coronary chronic total occlusions, percutaneous coronary intervention, medical therapy, predictors, MACE

Introduction

Coronary chronic total occlusion (CTO) occurs in about 10–20% of patients with coronary artery disease who underwent coronary angiography, limiting coronary intervention.[1,2] However, procedural success rates of CTO percutaneous coronary intervention (PCI) have significantly improved to 80–90% (experienced operators) due to the availability of new techniques and dedicated devices.[3] Successful CTO intervention improves short and long-term clinical outcomes.[4,5] However, PCI is performed in only 10–15% of patients undergoing CTO angioplasty procedures.[6–8] Nonetheless, there are limited data on the predictors of major cardiovascular events after a successful CTO intervention. Furthermore, the factors impacting the long-

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time prognosis of patients with medical therapy are unknown. This study aimed to identify predictors of major adverse cardiac events (MACE) in CTO patients undergoing successful recanalization and medical therapy.

Materials and Methods

Study Design and Population

This study included all patients with at least one coronary CTO lesion at our center between January 2007 and December 2018. Exclusion criteria were: patients with failed CTO-PCI or coronary artery bypass grafting (CABG), ST-segment elevation myocardial infarction (STEMI), a history of CABG, cardiogenic shock, or malignant tumor. A total of 2015 patients were included in the study (Figure 1). Patients were referred for PCI if they had CTO-related symptoms or objective evidence of viability/ischemia in the area of the CTO artery. Inducible myocardial ischemia was evaluated by echocardiography or myocardial perfusion scan and myocardial viability was assessed on cardiac magnetic resonance imaging. In symptomatic patients, even without information on viability or in asymptomatic patients with viability, PCI was preferred. In asymptomatic patients who did not have viability data available or in subjects with proved absence of viability, medical therapy was strongly preferred. The decision to perform PCI for CTO patients was also dependent on several factors, including co-morbidity, the extent of other coronary artery disease, CTO location, technical difficulty, doctors' and patients' preference.[9–11] Detailed data on demographic and clinical characteristics, procedures, complications were recorded and reviewed in the hospital database. Follow-up data were obtained through inpatient observation, telephone contact or outpatient visit.

Ethics

This was a single-center, retrospective observational study approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. The protocol followed the ethical principles in the Declaration of Helsinki. All patients gave their written informed consent prior to any study procedures.

Endpoint and Definitions

CTO was defined as complete coronary occlusion with thrombolysis in myocardial infarction (TIMI) grade 0 flow for three months or longer.[12] Duration of occlusion was defined as the time from sudden symptom onset to myocardial infarction (MI) or based on previous angiographic reports. Technical success was defined as restoration of TIMI 3 flow with residual stenosis <30% within the treated segment. The primary endpoint was defined as MACE occurrence, including cardiac death, MI, and target-vessel revascularization (TVR). Cardiac death was defined as a death caused by cardiovascular diseases in the absence of established cardiovascular etiology. MI was defined as the presence of clinical symptoms, ECG change and elevation of CK-MB, troponin I or T levels >3 fold of the upper limit of the normal value.[13] TVR was defined as the repeated revascularization of the target vessel via PCI or CABG. HF was defined as symptoms resulting from the left ventricle (LV) systolic dysfunction confirmed via resting transthoracic echocardiography, with left ventricular ejection fraction (LVEF) <35%.

Interventional Procedure and Medical Treatment

All patients were given aspirin (300 mg) (orally), clopidogrel loading dose (300 mg), and weight-adjusted unfractionated heparin (80–100 U/kg) (intravenously) before the procedure. CTO PCI was performed using standard techniques. The post-procedural antiplatelet regimen consisted of lifelong aspirin and clopidogrel (75 mg/day) for at least one year. Statins, antiplatelet medication, β-blockers, nitrate, and renin-angiotensin system blockade, were the medical therapies.[14]

Statistical Analysis

Continuous variables were expressed as means ± standard deviation and compared using Student's *t*-test, Mann–Whitney or Wilcoxon tests. The Kolmogorov–Smirnov test was used to assess whether there was a normal distribution. Categorical data were expressed as frequencies and percentages and were compared using the chi-square test and Fisher's exact tests. Cox regression proportional hazard model was used to construct univariate and multivariate survival analyses to identify predictors of MACE occurrence. The following variables were included in the Cox regression model: ≥65 years, males, smoking, hypertension, diabetes mellitus, hyperlipidemia, previous MI, chronic kidney disease (CKD), heart failure, LVEF <40%, left ascending coronary artery (LAD) CTO, Japanese-chronic total occlusion (J-CTO) score (per point increment) and multivessel disease. Variables with a univariate P-value <0.1 were included in the multivariate analyses. Hazard ratios (HR) with 95% confidence intervals (CI) and the p-values were determined. All p-values were from two-sided tests, and the level of statistical significance was set at 0.05. SPSS V.24.0 (SPSS Inc, Chicago, IL) and Stata 15

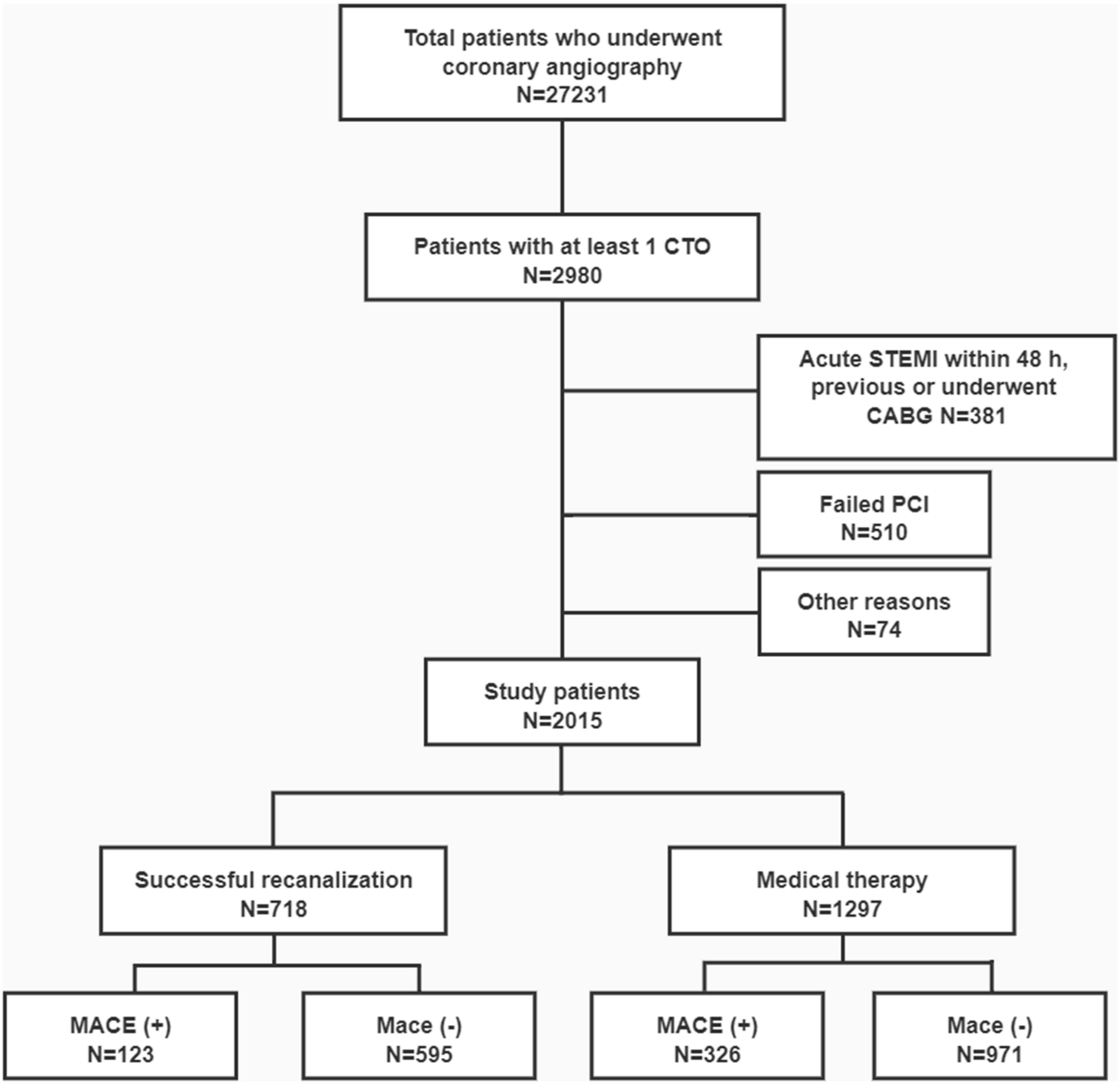

Figure 1 Study flow chart.
Abbreviations: CABG, coronary artery bypass grafting; CTO, chronic total occlusion; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

(StataCorp, College Station, TX, USA) were used for all statistical analyses.

Results

Baseline, Angiographic and Procedural Characteristics of Patients

A total of 718 patients underwent successful CTO recanalization, and 1297 patients received medical therapy. The baseline characteristics of the two groups are summarized in Table 1. MACE occurred in 123 (17.1%) patients in the successful CTO recanalization group. MACE patients had a higher prevalence of previous MI, heart failure, calcified lesion, and low LVEF than those without MACE. There were no significant differences in procedural characteristics and complications and in-hospital death between the MACE and non-MACE patients. Besides, MACE occurred in 326 (25.1%) patients in the medical therapy group. The patients had prior MI, left circumflex coronary artery (LCX) CTO

Table 1 Baseline Clinical, Angiographic and Procedural Characteristics and in-Hospital Outcome of All Patients According to the Occurrence of MACE in the Successful Recanalization and Medical Therapy Groups

Variables	Successful Recanalization (n=718)			Medical Therapy (n=1297)		
	MACE (+) (n = 123)	MACE (-) (n = 595)	P value	MACE (+) (n = 326)	MACE (-) (n = 971)	P value
Age, years	65.2 ± 9.6	62.9 ± 9.7	0.099	60.7 ± 10.0	60.2 ± 8.9	0.434
Male	91 (74.0)	450 (75.6)	0.700	555 (83.5)	340 (79.8)	0.126
Smoking	52 (42.3)	254 (42.7)	0.933	315 (47.4)	198 (46.5)	0.774
Hypertension	86 (69.9)	392 (65.9)	0.388	419 (63.0)	269 (63.1)	0.963
Diabetes mellitus	46 (37.4)	203 (34.1)	0.486	256 (38.5)	157 (36.9)	0.585
Hyperlipidemia	88 (71.5)	433 (72.8)	0.781	500 (75.2)	317 (74.4)	0.664
Familial history of CAD	9 (7.3)	74 (12.4)	0.106	77 (11.6)	47 (11.0)	0.782
Previous MI	45 (36.6)	161 (27.1)	0.033	238 (35.8)	116 (27.2)	0.003
CKD	13 (10.7)	38 (6.5)	0.103			
Heart failure	24 (19.5)	66 (11.1)	0.010	77 (11.6)	47 (11.0)	0.782
LVEF, %	52.1 ± 8.9	55.1 ± 7.2	0.001	60.7 ± 10.0	60.2 ± 8.9	0.434
Baseline medication						
Aspirin	121 (98.4)	579 (97.3)	0.492	650 (97.7)	420 (98.6)	0.320
Clopidogrel	116 (94.3)	579 (97.3)	0.085	609 (91.6)	410 (96.2)	0.002
Statin	114 (92.7)	574 (96.5)	0.056	645 (97.0)	409 (96.0)	0.381
β blocker	94 (76.4)	452 (76.0)	0.914	511 (76.8)	316 (74.2)	0.316
ACEI or ARB	78 (63.4)	357 (60.0)	0.481	426 (64.1)	254 (59.6)	0.140
One CTO lesion	99 (80.5)	517 (86.9)	0.064	586 (88.1)	375 (88.0)	0.963
Two CTO lesions	22 (17.9)	73 (12.3)	0.094	75 (11.3)	47 (11.0)	0.900
LAD	52 (42.3)	238 (40.0)	0.640	214 (32.2)	163 (38.3)	0.039
LCX	28 (22.8)	138 (23.2)	0.918	219 (32.9)	87 (20.4)	<0.001
RCA	63 (51.2)	280 (47.1)	0.400	311 (46.8)	216 (50.7)	0.204
Multivessel disease	92 (74.8)	399 (67.1)	0.093	566 (85.1)	287 (67.4)	<0.001
Proximal or mid CTO	95 (77.2)	438 (73.6)	0.403	442 (66.5)	317 (74.4)	0.005
Calcification	25 (20.3)	69 (11.6)	0.009	104 (15.6)	39 (9.2)	0.002
Long lesions (≥20 mm)	83 (67.5)	379 (63.7)	0.780	401 (60.3)	277 (65.0)	0.117
J-CTO score	1.42 ± 1.05	1.45 ± 1.01	0.995	1.71 ± 1.22	1.44 ± 1.01	<0.001
SYNTAX score	20.6 ± 8.0	19.3 ± 6.7	0.367	22.1 ± 9.1	18.1 ± 7.9	0.062
Dual injection	34 (27.6)	154 (25.9)	0.686			
Microcatheter use	43 (34.9)	184 (30.9)	0.381			
Radial access	83 (67.4)	386 (64.8)	0.580			
Femoral access	40 (32.6)	209 (35.2)	0.580			
IVUS use	17 (13.8)	66 (11.1)	0.389			
Number of stents	1.48 ± 0.72	1.45 ± 0.76	0.998			
Total stent length, mm	42.8 ± 22.2	43.7 ± 21.8	0.554			
Contrast volume, mL	228 ± 73	226 ± 81	0.999			
Coronary dissection	6 (4.8)	20 (3.4)	0.425			
Coronary perforation	2 (1.6)	6 (1.0)	0.631			
In-hospital death	1 (0.8)	2 (0.3)	0.646	2 (0.6)	5 (0.5)	0.834

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; CTO, chronic total occlusion; IVUS, intravascular ultrasound; J-CTO, Japanese-chronic total occlusion; LAD, left ascending coronary artery; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; RCA, right coronary artery.

lesion, multivessel disease, calcified lesion, and high J-CTO score. The prevalence of clinical characteristics was not significantly different between the MACE and non-MACE patients except for the history of MI.

Clinical Follow-Up and Multivariate Analysis

Long-term clinical outcomes are shown in Table 2. The median follow-up time was 2.6 (interquartile range (IQR),

Table 2 Clinical Outcomes of All Patients with CTOs in the Successful Recanalization and Medical Therapy Groups

Variables	Successful Recanalization	Medical Therapy
	n = 718	n = 1297
MACE	123 (17.1)	326 (25.1)
Cardiac death	23 (3.2)	74 (5.7)
MI	49 (6.8)	106 (8.2)
TVR	80 (11.1)	188 (14.5)

Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PSM, propensity score matching; TVR, target-vessel revascularization.

1.2–4.7) years. Kaplan-Meier analyses for the occurrence MACE and cardiac deaths during follow-up are shown in Figure 2. MACE and cardiac deaths were less in patients with successful CTO recanalization than in patients in the medical therapy group (17.1% vs 25.1%, $p < 0.001$; 3.2% vs 5.1%, $p = 0.007$, respectively). Multivariate analysis was conducted to identify the risk factors of MACE occurrence. Heart failure (hazard ratio [HR] 1.77, 95% confidence interval [CI]: 1.04–3.04, $p = 0.036$) was identified as the independent predictor for MACE in successful CTO recanalization (Table 3). Additionally, male gender (HR 1.53, 95% CI: 1.13–2.05, $p = 0.005$), diabetes mellitus (HR 1.39, 95% CI: 1.11–1.74, $p = 0.003$), heart failure (HR 1.44, 95% CI: 1.10–1.87, $p = 0.007$), J-CTO score (HR 1.17, 95% CI: 1.07–1.28, $p = 0.001$) and multivessel disease (HR 2.20, 95% CI: 1.42–3.39, $p < 0.001$) were independently associated with MACE in medical therapy group (Table 4).

Discussion

Herein, (1) successful CTO PCI group significantly reduced the risk of MACE and cardiac death compared with the medical therapy group. Also, (2) Heart failure after a successful CTO intervention increased MACE occurrence. (3) Male gender, diabetes mellitus, heart failure, J-CTO score, and multivessel disease were predictors of MACE in CTO patients treated with medical therapy.

CTO patients with heart failure had a higher risk profile with more comorbidities and more diffuse and complex coronary lesions. Moreover, they were associated with poor prognosis, an increased risk of sudden death, ventricular arrhythmias based on the COMMIT-HF (COnteMporary Modalities In Treatment of Heart Failure) registry.[15,16] Notably, Galassi et al reported that LVEF ≤35% could not predict the occurrence of major cardiac and cerebrovascular events (MACCE) (HR: 1.52; 95% CI: 0.66 to 2.92; $p = 0.398$) in patients undergoing CTO PCI,[17] consistent with this study. Previous studies have also demonstrated that heart failure is associated with MACE in CTO patients.[18,19] CTO patients with heart failure may have a high ischemic burden caused by CTO and relevant donor vessels. A retrospective study showed that multivessel disease is the most effective predictor of 5-year MACE.[20] CTO patients with heart failure or multivessel disease are associated with a high risk of ventricular tachycardia or ventricular fibrillation.[16,21] Therefore, implantable cardioverter-defibrillator (ICD) may benefit these patients, especially those with ischemic cardiomyopathy or low LVEF.[22]

However, no study has reported on MACE predictors among patients treated with medication alone. Male patients are frequent smokers, have a history of MI, chronic obstructive pulmonary disease, multivessel disease, long and tortuosity lesions compared with female patients, which may increase MI in CTO patients.[19,23] Additionally, the CAD process may

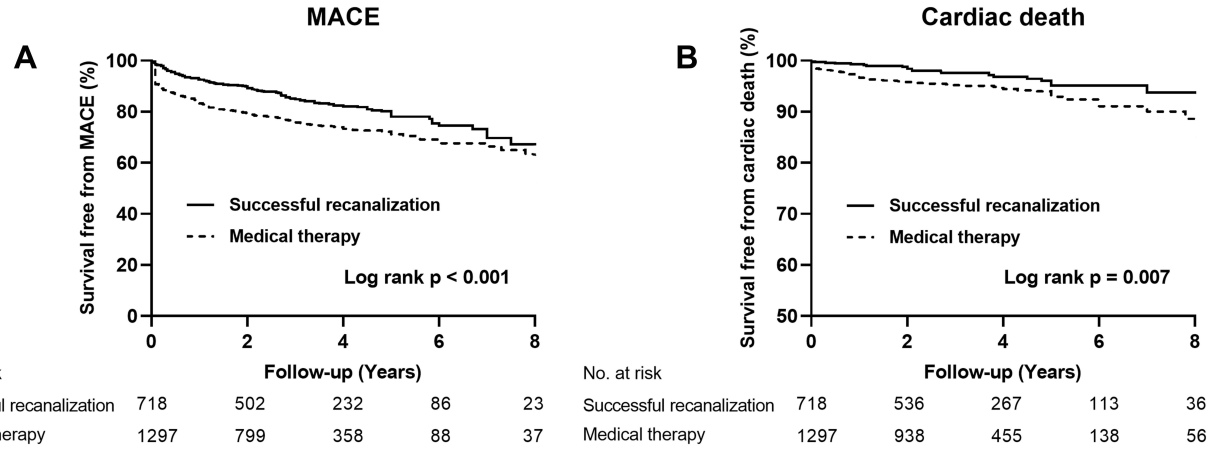

Figure 2 Kaplan–Meier curves for MACE (**A**) and cardiac death (**B**) during follow-up for successful recanalization versus medical therapy in total patients.
Abbreviation: MACE, major adverse cardiovascular events.

Table 3 Univariate and Multivariate Analyses of the MACE in Patients Who Underwent Successful Recanalization for CTOs

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age≥65 yrs	1.36 (0.96–1.94)	0.084	1.25 (0.86–1.82)	0.244
Male	0.97 (0.65–1.45)	0.894		
Smoking	1.06 (0.74–1.51)	0.757		
Hypertension	1.19 (0.81–1.75)	0.369		
Diabetes mellitus	1.22 (0.84–1.76)	0.290		
Hyperlipidemia	1.04 (0.81–1.33)	0.793		
Previous MI	1.13 (0.78–1.63)	0.514		
CKD	1.70 (0.95–3.02)	0.071	1.16 (0.61–2.19)	0.645
Heart failure	1.98 (1.26–3.09)	0.003	1.77 (1.04–3.04)	0.036
LVEF <40%	1.64 (0.92–2.94)	0.090	1.19 (0.62–2.28)	0.593
LAD CTO	1.06 (0.74–1.52)	0.743		
J-CTO score (per point increment)	0.99 (0.83–1.91)	0.977		
Multivessel disease	1.44 (0.96–2.16)	0.079	1.36 (0.89–2.10)	0.155
Total stent length ≥ 20 mm	0.87 (0.71–1.14)	0.732		

Abbreviations: CKD, chronic kidney disease; CTO, chronic total occlusion; J-CTO, Japanese-chronic total occlusion; LAD, left ascending coronary artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction.

Table 4 Univariate and Multivariate Analyses of the MACE in Patients Who Underwent Medical Therapy for CTOs

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age≥65 yrs	1.08 (0.87–1.35)	0.451		
Male	1.42 (1.06–1.90)	0.017	1.53 (1.13–2.05)	0.005
Smoking	1.14 (0.92–1.42)	0.221		
Hypertension	0.99 (0.79–1.26)	0.974		
Diabetes mellitus	1.37 (1.10–1.70)	0.005	1.39 (1.11–1.74)	0.003
Hyperlipidemia	1.01 (0.79–1.30)	0.898		
Previous MI	1.25 (1.00–1.55)	0.048	1.05 (0.83–1.33)	0.648
CKD	1.43 (1.04–1.96)	0.026	1.22 (0.88–1.70)	0.222
Heart failure	1.66 (1.30–2.12)	<0.001	1.44 (1.10–1.87)	0.007
LVEF <40%	1.29 (0.95–1.77)	0.101		
LAD CTO	1.05 (0.83–1.32)	0.669		
J-CTO score (per point increment)	1.19 (1.08–1.30)	<0.001	1.17 (1.07–1.28)	0.001
Multivessel disease	2.35 (1.52–3.61)	<0.001	2.20 (1.42–3.39)	<0.001

Abbreviations: CKD, chronic kidney disease; CTO, chronic total occlusion; J-CTO, Japanese-chronic total occlusion; LAD, left ascending coronary artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction.

be delayed in women, possibly due to the potential protective effects of estrogen against coronary atherosclerosis until menopause. Therefore, women with CTOs are more likely to be older than men with CTO.[24] Herein, diabetes mellitus was associated with MACE, consistent with previous reports.[25,26] Diabetic patients have more comorbidities, significant atherosclerotic burden, longer and more complex coronary lesions, and more adverse cardiovascular events, probably due to frequent hyperplasia, platelet hyperreactivity, increased fibrinogen levels, thromboxane, proinflammatory states, systemic endothelial dysfunction, and metabolic disorders.[27,28] Notably, collateral circulation development is less common in diabetic patients than in non-diabetic patients when coronary arteries become occluded. Particularly, well-developed coronary collateral circulation can supply the downstream perfusion area in CTO patients, thereby alleviating myocardial ischemia, preserving viable myocardium, reducing infarct area, improving left ventricular function, and decreasing cardiovascular mortality.[29,30] This may indicate the worse outcome of CTO patients with DM.

Prior study demonstrated that the age, creatinine, ejection fraction (ACEF) score might have a sufficient

predictive value for in-hospital death in patients with cardiogenic shock secondary to STEMI.[31] Furthermore, acute kidney injury (AKI) was an independent prognostic factor for long-term mortality among these patients treated with primary PCI.[32] Interestingly, for CTO patients, age and CKD had no predictive value,[33–35] possibly due to the different study populations. Besides, CKD was not routinely evaluated among CTO patients in previous studies.[26,33,36] In present study, only 51 (7%) patients were with CKD in successful CTO PCI group in our study, and the mean contrast volume was 227mL. Hydration, before and after the CTO procedure, was effective to reduce the occurrence of CIN.[35] For the rare patients who need dialysis, it was done immediately after procedure. Therefore, after hydration or dialysis, AKI rate was very low among these patients.

LAD CTO was also not correlated with subsequent adverse clinical outcomes, consistent with previous studies.[25,37] However, a high J-CTO score was correlated with the occurrence of composite cardiovascular events. The J-CTO score system is one of the most useful tools to predict CTO PCI success.[38] Occlusion length >20 mm represents a higher ischemic burden caused by CTO, and relevant donor vessels and calcification represent an increased atherosclerosis progression.[38]

Limitations

This study has some limitations. First, this was a non-randomized study. Although the CTO registries have some limitations, this study included several CTO PCI patients. Second, regular angiographic follow-up was not conducted, and thus some adverse events, such as TVR, might not be accurately recorded. Third, the estimated glomerular filtration rate (eGFR) after CTO procedure was not evaluated routinely for all patients at our center, and the data of AKI rate was not recorded in our study. Fourth, symptom improvement, as assessed using the Seattle angina questionnaire, was not assessed before and after revascularization. Fifth, femoral artery is an important vascular approach, especially for CTO procedures due to more dual injection application. The rate of femoral approach was relatively low in the present study. Tokarek et al reported that higher experience in radial approach might be linked to worse outcome in PCI via femoral approach and operators on training should be encouraged to develop proficiency in both radial approach and femoral approach.[39] However, most CTO patients were treated with conservative therapy. Therefore, the findings on the high-risk subset may be meaningful.

Conclusion

Heart failure increased the occurrence of MACE in patients with successful recanalized CTO. Male gender, diabetes mellitus, heart failure, J-CTO score, and multivessel disease were MACE predictors in CTO patients treated with medical therapy.

Abbreviations

CTO, chronic total occlusion; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Data Sharing Statement

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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