The Impact of Successful Chronic Total Occlusion Percutaneous Coronary Intervention on Long-Term Clinical Outcomes in Real World

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Research article

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Abstract

**Background:** Coronary chronic total occlusions (CTOs) are correlated with increased risk of adverse clinical outcomes. The optimal treatment strategy for CTO has not been well established. We sought to examine the impact of CTO percutaneous coronary intervention (PCI) on long-term clinical outcome in the real world.

**Methods:** A total of 592 consecutive patients with CTO in Beijing Friendship Hospital from June 2017 to December 2019 were enrolled, 29 patients were excluded due to Coronary artery bypass grafting (CABG). After exclusion, 563 patients were divided into the no-revascularized group (CTO-NR group, n=263) and successful revascularized group (CTO-R group, n=300). The primary endpoint was cardiac death; Secondary endpoint was major adverse cardiac and cerebrovascular events (MACCE), a composite of all-cause death, cardiac death, recurrent myocardial infarction, target lesion revascularization, re-hospitalization, heart failure, and stroke.

**Results:** Percent of Diabetes mellitus (53.2% vs 39.7), Chronic kidney disease (8.7% vs 3.7%), CABG history (7.6% vs 1%), three vessel disease(96.2% vs 90%) and left main coronary artery disease (25.1% vs 13.7%) was significantly higher in the CTO-NR group than in success PCI group (all P<0.05). Moreover, the CTO-NR group has lower EF (0.58±0.11 vs 0.61±0.1, p=0.001) and FS (0.31±0.07 vs 0.33±0.07, p=0.002). At a median follow-up of 12 months, CTO revascularization was superior to CTO no-revascularization in terms of cardiac death (adjusted hazard ratio [HR]: 0.27, 95% conference interval [CI] 0.11-0.64). The superiority of CTO revascularization was consistent for MACCE (HR: 0.55, 95% CI 0.35-0.79). At multivariable Cox hazards regression analysis, CTO revascularization remains one of the independent predictors of lower risk of cardiac death and MACCE.

**Conclusions:** Successful revascularization by PCI may bring more clinical benefits. The presence of LVEF <0.5 and LM-disease was associated with an incidence of cardiac death; CTO revascularization was a protected predictor of cardiac death.

**Background**

Coronary chronic total occlusions (CTOs) are common and have been associated with adverse clinical outcomes. With the development of devices and technologies, percutaneous coronary intervention (PCI) of CTO is increasingly pursued, and the success rate of CTO is getting higher and higher. However, its beneficial effect remains debatable. Some observational studies comparing successful versus failed PCI have demonstrated better outcomes associated with PCI, while a few randomized controlled trials (RCTs)'s conclusions did not consistently support the benefit of CTO PCI. Moreover, this benefit is only the improvement of clinical symptoms [1, 2]. Overall, it remains unclear whether CTO revascularization brings long-term clinical benefit. Therefore, by using the Cardiovascular Center Beijing Friendship Hospital Database Bank, we attempted to determine whether successful revascularization offers a clinical benefit in the CTO patients. This study focused on the major adverse cardiac and cerebrovascular events.
(MACCE), the MACCE includes all-cause death, cardiac death, recurrent myocardial infarction, heart failure, target lesion revascularization, re-hospitalization, and stroke.

**Methods**

**Study design and population**

The retrospective study was based on the data from the Cardiovascular Center of Beijing Friendship Hospital Data Bank (CBD Bank). The protocol was approved by the ethical committee of Beijing Friendship Hospital. From June 2017 to October 2019, a total of 592 consecutive patients with CTO were enrolled in this study. 29 patients were excluded from this study because they received CABG treatment after the CTO diagnosis. Finally, a total of 563 patients were included in the final analysis. All patients included in the study were prospectively followed and a minimum of 6-month follow-up was warranted in order to be included in the present survival analysis. The patient flow of the study is shown in Fig. 1.

**Definitions of variables and clinical endpoints**

The patients’ demographic data, past medical history (hypertension, coronary heart disease, diabetes, hyperlipemia and other diseases), and the conditions of smoking and drinking, were collected from medical records. BMI was calculated by weight (kilograms) divided by the square of height (meters). The estimated glomerular filtration rate (eGFR) was calculated by standard calculations (GFR based on levels of creatinine [GFR(epi)]) [3].

For the angiogram data, experienced, interventional physicians rescanned the cine angiograms by using standard definitions in order to reduce bias. The definition of CTO was a TIMI flow grade of 0 and an estimated duration of at least 3 months. CTO revascularization (CTO-R) was defined as final residual stenosis less than 20%, with TIMI grade ≥ 2 flow on visual assessment [4]. CTO no-revascularization (CTO-NR) included patients who not PCI and failed PCI.

The primary endpoint was cardiac death, defined as previously reported including death from acute MI, heart failure, arrhythmia and unexplained sudden death [5]. The secondary endpoint was major adverse cardiac and cerebrovascular events (MACCE), a composite of all-cause death, cardiac death, recurrent myocardial infarction, target lesion revascularization, re-hospitalization, heart failure, and stroke.

All the information was recorded from new hospitalizations or by telephone calls and/or ambulatory visits performed 6 months after PCI and at least one time per year. Clinical follow-up was censored at the date of last follow-up or at 2 years, whichever came first.

**Statistical analysis**

Demographic and clinical factors were compared between cohorts of patients depending on the result of CTO revascularization and the different coronary artery CTO lesions. Baseline characteristics are described with mean±SD (or medians and first and third IQRs) for continuous variables and compared...
with Student's t test or Mann–Whitney or Wilcoxon tests, based on the normality of the data. Categorical variables are expressed as frequencies and percentages, and were compared by Chisquare or Fisher's exact statistics.

Survival curves were conducted using Kaplan–Meier estimates and compared with the log-rank test. Cox proportional hazards methods were used to estimate the independent effect of multiple independent variables on the risk of adverse clinical events in both CTO-R and CTO-NR patients. All factors showing significance in the univariate analysis ($p < 0.05$) were then examined by a multivariate analysis. The results are reported as adjusted hazard ratios (HR) with associated 95% Confidence Intervals (CI). All analyses were 2-tailed and a P value $< 0.05$ was considered statistically significant. All analyses were performed by using SPSS (version 25.0, Chicago, IL, USA) and Metaninf function in Stata 12.0; Kaplan–Meier survival curves were generated with the use of GraphPad Prism software (version 5; GraphPad, Inc, San Diego, CA).

**Results**

From June 2017 to December 2019, a total of 592 CTO patients were consecutively enrolled in the present study (Fig. 1). Of these patients, 29 (4.9%) patients were excluded due to CABG, 300 (50.7%) were managed by successful PCI revascularization (CTO-R group) and 263 (44.4%) were not revascularized (CTO- NR group). The CTO-NR group included patients who initial CTO-no PCI ($n=172$) and failed CTO-PCI ($n=91$).

**Baseline characteristics**

The baseline clinical characteristics of different coronary artery CTO lesions are reported in Table 1. LAD-CTO 163 cases (27.5%), LCX-CTO 148 cases (25%), RCA- CTO 218 cases (36.5%), $\geq 2$ vessel CTO 61 cases (11%). Previous history of CABG, the probability of choosing CABG treatment after CTO and successful PCI to open the vessel were different. Compared LAD-CTO, LCX-CTO and RCA-CTO group, the history of CABG and the proportion of choosing CABG treatment after CTO in $\geq 2$ vessel CTO group were high, and the proportion of successful PCI in LAD group was the highest.

Differences in terms of clinical characteristics with CTO-R group and CTO-NR group are reported in Table 2. Compared to CTO revascularized patients, those not revascularized had a higher prevalence of diabetes, chronic kidney disease, prior CABG, three-vessel disease and LM disease, moreover, these patients were significantly older ($67 \pm 11$ vs $63 \pm 10$ years; $p=0.000$), with lower mean ejection fraction ($0.58 \pm 0.11$ vs $0.61 \pm 0.1$; $p=0.001$) and fraction shortening ($0.31 \pm 0.07$ vs $0.33 \pm 0.07$; $p=0.002$), the level of CHOL and LDL-C were also lower. Whereas the peak concentration of NT-proBNP was higher ($487$ vs $278$, $p=0.001$) in the CTO-NR group. For the other variables, there were no significant differences between the groups.

Significant correlates of CTO revascularized in multivariable analysis are shown in Fig. 2. Compared with CTO-R group, no revascularized patients were more likely to be older (age $\geq 65$ years), and the proportion
of diabetes, three-vessel disease and LM disease is higher. Also, the CTO-R group was more likely to be in-stent (IS) CTO.

**Clinical follow-up**

Up to 2-year follow-up (median 1 years, IQR 6–12 months), compared with CTO-R patients, those with CTO-NR had significantly higher rate of cardiac death (6.1% vs 1.3%; \( P_{\text{log-rank}}=0.003 \)) and of MACCE (22.1% vs 12%; \( P_{\text{log-rank}}=0.002 \)) (Fig 3 A, B respectively). Re-hospitalization tended to occur more frequently in CTO-NR patients than in CTO-R patients (17.5% vs 11.3%, \( p=0.037 \)). Moreover, no revascularized CTO patients suffered more often from target vessel revascularization (2.3% vs 0.3%, \( p=0.037 \)), and have therefore a higher MACCE rate (\( p=0.001 \)). Other clinical events are reported in table 3.

**Predictors of survival**

Considering all CTO patients, a multivariable Cox regression analysis (table 4) was used to identify clinical and angiographic independent predictors of cardiac death and MACCE. For MACCE, the final multivariable mode included LVEF \( \leq 0.5 \) and CTO-R. For cardiac death, the final multivariable mode included LVEF \( \leq 0.5 \), CTO-R and LM disease.

By multivariate analysis (Fig. 4), CTO-R was a protected predictor of cardiac death (HR: 0.239, 95% CI 0.076-0.751) and MACCE (HR: 0.541, 95% CI 0.353-0.83). Additionally, lower LVEF (LVEF \( \leq 0.5 \), HR: 4.804, 95% CI 1.895-12.177) and LM disease (HR: 3.884, 95% CI 1.544-9.771) predicted a worse probability for cardiac death.

**Effects of different CTO lesion vessels (LAD, LCX and RCA) on MACCE**

In Fig. 5, the effect of different CTO vessels (LAD, LCX and RCA) revascularization on MACCE was studied, there was no difference in the effect of different CTO lesion vessels revascularization on MACCE (\( p=0.58 \)). Although there was no statistical difference, the cumulative survival rate of LCX-CTO revascularization is still the lowest.

**Discussion**

The present study showed patients with CTO not revascularised by PCI had worse outcomes compared with those with CTO revascularised, with higher incidence of cardiac death and MACCE. The presence of LVEF \( \leq 0.5 \), LM-disease was associated with an incidence of cardiac death, CTO revascularised was a protected predictor of cardiac death.

In our study population, the proportion of older (age \( \geq 65 \) years), diabetes, LM disease and three-vessel disease was higher in the no-revascularised CTO patients. This suggests that CTO with the above characteristics is more difficult to open. More importantly, previous studies have shown that age is an independent risk factor for cardiovascular mortality [6]. Elderly patients with decreased body function are more likely to have hypertension and diabetes, which promote atherosclerosis. In addition, the treatment
strategy of CTO will also take into account the age factor; older patient tend to choose conservative treatment rather than PCI intervention. Meanwhile, there were more patients with in-stent restenosis (ISR) CTO in the revascularised group, which is also consistent with clinical practice; the ISR-CTO is easier to open because of the contour of the stent.

Evaluation of cardiac function in patients with CTO is of great significance for their prognosis. Serum NTproBNP is an important biomarker in our clinical practice. Abnormal elevation of NTproBNP can accurately reflect the degree of heart failure[7], and its combination with LVEF can comprehensively reflect the state of cardiac function. In our study, the peak of NTproBNP was higher and the LVEF was lower in the no-revascularised CTO patient. Moreover, low-LVEF was a harmful predictor of cardiac death, we found that the presence of LVEF<0.5 was associated with an incidence of cardiac death at least 4 times higher than those with LVEF ≥ 0.5. Overall, cardiac dysfunction is more unfavorable to the clinical prognosis of CTO patients, which can significantly increase the incidence of major adverse cardiovascular events.

CTO are a common clinical finding among patients undergoing coronary angiography, approximately 1 in 4 patients with obstructive coronary artery disease on coronary angiography had CTOs [8]. CTO have been referred to as the “final frontier” in interventional cardiology, which are complex and difficult to open [9]. Although overall success rates remain low, with improvement in equipment and techniques, high success rates can be achieved at experienced centers; PCI for CTOs has been rapidly evolving during recent years. Our study compared the opening rates of different CTO sites, the results showed that the opening rates of LAD, LCX, RCA, and > 2 vessels were 68.2%, 40.6%, 53.9% and 42.1%, respectively. There were significant differences in the opening rate of different CTO vessels (p = 0.000).

We can found that the opening rate of LAD-CTO is the highest, the LAD coronary artery supplies a major portion of the left ventricle, its diagonal branches perfuse the entire anterior wall, and its septal branches supply the anterior 2/3 of the septum. Especially a proximal LAD-CTO will affect the entire anterior and anteroseptal wall from base to apex. Typically such a lesion, if not revascularized, will compromise overall LV systolic function and reduces the overall LVEF to at least 35–40%; which will lead to hypotension and heart failure[10]. Therefore, clinicians are more willing to try to open LAD-CTO. This may be one of the reasons for the high opening rate of LAD-CTO. Nevertheless, the success rate of CTO with more than 2 vessels was low, and the probability of choosing CABG treatment is higher (p = 0.03). This result is also consistent with the clinical practice; CABG is the first choice for multi-vessel coronary artery disease. Many studies have suggested a long-term survival advantage for CABG compared with PCI in patients with multi-vessel coronary artery disease [11]. Moreover, the success rate of LCX-CTO was the lowest; many studies have confirmed that the successful opening of LCX-CTO has not seen obvious clinical benefits [12], and LCX-CTO is more difficult to open, one of the diagnostic criteria of the PROGRESS-CTO score is LCX-CTO [13].

Although the successful opening of CTO lesion vessels was significantly associated with the decrease of MACCE, in the CTO-R group, different target vessel lesions (LAD, LCX and RCA) revascularization did not
affect MACCE. It can be seen from Fig. 5 that successfully opened the LCX-CTO has the least effect on prognosis and the lowest cumulative survival rate. This confirmed the limited clinical significance of opening the LCX-CTO.

Our result showed that successful CTO PCI is associated with a statistically significant improvement in cardiac death and MACCE, CTO revascularised was a protected predictor of cardiac death (HR: 0.239, 95% CI 0.076–0.751) and MACCE (HR: 0.541, 95% CI 0.353–0.83). It may be that the successful opening of CTO can improve cardiac function and ultimately improve the clinical outcome. A previous meta-analysis of 34 studies with 2735 patients on the impact of CTO PCI on LV function was performed in 2018 by Michael Megaly et al and showed a statistically significant increase in LVEF (3.8%, 95% CI 3.0-4.7, P < 0.0001) as compared with baseline[14]. Additionally, in our study, lower LVEF (LVEF<0.5) and LM disease predicted a worse probability for cardiac death. In summary, the predictive risk factors of cardiac death in CTO patients include vascular not revascularised, LM lesions and low LVEF.

**Limitations**

The following limitations were present in this study. (1) This study was a retrospective cohort study. The evidence grade is lower than that of a randomized controlled trial. (2) The signs of a viable myocardium were not evaluated in our study. (3) Although we used multivariate Cox regression analysis to adjust for differences in baseline characteristics, there may still be unknown confounding factors, therefore, the research results should be reasonably interpreted. Moreover, the randomized clinical trials should be conducted to verify the results in the future.

**Conclusions**

In summary, compared with CTO not revascularised, successful revascularization offered patients more clinical benefits, manifested by lower incidence of cardiac death and MACCE during follow-up. Moreover, the presence of LVEF<0.5 and LM-disease was associated with an incidence of cardiac death; CTO revascularization was a protected predictor of cardiac death. Further RCTs are needed to investigate the role of PCI for management of patients with CTO.

**Abbreviations**

CTO: chronic total occlusion; PCI: percutaneous transluminal coronary intervention; ISR: in-stent restenosis; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; TVR: target vessel revascularization; LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery; CHD: coronary heart disease; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; BMI: body mass index; CHOL: cholesterol; LDL-C: low-density lipoprotein-cholesterol; HR: hazard ratio; CI: confidence interval; RCTs: randomized controlled trials.
Declarations

Ethics approval and consent to participate

Ethical approval was obtained from Beijing Friendship Hospital ethics committee. This retrospective study was conducted without informed consent for some objective reasons and was approved by the ethics committee. All procedures performed in studies were in accordance with Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data and materials can be found from the first author and corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

LH and CH designed the protocol, DX and ZL participated in the clinical data collection, GX drafted the manuscript. All authors read and approved the final manuscript.

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Tables
Table 1: Baseline characteristics of the study population grouped by the different coronary artery CTO lesions

| Variable         | LAD (n = 163) | LCX (n = 148) | RCA (n = 216) | ≥ 2 vessel (n = 65) | P    |
|------------------|---------------|---------------|--------------|---------------------|------|
| Age (years)      | 64.74 ± 9.98  | 64.37 ± 10.23 | 64.66 ± 10.7 | 64.25 ± 11.67       | 0.982|
| Male             | 136(83.4)     | 119(80.4)     | 172(79.6)    | 52(80)              | 0.811|
| Days             | 7(5,9)        | 6(5,8)        | 7(5,9)       | 7(5,10.5)           | 0.291|
| BMI (kg/m²)      | 25.83 ± 3.3   | 26.25 ± 3.33  | 25.94 ± 3.37 | 26.16 ± 4.16        | 0.717|
| AC (cm)          | 93.14 ± 9.7   | 94.06 ± 10.08 | 93.32 ± 9.44 | 93.29 ± 12.11       | 0.868|
| Smoke            | 102(62.6)     | 94(63.5)      | 153(70.8)    | 42(64.6)            | 0.312|
| Drink            | 31(19)        | 20(13.5)      | 54(25)       | 14(21.5)            | 0.059|
| HT               | 113(69.3)     | 112(75.7)     | 162(75)      | 47(72.3)            | 0.553|
| DM               | 78(47.9)      | 72(48.6)      | 87(40.3)     | 37(56.9)            | 0.086|
| Hyperlipemia     | 91(55.8)      | 92(62.2)      | 118(54.6)    | 35(53.8)            | 0.486|
| CHD              | 94(57.7)      | 88(59.5)      | 140(64.8)    | 40(61.5)            | 0.525|
| OMI              | 32(19.6)      | 29(19.6)      | 56(25.9)     | 16(24.6)            | 0.375|
| HF               | 2(1.2)        | 1(0.7)        | 3(1.4)       | 2(3.1)              | 0.577|
| CKD              | 8(4.9)        | 10(6.8)       | 13(6)        | 3(4.6)              | 0.879|
| PAD              | 9(5.5)        | 13(8.8)       | 20(9.3)      | 4(6.2)              | 0.519|
| Stroke           | 36(22.1)      | 38(25.7)      | 42(19.4)     | 12(18.5)            | 0.486|
| History of PCI   | 49(30.1)      | 48(32.4)      | 64(29.6)     | 19(29.2)            | 0.94 |
| History of CAGB  | 3(1.8)        | 2(1.4)        | 8(3.7)       | 10(15.4)            | 0.000|
| ISR              | 15(9.2)       | 5(3.4)        | 17(7.9)      | 2(3.1)              | 0.104|
| PCI open         | 107(68.2)     | 58(40.6)      | 111(53.9)    | 24(42.1)            | 0.000|
| CABG             | 6(3.7)        | 5(3.4)        | 10(4.6)      | 8(12.3)             | 0.03 |

Data are presented as absolute numbers and percentages (for categorical variables) or mean value ± SD (for continuous variables) unless otherwise specified. BMI, body mass index; AC, Abdominal circumference; HT, hypertension; DM, diabetes mellitus; HF, heart failure; CHD, coronary heart disease; OMI, old myocardial infarction; CKD, Chronic kidney disease; PAD, Peripheral arterial disease; CABG, coronary artery bypass grafting; CTO, coronary chronic total occlusion; PCI, percutaneous coronary intervention; ISR, In stent restenosis.
Table 2
Baseline characteristics of patients stratified for CTO lesion Revascularized or Not.

| Variable      | CTO-R group (n = 300) | CTO-NR group (n = 263) | P     |
|---------------|-----------------------|------------------------|-------|
| Age           | 63 ± 10               | 67 ± 11                | 0.000 |
| Male          | 248(82.7)             | 208(79.1)              | 0.28  |
| Days          | 7(5,9)                | 6(5,8)                 | 0.721 |
| BMI(kg/m^2)   | 26.19 ± 3.59          | 25.85 ± 3.2            | 0.242 |
| AC(cm)        | 93.36 ± 9.96          | 93.67 ± 9.77           | 0.721 |
| Smoke         | 200(66.7)             | 171(65)                | 0.681 |
| Drink         | 63(21)                | 50(19)                 | 0.557 |
| HT            | 220(73.3)             | 193(73.4)              | 0.989 |
| DM            | 119(39.7)             | 140(53.2)              | 0.001 |
| Hyperlipemia  | 162(54)               | 157(59.7)              | 0.174 |
| CHD           | 177(59)               | 167(63.5)              | 0.275 |
| OMI           | 58(19.3)              | 68(25.9)               | 0.064 |
| HF            | 4(1.3)                | 4(1.5)                 | 0.851 |
| CKD           | 11(3.7)               | 23(8.7)                | 0.012 |
| PAD           | 21(7)                 | 21(8)                  | 0.657 |
| Stroke        | 63(21)                | 58(22.1)               | 0.761 |
| History of PCI| 88(29.3)              | 88(33.5)               | 0.292 |
| History of CABG | 3(1)                  | 20(7.6)                | 0.000 |
| CHOL(mmol/L)  | 4.13 ± 1.09           | 3.9 ± 1.01             | 0.013 |
| LDL-C(mmol/L) | 2.34 ± 0.76           | 2.2 ± 0.73             | 0.036 |
| eGFR(ml/min)  | 86.24 ± 20.57         | 80.15 ± 23.37          | 0.001 |
| NT-proBNPmax(Pg/ml) | 278(81,1034.75)        | 487(144,2223)          | 0.001 |
| LVEDD         | 5.23 ± 0.64           | 5.27 ± 0.59            | 0.43  |

Values are n (%), mean ± SD or median with interquartile range. CHOL, cholesterol; LDL-c, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide, eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic dimension, LVEF, left ventricular ejection fraction; FS, fraction shortening, LM disease, Left main disease.
| Variable                  | CTO-R group (n = 300) | CTO-NR group (n = 263) | P   |
|--------------------------|-----------------------|------------------------|-----|
| LVEF                     | 0.61 ± 0.1            | 0.58 ± 0.11            | 0.001 |
| FS                       | 0.33 ± 0.07           | 0.31 ± 0.07            | 0.002 |
| ISR                      | 25(8.3)               | 12(4.6)                | 0.072 |
| three vessel disease     | 270(90)               | 253(96.2)              | 0.004 |
| LM disease               | 41(13.7)              | 66(25.1)               | 0.001 |

Values are n (%), mean ± SD or median with interquartile range. CHOL, cholesterol; LDL-c, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide, eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic dimension, LVEF, left ventricular ejection fraction; FS, fraction shortening, LM disease, Left main disease.

Table 3
Comparison of clinical outcome between CTO-R group and CTO-NR group

| Event, n (%)                        | CTO-R group (n = 300) | CTO-NR group (n = 263) | P   |
|-------------------------------------|-----------------------|------------------------|-----|
| MACCE                               | 36(12)                | 58(22.1)               | 0.001 |
| All-cause death                     | 7(2.3)                | 17(6.5)                | 0.016 |
| Cardiac death                       | 4(1.3)                | 16(6.1)                | 0.002 |
| Re-hospitalization                  | 34(11.3)              | 46(17.5)               | 0.037 |
| Heart failure                       | 8(2.7)                | 4(1.5)                 | 0.348 |
| Target vessel revascularization     | 1(0.3)                | 6(2.3)                 | 0.037 |
| Recurrent myocardial infarction     | 6(2)                  | 5(1.9)                 | 0.933 |
| Stroke                              | 1(0.3)                | 3(1.1)                 | 0.255 |

MACCE: major adverse cardiac and cerebrovascular events, a composite of all-cause death, cardiac death, recurrent myocardial infarction, target vessel revascularization, re-hospitalization, heart failure, and stroke.
Table 4
Multivariate Cox regression analysis in the overall CTO patients

| Predictor variable | HR (95% CI)      | P   |
|--------------------|------------------|-----|
| **MACCE**          |                  |     |
| Age ≥ 65 years     | 0.92(0.58–1.465) | 0.729 |
| Male               | 0.663(0.398–1.106) | 0.116 |
| HT                 | 0.954(0.594–1.532) | 0.845 |
| DM                 | 0.822(0.537–1.26) | 0.369 |
| HP                 | 0.89(0.588–1.346) | 0.581 |
| OMI                | 0.85(0.508–1.422) | 0.536 |
| PAD                | 1.317(0.674–2.575) | 0.42 |
| Stroke             | 1.028(0.632–1.672) | 0.912 |
| eGFR<90            | 0.999(0.639–1.561) | 0.996 |
| **LVEF<0.5**       | 2.121(1.304–3.452) | 0.002 |
| **CTO-R**          | 0.541(0.353–0.83) | 0.005 |
| LM disease         | 1.211(0.734–2.001) | 0.454 |
| **Cardiac death**  |                  |     |
| Age ≥ 65 years     | 0.501(0.172–1.459) | 0.205 |
| Male               | 0.437(0.148–1.288) | 0.133 |
| HT                 | 1.548(0.501–4.778) | 0.447 |
| DM                 | 0.781(0.295–2.065) | 0.618 |
| HP                 | 0.948(0.365–2.461) | 0.913 |
| OMI                | 0.548(0.171–1.75) | 0.31 |
| PAD                | 2.332(0.739–7.364) | 0.149 |
| Stroke             | 0.925(0.31–2.758) | 0.889 |
| eGFR<90            | 1.369(0.485–3.861) | 0.553 |
| **LVEF<0.5**       | 4.804(1.895–12.177) | 0.001 |
| **CTO-R**          | 0.239(0.076–0.751) | 0.014 |
| LM disease         | 3.884(1.544–9.771) | 0.004 |