Long-term outcomes of percutaneous coronary intervention for in-stent chronic total occlusion

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Abstract

Background: The development of the technique has improved the success rate of percutaneous coronary intervention (PCI) for in-stent chronic total occlusion (IS-CTO). However, long-term outcomes remain unclear. The present study sought to investigate long-term outcomes of PCI for IS-CTO.

Methods: A total of 474 IS-CTO patients were enrolled at two cardiac centers from 2015 to 2018 retrospectively. These patients were allocated into either successful or failed IS-CTO PCI groups. The primary endpoint (major adverse cardiac events [MACE]) consisted of recurrent angina pectoris (RAP), target-vessel myocardial infarction (MI), heart failure, cardiac death, or ischemia-driven target-vessel revascularization (TVR) at follow-up. Multivariable Cox regression analysis was used to investigate the association between treatment appropriateness and clinical outcomes.

Results: A total of 367 patients were successfully treated with IS-CTO PCI while 107 patients had failed recanalization. After a median follow-up of 30 months (interquartile range: 17–42 months), no significant difference was observed between the two groups for the following parameters: cardiac death (successful PCI *vs.* failed PCI: 0.9% *vs.* 2.7%; adjusted hazard ratio [HR]: 1.442; 95% confidence interval [CI]: 0.21–9.887; $P = 0.709$), RAP (successful PCI *vs.* failed PCI: 40.8% *vs.* 40.0%; adjusted HR: 1.025; 95% CI: 0.683–1.538; $P = 0.905$), heart failure (successful PCI *vs.* failed PCI: 6.1% *vs.* 2.7%; adjusted HR: 0.281; 95% CI: 0.065–1.206; $P = 0.088$), target-vessel related MI (successful PCI *vs.* failed PCI: 1.5% *vs.* 2.7%; adjusted HR: 1.150; 95% CI: 0.221–5.995; $P = 0.868$), MACE (successful PCI *vs.* failed PCI: 44.2% *vs.* 45.3%; adjusted HR: 1.052; 95% CI: 0.717–1.543; $P = 0.797$). More patients were free of angina in the successful IS-CTO PCI group compared with failed PCI in the first (80.4% *vs.* 60%, $P < 0.01$) and second years (73.3% *vs.* 60.0%, $P = 0.02$) following up. Successful IS-CTO PCI had a lower incidence of MACE in the first and second years (20.2% *vs.* 40.0%, $P < 0.01$; 27.9% *vs.* 41.3%, $P = 0.023$) compared with failed PCI. After a median follow-up of 30 months, the reocclusion rate was 28.5% and TVR was 26.1% in the successful IS-CTO PCI group. Receiving >18 months of dual antiplatelet therapy (DAPT) was an independent predictor of decreased risk of TVR (HR: 2.682; 95% CI: 1.295–5.578; $P = 0.008$) or MACE (without TVR) (HR: 1.898; 95% CI: 1.036–3.479; $P = 0.038$) in successful IS-CTO PCI.

Conclusions: After a median follow-up of 30 months, the successful IS-CTO PCI group had MACE similar to that of the failed PCI group. However, the successful IS-CTO PCI group had improved angina symptoms and were free from requiring coronary artery bypass grafting in the first or second years. To decrease MACE, DAPT was found to be essential and recommended for at least 18 months for IS-CTO PCI.

Keywords: In-stent chronic total occlusion; Percutaneous coronary intervention; Predictive factor; Prognosis

Introduction

Percutaneous coronary intervention (PCI) for in-stent chronic total occlusion (IS-CTO) accounts for 5% to 25% of all CTOs and is the most difficult and challenging subset of lesions treated using PCI. Due to the development of new equipment and the techniques, IS-CTO PCI has achieved high technical and procedural rates of success (86%).[1] Although clinicians should be pleased with the apparent technological success, such achievements must be translated into long-term patient well-being. Little literature has so far been published on the subject.

As is well known, PCI for non-occlusive in-stent restenosis (ISR) yields worse outcomes than PCI in *de novo* lesions, even in the era of drug-eluting stents (DES).[2-4] The pre-existed artificial stent structure makes IS-CTO lesion's long-term outcome more pessimistic than *de novo* CTO reasonably. IS-CTO has been identified as an independent predictor of target-vessel revascularization (TVR).[5] Until now, few

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reports have been published of clinical long-term outcomes for IS-CTO PCI. It is the aim of the present study to examine the long-term outcomes and predictors of adverse events in PCI for IS-CTO. The results should assist clinicians in taking the most appropriate clinical decisions and improve the long-term outcomes of this challenging patient population.

Methods

Ethical approval

The study complied with the principles of the *Declaration of Helsinki* and was approved by the Ethics Committees of two participating centers (Fuwai Hospital and Beijing Anzhen Hospital). All eligible patients provided informed consent for this study before undergoing coronary angiography.

Patient population

The CTO database was retrospectively queried and 474 cases who had undergone PCI for IS-CTO in two participating centers (Chinese Academy of Medical Science National Center for Cardiovascular Disease Fuwai Hospital and Beijing Anzhen Hospital) consecutively from January 2015 to December 2018 were selected. The IS-CTO PCI procedure was based on current PCI recommendations.[6,7] Cases were divided into successful and failed IS-CTO PCI groups, of which detailed clinical and procedural data were collected. Patients had been questioned about their symptoms, angina status (Canadian Cardiovascular Society [CCS] grading of angina pectoris [AP]), and dyspnea class (New York Heart Association functional classification). Follow-up was performed by telephone interviews, a review of hospital records, or in outpatient visits. Information about each patient in the failed PCI and successful PCI groups included which medications had been used, such as antiplatelet, β-blockers, statin lipid-lowering therapy, angiotensin converting enzyme inhibitor (ACEI), or nitrates. Baseline, procedural, and hospitalization data were recorded for further analysis. The institutional review boards of each of the two participating hospitals approved the study.

Definitions

A CTO was defined as an occluded coronary lesion with thrombosis in the myocardial infarction (MI)-related artery with antegrade blood flow grade thrombolysis in myocardial infarction (TIMI) 0 and an estimated duration of >3 months. Occlusions located within a previously implanted stent or up to 5 mm from the edge of the stent was defined as IS-CTO.[1]

Technical success in PCI for CTO was defined as successful CTO revascularization with <30% residual stenosis and restoration of antegrade thrombolysis in myocardial infarction flow grade 3 in the CTO segment. Procedural success was defined as technical success without any in-hospital adverse events (all-cause death, Q-wave MI, stroke, recurrent angina requiring TVR with PCI, or coronary artery bypass grafting [CABG]). Major procedural complications included: procedure-related death, stroke, periprocedural type 4a MI, major bleeding (bleeding requiring transfusion, vasopressors, surgery, or percutaneous intervention), or coronary perforation with cardiac tamponade requiring intervention (pericardiocentesis, coiling, covered stent implantation, or surgery).

Long-term dual antiplatelet therapy (DAPT) was defined as longer than 18 months on DAPT. Major adverse cardiac events (MACE) at follow-up were defined as recurrent angina pectoris (RAP) (CCS grading), target-vessel MI, heart failure, cardiac death, or ischemia-driven TVR.

AP was defined as typical symptoms with a corresponding change in electrocardiogram or stress test. Symptoms were graded as I to IV using the CCS classification — class I: angina with strenuous exertion; class II: angina with moderate exertion; class III: angina with mild exertion; class IV: angina with any level of physical exertion.

Statistical analysis

Continuous variables are reported as mean ± standard deviation and compared using a Student's *t* test. Categorical variables are expressed as frequency (percentage) and were tested using a Chi-square test. Event-free survival was assessed using the Kaplan-Meier plots and compared with log-rank tests. Covariates that were significant by univariate analysis or those that were clinically relevant were included in multivariate models. Variable selection was performed by fitting a penalized Cox regression model. The results of this analysis are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). *P* values < 0.05 were considered statistically significant. Statistical analysis was conducted using SPSS version 25 (IBM Corporation, Armonk, NY, USA).

Results

Baseline clinical characteristics

A total of 474 patients were recruited to the study, of which 395 (82.8%) were male. Of the total, 313 (65.6%) had a history of hypertension, 409 (86.3%) had a history of dyslipidemia, 303 (63.9%) were current smokers, and 279 (59%) had a previous MI. A total of 367 patients were successfully treated with PCI and ISO-CTO PCI failed in 107 patients. There were no significant differences between the successful and failed IS-CTO PCI groups with respect to age, the prevalence of cardiovascular risk factors, renal function, ejection fraction, previous MI, previous CABG history, procedural complications, or indications for CTO PCI [Table 1]. Both the successful and failed groups received standard medical therapy (MT).

Baseline angiographic characteristics

The majority of IS-CTOs were located in the right coronary artery (RCA, 43.9%), the left anterior descending artery (LAD, 35.2%), or the left circumflex artery (17.4%). The failed IS-CTO group had a greater number of IS-CTOs in the RCA ($P = 0.000$) and fewer in the LAD ($P = 0.002$) than the successful group. No difference was observed in the left ventricular end-diastolic diameter or left ventricular ejection fraction (LVEF) between the two

Table 1: Baseline characteristics of the overall population of PCI.

Characteristics	Overall ($N = 474$)	Successful PCI ($n = 367$)	Failed PCI ($n = 107$)	Statistical values	P
Age (years)	61.00 ± 10.50	60.85 ± 9.97	60.72 ± 12.09	2.968*	0.910
BMI (kg/m^2)	26.40 ± 4.10	26.23 ± 4.26	27.00 ± 3.51	1.024*	0.089
Male	395 (82.8)	298 (81.2)	97 (90.7)	5.333†	0.021
EF (%)	58.30 ± 8.30	58.54 ± 8.29	57.96 ± 8.50	0.577*	0.533
LVEDd (mm)	50.20 ± 6.20	50.05 ± 46.11	50.72 ± 6.36	0.252*	0.329
TC (mmol/L)	3.95 ± 1.20	4.00 ± 1.21	3.75 ± 1.02	3.774*	0.045
LDL-C (mmol/L)	2.18 ± 1.00	2.22 ± 1.06	2.02 ± 0.92	3.103*	0.065
Lipoprotein a (mg/L)	351.28 ± 336.90	361.78 ± 337.53	315.58 ± 333.97	0.146*	0.228
During of first PCI (years)	5.70 ± 3.80	5.74 ± 3.75	5.37 ± 3.46	0.694*	0.366
eGFR (mL/min/1.73 m^2)				0.789†	0.853
eGFR >90 mL/min/1.73 m^2	367 (76.9)	281 (65.6)	81 (76.4)		
eGFR (60–90) mL/min/1.73 m^2	96 (20.1)	73 (19.9)	23 (21.7)		
eGFR (30–60) mL/min/1.73 m^2	13 (2.7)	11 (3.0)	2 (1.9)		
eGFR <30 mL/min/1.73 m^2	1 (0.2)	1 (0.3)	0 (0)		
Hypertension	313 (65.6)	240 (65.6)	73 (68.9)	0.399†	0.527
Dyslipidemia	409 (86.3)	317 (86.4)	92 (86.0)	0.011†	0.917
Diabetes	162 (34.0)	122 (33.3)	40 (37.7)	0.707†	0.401
Current smoking	303 (63.9)	232 (63.2)	71 (66.4)	0.354†	0.552
Previous MI	279 (59.0)	210 (57.4)	69 (64.5)	1.730†	0.188
Previous CABG	11 (2.3)	9 (2.5)	2 (1.9)	0.118†	0.731
Prior attempt	31 (6.6)	19 (5.2)	12 (11.2)	4.905†	0.027
Dual injection	28 (5.9)	22 (6.0)	6 (5.6)	0.270†	0.870
CTO site					
LAD	166 (35.2)	142 (39.0)	24 (22.4)	9.961†	0.002
LCX	82 (17.4)	69 (19.0)	13 (12.1)	2.664†	0.103
RCA	207 (43.9)	142 (39.0)	65 (60.7)	15.861†	0.000
Branch vessel CTO	19 (3.5)	18 (4.9)	1 (0.9)	5.333†	0.000
Occlusion length (mm)	24.10 ± 20.10	17.81 ± 13.27	45.54 ± 26.44	84.338*	0.000
Prox-cap ambiguity/blunt	409 (86.3)	312 (85.0)	97 (90.7)	2.228†	0.136
Prox bifurcation	46 (9.6)	18 (4.9)	28 (26.2)	42.746†	0.000
Ostial CTO	48 (10.1)	13 (3.5)	35 (32.7)	77.445†	0.000
Good interventional collaterals	116 (24.5)	90 (24.5)	26 (24.3)	0.002†	0.962
Proximal bending	73 (15.4)	16 (4.4)	57 (53.3)	152.118†	0.000
Moderate or severe tortuosity	120 (25.3)	29 (7.9)	91 (85.0)	260.770†	0.000
Underexpansion	120 (25.3)	26 (7.1)	94 (87.9)	285.825†	0.000
Poor distal target	49 (10.3)	16 (4.4)	33 (30.8)	62.680†	0.000
Success	367 (77.4)				
Failure	107 (22.6)				
Successful crossing technique					
Antegrade wire escalation	455 (96.0)	354 (96.5)	101 (99.4)	0.918†	0.338
Retrograde wire escalation	19 (4.0)	13 (3.5)	6 (5.6)	0.918†	0.338
Use of crossboss	9 (1.9)	9 (2.4)	0 (0.0)	Fisher	0.219
Use of intravascular ultrasound	27 (5.7)	25 (6.8)	2 (1.9)	2.904†	0.088
Type of treatment					
POBA	50 (13.6)				
DEB	125 (34)				
DES	219 (59.7)				
Contrast volume (mL)	199.80 ± 72.60	202.71 ± 72.15	189.91 ± 73.77	0.179*	0.111
Total procedural time (min)	63.40 ± 50.60	65.84 ± 51.40	55.13 ± 47.08	0.188*	0.056
Major procedural complications					
Side branch loss	19 (4.0)	18 (4.9)	1 (0.9)	2.440†	0.118
Low flow	30 (6.3)	29 (7.9)	1 (0.9)	5.636†	0.018
Perforation	4 (0.8)	2 (0.5)	2 (1.9)	0.514†	0.473
Dissection	5 (1.0)	4 (1.1)	1 (0.9)	0.000†	1.000

Values are mean ± standard deviation, or n (%). *F values. †x^2 values. PCI: Percutaneous coronary intervention; BMI: Body mass index; LVEDd: Left ventricular end-diastolic diameter; MI: Myocardial infarction; CABG: Coronary artery bypass graft surgery; CTO: Chronic total occlusion; LAD: Left anterior descending coronary artery; LCX: Left circumflex coronary artery; RCA: Right coronary artery; POBA: plain old balloon angioplasty; DEB: Drug-eluting balloon; DES: Drug-eluting stent; EF: Ejection fraction; TC: Total cholesterol.

groups ($P > 0.05$). The failed PCI group exhibited a longer occlusion length than the successful IS-CTO PCI group (45.54 ± 26.44 *vs.* 17.81 ± 13.27; $P < 0.001$), a larger rate of ostial CTO (32.7% *vs.* 3.5%; $P = 0.000$), proximal bifurcation (26.2% *vs.* 4.9%; $P < 0.001$), moderate or severe tortuosity (85% *vs.* 7.9%; $P < 0.001$), proximal bending (53.3% *vs.* 4.4%; $P < 0.001$), under expansion (87.9% *vs.* 7.1%; $P < 0.001$), poor distal target (30.8% *vs.* 4.4%; $P < 0.001$), and higher *J* scores (2.56 ± 0.71 *vs.* 2.15 ± 0.88, $P < 0.001$). No difference was observed in syntax score between the two groups ($P = 0.221$) [Table 1].

Procedural characteristics

The overall procedural success rate was 77.4%. In all successful IS-CTO PCI procedures, a true-to-true crossing of the occlusion was conducted and in no case did subintimal crushing of the previous stent occur. The most frequent successful crossing strategy (96.0%) was antegrade wire escalation. The retrograde approach is used rarely in IS-CTO patients (4.0%). Intravascular ultrasound (IVUS) was relatively infrequently utilized, principally due to its expense and time inefficiency [Table 1].

The incidence of major procedural complications was 12.1%. No deaths, strokes, stent thrombosis, or emergent TVR occurred during hospitalization. Four perforations, 19 cases of side branch loss, 30 of low/no flow, and five of dissection were observed in the successful IS-CTO PCI group. One of four patients with tamponade received pericardiocentesis. No differences were observed between the successful and failed IS-CTO PCI groups regarding side branch loss, perforation, or dissection [Table 1].

Clinical outcomes on follow-up

Follow-up data were available for 411 (86.7%) patients. Median follow-up was 30 months (interquartile range: 17–42 months). In the failed group ($n = 92$), ten patients received a CABG, due to the patients' wishes and their unacceptable symptoms of AP, and seven underwent a second PCI within 1 month that was subsequently successful, who were transferred to the successful IS-CTO PCI group ($n = 326$). In all, 75 cases were assigned to the failed PCI group. They all received standard MT with a prescription for aspirin, clopidogrel/ticagrelor, ACEI, beta-blockers, and statins. There was no difference in MT between the two groups ($P > 0.05$) [Table 2].

Kaplan-Meier analysis of MACE-free survival curves of the failed and successful IS-CTO PCI groups is displayed in Figure 1. The plots crossed at 36 months with an HR value of 1.052 (95% CI: 0.717–1.543; $P = 0.797$).

Clinical outcomes on follow-up are displayed in Table 3. No significant differences were observed in the following parameters between the two groups: cardiac death (failed *vs.* successful PCI: 2.7% *vs.* 0.9%; adjusted HR: 1.442; 95% CI: 0.21–9.887; $P = 0.709$), RAP (failed *vs.* successful PCI: 40% *vs.* 40.8%; HR: 1.025; 95% CI: 0.683–1.538; $P = 0.905$), heart failure (failed *vs.* successful PCI: 2.7% *vs.* 6.1%; HR: 0.281; 95% CI: 0.065–1.206; $P = 0.088$), target-vessel related MI (failed *vs.* successful PCI: 2.7% *vs.* 1.5%; HR: 1.150; 95% CI: 0.221–5.995; $P = 0.868$), and MACE (failed *vs.* successful PCI: 45.3% *vs.* 44.2%; HR: 1.052; 95% CI: 0.717–1.543; $P = 0.797$). In the IS-CTO PCI group, reocclusion occurred in 28.5% of cases and TVR in 26.1%. Over the following 30 months, 12 cases in the successful PCI group received CABG due to restenosis/reocclusion. The incidence of MACE in the failed PCI ($n = 75$), successful IS-CTO PCI ($n = 326$), and CABG ($n = 22$) groups was 45.3%, 44.2%, and 13.6%, respectively.

Multivariate predictors of restenosis/reocclusion are displayed in Table 4 on follow-up. Long-term DAPT therapy was an independent predictor of decreased restenosis/reocclusion (HR: 2.682; 95% CI: 1.295–5.578; $P = 0.008$). Small vessels (HR: 0.588; 95% CI: 0.348–0.995; $P = 0.048$), being female (HR: 0.506; 95% CI: 0.309–0.829; $P = 0.007$), and a higher body mass index (BMI) (HR: 1.053; 95% CI: 1.007–1.102; $P = 0.025$) were independent predictors of restenosis/reocclusion. Long-term DAPT remained independently associated with decreasing MACE (not driven by TVR) (HR: 1.898; 95% CI: 1.036–3.479; $P = 0.038$). Prior CABG was independently associated with MACE (not driven by TVR) (HR: 0.204; 95% CI: 0.062–0.673; $P = 0.009$). Figure 2 presents the adjusted 3-year survival curves from TVR. Patients prescribed long-term DAPT had a >2-fold decreased risk of TVR with no major bleeding events throughout follow-up.

Discussion

The principal findings of the present study were as follows. (1) The long-term outcomes of successful IS-CTO PCI showed a surprisingly high incidence of MACE (44.2%)

Table 2: Medication at 30-month follow-up of failed IS-CTO PCI *vs.* successful IS-CTO PCI groups.

Medication	Failed PCI ($n = 75$)	Successful PCI ($n = 326$)	Statistical values	*P* value
Aspirin (%)	74 (98.7)	323 (99.1)	0.000*	1.000
ADP receptor inhibitor (%)	10 (13.3)	75 (23.0)	0.025*	0.874
ACE-inhibitor or ARB (%)	52 (70.3)	225 (69.7)	0.234*	0.890
Beta-blocker (%)	63 (84.0)	296 (82.5)	3.318*	0.069
Calcium antagonist (%)	20 (26.7)	97 (30.1)	0.839*	0.657
Statin (%)	75 (100.0)	324 (99.4)	Fisher	1.000
Nitrate (%)	72 (96.0)	322 (98.8)	1.356*	0.244

* x^2 values. IS-CTO: In-stent chronic total occlusion; PCI: Percutaneous coronary intervention; ADP: Adenosine diphosphate; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker.

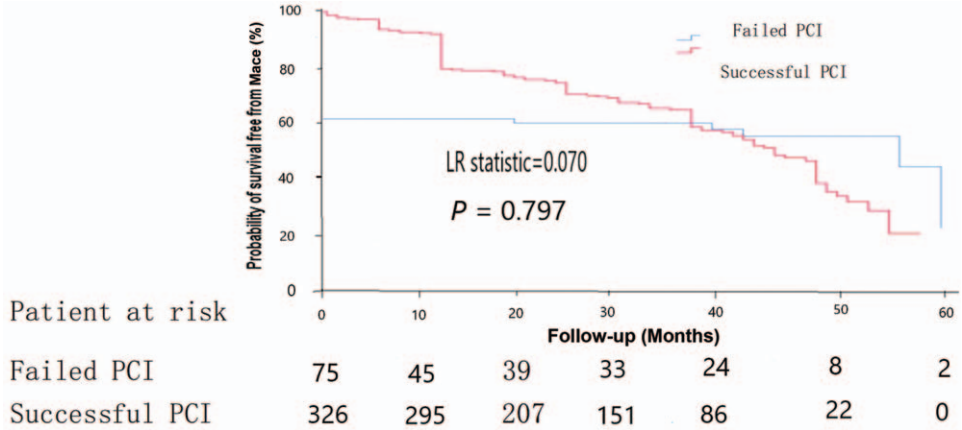

Figure 1: Long-term MACE. Kaplan-Meier curves for MACE; hazard ratios and *P* values are derived from Cox proportional hazard methods. CI: Confidence interval; HR: Hazard ratio; MACE: Major adverse cardiac events; PCI: Percutaneous coronary intervention.

Table 3: Clinical outcomes of patients with in-stent chronic total occlusion on follow-up, *n* (%).

Clinical outcomes	Failed PCI (*n* = 75)	Successful PCI (*n* = 326)	Adjusted HR (95% CI)	*P*
Major adverse cardiac events	34 (45.3)	144 (44.2)	1.052 (0.717–1.530)	0.797
Angina	30 (40.0)	133 (40.8)	1.025 (0.683–1.538)	0.905
Re-infarction	2 (2.7)	5 (1.5)	1.150 (0.221–5.995)	0.868
Heart failure	2 (2.7)	20 (6.1)	0.281 (0.065–1.206)	0.088
Cardiac mortality	2 (2.7)	3 (0.9)	1.442 (0.21–9.887)	0.709
Restenosis/re-occlusion		93 (28.5)		
TVR		85 (26.1)		

Major adverse cardiac events adjusted covariates: age, BMI, sex, prior MI, CABG, LVEF, eGFR, dyslipidemia, diabetes, hypertension, smaller vessel diameter, long-term DAPT, CTO site. Angina adjusted covariates: age, dyslipidemia, diabetes, hypertension, long-term DAPT. Re-infarction adjusted covariates: age, dyslipidemia, diabetes, hypertension, long-term DAPT. Heart failure adjusted covariates: age, sex, hypertension, prior MI, LVEF, LVEDd, eGFR, CTO site. Cardiac mortality adjusted covariates: age, sex, prior MI, CABG, LVEF, eGFR, CTO site, long-term DAPT. Values are *n* (%). PCI: Percutaneous coronary intervention; HR: Hazard ratio; CI: Confidence interval; TVR: Target-vessel revascularization; BMI: Body mass index; MI: Myocardial infarction; CABG: Coronary artery bypass graft surgery; LVEF: Left ventricular ejection fraction; DAPT: Dual antiplatelet therapy; CTO: Chronic total occlusion; LVEDd: Left ventricular end-diastolic diameter.

Table 4: Multivariable Cox proportional analysis for predictors of restenosis/re-occlusion on follow-up.

Model	Adjusted HR	95% CI	*P* value
Female	0.506	0.309–0.829	0.007
BMI	1.053	1.007–1.102	0.025
Smaller vessel diameter	0.588	0.348–0.995	0.048
Long-term DAPT	2.682	1.295–5.578	0.008

Hazard ratios and *P* values were calculated from Cox proportional hazard methods. Adjusted covariates: age, prior MI, LVEF, eGFR, dyslipidemia, diabetes. HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; DAPT: Dual antiplatelet therapy; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction.

and traceable restenosis and reocclusion (28.5%) after a median follow-up of 30 months. (2) Angina and MACE in the successful IS-CTO PCI group occurred significantly less frequently than in the failed PCI group in the first and second years. Over the first and second years, successful IS-CTO PCI improved symptoms of angina and reduced the need for coronary artery bypass grafting. (3) More than 18 months of DAPT decreased MACE in IS-CTO PCI.

IS-CTOs constitute 5% to 25% of all PCIs for CTO[8-11] and so are frequently observed during PCI procedures. Although IS-CTO is apparently different from *de novo* CTO due to the artificial implanted stent structure, clinicians rarely treat them differently. The long-term outcomes of IS-CTO are as yet unknown, and so this is the focus of the present study.

After a median follow-up of 30 months, the successful IS-CTO PCI group had a surprisingly high rate of MACE (44.2%) and traceable restenosis and reocclusion (28.5%). Azzalini *et al*[5] reported that over a 15-month follow-up period, MACE were observed in 20.8% *vs.* 13.9%; $P = 0.07$ in the IS-CTO group compared with the *de novo* group and driven by TVR (16.7% *vs.* 9.4%; $P = 0.03$), where IS-CTO was found to be an independent predictor of MACE. Indeed, we found a similar incidence of MACE after 15 months [Figure 1]. Traceable restenosis and reocclusion occurred in 28.5%, without considering asymptomatic ISR or reocclusion, suggesting that almost one-third of the benefit of IS-CTO PCI had disappeared by month 30.

Kaplan-Meier curve analysis, as shown in Figure 1, demonstrated that the MACE-free survival curves in the two groups apparently separated during the first year following treatment. Significantly, more patients with MACE were in the failed PCI group. But after nearly 1-year, MACE

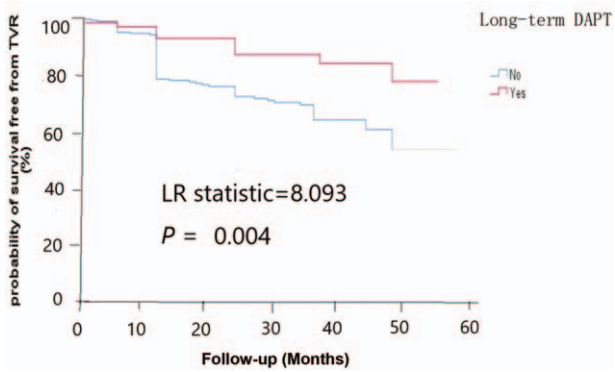

Figure 2: Long-term outcome of IS-CTO PCI. Kaplan-Meier curves for TVR, for patients with and without long-term DAPT; hazard ratios and *P* values are derived from Cox proportional hazard methods. CI: Confidence interval; DAPT: Dual antiplatelet therapy; HR: Hazard ratio; IS-CTO: In-stent chronic total occlusion; PCI: Percutaneous coronary intervention; TVR: Target-vessel revascularization.

in the successful IS-CTO group increased rapidly. By the 36th month, the two curves crossed, after which the MACE in the successful IS-CTO PCI group increased even more rapidly than the failed PCI group. After a median follow-up of 30 months, no difference in cardiac death was observed (0.9% *vs.* 2.7%; $P = 0.709$) between the successful and failed IS-CTO PCI groups. de la Torre Hernandez *et al*[12] also reported that after a median follow-up of 20 months, cardiac death in failed *vs.* successful groups was 8.3% and 3%, respectively ($P = 0.09$). They observed no difference between the successful and failed IS-CTO PCI groups for long-term mortality, in support of the findings in the present study.

In the successful IS-CTO group in the present study, the recanalization of the IS-CTO instantly mitigated ischemia, relieving the symptoms of angina. As time passed, more patients presented symptoms of angina. After a median follow-up of 30 months, no differences in reports of angina between the failed and successful IS-CTO groups were found (40% *vs.* 40.8%; HR: 1.025; 95% CI: 0.683–1.538; $P = 0.905$). The current guidelines for myocardial revascularization recommend that treatment for CTO should be considered depending on symptoms or objective evidence of myocardial viability/ischemia in the territory of the occluded artery.[13] Improvement in symptoms is considered the principal benefit of CTO PCI. The present study found no difference in heart failure (2.7% *vs.* 6.1%; $P = 0.088$) or target-vessel MI (2.7% *vs.* 1.5%; $P = 0.868$) between the failed and successful IS-CTO PCI groups.

The benefits of CTO PCI are controversial. A number of observational, uncontrolled studies have suggested that successful CTO PCI can improve angina, dyspnea, depression, capacity for exercise, and risk of arrhythmias. The OPEN-CTO trial reported that a great improvement in the Seattle Angina Questionnaire subscales was observed in successful *vs.* unsuccessful procedures ($P < 0.001$). An Italian multi-center registry reported that of 1777 patients with CTOs, 1-year follow-up examinations indicated that PCI (43.7%), MT (46.5%), or surgery (9.8%) were performed, with rates of cardiac death of 1.4% *vs.* 4.7% and 6.3% $P < 0.001$, and MACE was 2.6% *vs.* 8.2% and 6.9%; $P < 0.001$, respectively, significantly lower in the PCI group than for MT or CABG.[14]

Conversely, long-term outcomes for CTO in randomized controlled trials are suboptimal. The EXPLORE trial failed to find any differences in LVEF between the two groups and demonstrated that there were more patients free from angina in the CTO-PCI arm after 1 year (94% *vs.* 87%, $P = 0.03$).[15] The DECISION-CTO trial demonstrated no difference in the primary composite endpoint of MACE after 3 years (all-cause mortality, MI, stroke, repeat revascularization) between PCI and MT groups, suggesting that MT was not inferior to PCI as an initial strategy (NCT01078051).

In conclusion, the studies described above showed, in the short-term, that PCI is effective in relieving the symptoms of CTO, but over the long-term, especially after 30 months, all indices revert to their original trend, consistent with the findings in the present study. The decision of approach to IS-CTO should include the evaluation of symptoms, ischemic burden, and myocardial viability. In asymptomatic CTO patients with no available viability data, MT is strongly recommended, while PCI or CABG are preferred for symptomatic patients or asymptomatic patients with proven viability issues.

In the present study, CABG exhibited a low incidence of MACE, 13.6%. CABG should be considered as an initial treatment option for IS-CTO patients with significant concomitant LM disease, multivessel disease, more complex coronary artery disease, or a high SYNTAX score. CABG may reduce the risk of TVR and provide complete arterial revascularization.

The present study also demonstrated that in the IS-CTO PCI group, TVR was 26.1%. It can be reasonably inferred that a patient's biological factors that caused the first in-stent occlusion may be triggered once again where a fresh stent is implanted in the same lesion. These factors may include abnormal local morphology inflammatory reaction, adverse reactions to stent polymers, antiplatelet drug resistance, under expansion/malposition, or the presence of other immune diseases, etc. The high risk of TVR was also correlated with lower utilization of IVUS or OCT. A meta-analysis of randomized trials indicated that after a mean of 15 months, routine IVUS-guided PCI could reduce the risk of MACE (6.5% *vs.* 10.3%; odds ratio: 0.60; 95% CI: 0.46–0.77; $P < 0.0001$), principally because of a reduction in the risk of TVR (4.1% *vs.* 6.6%; odds ratio: 0.60; 95% CI: 0.43–0.84; $P = 0.003$).[16]

The practical challenges of how to achieve a balanced platelet inhibition and reduce the incidence of bleeding or other adverse events have been discussed.[17] Campo *et al*[18] reported that patients undergoing a PCI procedure for ISR may benefit from long-term administration of aspirin plus clopidogrel. Additionally, the present study indicated that the administration of >18 months of DAPT could independently decrease MACE (driven by TVR and not driven by TVR). Our adjusted analysis indicated that >18 months of DAPT was an independent predictor of decreased TVR (HR: 2.682; 95% CI: 1.295–5.578;

$P = 0.008$), small vessels were an independent predictor of restenosis/reocclusion (HR: 0.588; 95% CI: 0.348–0.995; $P = 0.048$), in addition to being female (HR: 0.506; 95% CI: 0.309–0.829; $P = 0.007$), and having a higher BMI (HR: 1.053; 95% CI: 1.007–1.102; $P = 0.025$). Additionally, >18 months of DAPT was found to decrease the risk of MACE for IS-CTO PCI. Rathore and Kaul[18] reported that small vessel (<3 mm) coronary artery disease is common and was identified as an independent predictor of restenosis following PCI. The present study also indicated that prior CABG was an independent predictor of MACE (not driven by TVR) on follow-up. Azzalini *et al*[5] reported that previous CABG was an independent risk factor of MACE on follow-up for IS-CTO PCI. A number of novel findings were achieved in the present study.

Study limitations

The following were limitations of the present study. (1) This was a retrospective observational study rather than a randomized clinical trial. (2) The number of patients included was relatively small compared with other *de novo* CTO studies. (3) Operator-related bias could have affected the assessment of angiographic parameters due to the absence of quantitative analysis to some degree. (4) IVUS was not utilized in many cases due to cost and efficiency, not optimal for the outcome of IS-CTO PCI.

Conclusions

After a median follow-up of 30 months, a similar number of MACE were observed in the successful IS-CTO PCI group compared with the failed PCI group. However, successful IS-CTO PCI improved symptoms of angina and reduced coronary artery bypass grafting during the first and second years. To decrease MACE, DAPT was essential and recommended for at least 18 months for IS-CTO PCI patients.

Conflicts of interest

None.

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