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Long-Term Outcomes of Percutaneous Coronary Intervention for Patients With In-Stent Chronic Total Occlusion Versus De Novo Chronic Total Occlusion

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Abstract

Limited data are available on long-term outcomes and health status in the treatment of in-stent coronary chronic total occlusion (IS-CTO) and de novo coronary chronic total occlusion (de novo CTO). This study compared the long-term clinical outcomes and health status of percutaneous coronary intervention (PCI) for patients with IS-CTO versus patients with de novo CTO in the drug-eluting stent era. We screened 483 consecutive patients with 1 CTO lesion, including 81 patients with IS-CTO and 402 patients with de novo CTO. Propensity score matching was used to balance baseline characteristics between the 2 groups. The clinical end point was major adverse cardiac events (MACE). The success rates of CTO lesion revascularization were similar in both groups. In the propensity score-matched patients, after a median follow-up of 36 months, MACE was observed in 32.8% of patients with IS-CTO versus 13.5% of the patients with de novo CTO ($P < .001$), mainly driven by target-vessel revascularization (21.9% vs 6.7%; $P < .01$). Moreover, patients with IS-CTO had significantly worse Seattle Angina Questionnaire anginal stability scores than the patients with de novo CTO. In conclusion, patients with IS-CTO after PCI had a worse clinical outcome, mainly MACE, and a poorer anginal stability in the long term than patients with de novo CTO.

Keywords

chronic total occlusion, in-stent chronic total occlusion, major adverse cardiac events, Seattle Angina Questionnaire

Introduction

Percutaneous coronary intervention (PCI) for patients with in-stent coronary chronic total occlusion (IS-CTO) or de novo coronary chronic total occlusion (de novo CTO) is one of the major technical challenges in contemporary interventional cardiology. These complex lesions are identified in approximately 15% to 30% of all coronary angiography.[1-4] Among these CTOs, the prevalence of IS-CTO is approximately 5% to 10%.[1,5] Albeit the procedural success rate has improved during the past few years, PCI in IS-CTOs have been associated with suboptimal success rates.[5–8] Successful CTO-PCI has been shown to reduce the risks of angina and postoperative myocardial infarction (MI) and improve long-term survival compared with failed CTO-PCI.[1,9,10] But several studies have reported that 20% to 35% of CTOs are still not revascularized by PCI even when performed by experienced operators.[1,11,12] Additionally, treatment of in-stent occlusive segments has been identified as an independent predictor of the need for target-vessel revascularization (TVR) and subsequent adverse cardiac outcomes at short- and medium-term follow-up.[13,14]

To date, few studies have compared the long-term clinical outcomes of patients with IS-CTO versus de novo CTO who undergo revascularization in the drug-eluting stent era,[13,15] especially in Chinese individuals. Similarly, the long-term status quantified by the Seattle Angina Questionnaire (SAQ) of

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this patient subgroup on follow-up is poorly characterized. The aim of this study is to address these important questions.

Methods

Study Population

Patients with CTO lesions were confirmed by coronary angiography in the Cardiology Department of the First Affiliated Hospital of Xi'an JiaoTong University (Xi'an, Shaanxi, China) between June 2013 and October 2017. The inclusion criteria for the present study were: (1) only 1 CTO lesion/patient detected on diagnostic coronary angiography and (2) symptomatic angina and/or functional ischemia. Exclusion criteria were: (1) previous coronary artery bypass graft surgery; (2) history of cardiogenic shock or cardiopulmonary resuscitation; (3) self-identified history of stroke, renal failure, or severe arrhythmia; and (4) presence of a malignant tumor. Finally, a total of 483 patients were included in the study. Participants were divided into IS-CTO group (n = 81) and de novo CTO group (n = 402). The periodic follow-up for adverse events was carried out via telephone contacts or outpatient visit every year between 2014 and 2018. The study was approved by both the Research and Ethics Committees of the First Affiliated Hospital of Xi'an Jiaotong University.

Definitions

For all of the patients, qualitative and quantitative coronary angiographic analyses were carried out according to the standard methods. Two experienced cardiovascular interventional physicians conducted blind analysis of the angiography results. The treatment strategy, stenting techniques, and use of glycoprotein IIb/IIIa receptor inhibitors or intravascular ultrasound used was at the discretion of the operators. All medications were determined according to the guidelines and patient requirements.[16,17] Written informed consent was obtained from all study participants. A "CTO lesion" was defined as 100% luminal obstruction with an estimated duration of occlusion of at least 3 months with no antegrade flow through the lesion (thrombolysis in myocardial infarction [TIMI] flow grade 0).[5] In-stent coronary chronic total occlusion was considered if the occlusion was located within a previously deployed stent or within 5 mm of its proximal and distal ends.[5,13] The estimated duration of occlusion was based on the first onset of angina, previous history of MI in the target vascular region, or proven by prior angiographic results. The Japanese-Chronic Total Occlusion (J-CTO) score was calculated for each lesion. Independent angiographic predictors of unsuccessful guide wire crossing through CTO lesions (each given 1 point) that made up the J-CTO score included prior failed attempt, angiographic evidence of heavy calcification, bending $\geq 45^\circ$ within the occluded segment, blunt stump, and occlusion length >20 mm. Angiographic morphology of the entry point was classified as "tapered" if the occluded segment ended in a funnel-shaped form or "blunt stump" if it did not.[18] Then, contemporary PCI techniques for CTO lesions, such as the antegrade wire escalation, reversal wire escalation, antegrade dissection re-entry techniques, reversal dissection re-entry techniques, the "hybrid" approach, hydrophilic wire with a tapered tip, and microcatheters, were used based on the physician's choice. Restenting may be hindered by trapping of the new stent in the struts of the prior stent, or in cases of subintimal crossing of the CTO, true lumen re-entry may be hindered.[5] In challenging cases, special maneuvers may be required involving either antegrade or retrograde penetration of the occluded stent and subsequent strut dilatation with "crushing" of the prior stents when new stents are deployed. Technical success was defined as residual stenosis <30% with antegrade flow TIMI 3. Procedural success was defined as technical success plus no inhospital adverse cardiac effects, including MI, all-cause mortality, and recurrence of cardiac symptoms requiring repeat target vessel PCI.[1,5,13] Quantitative angiographic minimum luminal diameters (MLDs) and diameter stenosis (DS) post-PCI were measured in matched views before and after main vessel stenting, if applicable. For the main vessel, the reference diameter (RD) was the average of the proximal and distal reference lumen diameters. For the side branch, the RD was the distal reference lumen diameter. Diameter stenosis was calculated as: $100 \times (RD - MLD)/RD$.[10] The composite clinical end point of major adverse cardiac events (MACE) on follow-up was defined as a composite of target-vessel MI, cardiac death, and ischemia-driven TVR in the treated CTO vessel.[10] All deaths were considered to have been from cardiac causes unless an explicit noncardiac cause could be documented.

Seattle Angina Questionnaire

The SAQ is frequently used for measuring the health status of patients with coronary artery disease (CAD). It has been commonly used in clinical trials and is recognized as a performance indicator for assessing the health status of patients with CAD.[19] Scores were calculated for each domain, ranging from 0 to 100, with 0 representing the worst status and 100 representing the best status. In this study, all patients' views on the impact of CAD on their health status were quantified using the SAQ at the last follow-up.

Measurements of Clinical Parameters

We collected several demographics, clinical, and analytical parameters. Age, gender, height, and weight were recorded, and body mass index (kg/m^2) was calculated. Patients either with persistent blood pressure >140/90 mm Hg or those currently taking antihypertensive drugs were considered hypertensive. Several biochemical parameters, including serum uric acid, blood glucose, lipid levels, high sensitivity C-reactive protein, and the estimated glomerular filtration rate (eGFR), were measured.[20]

Table 1. Baseline Clinical Characteristics.[a]

Variable	Total population (n = 483)			Propensity-matched population (n = 256)		
	De novo CTO (n = 402)	In-stent CTO (n = 81)	*P*	De novo CTO (n = 192)	In-stent CTO (n = 64)	*P*
Age, years	68 (60-74)	66 (61-73)	0.770	69 (62-75)	67 (61-74)	.559
Male, n (%)	248 (61.7)	65 (80.2)	0.001	162 (84.2)	51 (79.7)	.251
Body mass index, kg/m^2	23.7 ± 3.0	24.1 ± 2.6	0.431	23.9 ± 3.6	24.4 ± 2.5	.432
Current smoker, n (%)	128 (31.8)	46 (56.8)	<0.001	89 (46.3)	35 (54.7)	.311
Hypertension, n (%)	186 (46.3)	16 (19.8)	<0.001	59 (30.5)	14 (21.9)	.158
Diabetes mellitus, n (%)	85 (21.1)	20 (24.7)	0.480	38 (19.7)	16 (25.0)	.388
Prior MI, n (%)	109 (27.1)	47 (58.0)	<0.001	81 (42.2)	32 (50.0)	.302
Indication of CTO-PCI, n (%)						
Stable angina pectoris	82 (20.4)	10 (12.3)	0.324	22 (11.5)	8 (12.5)	.500
Unstable angina pectoris	197 (49.0)	43 (53.1)		122 (63.5)	35 (54.7)	
Acute MI	49 (12.2)	9 (11.1)		13 (6.8)	7 (10.9)	
Other	74 (18.4)	19 (23.5)		35 (18.2)	14 (21.9)	
Cardiovascular medications, n (%)						
DAPT	380 (94.5)	68 (83.9)	0.064	181 (94.2)	58 (90.6)	.246
Statins	398 (99.2)	81 (100)	0.180	192 (100)	64 (100)	-
β-Blockers	348 (86.6)	71 (87.7)	0.786	162 (84.3)	55 (85.9)	.724
ACEI/ARB	348 (86.6)	70 (86.4)	0.220	155 (80.7)	59 (92.2)	.073
Cardiovascular medications, n (%)						
Calcium channel blocker	86 (21.4)	15 (18.5)	0.590	28 (14.6)	15 (23.4)	.189
Nitrate	115 (28.6)	20 (24.6)	0.410	47 (24.5)	13 (20.3)	.467
Ejection fraction	62 (51-69)	54 (44-65)	0.025	60 (47-67)	59 (43-66)	.325

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a]Data are presented as n (%), mean ± standard deviation, or median and interquartile range.

Statistical Analysis

Data are presented as means ± standard deviation or median and interquartile range for continuous variables and percentages for categorical variables. Continuous variables with normal distribution were evaluated using the Student *t* test, whereas the Mann-Whitney test was used for non-normally distributed data. Categorical variables and frequencies were compared with the chi-square test. To adjust for differences in related potential confounding factors, we performed a 1:3 matched analysis based on the propensity score of each patient.[10,16] To do this, propensity scores were estimated using logistic regression analysis.[21] The log odds of the probability that a patient had IS-CTO were modeled as a function of the identified confounders. The propensity score included all the variables listed in Table 1. Using the estimated logits, we first randomly selected a patient with IS-CTO and then matched that patient with 3 patients in the de novo CTO group with the closest estimated logit value. Finally, we were able to successfully match 64 patients having IS-CTO with 192 patients having de novo CTO. After the propensity score matching, the clinical outcomes occurring over time for MACE and all-cause mortality were described by Kaplan-Meier survival curves and compared by the log-rank test. In all cases, a 2-sided $P < .05$ was considered significant. All statistical analysis was performed using SPSS Version 25.0 (SPSS, Inc) and R 3.1.0 (R Foundation for Statistical Computing).

Results

Study Population and Baseline Characteristics

The study population consisted of 483 patients with CTO after PCI. Among them, the prevalence of IS-CTO was 16.8%. Baseline clinical characteristics and preoperative laboratory results of all participants are summarized in Tables 1 and 2. Compared with patients in the de novo CTO group, those in the IS-CTO group were more often men with a higher prevalence of smoking and prior MI, and a higher level of serum uric acid, but with a lower prevalence of hypertension and a lower left ventricular ejection fraction, eGFR, and low-density lipoprotein cholesterol level.

Baseline Angiographic and Procedural Characteristics

Table 3 presents the angiographic and procedural characteristics of all patients. Compared with the de novo CTO group, patients with IS-CTO had a higher prevalence of occlusion length >20 mm. No differences were observed regarding the number of diseased vessels, the target CTO vessel, side branch, and the amount of blunt stump. Procedural success rates were similar between the IS-CTO and de novo CTO groups (79.0% vs 75.1%; $P = .503$), and all patients with successful PCI underwent drug-eluting stent implantation. Moreover, the periprocedural complication rates were also similar in both groups (1.2% vs 2.0%; $P = .741$). In patients with IS-CTO, 1 case of

Table 2. Results of Preoperative Laboratory Measurements.[a]

Variable	Total population (n = 483)			Propensity-matched population (n = 256)		
	De novo CTO (n = 402)	In-stent CTO (n = 81)	*P*	De novo CTO (n = 192)	In-stent CTO (n = 64)	*P*
Blood glucose, mmol/L	5.85 (5.40-6.70)	5.70 (5.20-6.46)	.795	5.7 (5.3-6.7)	5.8 (5.3-7.5)	.490
HbA_{1c}, %	5.6 (4.8-6.8)	5.3 (4.4-7.0)	.050	5.6 (4.9-7.1)	5.2 (4.4-6.9)	.172
Serum uric acid, μmol/L	292 (261-353)	342 (293-384)	.038	329 ± 93	348 ± 78	.936
eGFR, mL/min/1.73m^2	102.6 ± 28.6	92.3 ± 30.6	.012	99.0 ± 26.4	95.4 ± 23.4	.261
Total cholesterol, mmol/L	3.7 (3.1-4.4)	3.6 (3.1-4.0)	.281	3.6 (3.1-4.3)	3.6 (3.3-4.4)	.527
Total triglycerides, mmol/L	1.5 (1.2-1.9)	1.4 (1.0-2.5)	.815	1.4 (1.0-1.9)	1.3 (1.0-2.3)	.630
Low-density lipoprotein cholesterol, mmol/L	2.1 (1.7-2.7)	1.9 (1.3-2.3)	.034	2.1 (1.6-2.6)	1.9 (1.5-2.6)	.365
High-density lipoprotein cholesterol, mmol/L	1.0 (0.8-1.1)	0.9 (0.8-1.1)	.413	0.9 (0.8-1.1)	1.0 (0.8-1.2)	.109
High-sensitivity C-reactive protein, mg/L	1.49 (0.65-3.35)	1.55 (0.82-3.59)	.900	1.42 (0.55-3.34)	1.86 (0.81-3.62)	.359

Abbreviations: CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin.
[a]Data are presented as mean ± standard deviation or median and interquartile range.

Table 3. Angiographic and Procedural Characteristics.[a]

Variable	Total population (n = 483)			Propensity-matched population (n = 256)		
	De novo CTO (n = 402)	In-stent CTO (n = 81)	*P*	De novo CTO (n = 192)	In-stent CTO (n = 64)	*P*
Number of diseased vessels, n (%)						
1	39 (9.7)	5 (6.2)	.544	24 (12.5)	5 (7.8)	.351
2	55 (13.7)	10 (12.3)		25 (13.0)	6 (9.4)	
3	308 (76.6)	66 (81.5)		143 (74.5)	53 (82.8)	
Number of CTOs	402	81	-	192	64	-
Target-vessel CTO, n (%)						
Right coronary artery	182 (45.3)	37 (45.7)	.903	86 (44.8)	30 (46.9)	.866
Left anterior descending	127 (31.6)	27 (33.3)		64 (33.3)	22 (34.3)	
Left circumflex	93 (23.1)	17 (21.0)		42 (21.9)	12 (18.8)	
Side branch, n (%)	142 (35.3)	25 (30.9)	.441	57 (29.7)	17 (26.6)	.890
Blunt stump, n (%)	156 (38.8)	37 (45.7)	.249	83 (42.2)	25 (39.1)	.679
Lesion length >20 mm, n (%)	170 (42.2)	53 (65.4)	.000	108 (56.3)	40 (62.5)	.320
Moderate or severe calcifications, n (%)	125 (30.4)	24 (29.6)	.829	60 (31.0)	19 (29.7)	.878
J-CTO score	1.89 ± 1.15	1.95 ± 1.23	.841	1.91 ± 1.30	2.00 ± 1.21	.101
Reference diameter, mm	3.43 ± 0.42	3.34 ± 0.52	.423	3.11 ± 0.23	3.40 ± 0.52	.081
After intervention						
Lesion MLD, mm	2.60 ± 0.41	2.72 ± 0.44	.123	2.43 ± 0.16	2.65 ± 0.37	.071
Diameter stenosis, %	24.8 ± 8.0	21.5 ± 9.30	.177	21.8 ± 4.2	19.7 ± 5.2	.231
Number of stents implanted	2.20 ± 1.20	2.40 ± 1.40	.384	2.30 ± 1.20	2.50 ± 1.30	.380
Use of intravascular ultrasound, n (%)	25 (6.2)	5 (6.1)	.794	11 (5.7)	3 (4.6)	.473
Procedural complications, n (%)	8 (2.0)	1 (1.2)	.741	2 (1.0)	1 (1.5)	.330
Procedural success, n (%)	302 (75.1)	64 (79.0)	.503	146 (76.0)	50 (78.1)	.740

Abbreviations: CTO, chronic total occlusion; J-CTO, Japanese-CTO; MLD, minimum luminal diameter.
[a]Data are presented as n (%), mean ± standard deviation or median and interquartile range.

periprocedural MI occurred. In de novo CTO group, we observed 3 cases of coronary perforation with cardiac tamponade, 2 cases of stroke, and 3 periprocedural MI.

Clinical Outcomes in Total Population

The median follow-up period was 36 months (interquartile range: 28-51 months). Follow-up was available for 445 (92.1%) of 483 patients. The clinical outcomes of all patients with CTO on follow-up are shown in Table 4. The overall number of MACE was 107 (24.1%)/445, and there were more MACE in the IS-CTO group than in the de novo CTO group (34.2% vs 21.9%; $P = .020$). The incidence of ischemia-driven TVR was significantly higher in patients with IS-CTO ($P = .002$).

Propensity-Score Matched Analysis

To further investigate this finding comprehensively and accurately, patients having IS-CTO were matched with patients having de novo CTO with 1:3 ratio. The propensity score

Table 4. Clinical Outcomes on Follow-Up in All Study Patients.[a]

Variable	Total population (n = 445)			Propensity-matched population (n = 256)		
	De novo CTO (n = 366)	In-stent CTO (n = 79)	*P*	De novo CTO (n = 192)	In-stent CTO (n = 64)	*P*
MACE	80 (21.9)	27 (34.2)	.020	26 (13.5)	21 (32.8)	<.001
Cardiac mortality	28 (7.7)	5 (6.3)	.684	12 (6.3)	4 (6.3)	.795
Target-vessel MI	29 (7.9)	7 (8.9)	.782	11 (5.7)	6 (9.4)	.122
Ischemia-driven TVR	37 (10.1)	18 (22.8)	.002	13 (6.7)	14 (21.9)	<.01
All-cause mortality	36 (9.8)	9 (11.4)	.677	22 (11.5)	7 (10.9)	.773

Abbreviations: CTO, chronic total occlusion; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target-vessel revascularization.
[a]Data are presented as n (%).

included all the variables listed in Table 1. The clinical outcomes of propensity score-matched patients are shown in Table 4. In these patients, MACE was observed in 32.8% of patients with IS-CTO versus 13.5% of patients with de novo CTO ($P < .001$), mainly driven by TVR (21.9% vs 6.7%; $P < .01$). However, there were no statistical differences in incidence of all-cause mortality, cardiac mortality, and target-vessel MI between groups. Kaplan-Meier curves show the cumulative incidence occurring over time for propensity-matched patients (Figure 1). Patients with IS-CTO had a significantly worse survival outcome free from MACE (log rank 11.073, $P < .001$), driven by TVR (log rank 10.449, $P < .01$), than patients with de novo CTO.

Seattle Angina Questionnaire

A total of 400 patients' views on their health status were quantified by the SAQ scores on follow-up. As shown in Table 5, patients with IS-CTO had significantly lower SAQ angina stability scores than patients with de novo CTO (64.1 $\pm$ 26.2 vs 79.8 $\pm$ 24.9; $P < .001$). No statistical differences were observed regarding physical limitation, angina frequency, treatment satisfaction, and quality of life between the 2 groups. For propensity-matched cohort analysis, SAQ scores were available for 227 participants. The score of 5 domains of SAQ between the 2 groups after the propensity score matching was similar with those before propensity matching, and the angina stability of patients with IS-CTO was worse than that of patients with de novo CTO (Table 5 and Figure 2).

Discussion

The study was designed to compare the long-term clinical outcomes and health status of patients with IS-CTO versus de novo CTO after PCI. The findings of the study were as follows: (1) procedural success rates were similar in patients with IS-CTO, as compared with patients with de novo CTO; (2) patients with IS-CTO after PCI tended to have a higher incidence of MACE, mainly driven by TVR, at long period of follow-up; (3) patients with IS-CTO had worse stability of angina symptom quantified by the SAQ angina stability scores than patients with de novo CTO in the long term.

Despite the advancement of technique and devices for CTO-PCI, CTO lesions are still a challenging subset for successful CTO revascularization, and procedural success rates of PCI for patients with IS-CTO were lower than that of PCI for de novo CTO in several previous studies.[7,22] Abbas et al reported a PCI success rate for de novo CTO of 75% and for IS-CTO of 63%.[22] Abdel-Karim et al reported a procedural success rate of 71% on 21 patients with IS-CTO.[7] With the improvement of technique and equipment for CTO revascularization in the later period, success rates of IS-CTO-PCI have remarkably increased. Azzalini et al[13] recently reported that nearly 12% of all consecutive CTO-PCI treated at their institution was IS-CTO, and success rates were high and similar to de novo CTO-PCI (86.5% vs 86.5%). Lee et al reported that successful PCI was achieved in 84.2% of the IS-CTO group and 78.4% of the de novo CTO group in Korea between 2008 and 2014.[15] In our study, success rates of PCI were achieved in 79.0% of the IS-CTO group and 75.1% of the de novo CTO group, which are close to the results of the aforementioned studies.

The major mechanism of PCI failure in IS-CTO lesions in all cases of the present study is that the guide wire cannot cross the lesion. Wiring often fails during PCI for de novo CTO due to the difficulty of determining precise vascular route, but it is easier in PCI for IS-CTO, because the previous stents serve as a route map for the target vessel.[7,15] Although vessel routes can be easily distinguished in IS-CTO cases, the wire and microcatheters are greatly undermined by the presence of the strut of the initial stent.[13] In patients with IS-CTO, subintimal tracing and re-entry of the wire into the true lumen are not easy, and it is difficult to advance the new stent if the previous stent deformed or fractured in the balloon passage.[7,15] Moreover, a newly implanted stent is frequently in conflict with the previous stent.

Even after successful revascularization, the clinical outcomes of IS-CTO is still worse than that of de novo CTO.[13,14,23] Our results showed that the incidence of MACE in the IS-CTO group at follow-up was higher than that in patients with de novo CTO. In-stent coronary chronic total occlusion and in-stent restenosis have been shown to be a worsening clinical condition.[15,24,25] Rinfret et al identified that the successful treatment of an in-stent occlusion was a strong predictor of subsequent adverse events at a median follow-up of

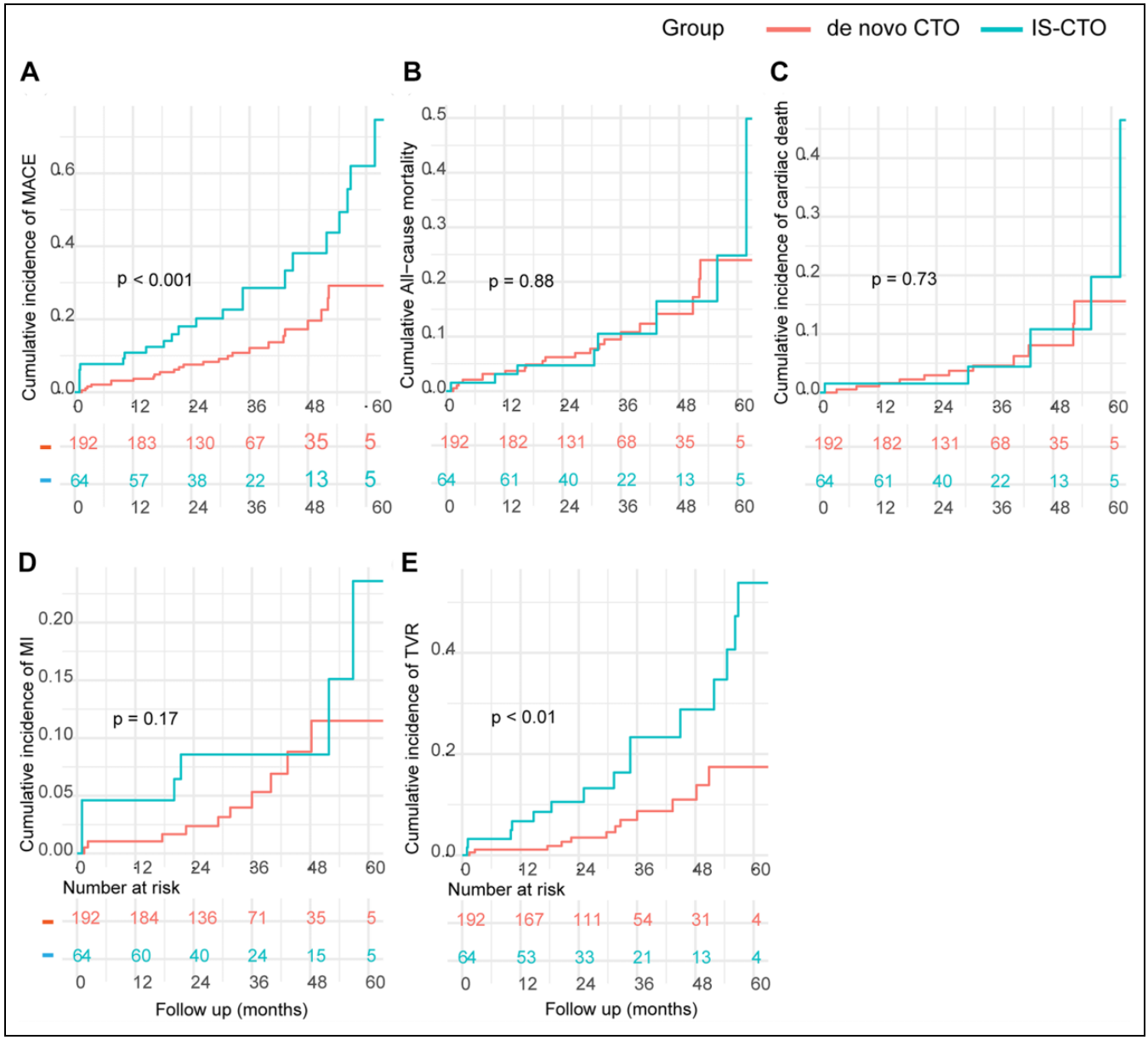

Figure 1. Kaplan-Meier curves for outcomes according to type of CTO after propensity score matching. Kaplan-Meier curves describing the risk of (A) MACE, (B) all-cause mortality, (C) cardiac death, (D) myocardial infarction, and (E) TVR. CTO indicates coronary chronic total occlusion; IS-CTO, in-stent coronary chronic total occlusion; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target-vessel revascularization.

398 days, including MI, ischemia or symptoms-driven TVR, and reocclusion.[14] Approximately one-fifth of the patients after PCI for in-stent restenosis presented with acute coronary syndrome, with 2% presenting as ST-elevation MI in the study by Rathore et al.[24] Azzalini et al found that IS-CTO was an independent and important risk factor for MACE, and the incidence of MACE was higher in IS-CTO versus de novo CTO after a median follow-up of 471 days.[13] After a median follow-up of 36 months, we found that even with similar procedural success rates of PCI, the incidence of MACE in patients with IS-CTO was higher than those in de novo CTO group, which was primarily driven by repeat TVR. After propensity score matching, no differences were observed regarding baseline variables between the 2 groups. But even in this case, Kaplan-Meier curves also showed significantly worse cumulative incidence of MACE in patients with IS-CTO.

The pathophysiological mechanism of such recurrent events after PCI with IS-CTO patients is largely unknown. Neointimal formation might be involved even though all patients were stented with drug-eluting stents. This recurrent phenomenon could also be explained by baseline biological factors that were also involved in the first stent occlusion, such as stent underexpansion or fracture, antiplatelet agent resistance leading to thrombosis, local inflammation, and atherosclerotic

Table 5. Seattle Angina Questionnaire Scores on Follow-Up.[a]

Variable	Total population (n = 400)			Propensity-matched population (n = 227)		
	De novo CTO (n = 330)	In-stent CTO (n= 70)	*P*	De novo CTO (n = 170)	In-stent CTO (n = 57)	*P*
Physical limitation scale	51.6 ± 17.0	50.4 ± 13.8	.606	51.7 ± 17.7	50.7 ± 14.5	.395
Angina stability scale	79.8 ± 24.9	64.1 ± 26.2	<.001	80.2 ± 26.1	63.8 ± 27.5	<.001
Angina frequency scale	91.0 ± 15.0	90.8 ± 12.3	.972	91.4 ± 15.8	91.1 ± 13.1	.884
Treatment satisfaction scale	71.5 ± 12.6	69.5 ± 13.9	.268	71.6 ± 13.3	69.1 ± 14.3	.220
Quality of life	76.2 ± 12.8	73.2 ± 16.3	.141	75.9 ± 13.4	72.9 ± 17.3	.171

Abbreviation: CTO, chronic total occlusion.
[a]Data are presented as mean ± standard deviation.

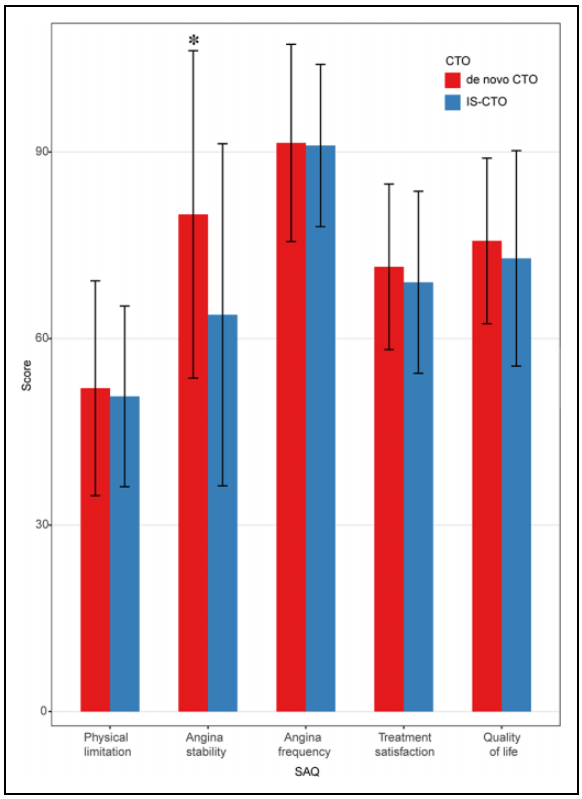

Figure 2. Seattle Angina Questionnaire scores in propensity-matched population. CTO indicates coronary chronic total occlusion; IS-CTO, in-stent coronary chronic total occlusion; SAQ, Seattle Angina Questionnaire. *$P < .001$.

progression.[13-15] In addition, excess stent length or multilayered stenting are risk factors for restenosis after PCI and associated with abnormal vascular responses and thrombosis.[26-28] Moreover, several studies identified that lower eGFR,[29] acute coronary syndrome presentation,[13] higher Prospective Global Registry for the Study of Chronic Total Occlusion Intervention-CTO score,[30,31] and higher number of diseased vessels are independent predictors of MACE after PCI with CTO. Above all, we cannot exclude that a more mechanistic approach to IS-CTO revascularization based on baseline intracoronary imaging (stent underexpansion, fracture, heavy calcification, etc). In this study, we failed to identify the mechanism of occlusive restenosis that might have guided subsequent treatment and could be a significant contributor to poor outcomes. Based on the above factors, it is important to precisely analyze the characteristics of CTO lesions, such as lumen and vessel size, lesion length, plaque burden, the severity of calcification, collateral circulation, and so on, which might be associated with long-term stent patency and cardiovascular events on follow-up.[15,32,33]

Few studies have measured the long-term health status of patients after PCI for IS-CTO versus de novo CTO. The SAQ, which quantifies 5 domains to measure the impact of angina on patient health status, has been shown to be effective, reproducible, and sensitive to changes in clinical symptoms.[34,35] Safley et al reported that all SAQ scores improved in patients with CTO and non-CTO patients after PCI, and there were no differences in physical limitation, quality of life, and angina frequency scores between these 2 groups.[36] Ybarra et al observed that patients having CTO with complex features such as those with dissection re-entry techniques, those with high complexity (Japanese CTO $\geq$3), or coronary artery bypass grafting had similar degrees of improvement in health status quantified by the SAQ scores compared with those with less complex CTOs.[37] In our study, we first found that the angina stability scores of SAQ at follow-up in patients with IS-CTO after stent implantation were significantly lower than patients with de novo CTO, indicating that patients with de novo CTO have better stability of angina symptom than patients with IS-CTO.

Our study has several limitations. First, it shares all the limitations of observational, single center studies, although we used propensity score-matched analyses to compensate for that. Second, although there were no statistically significant differences in these potential confounding factors between the 2 groups after propensity score matching, we were unable to correct for unmeasured potential variables. It is important to note that no propensity score method, including matching, adjusts for unmeasured confounders;[21] a true matched analysis would be more robust. Third, PCI for CTO usually involves some degree of dissection and re-entry, which can only be assessed by intravascular ultrasound. The use of intravascular ultrasound in the present study was low due to cost-related issues and the extended time of operation. Besides, quantitative angiographic analysis, such as angiographic MLD and DS, has

been reported to be associated with the clinical outcomes of patients with CTO after intervention.[38] In our study, we found that there were no statistical differences in angiographic MLD and DS after CTO-PCI between patients with IS-CTO and patients with de novo CTO. However, we were unable to assess the real effect of changes in MLD and DS on the long-term outcomes of patients with CTO after PCI. Because of these limitations, a larger sample and multicenter study is needed to provide more information on the long-term clinical outcomes and health status for patients with IS-CTO after PCI.

In conclusion,despite similar procedure success rates, IS-CTO was associated with higher rate of MACE at long period of follow-up, and the difference in MACE was mainly driven by requirement for repeat TVR. Moreover, patients with IS-CTO after PCI had a poorer long-term anginal stability than patients with de novo CTO.

Authors' Note

Ke Gao, MD, and Bo-Lin Li, MD, contributed equally to this work. HL, XZ, KG, and BL designed and supervised the study. LF, MZ, and QL extracted eligible patients. LY, WW, ZF, WY, JR, BL, and YW made a major contribution to data acquisition. KG, BL, and HL drafted and revised it critically for important intellectual content. All authors have read the final approval of the version to be published.

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References

1. Stojkovic S, Juricic S, Dobric M, et al. Improved Propensity-Score Matched Long-Term Clinical Outcomes in Patients with Successful Percutaneous Coronary Interventions of Coronary Chronic Total Occlusion. Int Heart J. 2018;59:719-26.
2. Ramunddal T, Hoebers LP, Henriques JP, et al. Chronic total occlusions in Sweden–a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). PLoS One. 2014;9:e103850.
3. Agrawal H, Lange RA, Montanez R, et al. The Role of Percutaneous Coronary Intervention in the Treatment of Chronic Total Occlusions: Rationale and Review of the Literature. Curr Vasc Pharmacol. 2019;17:278-90.
4. Vemmou E, Alaswad K, Karmpaliotis D, et al. Outcomes of Percutaneous Coronary Intervention for In-Stent Chronic Total Occlusions: Insights From the PROGRESS-CTO Registry. JACC Cardiovasc Interv. 2020;13:1969-71.
5. Christopoulos G, Karmpaliotis D, Alaswad K, et al. The efficacy of "hybrid" percutaneous coronary intervention in chronic total occlusions caused by in-stent restenosis: insights from a US multicenter registry. Catheter Cardiovasc Interv. 2014;84:646-51.
6. Azzalini L, Vo M, Dens J, Agostoni P.Myths to Debunk to Improve Management, Referral, and Outcomes in Patients With Chronic Total Occlusion of an Epicardial Coronary Artery. Am J Cardiol. 2015;116:1774-80.
7. Abdel-Karim AR, Lombardi WB, Banerjee S, Brilakis ES. Contemporary outcomes of percutaneous intervention in chronic total coronary occlusions due to in-stent restenosis. Cardiovasc Revasc Med. 2011;12:170-6.
8. de la Torre Hernandez JM, Rumoroso JR, Subinas A, et al. Percutaneous intervention in chronic total coronary occlusions caused by in-stent restenosis: procedural results and long-term clinical outcomes in the TORO (Spanish registry of chronic TOtal occlusion secondary to an occlusive in-stent RestenOsis) multicentre registry. EuroIntervention. 2017;13: e219-e26.
9. Teramoto T, Tsuchikane E, Yamamoto M, et al. Successful revascularization improves long-term clinical outcome in patients with chronic coronary total occlusion. Int J Cardiol Heart Vasc. 2017; 14:28-32.
10. Jang WJ, Yang JH, Choi SH, et al. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. JACC Cardiovasc Interv. 2015;8:271-9.
11. Rathore S, Matsuo H, Terashima M, et al. Procedural and in-hospital outcomes after percutaneous coronary intervention for chronic total occlusions of coronary arteries 2002 to 2008: impact of novel guidewire techniques. JACC Cardiovasc Interv. 2009;2:489-97.
12. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol. 2012;59: 991-7.
13. Azzalini L, Dautov R, Ojeda S, et al. Procedural and Long-Term Outcomes of Percutaneous Coronary Intervention for In-Stent Chronic Total Occlusion. JACC Cardiovasc Interv. 2017;10: 892-902.
14. Rinfret S, Ribeiro HB, Nguyen CM, Nombela-Franco L, Urena M, Rodes-Cabau J. Dissection and re-entry techniques and longer-term outcomes following successful percutaneous coronary intervention of chronic total occlusion. Am J Cardiol. 2014; 114:1354-60.
15. Lee SH, Cho JY, Kim JS, et al. A comparison of procedural success rate and long-term clinical outcomes between in-stent restenosis chronic total occlusion and de novo chronic total occlusion using multicenter registry data. Clin Res Cardiol. 2020;109: 628-37.
16. Guo L, Zhong L, Chen K, Wu J, Huang RC. Long-term clinical outcomes of optimal medical therapy vs. successful percutaneous

coronary intervention for patients with coronary chronic total occlusions. Hellenic J Cardiol. 2018;59:281-7.
17. Yan Y, Yuan F, Liu H, et al. Percutaneous Coronary Intervention Offers Survival Benefit to Stable Patients With One Single Chronic Total Occlusion and Diabetes: A Propensity Score-Matched Analysis. Angiology. 2020;71:150-9.
18. Morino Y, Abe M, Morimoto T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. JACC Cardiovasc Interv. 2011;4:213-21.
19. Patel KK, Arnold SV, Chan PS, et al. Validation of the Seattle angina questionnaire in women with ischemic heart disease. Am Heart J. 2018;201:117-23.
20. Zheng W, Mu J, Chu C, et al. Association of Blood Pressure Trajectories in Early Life with Subclinical Renal Damage in Middle Age. J Am Soc Nephrol. 2018;29:2835-46.
21. Andersen LW, Kurth T. Propensity scores - A brief introduction for resuscitation researchers. Resuscitation. 2018;125:66-9.
22. Abbas AE, Brewington SD, Dixon SR, Boura J, Grines CL, O'Neill WW. Success, safety, and mechanisms of failure of percutaneous coronary intervention for occlusive non-drug-eluting in-stent restenosis versus native artery total occlusion. Am J Cardiol. 2005;95:1462-6.
23. Mir T, Ullah W, Sattar Y, et al. Outcomes of percutaneous intervention in in-stent versus de-novo chronic total occlusion: a meta-analysis. Expert Rev Cardiovasc Ther. 2020;18:827-33.
24. Rathore S, Kinoshita Y, Terashima M, et al. A comparison of clinical presentations, angiographic patterns and outcomes of in-stent restenosis between bare metal stents and drug eluting stents. EuroIntervention. 2010;5:841-6.
25. Magalhaes MA, Minha S, Chen F, et al. Clinical presentation and outcomes of coronary in-stent restenosis across 3-stent generations. Circ Cardiovasc Interv. 2014;7:768-76.
26. Mauri L, O'Malley AJ, Cutlip DE, et al. Effects of stent length and lesion length on coronary restenosis. Am J Cardiol. 2004;93:1340-6, a5.
27. Galassi AR, Tomasello SD, Crea F, et al. Transient impairment of vasomotion function after successful chronic total occlusion recanalization. J Am Coll Cardiol. 2012;59:711-8.
28. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation. 2004;109:1366-70.
29. Lee MS, Lee AC, Shlofmitz RA, et al. ORBIT II sub-analysis: Impact of impaired renal function following treatment of severely calcified coronary lesions with the Orbital Atherectomy System. Catheter Cardiovasc Interv. 2017;89:841-8.
30. Wykrzykowska JJ, Garg S, Girasis C, et al. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. J Am Coll Cardiol. 2010;56:272-7.
31. Christopoulos G, Kandzari DE, Yeh RW, et al. Development and Validation of a Novel Scoring System for Predicting Technical Success of Chronic Total Occlusion Percutaneous Coronary Interventions: The PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) Score. JACC Cardiovasc Interv. 2016;9:1-9.
32. Uchida Y, Ichimiya S, Ishii H, et al. Impact of plaque burden in the left main coronary artery determined by intravascular ultrasound on cardiovascular events in a Japanese population undergoing percutaneous coronary intervention. Am J Cardiol. 2012;109:352-8.
33. Basir MB, Karatasakis A, Alqarqaz M, et al. Further validation of the hybrid algorithm for CTO PCI; difficult lesions, same success. Cardiovasc Revasc Med. 2017;18:328-31.
34. Abdallah MS, Wang K, Magnuson EA, et al. Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. Jama. 2013;310:1581-90.
35. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. Circ Cardiovasc Qual Outcomes. 2014;7:640-7.
36. Safley DM, Grantham JA, Hatch J, Jones PG, Spertus JA. Quality of life benefits of percutaneous coronary intervention for chronic occlusions. Catheter Cardiovasc Interv. 2014;84:629-34.
37. Ybarra LF, Dautov R, Gibrat C, Dandona S, Rinfret S. Midterm Angina-Related Quality of Life Benefits After Percutaneous Coronary Intervention of Chronic Total Occlusions. Can J Cardiol. 2017;33:1668-74.
38. Liu W, Wagatsuma K, Nii H, Toda M, Amano H, Uchida Y. Impact of diabetes on long term follow-up of elderly patients with chronic total occlusion post percutaneous coronary intervention. J Geriatr Cardiol. 2013;10:16-20.