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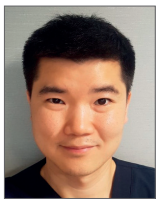
Special feature: Chronic total occlusion

Clinical outcomes after percutaneous coronary intervention for in-stent chronic total occlusion



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KEYWORDS

- chronic coronary total occlusion
- drug-eluting stent
- in-stent restenosis

Abstract

Aims: The aim of this study was to compare percutaneous coronary intervention (PCI) outcomes in relation to stent optimisation profiles between in-stent chronic total occlusions (CTOs) and *de novo* CTOs.

Methods and results: We evaluated 1,516 consecutive patients who underwent PCI for 147 in-stent CTOs (9.3%) and 1,439 *de novo* CTOs between 2007 and 2018. The primary endpoint was target vessel failure (TVF) consisting of a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularisation. The final post-stenting intravascular ultrasound (IVUS) images were analysed. Target lesion complexity reflected by the Japanese CTO score was similar, albeit calcification was more prevalent in *de novo* CTOs, whereas occlusion length >20 mm was more frequent in in-stent CTOs. The technical success (88.4% vs 87.5%, p=0.84) and in-hospital adverse event (1.4% vs 3.6%, p=0.26) rates were similar between CTO types. Among those who received drug-eluting stents, the five-year TVF (11.0% vs 10.7%, p=0.99) and target vessel revascularisation (4.2% vs 3.7%, p=0.81) rates were similar between groups. Total stent length, minimum stent area (5.4±1.8 vs 5.5±1.8 mm^2, p=0.77), and maximal plaque burden of the reference segments were largely comparable between groups.

Conclusions: In-stent CTO PCI with drug-eluting stents optimised by IVUS guidance offers as acceptable long-term clinical results as those achieved in *de novo* CTOs.

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Abbreviations

CTO	chronic total occlusion
DES	drug-eluting stent
IVUS	intravascular ultrasound
J-CTO	Japanese CTO
MI	myocardial infarction
PCI	percutaneous coronary intervention
TVF	target vessel failure

Introduction

Percutaneous coronary intervention (PCI) has become a preferred revascularisation strategy for patients with coronary artery disease, providing the benefit of effective relief for anginal symptoms and resolution of objective evidence of ischaemia[1]. However, although the incremental yearly rate of in-stent restenosis has become very low recently, it continues to occur over time, mitigating the advantages achieved by stent-based treatments. Although non-occlusive in-stent restenosis is readily treated by repeat PCI, its use for in-stent chronic total occlusions (CTOs) is technically challenging and was traditionally associated with suboptimal procedural success rates[2-4]. Accordingly, in-stent CTOs are often treated medically or surgically based on the disease extent of other coronary arteries.

With the various available devices and strategies, PCI has become more liberally used to treat in-stent CTOs, with the procedural success rate improving results as seen in more recent registries. Nevertheless, controversy persists about the efficacy of PCI for in-stent CTOs, mainly due to the perception of inferior treatment durability compared to that seen for *de novo* stenotic or CTO lesions[5,6]. Therefore, we evaluated the procedural and long-term outcomes of in-stent CTO PCI and compared them with those of contemporary *de novo* CTO PCI with specific focus on post-procedural stent optimisation.

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Methods

STUDY POPULATION

The study cohort included patients prospectively enrolled in the CTO registry of the Asan Medical Center, Seoul, South Korea, between January 2007 and June 2018. This registry enrolled patients who had angina or evidence of ischaemia and had a target CTO located in a major epicardial vessel with a reference vessel diameter ≥2.5 mm. Clinical, procedural, and outcome data were recorded in dedicated databases by independent research personnel. Telephone interviews and medical records of other hospitals were also obtained to ensure an accurate assessment of clinical endpoints as necessary. Coronary angiograms performed at baseline and after stenting were reviewed by independent angiographers in the angiographic core laboratory. CTO lesion complexity was assessed by calculating the Japanese CTO (J-CTO) score for each case. In each procedure, the use of specialised devices and techniques and the choice of drug-eluting stent (DES) type were left to the operator's discretion. Stent implantation was performed under intravascular ultrasonography (IVUS) guidance unless technically infeasible[7]. The usual manner of IVUS-guided PCI in our medical institution is as follows: 1) selection of the optimal landing zone and stent length to cover the residual disease adjacent to the lesion; 2) selection of an appropriate stent size considering the external elastic lamina diameters of the distal reference as well as the ability of the particular stent platform to accommodate expansion to the proximal reference diameter; and 3) maximisation of the final stent area using a non-compliant balloon (ideally to achieve a minimal stent area of ≥5.5 mm^2 based on our previous report)[8]. The local institutional review board approved this study and all patients provided written informed consent.

DEFINITIONS AND ENDPOINTS

The definition of CTO used for inclusion in the registry has been published elsewhere[9]. The database was reviewed to identify patients who underwent PCI for in-stent CTO, which was defined as a CTO lesion located within a previously implanted stent or involving the 5 mm segment proximal or distal to the stent edge.

Technical success was defined as the restoration of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 with residual stenosis <30% in the target lesions. In-hospital serious adverse events included any of the following before hospital discharge: death, myocardial infarction (MI), urgent target vessel revascularisation (TVR) with PCI or bypass surgery, cardiac tamponade requiring intervention, and stroke.

The primary endpoint of interest was target vessel failure (TVF), defined as a composite of cardiac death, target vessel-related MI, or TVR during follow-up after a successful procedure. Death was considered cardiac unless an unequivocal, non-cardiac cause was established. MI included procedure-related or spontaneous MI. Procedure-related MI was indicated by peak creatine kinase-myocardial band >10 times the upper reference limit within 48 hours post procedure, while spontaneous MI was defined as any creatine kinase-myocardial band or troponin increase above the upper limit of normal with ischaemic symptoms or signs during follow-up. Target vessel-related MI was defined as MI attributed to the vessel in which the CTO PCI was performed. TVR was defined as any repeat revascularisation using PCI or bypass surgery of the index CTO vessel. For all clinical endpoints, only the first procedure for each patient was considered in the analyses.

INTRAVASCULAR ULTRASOUND MEASUREMENTS

IVUS imaging was performed using motorised transducer pullback (0.5 mm/sec) and a commercial scanner (Boston Scientific Scimed, Minneapolis, MN, USA) consisting of a rotating 30- or 40-MHz transducer within a 3.2 Fr imaging sheath. The analysis of final post-stenting IVUS images was performed by independent personnel who were blinded to the patients' baseline characteristics and clinical outcomes. Computed planimetry (echoPlaque™ 3.0; Indec Systems, Santa Clara, CA, USA) was used to measure the minimal stent area and the lumen or external elastic membrane area of the proximal and distal reference segments and to identify the presence of dissection or haematoma at the stent edge or stent malapposition.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation, while categorical variables are shown as number (percentage). Continuous variables were compared using the Student's t-test or the Wilcoxon rank-sum test, while categorical variables were compared using the χ^2 or Fisher's exact test as appropriate. Cumulative event rates and probability curves were generated using the Kaplan-Meier method. Follow-up was censored at the date of the last follow-up or at five years, whichever came first. Cox proportional hazards models were used to estimate the risk of adverse events of the in-stent CTO group compared with that in the *de novo* CTO group. Risk-adjusting variables included age, sex, body mass index, hypertension, diabetes, chronic kidney disease, prior stroke, peripheral vascular disease, left ventricle ejection fraction, presence of left main disease, presence of multivessel disease, and J-CTO score. The final models for each endpoint were determined using backward stepwise elimination procedures in which the least significant variable was removed one at a time from the full model.

Propensity score-matching analysis was further performed to control for potential confounders and minimise any selection biases. The propensity score was estimated non-parametrically by fitting a logistic regression model using variables outlined in **Supplementary Table 1**. Matching was performed with the use of a 1:1 matching protocol with a calliper width equal to 0.2 of the standard deviation of the logit of the propensity score. Standardised differences were estimated for all the baseline covariates before and after matching; values of less than 10% for a given covariate indicate a relatively small imbalance. A Cox proportional hazards regression model with robust standard errors that accounts for the clustering of the pairs was used to compare the risks of outcomes in the matched cohort. The p-values were two-sided, and those <0.05 were considered significant. Data analyses were performed using R software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

INITIAL PROCEDURAL RESULTS

A total of 1,586 CTO PCI procedures were attempted in 1,516 patients during the study period. Among them, 147 (9.3%) procedures targeted in-stent CTOs. Seven (4.8%) in-stent CTO procedures were at least a second attempt for the index CTO lesion. The target lesion complexity reflected by the J-CTO score was similar between the in-stent and *de novo* CTO groups (2.0±1.1 and 1.9±1.1, respectively; p=0.32). The technical success rate for in-stent CTOs was similar to that for *de novo* CTOs (88.4% vs 87.5%; p=0.84). During the index hospitalisation, serious adverse events occurred at similar rates (1.4% vs 3.6%; p=0.26) between the two groups **(Table 1)**.

PATIENT AND PROCEDURAL CHARACTERISTICS

A total of 1,257 patients successfully underwent DES implantation for 1,278 CTO lesions and were included in the outcome analysis **(Figure 1)**. Among the 93 patients with in-stent CTO, the type of stent leading to in-stent CTO was a bare metal stent in 30 (32%) and a drug-eluting stent in 63 (68%). The cohort comprised 1,060 (84.3%) men; the mean patient age was 60.6 years.

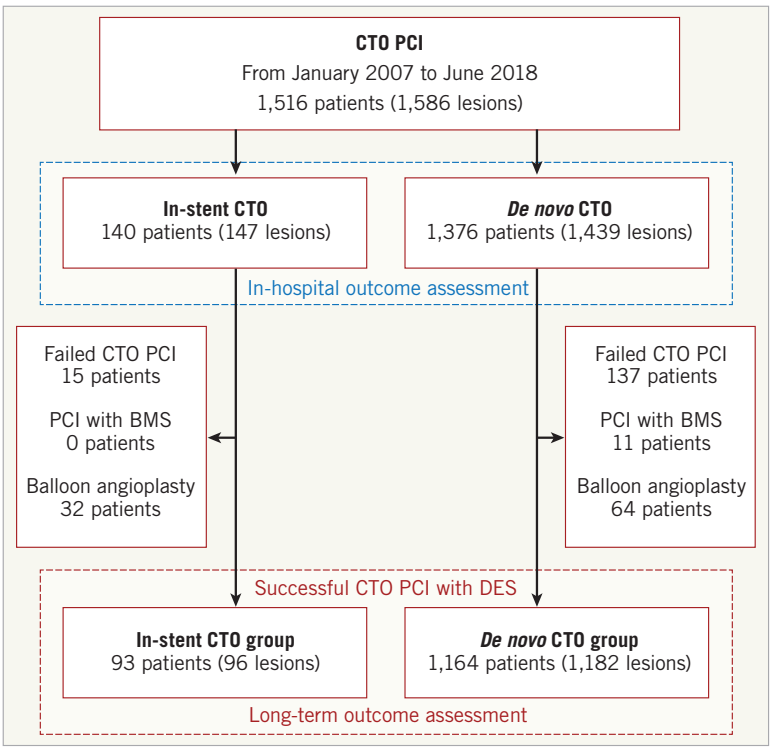

Figure 1. *Study flow chart.*

Table 1. Initial procedural results.

	In-stent CTO (n=140)	De novo CTO (n=1,376)	*p*-value
Technical success*	130 (88.4)	1,259 (87.5)	0.84
In-hospital serious adverse events	2 (1.4)	50 (3.6)	0.26
Death	0	1 (0.1)	>0.99
Procedure-related myocardial infarction	1 (0.7)	33 (2.4)	0.33
Urgent repeat revascularisation	1 (0.7)	13 (0.9)	>0.99
Cardiac tamponade requiring intervention	0	7 (0.5)	0.85
Stroke	0	2 (0.1)	>0.99
Contrast-induced nephropathy	0	10 (0.7)	0.64

Values are shown as number (%). *Values apply to 1,586 CTO lesions (147 in-stent CTO, 1,439 *de novo* CTO) for which PCI was attempted. CTO: chronic total occlusion

Overall, there was no significant difference in patient demographic or clinical characteristics between the in-stent and *de novo* CTO groups except that the former included more patients with prior MI, PCI, and bypass surgery **(Table 2)**. Baseline angiographic and procedural data are listed in **Table 3**. Although there were no differences in target CTO vessel, J-CTO score, or degree of collateralisation, calcification within the CTO was more prevalent in the *de novo* CTO group, while occlusion length >20 mm occurred more frequently in the in-stent CTO group. The primary antegrade approach was more commonly used for in-stent CTOs than for *de novo* CTOs (93.8% vs 86.7%; p=0.07). Accordingly, the final wire passage was successful with more frequent use of medium or high penetration force wires into in-stent CTOs than

Table 2. Demographic and clinical characteristics.

	In-stent CTO (n=93)	De novo CTO (n=1,164)	*p*-value
Age, years	60.9±10.7	60.6±10.5	0.81
Men	75 (80.6)	985 (84.6)	0.39
Body mass index, kg/m^2	25.1±2.6	25.5±3.1	0.23
Stable angina	75 (80.6)	947 (81.4)	0.98
Current smoker	16 (17.2)	316 (27.1)	0.05
Hypertension	60 (64.5)	709 (60.9)	0.57
Diabetes	27 (29.0)	368 (31.6)	0.69
Dyslipidaemia	78 (83.9)	878 (75.4)	0.09
Chronic kidney disease	1 (1.1)	30 (2.6)	0.58
Previous PCI	93 (100.0)	265 (22.8)	<0.01
Previous CABG	8 (8.6)	36 (3.1)	0.01
History of myocardial infarction	19 (20.4)	94 (8.1)	<0.01
History of stroke	6 (6.5)	73 (6.3)	>0.99
Peripheral vascular disease	5 (5.4)	29 (2.5)	0.19
Chronic lung disease	3 (3.2)	30 (2.6)	0.97
Atrial fibrillation	4 (4.3)	35 (3.0)	0.70
Left ventricular ejection fraction, %	57.3±8.3	57.8±8.5	0.56

Data are shown as mean±standard deviation or number (%). CABG: coronary artery bypass graft; CTO: chronic total occlusion; PCI: percutaneous coronary intervention

Table 3. Angiographic and procedural characteristics.

		In-stent CTO (n=93)	De novo CTO (n=1,164)	*p*-value
Multivessel disease		35 (37.6)	661 (56.8)	<0.01
Left main disease		4 (4.3)	70 (6.0)	0.66
Target CTO vessel*	Left anterior descending	44 (47.3)	507 (43.4)	0.79
	Left circumflex	7 (7.5)	144 (12.4)	
	Right coronary	42 (45.2)	509 (43.7)	
	Left main	0	1 (0.1)	
	Venous graft	0	3 (0.3)	
Japanese CTO score*		2.1±1.1	1.9±1.1	0.13
Blunt entry		57 (61.3)	682 (58.6)	0.69
Calcification		23 (24.7)	522 (44.8)	<0.01
Bending >45°		32 (34.4)	453 (38.9)	0.45
Length >20 mm		61 (65.6)	376 (32.3)	<0.01
Retry		19 (20.4)	154 (13.2)	0.08
Collateral grade, Rentrop scale*	Grade 0-1	14 (11.8)	227 (18.0)	0.18
	Grade 2-3	82 (88.2)	955 (82.0)	
Lesion-passaged wire*	Low penetration force	48 (51.6)	756 (64.9)	0.04
	Medium penetration force	18 (19.4)	171 (14.7)	
	High penetration force	27 (29.0)	237 (20.4)	
Stent type*	First-generation DES	19 (20.4)	193 (16.6)	0.42
	Second-generation DES	74 (79.6)	971 (83.4)	
Number of stents*		1.8±0.7	1.9±0.8	0.19
Total stent length, mm*		52.4±23.7	54.9±24.9	0.34
Average stent diameter, mm*		3.2±0.3	3.2±0.4	0.52
Post-intervention QCA data*				
Proximal reference vessel diameter, mm		3.0±0.4	3.2±0.6	0.05
Minimum stent diameter, mm		2.6±0.4	2.6±0.4	0.41
Distal reference vessel diameter, mm		2.0±0.5	2.1±0.6	0.69
Use of intravascular ultrasound*		89 (95.7)	1,072 (92.1)	0.29
Pre-stenting use		88 (94.6)	1,032 (88.7)	0.11
Post-stenting use		89 (95.7)	1,068 (91.8)	0.25
Fluoro time, min		50±36	45±43	0.24
Radiocontrast amount, mL		373±175	396±189	0.27

Data are shown as mean±standard deviation or number (%). *Information associated with the target CTO vessel. CTO: chronic total occlusion; DES: drug-eluting stent; QCA: quantitative coronary angiography

in *de novo* CTOs (48.4% vs 35.1%; p=0.01). No cases of in-stent CTO required subintimal crushing of the previous stent.

STENT OPTIMISATION

There was no significant intergroup difference in mean length (52.4±23.7 mm with in-stent CTO, 54.9±24.9 mm with *de novo* CTO; p=0.34) and nominal diameter (3.2±0.3 mm vs 3.2±0.4 mm; p=0.52) of the implanted stents at the target CTO lesion. IVUS was used for stent optimisation in more than 90% of the study cohort. Among them, full images of the pre- and the final post-stenting IVUS evaluations at the target vessel were available in 71 and 804 patients in the in-stent and *de novo* CTO groups, respectively **(Table 4)**. Among the in-stent CTOs, underexpansion of the initial stent (defined as an MSA <5.0 mm^2) was detected in 16 cases (22.5%). Although the absolute differences were small, minimum lumen area (difference of 1.1 mm^2) and maximal plaque burden (difference of 3.5%) at the proximal reference segment were in favour of the *de novo* CTO group. However, other important IVUS parameters such as the minimum stent area (5.4±1.8 vs 5.5±1.8 mm^2; p=0.77) and the maximal plaque burden of the distal reference segment (46.8% vs 46.9%; p=0.96) were similar between the two groups. Accordingly, quantitative coronary angiographic measurement showed similar minimum stent diameter between the groups. Also, there were no significant intergroup differences in the frequency of stent underexpansion, stent malapposition, or any degree of stent edge dissection or haematoma.

Table 4. IVUS measurements.

	In-stent CTO (n=71)	De novo CTO (n=804)	*p*-value
Proximal reference segments			
MLA, mm^2	8.7±3.2	9.8±3.7	0.02
EEM area at MLA site, mm^2	19.4±5.4	20.1±5.9	0.36
Maximum plaque burden, %	54.8±11.7	51.3±10.8	0.01
Distal reference segments			
MLA, mm^2	4.5±2.6	4.5±2.4	0.88
EEM area at MLA site, mm^2	9.0±4.8	8.9±4.7	0.85
Maximum plaque burden, %	46.8±16.0	46.9±17.8	0.96
In-stent segments			
MSA, mm^2	5.4±1.8	5.5±1.8	0.77
EEM area at MSA site, mm^2	11.9±4.8	11.7±5.0	0.65
Stent underexpansion*	33 (46.5)	365 (45.4)	0.96
Stent edge dissection	11 (15.5)	79 (9.9)	0.20
Any malapposition	7 (9.9)	113 (14.1)	0.41
Haematoma at stent edge	2 (2.8)	20 (2.5)	>0.99

Data are shown as mean±standard deviation or number (%). *Stent underexpansion was defined as an MSA <5.0 mm^2. *Results when different definition used; 1) minimal stent area/mean value of proximal and distal reference lumen area <80%, 44.9% versus 52.5%, *p*=0.30; 2) minimal stent area/distal reference EEM area <80%, 71.0% versus 71.2%, *p*>0.99; 3) minimal stent area/distal reference lumen area <100%, 23.2% versus 19.7%, *p*=0.59; 4) minimal stent area/distal reference lumen area <90%, 11.6% versus 10.7%, *p*=0.98
CTO: chronic total occlusion; EEM: external elastic membrane; IVUS: intravascular ultrasound; MLA: minimal lumen area; MSA: minimum stent area

CLINICAL OUTCOMES

The median follow-up period for the successful CTO PCI cohort was 5.2 years (interquartile range, 2.1-8.3 years). During the follow-up period, a total of 75 patients died, 49 of cardiac causes. MI occurred in 44 patients; TVR was performed in 36 of them. The Kaplan-Meier curves for the clinical endpoints are shown in **Figure 2**. The cumulative rates of TVF (11.0% vs 10.7%; p=0.99) and TVR (4.2% vs 3.7%; p=0.81) were similar between the in-stent and *de novo* CTO groups. The cumulative rates of death and target vessel MI were comparable between the two groups. During follow-up, there were 9 cases (2 in the in-stent CTO and 7 in the *de novo* CTO group) of definite stent thrombosis without a significant between-group difference (p=0.10). In the adjusted analysis using a multivariate Cox regression model, the risk of TVF remained comparable between the two groups, as did that for the other secondary study endpoints **(Table 5)**. After propensity score matching, there were 88 matched pairs of patients. The risks of TVF (hazard ratio [HR] 0.9, 95% confidence interval [CI]: 0.3-2.4, p=0.77), as

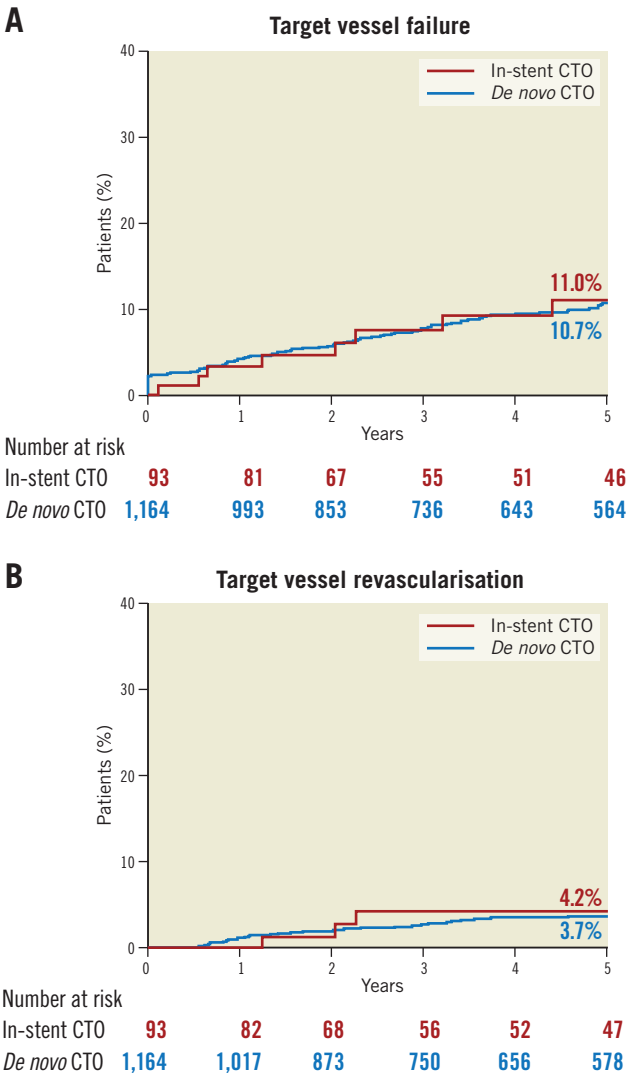

Figure 2. *Kaplan-Meier event curves. A) Cumulative incidence of target vessel failure. B) Target vessel revascularisation.*

Table 5. Hazard ratios of clinical outcomes.

	Event rates (%) at 5 years		Crude		Multivariate adjusted	
	In-stent CTO (n=93)	De novo CTO (n=1,164)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Target vessel failure	8 (11.0)	100 (10.7)	1.0 (0.5-2.1)	0.99	0.9 (0.5-1.9)	0.86
All-cause death	8 (10.5)	67 (7.6)	1.5 (0.7-3.2)	0.25	1.6 (0.8-3.3)	0.23
Cardiac death	4 (5.9)	45 (5.3)	1.1 (0.4-3.2)	0.80	1.1 (0.4-3.0)	0.89
Myocardial infarction	4 (6.0)	40 (3.9)	1.3 (0.5-3.5)	0.66	1.2 (0.4-3.4)	0.73
Target vessel myocardial infarction	3 (4.1)	32 (3.0)	1.2 (0.4-3.8)	0.79	1.2 (0.4-4.1)	0.74
Target vessel revascularisation	3 (4.2)	33 (3.7)	1.2 (0.4-3.8)	0.81	1.1 (0.3-3.7)	0.85

Event rates are shown as Kaplan-Meier estimates (number and percentage of events). Hazard ratios are for in-stent CTO versus *de novo* CTO group.
CI: confidence interval; CTO: chronic total occlusion; HR: hazard ratio

well as the individual outcomes, were in line with the results of the multivariable analysis **(Supplementary Table 1, Supplementary Table 2, Supplementary Figure 1)**.

Discussion

In this study we demonstrated that in-stent CTOs comprised approximately 10% of all the CTO PCI procedure cases and are characterised by less calcification but longer occlusion length with a similar overall CTO complexity and success rate compared with those for *de novo* CTOs. Among patients who underwent successful DES placement, the device-oriented composite endpoint of TVF was comparable between in-stent and *de novo* CTOs at five years, which should be viewed in the light of similar stent length and optimisation profiles achieved with IVUS guidance.

The prevalence of PCI for in-stent CTO varies from 5% to 25% in the published literature[2-6]. Perhaps technical difficulties to open the CTO effectively in an already stented segment and concerns about the long-term results after PCI are the main reasons why operators hesitate to attempt PCI for in-stent CTOs. Indeed, a recent analysis of a multicentre registry reported similar procedural success rates between in-stent and *de novo* CTO groups but a higher risk of adverse events during follow-up in the in-stent CTO group despite similar stent numbers and lengths[6]. However, nearly 90% of the total procedures were guided by angiography, and information regarding stent optimisation was unavailable. We believe that our report, which predominantly involves IVUS-guided CTO PCI, offers a practical guide for ensuring favourable long-term PCI results for in-stent CTOs.

The observation of comparable five-year post-stenting TVF rates between in-stent and *de novo* CTOs in our study could be reasonably explained by their comparable post-PCI IVUS parameters. The minimal stent area achieved in the two groups was notably similar. Accordingly, there was no difference in the frequency of stent underexpansion regardless of the definition used for the underexpansion. Moreover, the statuses of inflow or outflow track disease such as plaque burden and dissections were largely comparable. Because stent underexpansion and incomplete lesion coverage are well-known procedural factors responsible for stent failure, the association observed between the results of post-stenting IVUS measurements and clinical outcomes in our study seems plausible and is consistent with those of previous IVUS studies[10-12].

A practical implication of our analysis is that, even in cases in which CTO segments are surrounded by prior stents, operators would be able to optimise stent expansion and location such as that achieved in *de novo* CTOs with IVUS guidance. In previous studies, IVUS-supported PCI, compared with angiography-guided PCI, was associated with a significant reduction in major adverse cardiac events by decreasing the propensity of suboptimal stent implantation[13]. The contributor to this benefit seemed to be the larger minimal lumen diameter or area associated with IVUS over angiography guidance[14-17]. Considering the proximal and distal reference vessel diameter of ~3.0 mm and ~2.0 mm, respectively, in the post-PCI quantitative coronary angiographic analysis in our cohort, the average stent diameter of 3.2 mm used may be a result of IVUS guidance[14]. Together with somewhat aggressive stent sizing and mandatory use of adjunctive post-dilation guided by IVUS, we were able to achieve similar minimal stent area between in-stent and *de novo* CTOs. However, it would also be important to emphasise that a substantial proportion of patients still had stent underexpansion by IVUS criteria despite these strategies, probably because of the inherent features of CTOs associated with high atherosclerotic burden, site calcifications, and lesions frequently extended to distal vessels. In other words, with PCI guided by angiography alone, the propensity of suboptimal stenting may substantially increase, leading to adverse stent-related events. Because previous studies have demonstrated that the benefit of IVUS-guided PCI is pronounced in more complex coronary anatomies such as long lesions, left main lesions, and CTOs[14-17], the prognostic effect of this adjunctive tool may be maximised in in-stent CTOs. As advances in treatment algorithms and accumulating experience have increased the technical success of CTO PCI in recent years[18-20], increasing numbers of patients with in-stent CTO will undergo PCI. As long as operators consider that the optimal stenting versus wire-crossing strategy may more significantly affect stent-related outcomes after CTO PCI, the long-term outcomes of PCI will maintain it as an effective treatment option for patients with in-stent CTO.

Limitations

This study has several limitations. First, it was retrospective and observational in nature; thus, it was inherently subject to bias. Second, the number of in-stent CTO patients evaluated using IVUS and for the outcome analysis was relatively small. More robust evidence incorporating a larger number of patients is necessary. Third, the relatively lower clinical risk profile of our study population and a mandatory exclusion of patients with a target CTO vessel diameter of <2.5 mm may have contributed to the low TVF rates and the overall study results[21]. Fourth, our study focused on patients who received stent-based treatment; extrapolating our findings to all patients with in-stent CTOs would be inappropriate. The final treatment strategy of in-stent CTO is determined considering various anatomical and technical factors such as the mechanisms of prior stent failure, presence of disease extension beyond the prior stent, or the degree of negative remodelling or wire-based dissection of the outflow vessels[22,23]. Accordingly, a non-stenting strategy for in-stent CTOs is commonly used in reality, which is in line with the proportion seen in our registry (non-stenting treatment was used in 22.9% of the overall in-stent CTO cohort vs 4.7% of the *de novo* CTO cohort). However, because procedural optimisation using a drug-coated balloon for in-stent restenosis seems relevant[24], whether this concept is valid in in-stent CTO should be the subject of a future investigation.

Conclusions

The success and complication rates of contemporary PCI for in-stent CTOs are comparable to those for *de novo* CTOs. PCI with DES, optimised by IVUS guidance, offers acceptable long-term clinical results for in-stent CTOs.

Impact on daily practice

Previously, in-stent CTO PCI was related with lower success rates and worse long-term outcomes compared with *de novo* CTOs. However, our study showed a similar success rate and in-hospital outcome in both CTO groups. In addition, the long-term results of PCI were also comparable between in-stent CTO and *de novo* CTO, which is achieved by IVUS-guided optimisation with drug-eluting stents. Therefore, our data support IVUS-guided PCI for in-stent CTO.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Kaplan-Meier event curve for target vessel failure in the matched cohort.

Supplementary Table 1. Standardised mean difference of clinically relevant variables between the groups after propensity score matching.

Supplementary Table 2. Hazard ratios of clinical outcomes in the propensity score-matched population.

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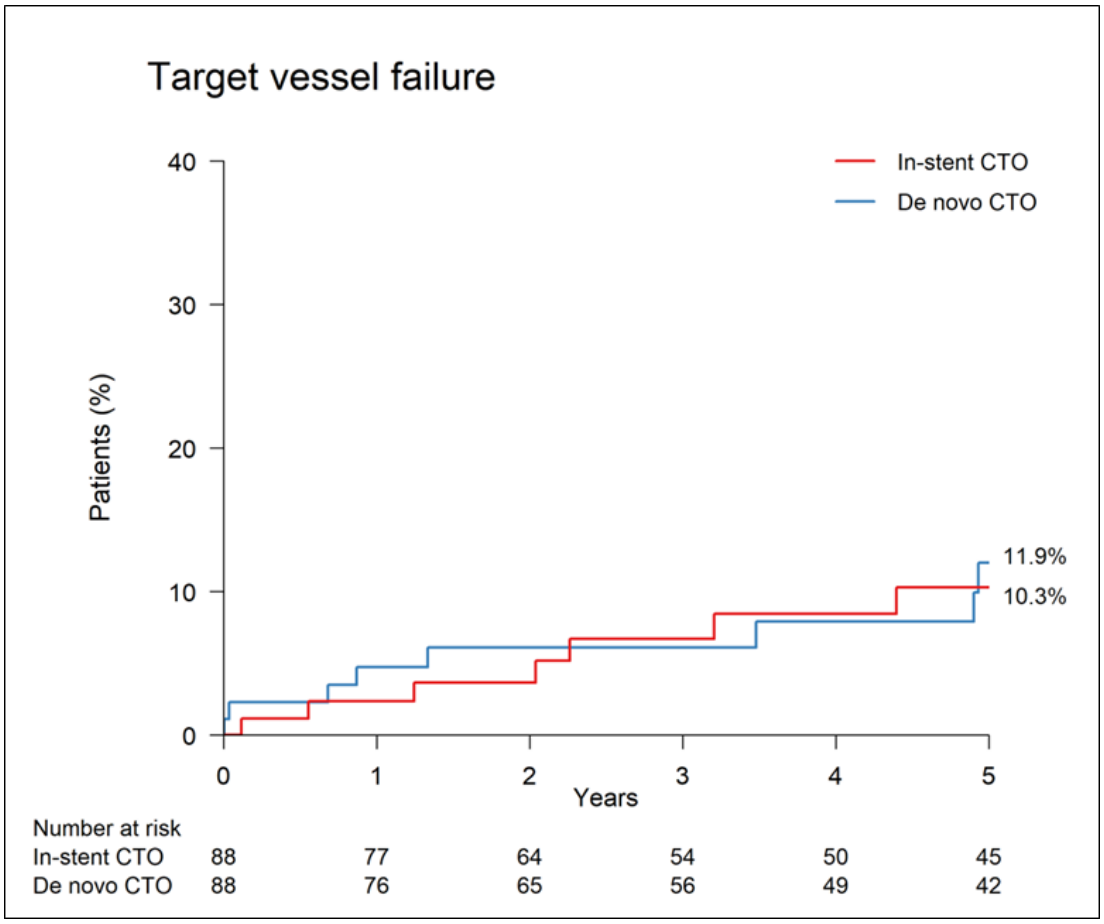
Supplementary data



Supplementary Figure 1. Kaplan-Meier event curve for target vessel failure in the matched cohort.

Supplementary Table 1. Standardised mean difference of clinically relevant variables between the groups after propensity score matching.

	In-stent CTO (n=88)	De novo CTO (n=88)	Standardised mean difference	*p*-value
Age, years	60.7±10.4	60.2±11.9	0.039	0.80
Men	72 (81.8)	72 (81.8)	<0.001	>0.99
Body mass index, kg/m^2	25.2±2.6	25.3±3.4	0.012	0.94
Stable angina	72 (81.8)	71 (80.7)	0.029	>0.99
Hypertension	58 (65.9)	57 (64.8)	0.024	>0.99
Diabetes	27 (30.7)	33 (37.5)	0.143	0.43
Dyslipidaemia	75 (85.2)	71 (80.7)	0.120	0.55
Chronic kidney disease	1 (1.1)	0	0.151	>0.99
Previous PCI	88 (100.0)	88 (100.0)	<0.001	
Previous CABG	7 (8.0)	7 (8.0)	<0.001	>0.99
History of MI	18 (20.5)	20 (22.7)	0.055	0.86
History of stroke	6 (6.8)	7 (8.0)	0.043	>0.99
Peripheral vascular disease	4 (4.5)	3 (3.4)	0.058	>0.99
LVEF, %	57.1±8.5	56.4±9.0	0.082	0.59
Atrial fibrillation	3 (3.4)	3 (3.4)	<0.001	>0.99
Multivessel disease	35 (39.8)	37 (42.0)	0.046	0.88
Collateral grade, 2-3	78 (88.6)	76 (86.4)	0.068	0.82
Retrograde success	10 (11.4)	9 (10.2)	0.036	>0.99
J-CTO score	2.0±1.1	1.9±1.0	0.087	0.57
Second-generation DES	70 (79.5)	71 (80.7)	0.028	>0.99
Stent number	1.8±0.7	1.8±0.8	0.015	0.92
Use of IVUS	84 (95.5)	85 (96.6)	0.058	>0.99

CABG: coronary artery bypass grafting; CTO: chronic total occlusion; DES: drug-eluting stent; IVUS: intravascular ultrasound; MI: myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 2. Hazard ratios of clinical outcomes in the propensity score-matched population.

	Event rates (%) at 5 years			
	In-stent CTO	De novo CTO	HR (95% CI)	*p*-value
Target vessel failure	7 (10.3)	8 (11.9)	0.9 (0.3-2.4)	0.77
All-cause death	7 (9.7)	5 (8.5)	1.4 (0.5-4.5)	0.54
Cardiac death	3 (4.9)	4 (7.0)	0.8 (0.2-3.4)	0.73
Myocardial infarction	4 (6.1)	4 (5.5)	1.0 (0.3-4.1)	0.97
Target vessel myocardial infarction	3 (4.3)	2 (2.3)	1.5 (0.3-9.0)	0.65
Target vessel revascularisation	3 (4.4)	3 (4.1)	1.0 (0.2-4.8)	0.97
Definite stent thrombosis	2 (3.1)	0	-	-

Event rates are shown as Kaplan-Meier estimates (number and percentage of events).

Hazard ratios are for in-stent CTO versus de novo CTO group.

CI: confidence interval; CTO: chronic total occlusion; HR: hazard ratio