Technical and procedural outcomes of the retrograde approach to chronic total occlusion interventions



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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00441

KEYWORDS

- chronic coronary total occlusion
- other techniques
- stable angina

Abstract

Aims: The retrograde approach is critical for achieving high success rates in chronic total occlusion (CTO) percutaneous coronary intervention (PCI), but has been associated with higher risk of complications. We examined the contemporary outcomes of the retrograde approach to CTO PCI aiming to identify areas in need of improvement.

Methods and results: We compared the technical and procedural outcomes of retrograde (n=1,515) and antegrade-only CTO PCIs (n=2,686) in a contemporary multicentre CTO registry. The mean age of patients undergoing retrograde PCI was 65±10 years and 86% were men, with high prevalence of prior myocardial infarction (51%), prior PCI (71%), and coronary artery bypass graft surgery (45%). The mean J-CTO score (3±1 vs 2±1, p<0.001) was higher in retrograde PCIs. The most commonly used collateral channels were septals (65%), epicardials (32%), saphenous venous grafts (14%) and left internal mammary artery grafts (2%). Overall technical (79% vs 91%, p<0.001) and procedural (75% vs 90%, p<0.001) success rates were lower with the retrograde approach, and these patients had a higher rate of in-hospital major complications than antegrade-only PCI patients (5.1% vs 0.8%, p<0.001), due to higher mortality (1.1% vs 0.1%, p<0.001), acute myocardial infarction (1.9% vs 0.2%, p<0.001), repeat PCI (0.7% vs 0.1%, p=0.001), and pericardiocentesis (1.7% vs 0.3%, p<0.001).

Conclusions: In summary, the retrograde approach to CTO PCI is performed in higher complexity lesions and is associated with lower success rates and a higher rate of major complications. Clinical Trial Registration: NCT02061436, Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS-CTO)

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Abbreviations

CABG coronary artery bypass graft **CTO** chronic total occlusion

J-CTO Japanese chronic total occlusion
MACE major adverse cardiac events

MI myocardial infarction

PCI percutaneous coronary intervention

PROGRESS-CTO Prospective Global Registry of Chronic Total

Occlusion Interventions

Introduction

Since its introduction more than a decade ago^{1,2}, the retrograde approach has become an essential tool for chronic total occlusion (CTO) percutaneous coronary intervention (PCI), and has been instrumental in improving technical success to ~85-90% from ~80% achieved with antegrade-only interventions^{3,4}. The retrograde approach usually requires two guide catheters and has four key technical steps: (a) advancing a guidewire and microcatheter through a collateral vessel or a bypass graft distal to the occlusion, (b) crossing the occlusion, (c) wire externalisation, and (d) balloon angioplasty with stent implantation⁵. In the hybrid approach⁶, upfront retrograde crossing in CTOs with proximal cap ambiguity and/or poor distal target as well as after failure of antegrade crossing, if there are interventional collaterals, is recommended. We examined the contemporary outcomes of the retrograde approach to CTO PCI aiming to identify areas in need of improvement.

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Material and methods

We analysed the clinical, angiographic, and procedural characteristics of 4,201 CTO PCIs performed in 4,108 patients enrolled in the PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; NCT02061436) registry between May 2012 and November 2018 at 21 US, one European, and one Russian centres (Supplementary Appendix 1). Some centres only enrolled patients during part of the study period due to participation in other studies. The study was approved by the institutional review board of each centre.

Coronary CTO was defined as a coronary lesion with Thrombolysis In Myocardial Infarction (TIMI) grade 0 flow of at least three months duration. Estimation of the duration of occlusion was clinical, based on the first onset of angina, prior history of myocardial infarction (MI) in the target vessel territory, or comparison with a prior angiogram. Calcification was assessed by angiography as mild (spots), moderate (involving ≤50% of the reference lesion diameter) and severe (involving >50% of the reference lesion diameter). Moderate proximal vessel tortuosity was defined as the presence of at least two bends >70° or one bend >90° and severe tortuosity as two bends >90° or one bend >120° in the CTO vessel. Blunt or no stump was defined as lack of tapering or lack of a funnel shape at the proximal cap. Interventional collaterals were defined as collaterals considered amenable to crossing by a guidewire and a microcatheter by the operator. Werner classification was

used for collateral channel assessment⁷. Additional angiographic definitions are described in **Supplementary Appendix 2**.

A procedure was defined as "retrograde" if an attempt was made to cross the lesion through a collateral vessel or bypass graft supplying the target vessel distal to the lesion; if not, the procedure was classified as "antegrade-only". Antegrade dissection/reentry was defined as antegrade PCI during which a guidewire was intentionally introduced into the subintimal space proximal to the lesion, or re-entry into the distal true lumen was attempted following intentional or inadvertent subintimal guidewire crossing.

Technical success was defined as successful CTO revascularisation with achievement of <30% residual diameter stenosis within the treated segment and restoration of TIMI grade 3 antegrade flow. Procedural success was defined as the achievement of technical success without any in-hospital complications. In-hospital major adverse cardiac events (MACE) included any of the following adverse events prior to hospital discharge: death, MI, recurrent symptoms requiring urgent repeat target vessel revascularisation with PCI or coronary artery bypass graft surgery (CABG), tamponade requiring either pericardiocentesis or surgery, and stroke. MI was defined using the third universal definition of myocardial infarction (type 4a MI). Major bleeding was defined as bleeding causing reduction in haemoglobin >3 g/dl or bleeding requiring transfusion or surgical intervention. The J-CTO score was calculated as described by Morino et al8, the CASTLE score as described by Szijgyarto et al9, the PROGRESS CTO score as described by Christopoulos et al¹⁰, and the PROGRESS-CTO Complications score as described by Danek et al11.

STATISTICAL ANALYSIS

Categorical variables are expressed as percentages and were compared using Pearson's chi-square test or Fisher's exact test. Continuous variables are presented as mean±standard deviation or median (interquartile range [IQR]) unless otherwise specified and were compared using the t-test and one-way analysis of variance (ANOVA) for normally distributed variables; the Wilcoxon rank-sum test and the Kruskal-Wallis test were applied for non-parametric continuous variables, as appropriate. Multivariable logistic regression was used to examine the association between use of the retrograde approach and in-hospital MACE, as well as to identify variables associated with retrograde technical failure. Variables with significant univariable association (p<0.1) were entered into the models. All statistical analyses were performed with JMP 13.0 (SAS Institute, Cary, NC, USA). A two-sided p-value of 0.05 was considered statistically significant.

Results

Retrograde CTO PCI was attempted in 1,505 patients (36.7%) undergoing 1,515 interventions that were compared to 2,686 antegrade-only CTO PCIs performed in 2,603 patients (63.3%).

Patients undergoing retrograde CTO PCI were older and had higher prevalence of coronary risk factors, prior MI, history of prior PCI and CABG (**Table 1**).

Table 1. Baseline characteristics of patients undergoing retrograde and antegrade-only CTO PCI.

Variable		Overall (n=4,108)	Retrograde (n=1,505)	Antegrade- only (n=2,603)	<i>p</i> -value
Age (years) *		64.5±10.1	65.0±10.2	64.2±10.0	0.028
Male gender		84.2%	85.7%	83.4%	0.066
Coronary artery disease	Stable angina	65.0%	66.3%	64.4%	
presentation	Acute coronary syndrome	25.0%	24.8%	25.1%	0.277
	Other	9.9%	8.9%	10.5%	
Diabetes mellitus		42.1%	42.3%	42.0%	0.874
Dyslipidaemia		89.4%	92.6%	87.6%	<0.001
Hypertension		90.6%	90.4%	90.7%	0.798
Prior myocardia	I infarction	47.6%	50.8%	45.8%	0.004
Congestive hea	rt failure	30.7%	31.7%	30.2%	0.356
Prior percutane coronary interve		64.3%	71.2%	60.4%	<0.001
Prior coronary a graft surgery	rtery bypass	31.9%	44.8%	24.6%	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m²) *		72.7±21.7	71.7±21.7	73.3 ± 21.8	0.065
Peripheral arter	y disease	14.0%	16.6%	12.6%	<0.001
Left ventricular fraction (%) **		54 (42, 60)	54 (40, 60)	54 (43, 60)	0.246

^{*} mean±standard deviation. ** median (interquartile range). CTO: chronic total occlusion; PCI: percutaneous coronary intervention

In the retrograde group, lesions were significantly more complex **(Table 2)**. Retrograde cases had better developed collaterals (Werner Class 1: 58.1% vs 49.0%; Werner Class 2: 31.8% vs 20.7%, both p<0.001).

The main technical characteristics are summarised in **Table 3**. In primary retrograde cases the main indications for selection of the retrograde approach were the following: long occlusion length (36.6%), ostial occlusions (27.5%), side branch at proximal cap (25.6%), poor distal target vessel (24.6%), bifurcation at distal cap (22.1%), proximal cap ambiguity (15.8%), and tortuosity (14.2%). The retrograde approach was more successfully applied as the crossing strategy in more complex lesions (**Figure 1**).

Overall technical and procedural success in the retrograde group was 79.2% and 75.4%, respectively, and was significantly lower compared with antegrade-only cases (90.5% and 90.0%, both p<0.001). In cases with successful retrograde CTO crossing, technical success was 98.4%, whereas in CTOs with retrograde wire crossing failure successful CTO revascularisation was achieved in 49.4% (Supplementary Table 1). The following collateral pathways were used: septal collaterals (62.0%), contralateral epicardial collaterals (29.9%), and saphenous vein grafts (13.5%) (Figure 2A). Successful collateral channel crossing was achieved in 75.3% (Figure 2B). Epicardial collaterals were more likely to be attempted

Table 2. Angiographic characteristics of chronic total occlusions undergoing retrograde and antegrade-only PCI.

Circumflex artery	Vari	iable	Overall (n=4,201)	Retrograde (n=1,515)	Antegrade- only (n=2,686)	<i>p</i> -value	
descending artery	Target vessel	, ,	54.8%	67.0%	47.8%		
artery 19.4% 15.7% 21.5% Order 13.4% 15.7% 21.5% Other 1.3% 1.0% 1.5% 21.5% Order 1.3% 1.0% 2.0.00 Proviously failed attempt 20.9% 26.3% 17.5% 21.5% Occlusion length, mm 32.7±23.0 41.8±26.6 28.0±19.3 20.00 Morray 45.1% 40.00 Morray 6.8% 10.1% 30.3% 20.00 Moderate/severe calcification 52.9% 68.3% 43.6% 20.00 Moderate/severe tortuosity 34.2% 46.6% 26.7% 20.00 In-stent restembers <t< td=""><td></td><td>descending</td><td>24.5%</td><td>16.3%</td><td>29.2%</td><td><0.001</td></t<>		descending	24.5%	16.3%	29.2%	<0.001	
Occlusion length, mm 32.7±23.0 41.8±26.6 28.0±19.3 <0.00 Proximal cap ambiguity 36.2% 55.6% 25.9% <0.00			19.4%	15.7%	21.5%		
Proximal cap ambiguity 36.2% 55.6% 25.9% <0.00 Interventional collaterals 57.0% 79.4% 45.1% <0.00		Other	1.3%	1.0%	1.5%		
Interventional collaterals 57.0% 79.4% 45.1% <0.00	Occlusion length, mm		32.7±23.0	41.8±26.6	28.0±19.3	<0.001	
Werner collateral classification Class 0 (Lass 1) 24.6% 10.1% 30.3% 49.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% 40.0% </td <td colspan="2">Proximal cap ambiguity</td> <td>36.2%</td> <td>55.6%</td> <td>25.9%</td> <td><0.001</td>	Proximal cap ambiguity		36.2%	55.6%	25.9%	<0.001	
Collateral classification Class 1 51.6% 58.1% 49.0% Class 2 23.8% 31.8% 20.7% Moderate/severe calcification 52.9% 68.3% 43.6% <0.00	Interventional collaterals		57.0%	79.4%	45.1%	<0.001	
Class I Class I 51.6% 58.1% 49.0% <0.00 Moderate/severe calcification 52.9% 68.3% 43.6% <0.00		Class 0	24.6%	10.1%	30.3%		
Class 2 23.8% 31.8% 20.7%		Class 1	51.6%	58.1%	49.0%	<0.001	
Moderate/severe tortuosity 34.2% 46.6% 26.7% <0.00 In-stent restenosis 16.6% 13.6% 18.3% <0.00	oladollidation	Class 2	23.8%	31.8%	20.7%		
In-stent restenosis 16.6% 13.6% 18.3% <0.00	Moderate/seve	ere calcification	52.9%	68.3%	43.6%	<0.001	
Previously failed attempt 20.9% 26.3% 17.8% <0.00 J-CTO score * 2.4±1.3 3.2±1.1 2.0±1.2 <0.00	Moderate/seve	ere tortuosity	34.2%	46.6%	26.7%	<0.001	
J-CTO score * 2.4±1.3 3.2±1.1 2.0±1.2 <0.00 PROGRESS CTO score * 1.3±1.0 1.4±1.0 1.3±1.1 0.02	In-stent rester	nosis	16.6%	13.6%	18.3%	<0.001	
PROGRESS CTO score * 1.3±1.0 1.4±1.0 1.3±1.1 0.02	Previously failed attempt		20.9%	26.3%	17.8%	<0.001	
	J-CTO score *		2.4±1.3	3.2±1.1	2.0±1.2	<0.001	
CASTLE score * 2.1±1.3 2.8±1.3 1.7±1.2 <0.00	PROGRESS CTO score *		1.3±1.0	1.4±1.0	1.3±1.1	0.020	
	CASTLE score	*	2.1±1.3	2.8±1.3	1.7±1.2	<0.001	
PROGRESS CTO complication score * 3.0±1.9 4.0±1.7 2.4±1.8 <0.00		O complication	3.0±1.9	4.0±1.7	2.4±1.8	<0.001	

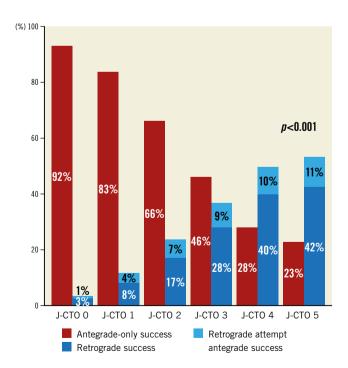


Figure 1. Technical success of CTO interventions with the retrograde approach (n=1,515) compared to antegrade-only interventions (n=2,686) stratified by the J-CTO score.

Table 3. Technical characteristics of CTO interventions in cases with the retrograde and antegrade-only approaches.

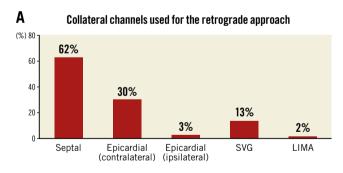
Variable		Overall (n=4,201)	Retrograde (n=1,515)	Antegrade- only (n=2,686)	<i>p</i> -value
Dual injection		68.9%	85.9%	59.3%	< 0.001
Crossing	AWE	84.4%	68.5%	93.5%	< 0.001
strategy used	ADR	28.6%	36.1%	24.4%	< 0.001
uscu	Retrograde	36.1%	100.0%	0.0%	< 0.001
First	AWE	78.9%	55.4%	92.2%	
crossing strategy	ADR	7.0%	5.5%	7.8%	< 0.001
Strategy	Retrograde	14.1%	39.1%	0.0%	
Final	AWE	49.4%	7.9%	72.7%	
crossing strategy	ADR	17.2%	12.6%	19.8%	<0.001
Stratogy	Retrograde	22.0%	61.0%	0.0%	
	None	11.5%	18.4%	7.6%	
Access	Right femoral	75.0%	82.8%	70.7%	< 0.001
site	Left femoral	46.5%	61.1%	38.2%	< 0.001
	Right radial	38.9%	39.2%	38.7%	0.737
	Left radial	19.8%	24.5%	17.2%	< 0.001
Technical success		86.4%	79.21%	90.51%	< 0.001
Number of stents *		2.4±1.1	2.9±1.1	2.1±1.1	<0.001
Overall sten	t length, mm *	70.4±36.3	89.4±36.5	61.5±32.7	<0.001

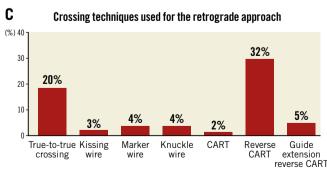
^{*} mean±standard deviation. ADR: antegrade dissection and re-entry; AWE: antegrade wire escalation

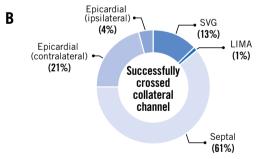
as a second or third collateral, and low-profile microcatheters were used more frequently (**Figure 3**). The most commonly used crossing techniques are summarised in **Figure 2C**. In lesions with successful

retrograde attempt, the most commonly used crossing technique was the reverse controlled antegrade and retrograde tracking (CART) (53.2%) (Figure 2D). In eight cases retrograde wire crossing was achieved with various retrograde techniques (marker wire technique [n=4]; CART [n=2]; true-to-true wiring [n=1]; reverse CART [n=1]); however, externalisation failed leading to technical failure. The predictors of retrograde technical failure are summarised in Supplementary Table 2. Retrograde cases required longer procedure and fluoroscopy times, higher volume of contrast and air kerma radiation dose compared with antegrade-only procedures (Figure 4).

The overall in-hospital MACE rate of retrograde CTO PCI was 5.1%, and any procedure-related complication occurred in 18.9% (Figure 5A, Figure 5B, Table 4). The incidence of coronary perforation was significantly higher in retrograde cases (8.6% vs 2.2%, p<0.001), and perforations were more severe (Ellis Class III or Class III-cavity spilling 41.3% vs 22.9%, p=0.133). The incidence of tamponade requiring pericardiocentesis, however, was caused similarly by antegrade wiring (n=12, 46.2%) and retrograde wiring (n=14, 53.8%) attempts during retrograde interventions, and it occurred more frequently if the retrograde approach was the successful crossing technique (66.7% vs 33.3%, p=0.225). Covered stents were used in 10.0% (n=10) of all perforations during the retrograde approach (n=140), and in 11.5% (n=3) of all cases when pericardiocentesis was required (n=26). On multivariable logistic regression (Supplementary Table 3), the retrograde approach was independently associated with increased risk of in-hospital MACE (OR 3.94, 95% CI: 2.01-8.20, p<0.001). In-hospital MACE and periprocedural complication rates were similar in cases with retrograde success compared with retrograde attempt failure (Figure 6, Figure 7).







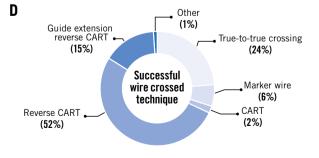


Figure 2. Technical outcomes of all the retrograde CTO interventions in terms of collateral crossing (A & B) and wire crossing techniques ($C \& D^*$). *Eight cases included with successful wire crossing, but retrograde failure due to failed wire externalisation.

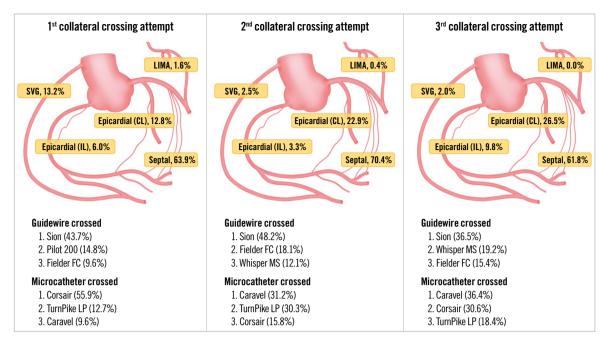


Figure 3. Technical characteristics of collateral channel crossing attempts during the retrograde approach in terms of collaterals used, successfully crossed guidewires and microcatheters. Manufacturer details: Asahi® SionTM, Caravel, Corsair, Fielder FCTM, all Asahi Intecc, Aichi, Japan; HI-TORQUE PILOT 200 and WHISPER® MS, Abbott Vascular, Santa Clara, CA, USA; Turnpike® LP, Teleflex Medical, Wayne, PA, USA/Vascular Solutions, Minneapolis, MN, USA.

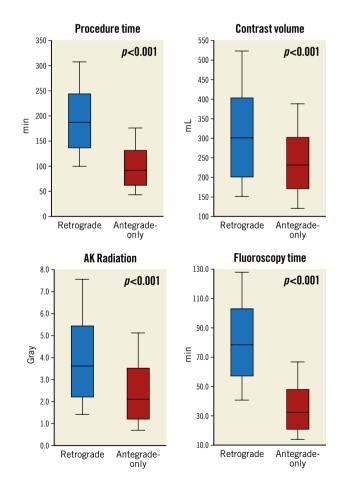


Figure 4. Procedural characteristics compared between retrograde CTO PCI and antegrade-only interventions.

The temporal trends of retrograde CTO PCI outcomes are presented in **Supplementary Table 4**. Additional procedural and patient characteristics are given in **Supplementary Table 5**.

Table 4. Procedural outcomes of retrograde and antegrade-only CTO PCIs.

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Va	riable	Overall (n=4,108)	Retrograde (n=1,505)	Antegrade- only (n=2,603)	<i>p</i> -value
Procedural s	success	84.80%	75.40%	90.00%	<0.001
In-hospital i cardiac ever	major adverse nt	2.36%	5.05%	0.81%	<0.001
Death		0.46%	1.06%	0.12%	< 0.001
Acute myoca infarction	nrdial	0.85%	1.93%	0.23%	<0.001
Stroke		0.22%	0.40%	0.12%	0.083
Emergency reintervention		0.29%	0.66%	0.08%	0.001
Emergency surgery		0.12%	0.20%	0.08%	0.363
Pericardiocentesis		0.80%	1.66%	0.31%	<0.001
Procedural o	complications	10.60%	18.90%	5.90%	<0.001
Perforation		4.53%	8.57%	2.19%	<0.001
Target v	essel	1.83%	2.86%	1.23%	<0.001
Collater	al vessel	0.58%	1.53%	0.04%	<0.001
Sep	tal	0.34%	0.86%	0.04%	<0.001
Epicardial		0.32%	0.86%	6% 0.00%	
Other		0.17%	0.07%	0.23%	0.434
Perforation	Ellis Class I	20.87%	17.50%	28.57%	
type	Ellis Class II	43.48%	41.25%	48.57%	0.133
	Ellis Class III	35.65%	41.25%	22.86%	

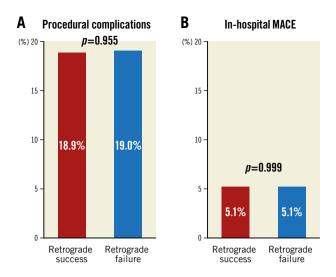


Figure 5. Distribution of periprocedural complications (A) and in-hospital major complications (B) of successful and failed retrograde CTO PCIs.

Discussion

Our study is one of the largest published to date examining the technical outcomes of retrograde CTO PCI. The major findings are as follows: (a) retrograde CTO PCI remains essential for CTO PCI, especially in complex lesions; (b) retrograde interventions are associated with higher in-hospital and periprocedural complications compared with antegrade-only interventions; (c) collateral crossing is successful in three quarters of cases, limiting retrograde CTO crossing success; (d) approximately half of the perforations requiring pericardiocentesis during retrograde CTO PCI were due to antegrade wiring attempts.

Antegrade wire escalation remains the most frequently used and most often successful CTO crossing strategy. The retrograde approach, however, remains essential for CTO PCI success, especially in complex occlusions when the antegrade approach fails or is not feasible³. The decreasing use of the retrograde approach in recent years may reflect improvements in antegrade wiring techniques and devices (especially novel, highly torquable guidewires).

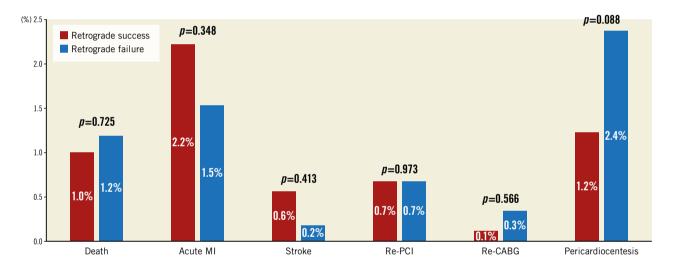


Figure 6. In-hospital major adverse cardiac events in failed and successful retrograde CTO PCIs.

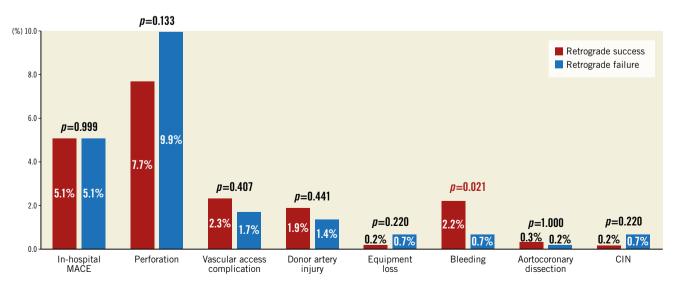


Figure 7. Periprocedural complications of failed and successful retrograde CTO PCIs.

In our study, the overall success rate of retrograde interventions was 79.2% with procedural success of 75.4%, which is similar to those of the European CTO Registry (n=1,582 CTO PCI, clinical success of 75.3%⁴). The slight decrease over time in technical and procedural success is probably explained by increasing CTO complexity (Supplementary Table 4) and a high prevalence of prior CABG.

Septal surfing and contrast-guided techniques (also known as distal tip injection technique) are currently used for collateral crossing¹². Dautov et al showed that septal collateral surfing was successful in 81% in 240 CTO PCIs, even if collaterals are invisible (Werner Class CC 0)¹³. Septal surfing was the most common collateral crossing strategy in cases with retrograde success (75.5%) in our study, whereas microcatheter tip injection guidance was used in 24.5%. The overall collateral channel crossing (by guidewire and microcatheter) success rate was 75.3%.

Once the guidewire and microcatheter cross the collateral channel, CTO crossing can also be challenging and is usually achieved using the reverse CART technique¹. In our cohort, reverse CART was the most commonly attempted and most commonly successful crossing strategy.

Retrograde CTO PCI has been reported to have a higher risk of complications in numerous cohorts compared with antegrade approaches (both antegrade wiring and/or antegrade dissection re-entry techniques). Similarly, in our study in-hospital MACE was 5.1% in the retrograde group (overall procedural complications 18.9%) and was significantly higher than in antegrade-only interventions. However, approximately half of the complications (46.2%) were caused by antegrade wiring, suggesting that a significant proportion of the higher retrograde CTO PCI risk is related to the complexity of the treated lesions. Furthermore, although coronary perforations were observed in 8.6% of the procedures treated with the retrograde approach, only 1.7% required pericardiocentesis, with the majority being treated conservatively.

Performing retrograde CTO PCI over the years has undergone significant changes with decreasing use of radiation and contrast despite increased lesion complexity, as reflected in the increasing J-CTO scores (**Supplementary Table 4**). Such improvements could be attributed to optimised imaging, use of contrast-saving equipment and techniques (such as the DyeVert™ system [Osprey Medical Inc., Minnetonka, MN, USA], use of IVUS) and continuous education. Although the retrograde approach carries increased risk of complications, our study shows that some of the complications attributed to the retrograde approach were actually due to antegrade crossing attempts during the same procedure and were probably related to high lesion complexity.

Limitations

Limitations of our study include the lack of core laboratory assessment of the study angiograms, lack of independent clinical events adjudication, and limited availability of follow-up for the study patients. Furthermore, the procedures were performed in dedicated, high-volume CTO centres by experienced operators, limiting the

extrapolation to less experienced operators and lower-volume centres. The selection of crossing strategy was made by each operator, probably reflecting local expertise and operator/patient preferences. The novel classification of the reverse CART techniques was not used in our current study; however, it was only introduced recently¹⁴. Procedure-related MI events are site reported without systematic post-procedural biomarker assessment, hence the rate of such complications may be underestimated.

Conclusions

The retrograde approach remains critical for the success of CTO PCI, especially in more complex occlusions. The retrograde approach should be performed by experienced operators and centres given its association with higher risk for complications.

Impact on daily practice

The retrograde approach is an important technique for crossing coronary chronic total occlusions, especially for more complex lesions. However, the retrograde approach carries increased risk of complications, especially perforation, even though some of the complications are related to antegrade crossing attempts during the same procedure. As a result, appropriate case selection, early recognition and, if necessary, timely treatment of coronary perforation are critical for reducing the rate of complications during retrograde chronic total occlusion interventions.

Appendix. Study collaborators

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Acknowledgements

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Minneapolis Heart Institute Foundation, Minneapolis, MN, USA. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Funding

The PROGRESS-CTO registry has received support from the Abbott Northwestern Hospital Foundation, Minneapolis, MN, USA and a gift from the Joseph F. and Mary M. Fleischhacker Foundation.

Conflict of interest statement

D. Karmpaliotis reports speaker honoraria from Abbott Vascular, Boston Scientific, Medtronic, and Vascular Solutions. K. Alaswad reports consulting fees from Terumo, and Boston Scientific, and being a consultant (non-financial) for Abbott Laboratories. F.A. Jaffer reports being a consultant for Abbott Vascular, Boston Scientific, Siemens, and Philips, and research grants from Canon, Siemens, and National Institutes of Health. R.W. Yeh reports receiving a Career Development Award (1K23HL118138) from the National Heart, Lung, and Blood Institute. M. Patel reports being on the speakers' bureau of AstraZeneca. E. Mahmud reports consulting fees from Medtronic and Corindus, speaker's fees from Medtronic, Corindus, and Abbott Vascular, educational programme fees from Abbott Vascular and clinical events committee fees from St. Jude. M.N. Burke reports consulting/speaking honoraria from Abbott Vascular and Boston Scientific. R.M. Wyman reports honoraria/consulting/speaking fees from Boston Scientific, Abbott Vascular, and Asahi. D. Kandzari reports research grant/consulting honoraria from Boston Scientific, and Medtronic Cardiovascular, and a research grant from Abbott. S. Garcia reports consulting fees from Medtronic. J. Khatri reports a research grant from Asahi Intece, and consultant/speaker honoraria from Abbott Vascular, Philips, and Abiomed. J. Moses reports being a consultant for Boston Scientific and Abiomed. N. Lembo reports being on the speaker bureau of Medtronic and the advisory board of Abbott Vascular and Medtronic. M. Parikh reports being on the speaker bureau of Abbott Vascular, Medtronic, CSI, BSC, and Trireme, and on the advisory boards of Medtronic, Abbott Vascular, and Philips. A. Kirtane reports receiving institutional research grants to Columbia University from Boston Scientific, Medtronic, Abbott

Vascular, Abiomed, St. Jude Medical, Vascular Dynamics, Glaxo SmithKline, and Eli Lilly. Z. Ali reports consultant fees/honoraria from St. Jude Medical, and AstraZeneca Pharmaceuticals, ownership interest/partnership/principal in Shockwave Medical, and VitaBx Inc, and research grants from Medtronic and St. Jude Medical. B. Rangan reports research grants from Infraredx, Inc., and The Spectranetics Corporation. S. Banerjee reports research grants from Gilead, and The Medicines Company, consultant/speaker honoraria from Covidien, and Medtronic, ownership of MDCARE Global (spouse), and intellectual property in HygeiaTel. E.S. Brilakis reports consulting/speaker honoraria from Abbott Vascular, American Heart Association (associate editor Circulation), Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), CSI, Elsevier, GE Healthcare, Infraredx, and Medtronic, research support from Regeneron, and Siemens, and being a shareholder in MHI Ventures. The other authors/study collaborators have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Centres participating in the current study.

Supplementary Appendix 2. Definitions.

Supplementary Table 1. Collateral channel crossing techniques during successful and failed retrograde CTO PCIs.

Supplementary Table 2. Multivariable analysis for predicting technical failure of retrograde CTO PCI.

Supplementary Table 3. Multivariable analysis for in-hospital major adverse cardiac events (MACE).

Supplementary Table 4. Temporal trends of technical and procedural outcomes of CTO PCI using the retrograde approach.

Supplementary Table 5. Baseline, angiographic, technical, and procedural characteristics of retrograde versus antegrade-only CTO PCI.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00441



Supplementary data

Supplementary Appendix 1. Centres participating in the current study

- 1. Appleton Cardiology, Appleton, WI, USA;
- 2. Baylor Heart and Vascular Hospital, Dallas, TX, USA;
- 3. Beth Israel Deaconess Medical Center, Boston, MA, USA;
- 4. Central Arkansas Veterans Health System, Little Rock, AR, USA;
- 5. Cleveland Clinic, Cleveland, OH, USA;
- 6. Columbia University, New York, NY, USA;
- 7. Emory University, Atlanta, GA, USA;
- 8. Henry Ford Hospital, Detroit, MI, USA;
- 9. Korgialeneio-Benakeio Hellenic Red Cross General Hospital of Athens, Athens, Greece;
- 10. Massachusetts General Hospital, Boston, MA, USA;
- 11. Medical Center of the Rockies, Loveland, CO, USA;
- 12. Meshalkin Siberian Federal Biomedical Research Center, Ministry of Health of Russian Federation, Novosibirsk, Russian Federation;
- 13. Minneapolis Heart Institute, Minneapolis, MN, USA;
- 14. Minneapolis VA Medical Center, Minneapolis, MN, USA;
- 15. Piedmont Heart Institute, Atlanta, GA, USA;
- 16. PeaceHealth St. Joseph Medical Center, Bellingham, WA, USA;
- 17. St. Luke's Health System's Mid-America Heart Institute, Kansas City, MO, USA;
- 18. The Heart Hospital Baylor Plano, Plano, TX, USA;
- 19. Torrance Memorial Center, Torrance, CA, USA;
- 20. Tristar Centennial Medical Center, Nashville, TN, USA;
- 21. VA North Texas Health Care System, Dallas, TX, USA;
- 22. UC San Diego/VA San Diego Healthcare System, San Diego, CA, USA;
- 23. UPMC Presbyterian, Pittsburgh, PA, USA.

Supplementary Appendix 2. Definitions

Adequate distal landing zone was defined as a distal vessel segment with a diameter larger than 2.0 mm, and without diffuse disease. Angiographic assessment of collateral channels was performed as described by Werner (CC0 grade: no continuous connection; CC1 grade: threadlike continuous connection; CC2: side branch-like continuous connection).

Reverse controlled antegrade and retrograde subintimal tracking and dissection (reverse CART) was defined as retrograde wire crossing facilitated by antegrade balloon inflation thus allowing retrograde wire re-entry to proximal true lumen, whereas the CART technique was defined as retrograde balloon advancement and inflation to facilitate antegrade wire re-entry. Guide extension reverse CART was defined as antegrade insertion of a guide catheter extension to serve as target for the advancement of the retrograde guidewire. True-to-true retrograde wiring was defined as intraluminal wire crossing from the distal to proximal cap of the occlusion, and marker wire technique was defined as advancement of a retrograde guidewire to facilitate antegrade wire escalation (AWE) or antegrade dissection re-entry (ADR).

Procedural complications are the composite of in-hospital MACE, perforation, pericardial tamponade, vascular access complications, bleeding, contrast nephropathy, donor vessel dissection/thrombosis, aortocoronary dissection, equipment loss.

Supplementary Table 1. Collateral channel crossing techniques during successful and failed retrograde CTO PCIs.

Variable	Overall (n=1,515)	Retrograde success (n=922)	Retrograde failure (n=593)	<i>p</i> -value
Technical success	79.2%	98.4%	49.4%	0.0001
Collateral channel used				
 Septal 	62.0%	62.6%	61.1%	0.5478
• Epicardial – contralateral	29.9%	27.3%	33.9%	0.0065
• Epicardial – ipsilateral	3.0%	2.0%	4.6%	0.0036
• Saphenous vein graft	13.5%	14.0%	12.7%	0.4546
• Left internal mammary artery	1.7%	1.6%	1.9%	0.7387
Number of collaterals used ^a	1.5±0.8	1.4 ± 0.7	1.8±0.8	0.0001
Collateral crossing attempt #1				
Crossing technique				0.0001
• Surfing-only	58.4%	65.3%	47.2%	
• Contrast-guided	41.6%	34.7%	52.8%	
Successful wire crossing	65.6%	87.3%	31.3%	0.0001
Successful microcatheter crossing	61.4%	84.8%	23.8%	0.0001
Collateral crossing attempt #2				
Crossing technique				0.1250
 Surfing-only 	61.0%	66.4%	56.3%	
• Contrast-guided	39.0%	33.7%	43.7%	
Successful wire crossing	35.1%	63.3%	12.5%	0.0001
Successful microcatheter crossing	32.5%	61.8%	8.3%	0.0001
Collateral crossing attempt #3				
Crossing technique				0.4460
• Surfing-only	55.1%	59.5%	51.8%	
• Contrast-guided	44.9%	40.5%	48.2%	

Successful wire crossing	50.5%	90.9%	21.3%	0.0001
Successful microcatheter crossing	48.0%	90.9%	15.5%	0.0001
Successful collateral crossing	75.3%	100.0%	35.0%	0.0001
Final collateral crossing technique				0.0482
 Surfing-only 	73.5%	75.5%	64.5%	
 Contrast-guided 	26.5%	24.5%	35.5%	
Collateral channel finally crossed				0.0001
• Septal	61.1%	63.1%	40.0%	
• Epicardial – contralateral	20.8%	18.3%	46.7%	
• Epicardial – ipsilateral	3.8%	4.2%	0.0%	
• Saphenous vein graft	13.1%	13.1%	13.3%	
Left internal mammary artery	1.1%	1.3%	0.0%	

^a mean±standard deviation.

Supplementary Table 2. Multivariable analysis for predicting technical failure of retrograde CTO PCI.

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	<i>p</i> -value
CASTLE score ^a [per 1-unit increase]	1.22	1.04	1.42	0.013
eGFR [per 1-unit increase]	0.99	0.99	1.00	0.154
PROGRESS CTO score ^b [per 1-unit increase]	1.28	1.05	1.56	0.017
Prior PCI	1.29	0.85	2.00	0.237
Prior failed CTO PCI attempt	1.46	0.96	2.22	0.077
Dual injection	0.59	0.35	1.00	0.050
Radial access used	0.67	0.46	0.98	0.039
Smoking	1.09	0.67	1.74	0.718
>2 CTO PCI during the same procedure	3.28	1.33	8.02	0.010
IVUS use for crossing	0.81	0.44	1.44	0.489

^a Described by Szijgyarto et al. ^b Described by Christopoulos et al. CI: confidence interval; CTO: chronic total occlusion; eGFR: estimated glomerular filtration rate; IVUS: intravascular ultrasound; PCI: percutaneous coronary intervention

Supplementary Table 3. Multivariable analysis for in-hospital major adverse cardiac events (MACE).

	Odds ratio	Lower 95% CI	Upper 95% CI	<i>p</i> -value
CASTLE score ^a [per 1-unit increase]	1.30	1.05	1.61	0.015
eGFR [per 1-unit increase]	0.99	0.98	1.00	0.054
>2 CTO lesions treated during the same procedure	3.21	1.04	8.13	0.043
Prophylactic LVAD use	2.53	0.96	5.81	0.060
Female gender	1.89	0.98	3.46	0.058
Retrograde approach	3.94	2.01	8.20	< 0.001
Peripheral artery disease	1.81	0.92	3.38	0.085
Prior MI	1.29	0.75	2.26	0.361
Interventional collaterals	1.61	0.85	3.26	0.150
Prior failed CTO PCI attempt	1.47	0.79	2.66	0.218

^a Described by Szijgyarto et al.

CI: confidence interval; CTO: chronic total occlusion; eGFR: estimated glomerular filtration rate; LVAD: left ventricular assist device; MI: myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 4. Temporal trends of technical and procedural outcomes of CTO PCI using the retrograde approach.

	2012	2013	2014	2015	2016	2017	2018	<i>p</i> -value
Overall CTO PCI success rate (including antegrade-only cases)	91.1%	88.1%	87.6%	84.6%	81.0%	82.7%	84.5%	<0.001
Outcomes of the retrograde approx	ach							
Prevalence *	39.3%	42.9%	36.8%	42.8%	40.2%	30.4%	29.9%	< 0.001
J-CTO score * a	3.1±0.9	3.2±1.0	2.7±1.1	3.3±1.0	3.2±1.1	3.0±1.1	3.4±1.1	< 0.001
Final successful crossing strategy *	:							0.010
• AWE	5.1%	11.6%	8.6%	5.6%	9.0%	7.4%	7.7%	
• ADR	13.0%	15.2%	13.7%	18.8%	13.4%	7.1%	9.8%	
• Retrograde	68.8%	60.4%	61.9%	54.9%	58.2%	65.5%	61.1%	
• None	13.0%	12.8%	15.8%	20.7%	19.5%	20.0%	21.4%	
Technical success	86.7%	86.6%	82.0%	77.5%	75.4%	78.1%	76.1%	0.014
Procedural success	85.4%	83.1%	78.1%	73.0%	72.8%	73.4%	69.6%	0.004
In-hospital MACE	1.46%	3.75%	6.57%	7.58%	6.33%	4.93%	3.52%	0.132
Procedural time (min) ^b	156 (114, 191)	160 (110, 211)	200 (142, 268)	225 (174, 272)	197 (150, 264)	183 (129, 245)	179 (146, 230)	< 0.001

Fluoroscopy time (min) ^b	64.8 (49.3, 90.5)	69.3 (46.5, 91.8)	82.4 (57.8, 107.2)	84.6 (66.7, 110.0)	77.8 (58.0, 103.0)	82.5 (62.4, 108.6)	82.1 (62.0, 99.8)	< 0.001
Contrast volume (ml) ^b	350 (225, 480)	275 (210, 395)	300 (220, 400)	350 (249, 450)	300 (229, 425)	300 (200, 396)	210 (150, 293)	<0.001
Air kerma radiation (Gray) ^b	5.7 (4.5, 8.2)	3.2 (2.2, 5.6)	4.1 (2.5, 5.8)	3.9 (2.5, 5.6)	2.9 (1.8, 4.3)	3.5 (2.0, 5.0)	3.2 (1.6, 4.9)	< 0.001

* per lesion based.

a mean±standard deviation. b median (interquartile range).

ADR: antegrade dissection re-entry; AWE: antegrade wire escalation; J: Japanese; MACE: major adverse cardiac events

Supplementary Table 5. Baseline, angiographic, technical, and procedural characteristics of retrograde versus antegrade-only CTO PCI.

Variable	Overall (n=4,108)	Retrograde (n=1,505)	Antegrade-only (n=2,603)	<i>p</i> -value
Baseline clinical characteristics				
Body mass index (kg/m²) b	30.6±6.3	30.7±6.1	30.5±6.3	0.367
Smoking (current)	26.2%	24.9%	26.9%	0.205
CCS angina classification				0.297
• CCS 2≤	89.7%	90.5%	89.2%	
• <ccs 2<="" th=""><th>10.3%</th><th>9.5%</th><th>10.8%</th><th></th></ccs>	10.3%	9.5%	10.8%	
Family history of coronary artery disease	34.4%	37.6%	32.7%	0.009
Prior valve surgery or procedure	3.0%	3.7%	2.5%	0.050
Baseline creatinine (mg/dL) ^c	1.0 (0.9, 1.2)	1.1 (0.9, 1.2)	1.0 (0.9, 1.2)	0.090
Currently on dialysis	2.4%	2.5%	2.3%	0.694
Prior cerebrovascular disease	11.2%	11.7%	11.0%	0.478
Chronic pulmonary disease	14.1%	16.2%	12.9%	0.007
Angiographic characteristics ^a				
Vessel diameter (mm) ^a	2.9±0.5	3.0±0.5	2.8±0.5	<0.001
Collateral filling ^a				<0.001
• Contralateral a	48.7%	64.0%	40.7%	
• Ipsilateral ^a	21.3%	12.5%	25.8%	
• Contralateral & ipsilateral ^a	27.4%	22.0%	30.2%	
• None ^a	2.7%	1.5%	3.3%	
Rentrop collateral filling ^a				0.022

• Rentrop 0 a	3.5%	2.1%	4.1%	
• Rentrop 1 a	17.0%	20.4%	15.6%	
• Rentrop 2 a	43.4%	40.8%	44.4%	
• Rentrop 3 a	36.1%	36.7%	35.9%	
Side branch at proximal cap ^a	52.7%	60.5%	48.5%	<0.001
Blunt/no stump ^a	52.4%	73.1%	41.7%	<0.001
Distal cap at bifurcation ^a	33.9%	48.4%	26.4%	<0.001
Adequate distal landing zone ^a	67.7%	53.4%	75.1%	<0.001
Technical ^a and procedural characteristics				
Intravascular ultrasound use ^a	29.1%	36.0%	25.2%	<0.001
• Facilitate wiring ^a	9.7%	15.7%	6.25%	<0.001
• Stent optimisation ^a	15.0%	16.8%	14.0%	0.012
• Other ^a	3.1%	3.3%	2.9%	0.473
Vascular access complication	1.46%	2.06%	1.11%	0.015
Equipment loss	0.22%	0.40%	0.12%	0.083
Donor artery dissection/thrombosis	0.97%	1.66%	0.58%	<0.001
Bleeding	0.97%	1.59%	0.61%	0.002
Aortocoronary dissection	0.17%	0.27%	0.12%	0.268
Contrast-induced nephropathy	0.27%	0.40%	0.19%	0.226

^a per lesion-based percentages.

^b mean±standard deviation.

^c median (interquartile range).