JACC: CARDIOVASCULAR INTERVENTIONS VOL. 17, NO. 20, 2024

ORIGINAL RESEARCH

CORONARY

Reclassification of CTO Crossing Strategies in the ERCTO Registry According to the CTO-ARC Consensus Recommendations

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ABSTRACT

BACKGROUND The CTO-ARC (Chronic Total Occlusion Academic Research Consortium) recognized that a nonstandardized definition of chronic total occlusion (CTO) percutaneous coronary intervention approaches can bias the complications' attribution to each crossing strategy.

OBJECTIVES The study sought to describe the numbers, efficacy, and safety of each final CTO crossing strategy according to CTO-ARC recommendations.

METHODS In this cross-sectional study, data were retrieved from the European Registry of Chronic Total Occlusions between 2021 and 2022.

RESULTS Out of 8,673 patients, antegrade and retrograde approach were performed in 79.2% and 20.8% of cases, respectively. The antegrade approach included antegrade wiring and antegrade dissection and re-entry, both performed with or without retrograde contribution (antegrade wiring without retrograde contribution: n = 5,929 [68.4%]; antegrade wiring with retrograde contribution: n = 446 [5.1%]; antegrade dissection and re-entry without retrograde contribution: n = 353 [4.1%]; antegrade dissection and re-entry with retrograde contribution: n = 137 [1.6%]). The retrograde approach included retrograde wiring (n = 735 [8.4%]) and retrograde dissection and re-entry (n = 1,073 [12.4%]). Alternative antegrade crossing was associated with lower technical success (70% vs 86% vs 93.1%, respectively; $P < 0.001$) and higher complication rates (4.6% vs 2.9% vs 1%, respectively; $P < 0.001$) as compared with retrograde and true antegrade crossing. However, alternative antegrade crossing was applied mostly as a rescue strategy (96.1%).

CONCLUSIONS The application of CTO-ARC definitions allowed the reclassification of 6.7% of procedures as alternative antegrade crossing with retrograde or antegrade contribution which showed higher MACCE and lower technical success rates, as compared with true antegrade and retrograde crossing. (JACC Cardiovasc Interv. 2024;17:2425–2437) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2024.09.002

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 17, NO. 20, 2024
OCTOBER 28, 2024:2425–2437

ABBREVIATIONS AND ACRONYMS

ADR = antegrade dissection and re-entry

ADR-0 = antegrade dissection and re-entry without retrograde contribution

ADR-R = antegrade dissection and re-entry with retrograde contribution

AW = antegrade wiring

AW-0 = antegrade wiring without retrograde contribution

AW-R = antegrade wiring with retrograde contribution

CART = controlled antegrade and retrograde tracking

CTO = chronic total occlusion

CTO-ARC = Chronic Total Occlusion Academic Research Consortium

ERCTO = European Registry of Chronic Total Occlusion

MACCE = major adverse cardiac and cerebrovascular event(s)

PCI = percutaneous coronary intervention

RDR = retrograde dissection and re-entry

RW = retrograde wiring

Although the success rate of chronic total occlusion (CTO) percutaneous coronary interventions (PCIs) today exceeds 80% to 90% in the hands of expert and dedicated operators, the incidence of complications remains non-negligible, particularly in the retrograde approach.[1-3] The CTO-ARC (Chronic Total Occlusion Academic Research Consortium) recognized consistent discordances in previous studies between the intended crossing technique and the real guidewire course, leading to inappropriate attribution of complications to the different crossing strategies.[4] Therefore, it was strongly recommended to adopt a standardized definition of crossing strategies in order to attribute the related complications properly, based on the time of their occurrence. However, if a such reclassification of crossing strategies leads to a reclassification of complication rates or prognosis was not still investigated.

The purpose of the present study was to classify consecutive CTO PCI procedures derived from the contemporary European Registry of Chronic Total Occlusion (ERCTO) according to the CTO-ARC consensus recommendations to report the corresponding rates of applied techniques and the related complication rates accurately. The study was reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[5]

METHODS

In this cross-sectional study, 8,673 CTO PCIs enrolled in the ERCTO registry between January 2021 and December 2022 were retrieved. The ERCTO registry is an electronically based nonrandomized retrospective observational multicenter registry including consecutive patients undergoing CTO PCI. It was developed by the Euro CTO non-profit association to collect data from patients treated by CTO PCI by expert operators at referral centers across Europe. The primary aim of the registry consists of the assurance and quality evaluation of the management of CTO PCI during routine clinical care. There are not exclusion criteria for patients' enrollment. Related to the retrospective study design, no written informed consent was deemed necessary. Patients' data were anonymized and managed according to the data safety protocols of the participating centers. The study was performed in accordance with the Declaration of Helsinki. The decision to treat CTO patients by PCI was based on clinical decision making during routine clinical care and according to international guidelines on myocardial revascularization.[6] The sequence of wiring techniques and the guidewire selection were left entirely to the operator's discretion. According to their credentials and as described previously, operators were classified as high-volume operators and mid-volume operators.[2]

DEFINITIONS. According to the CTO-ARC definitions,[4] CTOs were defined as the absence of antegrade flow through the lesion with a presumed or documented

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 26, 2024; revised manuscript received August 1, 2024, accepted September 3, 2024.

duration of >3 months with TIMI final CTO crossing strategies were taken to classify all CTO PCI procedures. The antegrade approach was defined as when the occlusion segment was approached from the proximal CTO cap with the intention of crossing the distal CTO cap into the distal true lumen. Retrograde was defined as when the occlusion segment was approached from the distal CTO cap with the intention of crossing the proximal CTO cap into true lumen.

Wiring of the CTO lesion was defined as follows: intraplaque means the CTO was intentionally crossed through the CTO body. Extraplaque means that the CTO was crossed through a dissection plane followed by re-entry into the true vessel lumen at or beyond the re-entry point.

Extraplaque wiring can be performed antegradely or retrogradely, defining the terms of antegrade dissection and re-entry (ADR) and retrograde dissection and re-entry (RDR), respectively.

The antegrade group included those procedures in which the CTO lesion was finally crossed by true anticipated antegrade wiring (AW) without retrograde or ADR contribution. Additionally, the antegrade group included alternative antegrade crossing strategies, the CTO lesion was finally crossed by antegrade wiring with retrograde contribution (AW-R) and those in which the CTO lesion was finally crossed by antegrade dissection and re-entry with retrograde contribution (ADR-R) or antegrade dissection and re-entry without retrograde contribution (ADR-0). The retrograde group included those procedures in which the CTO was finally crossed retrogradely, by retrograde wiring (RW) or RDR techniques. The term rescue or bailout approach in the context of CTO PCI reflects the final approach following other failed previous crossing attempts (**Figure 1**).

Technical success was defined as the successful recanalization of the CTO vessel with <30% residual stenosis and final TIMI flow grade 3. This definition is slightly different from the CTO-ARC definition, which includes as technical success even those cases with a final TIMI flow grade of 2. Procedural success was defined as technical success in the absence of major adverse cardiovascular and cerebrovascular events (MACCE), a composite of death, myocardial infarction, stroke, urgent repeated revascularization (re-PCI or surgery), or pericardiocentesis. Procedural myocardial infarction was defined according to the European Society of Cardiology guidelines on myocardial revascularization.[6] MACCE were documented occurring during the index CTO PCI procedure and within the index hospital stay. Bifurcations were defined by the presence of a side branch of diameter >2 mm within 5 mm of the proximal or distal cap of the CTO lesion.[7]

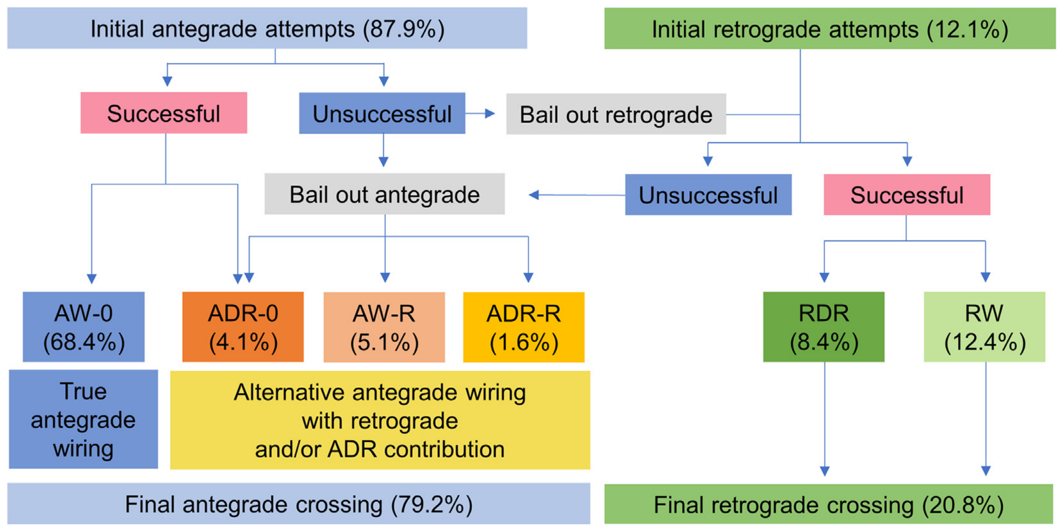
The collateral circulation was classified according to the collateral connection grade size-based classification by Werner et al.[8] CTO calcifications, assessed semi-quantitatively by angiography, were classified as mild (spots), moderate (radiopaque densities noted during the cardiac cycle involving only one side of the vascular wall), and severe (radiopaque densities noted without cardiac motion before contrast injection, generally involving both sides of the arterial wall).

STATISTICAL ANALYSIS. The statistical unit considered for the data analysis was the patient. Continuous variables were presented as mean ± SD or median (Q1-Q3), while categorical variables were presented as count and percentage. To assess the statistical significance, the chi-square test was used for categorical variables (or Fisher exact test when necessary). The Shapiro-Wilk test was used to assess the normality of the distribution, and subsequently analyzed employing either a 1-way analysis of variance or nonparametric tests such as the Kruskal-Wallis test. To explore pairwise multiple comparisons, Tukey's honestly significant difference or Dunn's post hoc test was conducted. These adjustments yield adjusted *P* values, which mitigate the risk of inflated *P* values resulting from multiple hypothesis testing at a predefined significance alpha level. Moreover, a logistic regression model, adjusting for clinical, procedural, and lesion characteristics, was employed to examine the OR for the occurrence of procedural and in-hospital complications across various clinical and procedural variables. Confounders were selected both with clinical and statistical relevance in mind. Significant variables identified in univariable analysis were incorporated into multivariable analysis, with results reported as adjusted ORs and their respective 95% CIs. A 2-sided *P* value <0.05 denoted statistical significance. The unadjusted estimates with their 95% CIs from the univariable models are included in the Supplemental Appendix. Data processing was performed using R software (version 4.3.3; R Foundation for Statistical Computing).

RESULTS

CLASSIFICATION AND TIMING OF CROSSING STRATEGIES. As outlined in the **Central Illustration**, the antegrade approach as the final CTO crossing strategy was performed most, in 79.2% (n = 6.865). Of these, true AW (antegrade wiring without retrograde contribution [AW-0]) was most frequent (68.4%). In

FIGURE 1 Application of CTO-ARC Definitions of Crossing Strategies to the ERCTO Registry



Flow chart from initial attempts to final crossing strategy. ADR = antegrade dissection and re-entry; ADR-0 = antegrade dissection and re-entry without retrograde contribution; ADR-R = antegrade dissection and re-entry with retrograde contribution; AW-0 = antegrade wiring without retrograde contribution; AW-R = antegrade wiring with retrograde contribution; CTO-ARC = Chronic Total Occlusion Academic Research Consortium; ERCTO = European Registry of Chronic Total Occlusion; RDR = retrograde dissection and re-entry; RW = retrograde wiring.

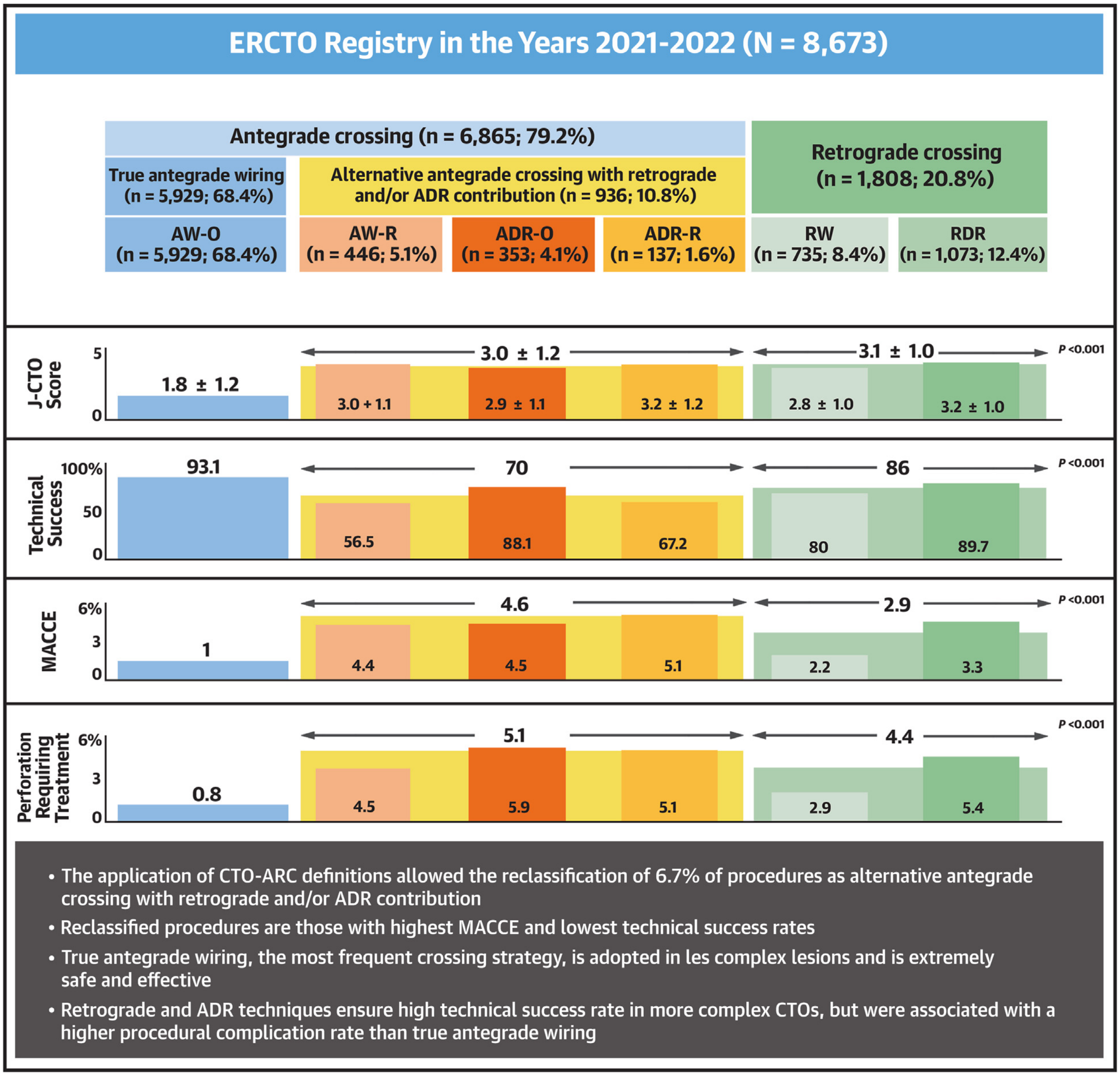
contrast, alternative antegrade crossing was performed in 10.8%. Here, AW-R was most common (5.1% [n = 446]), followed by ADR-0 (4.1% [n = 353]) and ADR-R (1.6% [n = 137]). Notably, retrograde contribution within alternative antegrade crossing was necessary in 6.7% either as AW-R or ADR-R. Final retrograde crossing was performed in 20.8% (n = 1,808).

ANALYSES ACCORDING TO FURTHER CROSSING ASPECTS. With respect to the first initial CTO crossing attempts, AW-0 was used in most cases (83%), followed by retrograde techniques and a small proportion of ADR-0. Regarding all CTO PCIs in which any retrograde technique per se was applied (n = 2,391), 37% were primary retrograde attempts, while the remaining 63% were bailout attempts after AW (58%) and ADR failure (5%). Focusing only on patients in which any ADR was performed (n = 537), ADR-0 and ADR-R were attempted primarily in 9.4%, while in the remaining 89.6%, those were applied as bailout after the failure of AW-0 (61.6%) or retrograde crossing (28%) (Supplemental Figure 1).

PATIENTS AND LESIONS CHARACTERISTICS. Population and lesion characteristics are shown in **Tables 1 and 2**. Most patients were males, and the mean age was 65 years. AW-0 showed a lower rate of previous coronary artery bypass grafting (AW-0 = 9%, ADR-0 = 21.8%, AW-R = 18.8%, ADR-R = 11.7%, RW = 14.9%, RDR = 19.2%; $P < 0.001$) and lower lesion complexity than other crossing strategies (J-CTO [Multicenter CTO Registry of Japan] score: AW-0 = 1.8 ± 1.2, AW-R = 3.0 ± 1.1, ADR-0 = 3.0 ± 1.1, ADR-R = 3.2 ± 1.0, RW = 2.8 ± 1.0, RDR = 3.2 ± 1.0; $P < 0.001$). In both antegrade and retrograde approaches, dissection and re-entry techniques had higher mean lesion length than other intraplaque crossing strategies (ADR-0 32.2 ± 17.4 mm vs AW-0 23.1 ± 14.4 mm; ADR-R 37.5 ± 18.8 mm vs AW-R 33.6 ± 18.6 mm; RDR 39.8 ± 19.1 mm vs RW 32.0 ± 17.4 mm; $P < 0.001$). Interventional collaterals (collateral connection grade >1) were mostly present in RW and RDR than AW-R and ADR-R (97.6% vs 95.2% vs 87% vs 86.1%, respectively; $P < 0.001$).

PROCEDURAL CHARACTERISTICS. Procedural details are reported in **Table 3**. AW-0 revealed highest technical success rates (93.1%), followed by RDR (89.7%), ADR-0 (88.1%), and RW (80%). ADR-R had the lowest technical success rate at 67.2%. Moreover, RDR had higher procedural success rate than RW (86.9% vs 77.7%). As compared with other crossing strategies, RDR was associated with increased stent lengths (RDR = 82.8 ± 40.4 mm), a higher number of implanted stents (RDR = 2.7 ± 1.4), and a higher proportion of CTO bifurcations attempted

CENTRAL ILLUSTRATION Performance of the Final Crossing Strategies Classified According to CTO-ARC Recommendations



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Description of crossing strategies' performance by grouping into true antegrade wiring, alternative antegrade crossing with retrograde and/or antegrade dissection and re-entry (ADR) contribution, and retrograde scenarios. Perforation requiring treatment includes perforations with and without tamponade. ADR-O = antegrade dissection and re-entry without retrograde contribution; ADR-R = antegrade dissection and re-entry with retrograde contribution; AW-O = antegrade wiring without retrograde contribution; AW-R = antegrade wiring with retrograde contribution; CTO-ARC = Chronic Total Occlusion Academic Research Consortium; ERCTO = European Registry of Chronic Total Occlusion; J-CTO = Japanese Multicenter CTO Registry; MACCE = major adverse cardiac and cerebrovascular event(s); RDR = retrograde dissection and re-entry; RW = retrograde wiring.

TABLE 1 Clinical Characteristics

	Overall (N = 8,673)	AW-O (n = 5,929)	AW-R (n = 446)	ADR-O (n = 353)	ADR-R (n = 137)	RW (n = 735)	RDR (n = 1,073)	*P* Value
Age, y	65.2 ± 11.2	64.8 ± 22.0	66.0 ± 10.6	67.1 ± 11.2	65.7 ± 9.0	64.2 ± 10.5	65.0 ± 10.4	0.118
Male	7,183 (82.8)	4,793 (80.8)	385 (86.3)	295 (83.6)	114 (83.2)	630 (85.7)	966 (90)	0.021
Hypertension	6,548 (75.5)	4,398 (74.2)	347 (77.8)	272 (77.1)	113 (82.5)	555 (75.5)	863 (80.4)	<0.001
Dyslipidemia	6,285 (72.5)	4,194 (70.7)	338 (75.8)	269 (76.2)	98 (71.5)	537 (73.1)	849 (79.1)	<0.001
Diabetes mellitus	2,682 (30.9)	1,802 (30.4)	149 (33.4)	100 (28.3)	41 (29.9)	239 (32.5)	351 (32.7)	0.334
ID diabetes mellitus	463 (5.3)	325 (5.5)	20 (4.5)	12 (3.4)	9 (6.6)	45 (6.1)	52 (4.8)	0.337
Smoker	1,951 (22.5)	1,299 (21.9)	92 (20.6)	68 (19.3)	45 (32.8)	185 (25.2)	262 (24.4)	0.003
Previous MI	2,876 (33.2)	1,909 (32.2)	179 (40.1)	106 (30)	45 (32.8)	261 (35.5)	376 (35)	0.004
Prior stroke	307 (3.5)	204 (3.4)	22 (4.9)	8 (2.3)	10 (7.3)	24 (3.3)	39 (3.6)	0.069
Previous CABG	1,027 (11.8)	535 (9)	84 (18.8)	77 (21.8)	16 (11.7)	109 (14.8)	206 (19.2)	<0.001
Previous PCI	4,482 (51.7)	2,938 (49.6)	255 (57.2)	201 (56.9)	73 (53.3)	415 (56.5)	600 (55.9)	0123
Atrial fibrillation	401 (4.6)	282 (4.8)	27 (6.1)	11 (3.1)	11 (8)	34 (4.6)	36 (3.4)	0.254
eGFR, mL/min/1.73 m^2	73.4 ± 300.0	76.1 ± 362.4	70.7 ± 25.0	61.8 ± 34.1	66.4 ± 27.0	71.1 ± 29.7	66.0 ± 29.3	0.875
Impaired LVEF								
≥50%	6,051 (69.7)	4,166 (70.3)	311 (69.7)	247 (70.3)	93 (67.9)	503 (68.4)	730 (68)	<0.001
≥35% and <50%	1,966 (22.7)	1,289 (21.7)	114 (25.6)	77 (21.8)	37 (27)	185 (25.2)	264 (24.6)	
<35%	656 (7.6)	474 (8)	21 (4.7)	28 (7.9)	7 (5.1)	47 (6.4)	79 (7.4)	
Clinical presentation								
Asymptomatic	1,401 (16.2)	936 (15.8)	99 (22.2)	63 (17.8)	30 (21.9)	126 (17.1)	147 (13.7)	<0.001
Stable angina	6,443 (74.3)	4,374 (73.8)	308 (69.1)	254 (72)	99 (72.3)	542 (73.7)	866 (80.7)	<0.001
Unstable angina	408 (4.7)	293 (4.9)	23 (5.2)	18 (5.1)	6 (4.3)	35 (4.8)	33 (3.1)	0.041
MI	244 (2.8)	180 (3)	13 (2.9)	10 (2.8)	3 (2.2)	16 (2.2)	21 (2)	0.185
CCS angina score >II	3,977 (45.9)	2,800 (47.2)	242 (54.3)	164 (46.5)	71 (51.8)	307 (41.8)	393 (36.6)	<0.001
NYHA functional class >I	5,893 (67.9)	3,973 (67)	306 (68.6)	253 (71.7)	98 (71.5)	488 (66.4)	775 (72.2)	0.009
Number of diseased vessels								
1	3,109 (35.8)	2,153 (36.3)	150 (33.6)	140 (39.7)	57 (41.6)	247 (33.6)	362 (33.7)	<0.001
2	2,555 (29.5)	1,779 (30)	133 (29.8)	96 (27.2)	35 (25.5)	215 (29.3)	297 (27.7)	
3	2,809 (32.4)	1,820 (30.7)	158 (35.4)	112 (31.7)	47 (34.3)	264 (35.9)	408 (38)	

Values are mean ± SD or n (%).

ADR-O = antegrade dissection and re-entry without retrograde contribution; ADR-R = antegrade dissection and re-entry with retrograde contribution; AW-O = antegrade wiring without retrograde contribution; AW-R = antegrade wiring with retrograde contribution; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CTO = chronic total occlusion; eGFR = estimated glomerular filtration rate; ID = insulin dependent; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RDR = retrograde dissection and re-entry; RW = retrograde wiring; STEMI = ST-segment elevation myocardial infarction.

(RDR = 30.4%). Notably, ADR-R was associated with longest procedural fluoroscopic time (79.3 minutes), followed by AW-R (72.1 minutes), RDR (71.3 minutes), ADR-O (53.1 minutes), and lowest in AW-O (48.4 minutes) alongside a corresponding sequence of injected contrast volume.

PROCEDURAL COMPLICATIONS. Table 4 and Supplemental Figure 2 report procedural complications and in-hospital outcomes according to the crossing strategies. In-hospital MACCE and overall perforations rates were lowest in AW-O and highest in ADR-R (MACCE: AW-O = 1%, AW-R = 4.4%, ADR-O = 4.5%, ADR-R = 5.1%, RW = 2.2%, RDR = 3.3%; $P < 0.001$; perforations: AW-O = 1.8%, AW-R = 10.1%, ADR-O = 8.8%, ADR-R = 10.9%, RW = 6.3%, RDR = 8.6%; $P < 0.001$).

From a total of 333 overall perforations (Figure 2), 20% led to cardiac tamponade resulting from involved collateral channels (31%) and the target coronary vessel (69%). Perforations responsible for cardiac tamponade were most frequently observed in ADR-O (2.8%), followed by AWR-R (2%) and RDR (2%), and were lowest in AW-O (0.3%) and RW (0.8%). All perforations with tamponade required at least 1 specific treatment. In contrast, perforations without cardiac tamponade were managed conservatively in 60% of the cases. Out of the 81 collateral channel perforations, 26% led to tamponade. Compared with the retrograde group, AW-R and ADR-R showed significantly higher collateral perforations (4.1% vs 3%; $P < 0.001$) (Supplemental Figure 3).

Side branch occlusion was highest in ADR-R (5.1%), followed by ADR-O (3.7%), RDR (2.0%), and AW-R (1.6%), and was lowest in AW-O (0.9%) (Table 4).

Specifically focusing on the comparison between RDR and RW, no differences were seen in the rates of

TABLE 2 Lesion Characteristics

	Overall (N = 8,673)	AW-O (n = 5,929)	AW-R (n = 446)	ADR-O (n = 353)	ADR-R (n = 137)	RW (n = 735)	RDR (n = 1,073)	*P* Value
Target vessel								
LAD	2,292 (26.4)	1,750 (29.5)	101 (22.6)	86 (24.4)	33 (24.1)	182 (24.8)	140 (13)	<0.001
LCX	1,287 (14.8)	1,019 (17.2)	47 (10.5)	66 (18.7)	10 (7.3)	64 (8.7)	81 (7.5)	
RCA	4,844 (55.9)	2,970 (50.1)	287 (64.3)	190 (53.8)	93 (67.9)	467 (63.5)	837 (78)	
IMA	4 (0)	4 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
SB	202 (2.3)	161 (2.7)	9 (2)	7 (2)	1 (0.7)	15 (2)	9 (0.8)	
SVG	11 (0.1)	8 (0.1)	0 (0)	1 (0.3)	0 (0)	1 (0.1)	1 (0.1)	
LMT	32 (0.4)	16 (0.3)	2 (0.4)	3 (0.8)	0 (0)	6 (0.8)	5 (0.5)	
CTO location								
Ostial	903 (10.4)	442 (7.5)	62 (13.9)	37 (10.5)	23 (16.8)	180 (24.5)	159 (14.8)	<0.001
Proximal	3,249 (37.5)	2,123 (35.8)	183 (41)	136 (38.5)	60 (43.8)	252 (34.3)	495 (46.1)	
Middle	3,753 (43.3)	2,736 (46.1)	163 (36.5)	165 (46.7)	50 (36.5)	262 (35.6)	377 (35.1)	
Distal	767 (8.8)	627 (10.6)	38 (8.5)	15 (4.2)	4 (2.9)	41 (5.6)	42 (3.9)	
Lesion length, mm	27.1 ± 16.9	23.1 ± 14.4	33.6 ± 18.6	32.2 ± 17.4	37.5 ± 18.8	32.0 ± 17.4	39.8 ± 19.1	<0.001
CTO diameter, mm	3.0 ± 1.2	2.9 ± 1.4	3.1 ± 1.1	3.1 ± 0.5	3.2 ± 0.4	3.1 ± 0.6	3.2 ± 0.5	<0.001
J-CTO score	2.2 ± 1.3	1.8 ± 1.2	3.0 ± 1.1	2.9 ± 1.1	3.2 ± 1.0	2.8 ± 1.0	3.2 ± 1.0	<0.001
Lesion length >20 mm	4,772 (55.1)	2,637 (44.5)	327 (73.3)	251 (71.1)	116 (84.7)	512 (69.7)	929 (86.7)	<0.001
Stump								
Tapered	3,633 (41.9)	3,055 (51.5)	98 (22)	111 (31.4)	31 (22.6)	136 (18.5)	202 (18.8)	<0.001
Blunt	3,393 (39.1)	1,982 (33.4)	228 (51.1)	180 (51)	62 (45.3)	349 (47.5)	592 (55.2)	
Tortuosity (severe)	227 (2.6)	132 (2.2)	14 (3.1)	10 (2.8)	7 (5.1)	29 (3.9)	35 (3.3)	0.009
≥1 previous attempt	1,885 (21.8)	1,044 (17.7)	129 (29)	110 (31.2)	43 (31.6)	217 (29.6)	342 (32)	<0.001
CC grade >1	7,776 (89.7)	5,212 (87.9)	388 (87)	285 (80.7)	118 (86.1)	700 (95.2)	1047 (97.6)	<0.001
Heavy calcifications	1,606 (18.5)	843 (14.2)	131 (29.4)	94 (26.6)	39 (28.5)	182 (24.8)	317 (29.5)	<0.001
In-stent CTO	805 (9.3)	624 (10.5)	38 (8.5)	21 (5.9)	11 (8)	60 (8.2)	51 (4.8)	<0.001

Values are n (%) or mean ± SD.

CC = collateral connection; IMA = internal mammary artery; J-CTO = Multicenter CTO Registry of Japan; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMT = left main trunk; RCA = right coronary artery; SB = side branch; SVG = saphenous venous graft; other abbreviations as in Table 1.

MACCE (2.8% vs 2.3%; $P = 0.210$), dissection of the donor artery (0.6% vs 1.4%; $P = 0.125$), and side branch occlusion (2% vs 1.5%; $P = 0.583$), whereas a trend was observed for overall perforations (8.6% vs 6.3%; $P = 0.083$) and with tamponade (0.8% vs 0.2%; $P = 0.077$).

Within a logistic regression model (Figure 3), retrograde crossing (OR: 2.65; 95% CI: 1.65-4.24;

TABLE 3 Procedural Characteristics

	Overall (N = 8,673)	AW-O (n = 5,929)	AW-R (n = 446)	ADR-O (n = 353)	ADR-R (n = 137)	RW (n = 735)	RDR (n = 1,073)	*P* Value
Technical success	7,727 (89.1)	5,521 (93.1)	252 (56.5)	311 (88.1)	92 (67.2)	588 (80)	963 (89.7)	<0.001
Procedural success	7,576 (87.4)	5,458 (92.1)	232 (52.1)	295 (83.6)	89 (65.0)	571 (77.7)	931 (86.9)	<0.001
Procedural metrics								
Fluoroscopic time, min	32.0 (18.3-55.0)	25.0 (15.0-37.3)	59.0 (43.0-84.0)	50.0 (32.7-68.0)	77.0 (55.7-98.4)	53.0 (35.0-73.0)	68.5 (49.1-90.0)	<0.001
Contrast volume, mL	200 (130-281)	180 (120-250)	300 (200-398)	250 (160-325)	300 (210-400)	230 (170-320)	250 (180-320)	<0.001
Procedural time, min	87.0 (55.0-129)	69.0 (47.0-100)	137 (112-180)	115 (75.0-150)	165 (130-197)	120 (90.0-160)	150 (113-180)	<0.001
Bifurcation stenting	2,233 (25.7)	1,528 (25.8)	100 (22.4)	76 (21.5)	30 (21.9)	173 (23.5)	326 (30.4)	<0.001
2-stent technique	402 (4.6)	260 (4.4)	20 (4.5)	13 (3.7)	5 (3.6)	37 (5)	67 (6.2)	0.607
Implanted stents	2.00 (1.00-3.00)	2.00 (1.00-3.00)	1.00 (0-3.00)	2.00 (1.00-3.00)	2.00 (0-3.00)	2.00 (1.00-3.00)	3.00 (2.00-4.00)	<0.001
Max stent diameter, mm	3.10 (2.75-3.50)	3.00 (2.75-3.50)	2.50 (0-3.50)	3.00 (2.64-3.50)	3.00 (0-3.50)	3.35 (0-3.70)	3.50 (3.00-4.00)	<0.001
Total stented length, mm	56.0 (31.0-86.0)	50.0 (30.0-76.0)	33.0 (0-81.0)	73.0 (38.0-100)	66.0 (0-100)	62.0 (23.0-90.0)	90.0 (62.0-110)	<0.001
IVUS-assisted procedure	1,844 (21.3)	1,128 (19)	93 (20.9)	79 (22.4)	32 (23.4)	170 (23.1)	342 (31.9)	<0.001

Values are n (%) or median (Q1-Q3).

IVUS = intravascular ultrasound; other abbreviations as in Table 1.

TABLE 4 Complications

	Overall (N = 8,673)	AW-O (n = 5,929)	AW-R (n = 446)	ADR-O (n = 353)	ADR-R (n = 137)	RW (n = 735)	RDR (n = 1,073)	*P* Value
MACCE	151 (1.7)	57 (1.0)	20 (4.4)	16 (4.5)	7 (5.1)	16 (2.2)	35 (3.3)	<0.001
Death	27 (0.3)	16 (0.3)	1 (0.2)	2 (0.6)	0 (0)	2 (0.3)	6 (0.6)	0.502
Overall MI	41 (0.5)	16 (0.3)	6 (1.3)	4 (1.1)	3 (2.2)	6 (1)	6 (0.6)	0.002
Urgent revascularization	11 (0.1)	4 (0.01)	1 (0.2)	0	2 (1.4)	2 (0.2)	2 (0.2)	0.984
Perforations with tamponade	67 (0.8)	19 (0.3)	9 (2.0)	10 (2.8)	2 (1.4)	6 (0.8)	21 (2.0)	<0.001
Stroke	5 (0.1)	2 (0.04)	3 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0.016
Other complications								
Side branch occlusion	110 (1.3)	51 (0.9)	7 (1.6)	13 (3.7)	7 (5.1)	11 (1.5)	21 (2)	<0.001
Stent thrombosis	15 (0.2)	12 (0.2)	0 (0)	1 (0.3)	0 (0)	2 (0.3)	0 (0)	0.574
Dissection of donor artery	37 (0.4)	12 (0.2)	7 (1.6)	2 (0.6)	0 (0)	10 (1.4)	6 (0.6)	<0.001
Major vascular complications	69 (0.8)	28 (0.5)	11 (2.5)	6 (1.7)	2 (1.5)	8 (1.1)	14 (1.3)	<0.001
Vascular access surgery	19 (0.2)	10 (0.2)	3 (0.7)	1 (0.3)	0 (0)	1 (0.1)	4 (0.4)	0.248
Major vascular complications	88 (1)	38 (0.7)	14 (3.2)	7 (2.0)	2 (1.5)	9 (1.2)	18 (1.7)	<0.001
Hb reduction >3 g/dL	11 (0.1)	5 (0.1)	3 (0.7)	0 (0)	1 (0.7)	0 (0)	2 (0.2)	0.004
Blood transfusions	17 (0.2)	4 (0.1)	3 (0.7)	2 (0.6)	1 (0.7)	3 (0.4)	4 (0.4)	<0.001
Contrast-induced nephropathy	73 (0.8)	41 (0.7)	3 (0.7)	1 (0.3)	3 (2.2)	10 (1.4)	15 (1.4)	<0.001
Perforations								
Overall	333 (3.9)	104 (1.8)	45 (10.1)	31 (8.8)	15 (10.9)	46 (6.2)	92 (8.6)	<0.001
Without tamponade	266 (3.0)	85 (1.5)	36 (8.1)	21 (6.0)	13 (9.5)	40 (5.4)	71 (6.6)	<0.001
At collateral channel site	81 (0.9)	0 (0)	17 (3.8)	0 (0)	7 (5.1)	14 (1.9)	43 (4.0)	<0.001
Requiring treatment	173 (2.0)	46 (0.8)	20 (4.5)	21 (5.9)	7 (5.1)	21 (2.9)	58 (5.4)	<0.001

Values are n (%).
MACCE = major adverse cardiac and cerebrovascular event(s); other abbreviations as in Table 1.

$P < 0.001$), ADR crossing (OR: 2.29; 95% CI: 1.29-3.96; $P = 0.003$), middle volume operators (OR: 1.72; 95% CI: 1.15-2.54; $P = 0.006$), and left ventricular ejection fraction <35% (OR: 1.81; 95% CI: 1.00-3.07) were demonstrated to be independently associated with the occurrence of in-hospital MACCE.

Finally, applying CTO-ARC definitions, 6.7% CTO PCIs that previously would have been classified as retrograde are now part of the antegrade approach (AW-R = 5.1% and ADR-R = 1.6%). In these 2 groups, a total of 27 MACCE, 60 coronary perforations, 7 dissections of donor artery, and 14 side branch occlusions occurred, corresponding to 17.9% of the total MACCE count (n = 27 of 151), 18% of overall perforations (n = 60 of 333), 19% of overall dissections of donor vessel (n = 7 of 37), and 12.7% of overall side branch occlusions (n = 14 of 110). Out of the 7 perforations with tamponade that occurred in this subgroup, 5 involved the collateral channels.

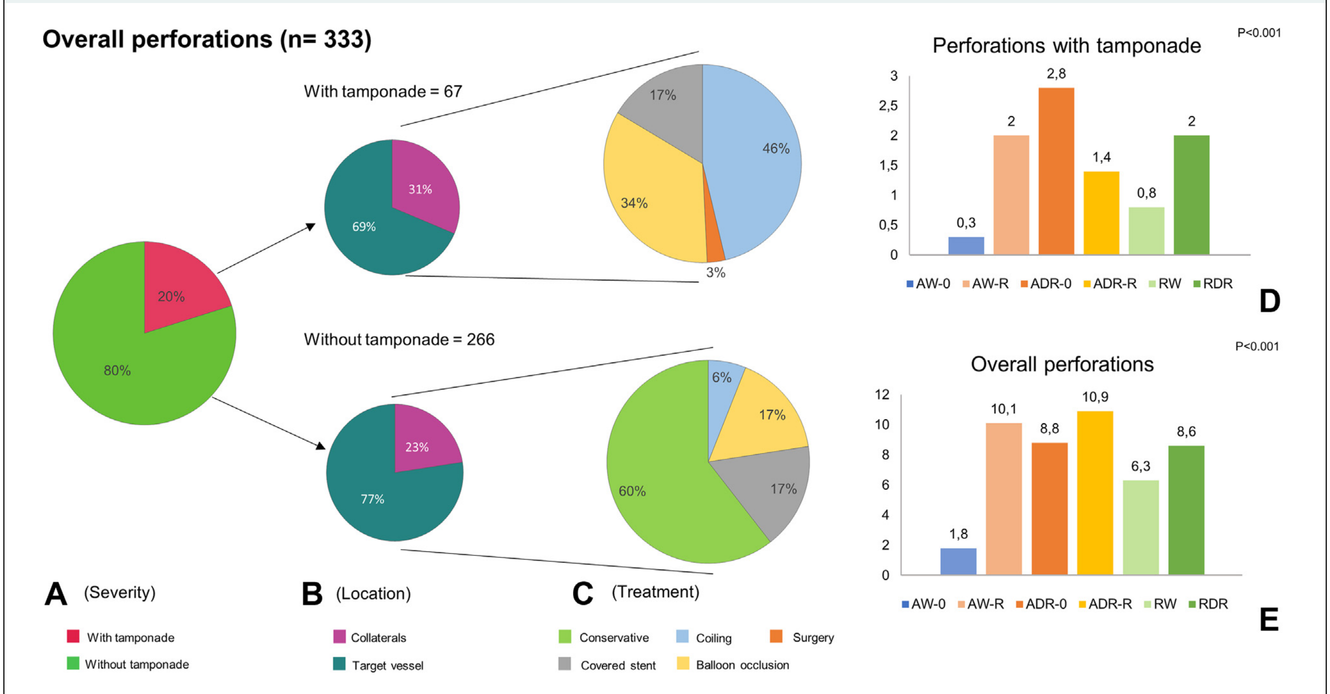
DISCUSSION

The main findings of the present study can be summarized as follows:

1. Following CTO-ARC definitions of crossing strategies, a non-negligible proportion of procedures with retrograde attempts, characterized by a high rate of MACCE and other procedural complications, have been reclassified as antegrade (ie, AW-R, ADR-O, or ADR-R).
2. True AW, retrograde crossing, and rescue antegrade are characterized by different lesion complexity and procedural success rates.
3. Both the retrograde approach and ADR techniques ensured a high technical success rate in more complex CTO lesions but were also associated with higher MACCE than AW-O.

RECLASSIFICATION OF CROSSING STRATEGIES AND ATTRIBUTION OF PROCEDURAL COMPLICATIONS. Many large prospective registries and trials have defined retrograde procedures not only when the CTO was crossed from distal to the proximal true lumen, but also when the CTO was crossed antegradely from the proximal to the distal true lumen, after unsuccessful retrograde attempts.[1-3,9-12] This may finally result in an additional misleading assignment of related complications. As demonstrated by the present study, the application of the CTO-ARC classification of crossing strategies has led to a reclassification of retrograde procedures with an antegrade rescue crossing strategy into the antegrade approach

FIGURE 2 Description of Perforations



Severity (A), location (B), and treatment (C) of perforation. Distribution of perforation with tamponade (D) and overall perforation (E) among crossing strategies. Abbreviations as in Figure 1.

(ie, AW-R and ADR-R). The proportion of reclassified procedures could be considered relatively small. However, its impact seems relevant, as it was associated with lower technical success and highest complication rates, affecting antegrade techniques rather than retrograde ones.

CLASSIFICATION ACCORDING TO THE 3 CTO CROSSING SCENARIOS MODEL. The application of CTO-ARC definitions of crossing strategies has outlined 3 specific CTO crossing scenarios, reflecting the contemporary approach to CTO PCI in daily practice: primary antegrade, retrograde, and alternative antegrade (Central Illustration). The latter comprised patients with AW-R, or ADR-0 or ADR-R.

True AW. The true antegrade approach covers roughly 70% of CTO procedures, representing the most frequently adopted initial crossing strategy. It is characterized in all cases by true anticipated AW (AW-0), by even 1 single wire in 86% of cases, in generally less complex CTO lesions. This group showed a high technical success rate (93.1%) and a very low MACCE rate (1%). Similarly, Suzuki et al[11] showed a technical success rate as high as 95% in the case of true antegrade wiring, performed by a single guidewire use in 81.5% of cases. In the PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) registry, Tajti et al[1] showed that antegrade wire escalation was more commonly applied as an initial crossing approach (74%) for less complex lesions (J-CTO score 2.24 ± 1.24, PROGRESS-CTO score 1.32 ± 0.87) with successful crossing (AW-0) in approximately half of the cases.

Retrograde crossing. Retrograde crossing covers roughly 20% of procedures and represents the second most frequent initial crossing strategy after AW-0. Furthermore, it includes 63% of bailout procedures, in which retrograde crossing generally occurs after AW failure and less frequently after ADR failure. Of note, despite the high complexity of CTO lesions attempted in the retrograde scenario, the procedural success rate was high (83%).

Importantly, RDR techniques were used with a more favorable risk/benefit balance than RW (Supplemental Table 1). Similarly, Allana et al[12] recently reported that in the retrograde approach, RDR techniques were associated with higher success than RW. Conversely, retrograde true lumen crossing or just a marker for antegrade crossing had a lower incidence of in-

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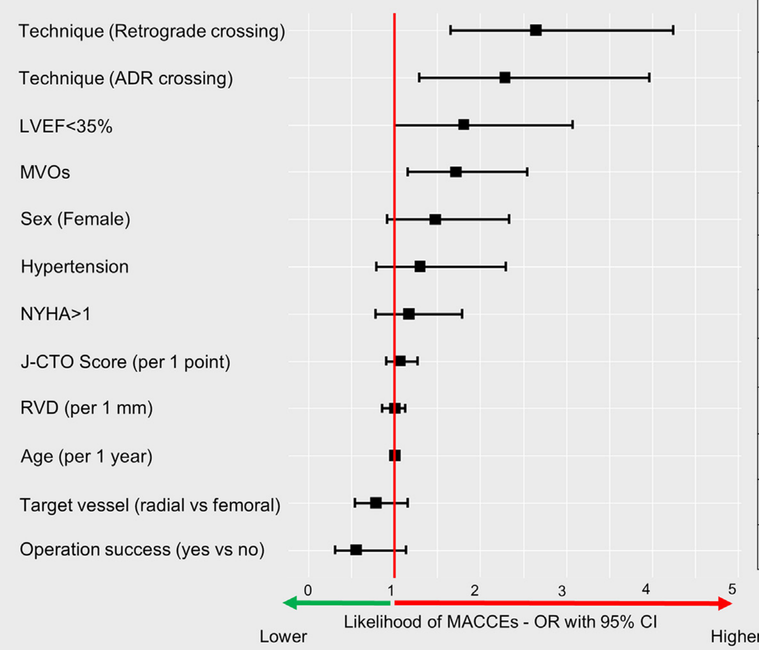
FIGURE 3 **Logistic Regression Model of Patient-Related and Procedure-Related Factors Associated With MACCE**



OR	95%CI	Pr(>|z|)
2.65	1.65-4.24	<0.001
2.29	1.29-3.96	0.003
1.81	1.00-3.07	0.036
1.72	1.15-2.54	0.006
1.48	0.91-2.33	0.097
1.30	0.79-2.29	0.330
1.17	0.78-1.79	0.464
1.07	0.90-1.27	0.464
1.01	0.86-1.12	0.862
1.01	1.00-1.03	0.121
0.79	0.54-1.15	0.225
0.56	0.31-1.13	0.082

Logistic regression model showing the association between different patient-related and procedure-related factors to procedural and in-hospital major adverse cardiac and cerebrovascular events (MACCE). J-CTO = Multicenter CTO Registry of Japan; LVEF = left ventricular ejection fraction; MVO = mid-volume operator; RVD = reference vessel diameter; other abbreviations as in Figure 1.

hospital major adverse cardiovascular event (MACE) (2.1% and 0.8%, respectively) than other RDR techniques such as conventional reverse controlled antegrade and retrograde tracking (CART), contemporary reverse CART, extended reverse CART, guide extension-assisted reverse CART, and CART (5.5%, 3.0%, 2.1%, 3.2%, and 4.1%, respectively; $P < 0.01$).[12]

Alternative antegrade crossing/rescue antegrade. Alternative antegrade crossing/rescue antegrade covers the remaining 10% of procedures, and represents a bailout scenario in most cases (96.1%). This group includes ADR-0, and all those procedures reclassified by CTO-ARC recommendation as AW-R and ADR-R. Although these 2 latter groups represent only 6.7% of CTO procedures, those are responsible for 17.9% of the total MACCE, 18% of overall perforations, and 19% of overall dissections of donor vessels. Of note, out of all AW-R and ADR-R perforations, 70% occurred at the site of collateral channels, while the remaining 30% were at the site of the target vessel and were part of the antegrade CTO crossing. Target vessel perforations occurred in AW-R and ADR-R would have been wrongly attributed to the retrograde approach if CTO-ARC classification had not been followed. This issue was faced in a previous study by Hirai et al,[13] in which 61% of perforations classified as due to retrograde approach by the operator actually were reclassified as related to antegrade techniques by the core lab.[13]

In our study, the rescue antegrade technical success rate was 70%, which is consistent with those reported in the Retrograde Summit General Registry and the Japanese CTO PCI Expert Registry (70.1 and 70%, respectively), in which the rescue antegrade procedures accounted for 8.4% and 10.6%, respectively. Unfortunately, in the Japanese studies, the procedural complications were only reported according to primary antegrade and primary retrograde approaches.[11,14] Therefore, comparing the safety of each CTO crossing scenario among these 2 Japanese studies and ours is impossible.

In the PROGRESS registry, Allana et al[12] reported a rescue antegrade proportion of 7.1% after failure of retrograde attempts with technical success of 50.3%

and an in-hospital MACE rate of 2.9%. However, once again, the rescue antegrade complications were considered part of retrograde approach complications.[12]

In summary, this 3 scenarios-based model is characterized by 2 ranks of lesion complexity (the lowest for primary antegrade and the highest for both rescue antegrade and retrograde) and 3 different ranks of procedural success (the highest for primary antegrade, the lowest for rescue antegrade, and the intermediate for retrograde) (Supplemental Table 2).

RETROGRADE AND ADR TECHNIQUES. We have identified the following procedure- and patient-related factors associated with MACCE: retrograde approach, ADR techniques, operator expertise, and severely impaired left ventricular ejection fraction (<35%) (**Figure 3**). Similarly, in the PROGRESS-CTO complication score, retrograde approach and ADR techniques have also been identified as independent predictors of complications beyond age >65 years, moderate-severe calcification, blunt stump, and female sex.[15]

Although retrograde approach and ADR techniques have higher complication rates than AW, as underlined in the latest global CTO crossing algorithm, such techniques are essential to ensure high CTO PCI success rates in more complex settings.[16] In our study, ADR techniques showed lower technical success and higher complication rates than AW-0; these results are similar to those reported in 2 large studies from the ERCTO and PROGRESS registries in which ADR was compared with AW and non-ADR procedures, respectively.[17,18]

This previously discussed complex situation should be clarified at the time of the informed consent of the patient, who should be made aware that in the presence of complex CTO lesions, ADR techniques and/or retrograde approach might be necessary to increase the likelihood of success, but at the prize of higher risk of complications.[19]

Another interesting finding raised in the present study is that while RDR techniques were used with a more favorable risk-benefit profile than intraplaque retrograde wiring (procedural success: RDR 86.4% vs RW 77.7%; $P < 0.001$), this was not seen when comparing ADR-0 with AW-0 (procedural success: ADR-0 83.6% vs AW-0 92.1%; $P < 0.001$). In addition to the lower CTO lesion complexity associated with AW-0, we believe that such a difference could also be related to the fact that an antegrade backup somehow controls re-entry attempts in RDR. In contrast, in ADR-0, distal re-entry is blind in most cases except for few procedures being supported by intravascular ultrasound-guided re-entry. In this regard, despite the need for a learning curve, extending intravascular ultrasound use might further improve efficacy and safety of such procedures.

STUDY LIMITATIONS. First, the ERCTO registry is subject to the limitations of observational studies. Second, the data presented in this manuscript reflect ERCTO practice, consisting of patients referred for CTO PCI at experienced European centers; therefore, these data may not be generalizable to all operators. Third, the ERCTO registry does not have core laboratory assessments of the patients' angiograms, CTO lesion characteristics, and final procedural approach. Furthermore, there is no independent angiographic and clinical event adjudication, which might lead to an overestimation of technical success and, conversely, an underestimation of procedural complications. Similarly, the complication timing is not validated by a core lab, but rather is left to the operator performing the procedure. Thus, each center was responsible for the accuracy and completeness of the data. In addition, the selection of guidewires and equipment was left to the operator's discretion, and its impacts on success and complication rates were not assessed. There is a potential patient selection bias since the decision to enroll a patient into the ERCTO registry is at the discretion of the operator and is not systematically followed by an oversight committee. Furthermore, despite CTO-ARC recommends reporting 30-day safety endpoint, in the present study it was reported the procedural and in-hospital MACCE rate only.

Moreover, despite intravascular imaging being mandatory to demonstrate unequivocally if the equipment position is intraplaque (wholly or in part) or extraplaque, it was not systematically used in the case of dissection and re-entry techniques. Therefore, the classification of dissection and re-entry procedures was left to the operator performing the procedure and was based on angiographic futures in most cases. However, the CTO-ARC recommendation recognized it as a common limitation of many studies. Finally, our results should be considered as hypothesis-generating and should be interpreted in the light that the external validity might be limited because, as compared with other large all-comer registries, our study population is younger and the proportion of males is lower.[20,21] This issue might be relevant because both age and female sex are associated with MACE.[15]

CONCLUSIONS

The application of CTO-ARC definition of crossing strategies to the contemporary ERCTO registry has allowed a simple and effective way to compare the efficacy and the safety of different crossing strategies, overcoming relevant biases of previous classifications. The reclassified patients were those with the highest MACCE rates. Furthermore, it has outlined 3 CTO crossing scenarios reflecting the contemporary practice of expert ERCTO operators. Retrograde and ADR techniques ensure a high technical success rate in more complex CTOs but were associated with a higher procedural complication rate than true anticipated AW.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Bufe has received speaker honoraria from Biotronik and Shockwave Medical. Dr Pyxaras has received consulting/speaker/proctorship honoraria from Abiomed, AstraZeneca, Asahi Intecc, Biotronik, Boston Scientific, and Terumo. Dr Ladwiniec has received consulting/speaker/proctoring honoraria from Abbott, Biotronik, Boston Scientific, Cordis, Shockwave Medical, and SMT. Dr Werner has received speaker honoraria from Abbott, Asahi Intecc, OrbusNeich, Philips, Siemens, and Terumo. Dr Mashayekhi has received consulting/speaker/proctoring honoraria from Abbott, Abiomed, Asahi Intecc, AstraZeneca, Biotronik, Boston Scientific, Cardinal Health, Daiichi-Sankyo, Medtronic, OrbusNeich, Shockwave Medical, Teleflex, and Terumo. Dr Ayoub has received consultant/proctor honoraria from Boston Scientific, Teleflex, Asahi Intecc, Cordis, Terumo, and SIS Medical. Dr Goktekin has received consulting/speaker/proctoring honoraria from Boston Scientific, Medtronik, MicroPort, and Asahi Inc. Dr Agostoni has received consulting honoraria from Abbott, Boston Scientific, Cordis, iVascular, Medtronic, Neovasc, Seven Sons, Teleflex, and Terumo. Dr Diletti has received consultant/proctoring honoraria from Asahi Intecc, Terumo, IMDS, Boston Scientific, Teleflex, and Philips. Dr Rathore has received honoraria for speaker and proctoring from Abbott Vascular and Translumina Therapeutics. Dr Bozinovic has served as a speaker or proctor and/or received honoraria from Orbus Neich and Medtronic. Dr Galassi has received consulting/speaker honoraria from Asahi Intecc and Ivascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? CTO-ARC recognized that a nonstandardized definition of CTO PCI approaches can bias the complications' attribution to each crossing strategy.

WHAT IS NEW? The application of CTO-ARC definitions allowed an effective way to compare the performances among CTO crossing techniques and outlined 3 CTO crossing scenarios (true AW, retrograde crossing, and rescue antegrade crossing) characterized by different ranks of lesion complexity and procedural success rates. Although true AW is the most frequent and safest crossing strategy, alternative antegrade crossing techniques, becoming more common, have a relevant impact on success and MACCE.

WHAT IS NEXT? A widespread adoption of the CTO-ARC definition among new studies will facilitate our understanding on when, how, and with what result to use the different crossing strategies.

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KEY WORDS chronic total occlusions percutaneous coronary intervention, CTO PCI, CTO PCI complications, Academic Research Consortium on CTO, ADR, antegrade dissection and re-entry, CTO-ARC, retrograde approach

APPENDIX For an expanded Methods section and supplemental figures and tables, please see the online version of this paper.