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Wire-based antegrade dissection re-entry technique for coronary chronic total occlusions percutaneous revascularization: Experience from the ERCTO Registry

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Abstract

Background: The recent development and widespread adoption of antegrade dissection re-entry (ADR) techniques have been underlined as one of the antegrade strategies in all worldwide CTO consensus documents. However, historical wire-based ADR experience has suffered from disappointing long-term outcomes.

Aims: Compare technical success, procedural success, and long-term outcome of patients who underwent wire-based ADR technique versus antegrade wiring (AW).

Methods: One thousand seven hundred and ten patients, from the prospective European Registry of Chronic Total Occlusions (ERCTO), underwent 1806 CTO procedures between January 2018 and December 2021, at 13 high-volume ADR centers. Among all 1806 lesions attempted by the antegrade approach, 72% were approached with AW techniques and 28% with wire-based ADR techniques.

Results: Technical and procedural success rates were lower in wire-based ADR than in AW (90.3% vs. 96.4%, $p < 0.001$; 87.7% vs. 95.4%, $p < 0.001$, respectively); however, wire-based ADR was used successfully more often in complex lesions as

For affiliations refer to page 875.

Abbreviations: ACT, activated clotting time; ADR, antegrade dissection and re-entry; AFR, antegrade fenestration and re-entry; APCTO, Asia Pacific CTO Club; AW, antegrade wire; AWE, antegrade wiring escalation; CASTLE, Coronary artery bypass grafting history, Age, Stump anatomy, Tortuosity degree, Length of occlusion and Extent of calcification; CC, collateral channels; CCS, Canadian Cardiovascular Society; CTO, chronic total occlusion; DES, drug-eluting stents; ERCTO, European Registry of CTOs; ICUS, intra-coronary ultrasound; J-CTO, Japanese Multicentre CTO Registry; LAST, limited antegrade subintimal tracking; MACCEs, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NYHA, New York Heart Association; OTW, over the wire; PCI, percutaneous coronary intervention; PROGRESS, Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; PW, parallel wire; STAR, subintimal tracking and re-entry; TIMI, thrombolysis in myocardial infarction.

compared to AW ($p = 0.017$). Wire-based ADR was used in most cases (85%) after failure of AW or retrograde procedures. At a mean clinical follow-up of 21 ± 15 months, major adverse cardiac and cerebrovascular events (MACCEs) did not differ between AW and wire-based ADR (12% vs. 15.1%, $p = 0.106$); both AW and wire-based ADR procedures were associated with significant symptom improvements.
Conclusions: As compared to AW, wire-based ADR is a reliable and effective strategy successfully used in more complex lesions and often after the failure of other techniques. At long-term follow-up, patient's MACCEs and symptoms improvement were similar in both antegrade techniques.

KEYWORDS
chronic total occlusion, mini-STAR, percutaneous coronary intervention, STAR, wire-based antegrade dissection re-entry

1 | INTRODUCTION

Percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) still represents a major challenge for interventional cardiologists. The advancement of equipment, skill, and training has determined an increase in success rate from historically 50%–60% to the 80%–90% now routinely quoted by expert operators.[1–3] The major reason for procedural failure has been represented by the inability to cross the body of occlusion, reaching the distal coronary true lumen with the guidewire. Other reasons are the creation of large dissection, the failure to deliver a balloon through the occlusion, and some procedural complications such as coronary perforation and intracoronary thrombosis. The recent development and widespread adoption of antegrade dissection and re-entry (ADR) techniques has been underlined as one of the antegrade strategies in all worldwide recent CTO consensus documents.[4–7] Such techniques are generally employed to force subintimal entry of more complex CTOs, in case of ambiguous proximal cap, adequate distal landing zone occlusion length >20 mm, and as bailout strategy after failure of conventional antegrade wiring (AW) techniques and/or no retrograde option. Antegrade wire-based ADR techniques were initially described by using the subintimal tracking and re-entry (STAR) technique and updated by the “modified STAR” using the contrast-guided technique; however, in both cases, disappointing long-term outcomes have been reported.[8,9] More recently an optimization of refined techniques such as limited antegrade subintimal tracking (LAST), mini-STAR, and antegrade fenestration and re-entry (AFR) showed better outcomes in a small group of patients.[10–14] Device-based ADR techniques by Stingray and Crossboss (Boston Scientific) showed good overall results in some center but at the expenses of increased costs.

In the present study, we assessed technical, procedural success, and long-term outcome of antegrade wire-based ADR techniques in comparison to AW.

2 | METHODS

2.1 | Population and design of the study

The main objective of the study was to compare technical success, procedural success, and long-term outcome of patients who underwent wire-based antegrade dissection re-entry (ADR) technique versus AW in the modern era.

The study population consists of patients enrolled in the European Registry of CTOs (ERCTO), a prospective real-world registry that includes patients treated via the retrograde or anterograde approach for one or more CTO lesions involving major native coronary arteries (>2.5 mm) or bypass conduits. Among all patients enrolled in the ERCTO between January 2018 and December 2021, at 13 European centers where ADR is widely performed (cut-off to be included: >50 ADR procedure/year), those who underwent antegrade CTO PCI were the object of the study. Furthermore, unsuccessful retrograde procedures, followed by the antegrade approach were included as well. On the other hand, successful retrograde procedures, device-based ADR procedures, and patients with missing data have been excluded. Antegrade CTO PCIs were included as first-attempt procedures or as procedures after prior failed antegrade or retrograde attempts in the same or other sessions. All procedures were scheduled (not ad hoc PCI), and patients were selected based on the presence of symptoms, viability of the myocardium subtended by the CTO artery, and significant inducible ischemia in the CTO artery territory, as demonstrated by functional imaging tests. In patients with more than one CTO, only one CTO vessel was attempted per procedure. The sequence of use of wiring techniques and the guidewire selection were left entirely to the operator's discretion.

Patient follow-up was performed either by a clinical visit or by a telephone interview. Informed consent was obtained from all patients; the study received the local ethical committee approval and was carried out in accordance with the principles of the Declaration of Helsinki.

2.2 | Definitions

We used the nomenclature suggested by the CTO-ARC Consensus Recommendation on the CTO crossing technique and clinical trials.[15] Coronary CTOs were defined as angiographic evidence of total occlusions of a native coronary artery or saphenous vein by-pass graft with TIMI (thrombolysis in myocardial infarction) flow Grade 0 and estimated durations of at least 3 months. Technical success was defined as angiographic success (final residual stenosis <30% by visual estimation and TIMI flow Grade 3 after CTO recanalization). Procedural success was defined as technical success with no in-hospital major adverse cardiac events (MACE) that is a composite endpoint of death, myocardial infarction (MI), hospitalization for heart failure, or clinically driven target vessel revascularization (TVR). MACCEs included cardiac death, MI, stroke, recurrent symptoms requiring repeat TVR (with either PCI or coronary artery bypass grafting).[16] Non-Q-wave MI was defined as creatine kinase–MB enzyme elevation >3 times the upper limit of normal.[16] Coronary perforations were defined and described as previously shown.[17] Contrast-induced nephropathy was defined as an increase of 25% or 0.5 mg/dL in serum creatinine level at 24–48 h after PCI in comparison with baseline values.[18] Serum creatinine was monitored at 24 and 48 h after the procedure. Procedural time was accounted from the engagement of coronary ostia until the removal of the guiding catheter. Procedural and fluoroscopy times and contrast load amounts were recorded by a technician at the end of the procedures.

The primary endpoint at follow-up was the MACCE rate. Secondary endpoints were the longitudinal evaluation of dyspnea and angina symptoms assessed according to New York Heart Association (NYHA) and Canadian Cardiovascular Society classifications (CCS), respectively, at baseline and at follow-up.

2.3 | Assessment of lesion complexity

To classify the attempted CTO lesions according to their complexity, the J-CTO, PROGRESS, and CASTLE scores, were calculated as previously described.[19–21] Variability in J-CTO, PROGRESS, and CASTLE scores reporting was assessed in a random sample of 10 CTO angiograms, which were evaluated by the same operator (for intraobserver variability) and another senior interventionalist (for interobserver variability). Both intraobserver and interobserver variability were less than 1%. The lesions were classified according to each different score and graded as easy, intermediate, difficult, or very difficult, respectively.

2.4 | Procedure description

2.4.1 | Initial strategies

Lesions were first attempted, in most cases, using AW approach defined as the use of a dedicated over-the-wire (OTW) device-supported microcatheter guidewire. The wire selection strategy was based on the antegrade wire escalation stiffness step-up method. This approach began with soft-polymeric guidewire series (up to 1 g), then in case of failure, changed with intermediate-stiffness guidewires (3–8 g), and finally hard-stiffness wires (≥9 g). If some anatomical lesion characteristics were recognized, the intravascular ultrasound (IVUS)-guided technique was selected as the initial strategy. Similarly, in the presence of a suitable collateral circulation retrograde approach with its refinements was used as the initial strategy.[21]

2.4.2 | Alternative antegrade strategies

Wire-based ADR techniques were performed either as a first-line approach or as a bailout procedure after the failure of anterograde or retrograde strategy. The wire-based ADR technique was performed among operators by different wires: soft polymeric wires such as Fielder FC, XT, and XTR (Asahi Intecc) according to the Mini-STAR technique[11]; intermediate/moderate/stiff polymeric wires such as Pilot 50, 150, and 200 (Abbott); the new stiff polymeric wire Mongo and Gladius (Asahi Intecc), or stiff hydrophilic wires followed by polymeric wires and vice versa to re-enter according to the LAST technique.[22]

2.5 | Concomitant medications

All procedures were scheduled, and all patients were on dual antiplatelet therapy. Patients received, the day before and after the PCI, an intra-venous hydration with 1 mL/kg/h of saline solution. At the beginning of the procedure, patients received intravenous unfractionated (UNF) heparin (80–100 IU/kg) to maintain activated clotting time (ACT) of more than 300 s, ACT time was measured every 30 min and, if required, an additional bolus of UFN heparin was administered. In all cases, after successful CTO recanalization drug-eluting stents (DES) were implanted. After DES implantation Aspirin (100 mg daily) was prescribed lifelong and clopidogrel (75 mg daily) for 12 months.

2.6 | Statistical analysis

Continuous variables were presented as mean ± SD, while categorical variables were presented as counts and percentages. To assess the statistical significance, the chi-squared test was used for categorical variables (or Fisher exact test when necessary) and the *t*-test for continuous variables. A logistic regression model was applied to assess whether the wire-based ADR technique showed a similar technical success rate of AW, adjusted for lesion complexity. Furthermore, the proportional hazards (PH) Cox model adjusted for clinical, procedural, and lesion characteristics was performed. A two-sided p value of less than 0.05 was considered to indicate statistical significance. All data were processed using R software (version 4.1.2).

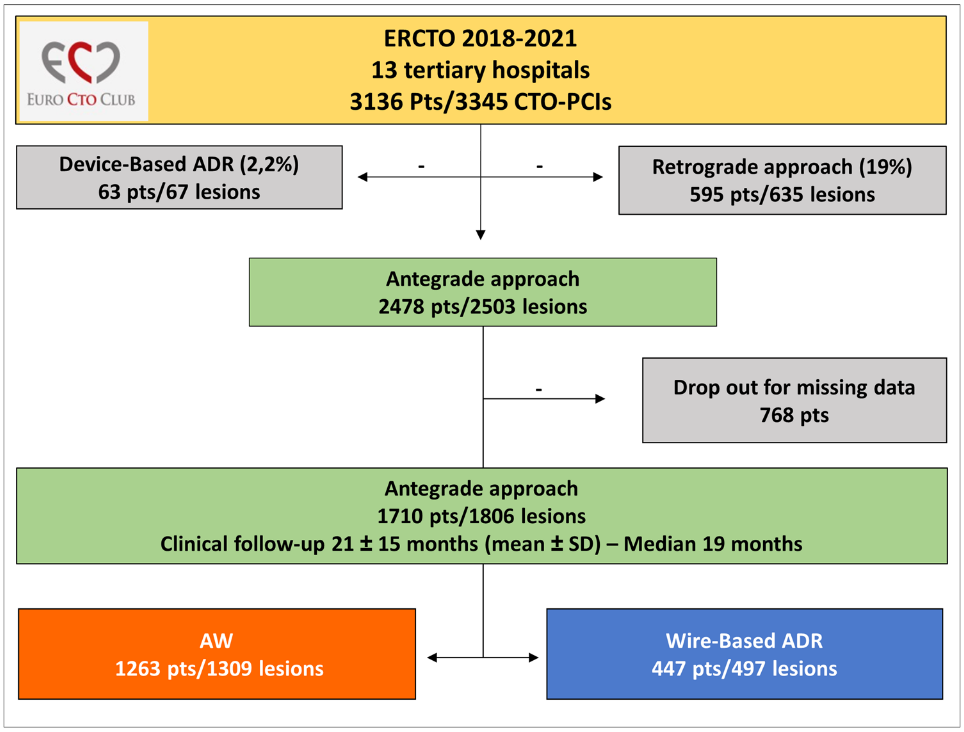


FIGURE 1 Study flow chart. ADR, antegrade dissection and re-entry; AW, antegrade wiring; FU, follow-up; MACCE, major adverse cardiac and cerebrovascular events.

3 | RESULTS

From January 2018 to December 2021, 3136 patients with CTO lesions underwent 3345 CTO procedures. Among all lesions, 635 (19%) were excluded as successfully crossed by the retrograde technique and 67 (2.2%) as approached by the Crossboss/Stingray device (Boston Scientific). Furthermore, 768 patients have been excluded from the analysis for missing data. Among these, 701 were lost in follow-up, while the remaining 67 had relevant missing database entries, which made the adopted recanalization technique or the used equipment unclear. The final study population consisted of 1710 patients, corresponding to 1806 lesions, treated by an antegrade approach. Among the 1806 lesions, 1309 (72%) were performed by AW techniques and 497 lesions (28%) by wire-based ADR techniques (Figure 1).

3.1 | Clinical characteristics

The study population characteristics are summarized in Table 1. The distribution of the majority of clinical factors was relatively homogeneous between AW and wire-based ADR. As compared to AW, the wire-based ADR group showed lower age (62.6 ± 10.6 vs. 62.9 ± 9.5 years, $p < 0.001$), prevalence of hypertension and asymptomatic status (65.4% vs. 75,4%, $p < 0.001$; 9.3% vs. 14.7, $p < 0.01$), lower proportion of patients with NYHA > 1 (35% vs. 56%, $p < 0.001$), and of 2-vessel disease (32.6% vs. 38.0%, $p = 0.036$). Conversely, as compared to AW, the wire-based ADR group showed a higher prevalence of previous CABG (15.7% vs. 8.7%, both $p = 0.001$) and stable angina (79.5% vs. 71.6%, $p = 0.005$) with a CCS > 2 (32% vs. 23%, $p < 0.001$).

3.2 | Lesion characteristics

The angiographic features of the CTO lesions attempted are summarized in Table 2. The RCA target vessel was attempted more frequently in the wire-based ADR group than in the AW group (51.3% vs. 40.5%, $p < 0.001$). Conversely, the LAD target vessel was attempted less frequently in the wire-based ADR group than in the AW group (27.4%, vs. 39.4%, $p < 0.001$). The lesion complexity as assessed by J-CTO, PROGRESS, and CASTLE score was higher for all the three scores in the wire-based ADR group as compared to the AW group (2.3 ± 1.2 vs. 2 ± 1.2, $p < 0.001$; 2.7 ± 1.4 vs. 2.3 ± 1.3, $p < 0.001$; 1.6 ± 0.9 vs. and 1.3 ± 1.0, $p < 0,001$, respectively).

3.3 | Procedural characteristics and complications

The procedural characteristics and complications are summarized in Table 3, while the type of guidewires finally crossing the CTOs are depicted in Figure 2. Among wire-based ADR procedures, mini-STAR, STAR, LAST, and AFR were used in 62, 28, 8, and 2 of the cases. The overall technical success rate was 94.7%; as compared with AW, wire-based ADR showed a lower technical success rate (90.3% vs.

TABLE 1 Clinical characteristics.

	CTO lesions (*N* = 1806)	AW (*N* = 1309)	ADR (*N* = 497)	*p*
Age	62.7 ± 9.7	62.9 ± 9.5	62.6 ± 10.6	**<0.001**
Men	1610 (89.1%)	1162 (88.8%)	448 (90.1%)	0.452
Hypertension	1312 (72.6%)	987 (75.4%)	325 (65.4%)	**<0.001**
Dyslipidaemia	1218 (67.4%)	882 (67.4%)	336 (67.6%)	0.971
Diabetes mellitus overall	575 (31.8%)	425 (32.4%)	150 (30.1%)	0.381
Diabetes mellitus ID	144 (7.9%)	107 (8.1%)	37 (7.4%)	0.679
Smoker	993 (54.9%)	727 (55.5%)	266 (54.2%)	0.473
Previous MI	770 (42.6%)	546 (41.7%)	224 (45.0%)	0.216
Previous NSTEMI	473 (26.1%)	327 (25%)	146 (29.4%)	0.066
Previous STEMI	297 (16.4%)	219 (16.7%)	78 (15.7%)	0.645
Previous CABG	192 (10.6%)	114 (8.7%)	78 (15.7%)	**<0.001**
Previous PCI	956 (52.9%)	687 (52.5%)	269 (54.1%)	0.567
LVEF > 50%	1185 (65.6%)	836 (63.9%)	349 (70.2%)	0.07
35% < LVEF < 50%	472 (2.1%)	356 (27.2%)	116 (23.3%)	
LVEF < 35%	141 (7.8%)	111 (8.5%)	30 (6%)	
Prior stroke	26 (1.4%)	20 (1.5%)	6 (1.2%)	0.772
Clinical presentation				
Asymptomatic	244 (13.5%)	193 (14.7%)	46 (9.3%)	**0.01**
Stable angina	1333 (73.8%)	937 (71.6%)	395 (79.5%)	**0.004**
Unstable angina	144 (8%)	110 (8.5%)	36 (7.2%)	0.37
MI	85 (4.7%)	68 (5.2%)	20 (4%)	0.223
CCS > 2	465 (26%)	306 (23%)	159 (32%)	**<0.001**
NYHA > 1	909 (50%)	735 (56%)	174 (35%)	**<0.001**
No. of vessels diseased				
1-vessel	622 (34.4%)	447 (34.1%)	175 (35.2%)	0.712
2-vessels	660 (36.5%)	498 (38.0%)	162 (32.6%)	**0.036**
3-vessels	497 (27.5%)	344 (26.2%)	153 (30.8%)	0.063

Note: Bold values indicate statistically significant values at $p < 0.05$.

Abbreviations: ADR, antegrade dissection re-entry; AW, antegrade wire; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CTO, chronic total occlusion; ID, insulin-dependent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; NYHA, New York heart association; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

96.4%; $p < 0.001$). Figure 3 depicts the proportion of successful procedures according to the lesion complexity in both groups. When corrected for lesion complexity, as defined by J-CTO score ≥3, the technical success rate was significantly higher in wire-based ADR as compared to AW ($p = 0.017$) (Central Illustration 1A). Wire-based ADR showed a similar proportion of unsuccessful procedures as defined by TIMI 0/1, TIMI 2, or TIMI 3 with final residual stenosis ≥30% as compared to the AW group (32% vs. 40%; 62% vs. 55%; 6% vs. 5%, respectively; $p = 0.051$).

Wire-based ADR was used in 68% of cases after the failed antegrade wiring approach, in 17% of cases after the failure of the retrograde approach while in the remaining 15% of cases as the first-line approach. Procedural success did not differ between the Wire-based ADR cases performed as bail-out or first-line strategy (86.6% vs. 88.2%; $p = 0.072$).

As compared to AW, wire-based ADR procedures showed higher number of total procedural time (111.7 + 63.1 vs. 98.4 + 56.8 min, $p < 0.001$), higher fluoroscopic time (48.7 + 33.8 vs. 38.4 + 26.9 min, $p < 0.001$), higher contrast volume (357.2 + 347.8 vs. 293.2 + 177.8 ml, $p < 0.001$), higher number of implanted stents (2.5 ± 1.4 vs. 2.4 ± 1.2, $p = 0.038$), and a higher total stented segment length (68.0 ± 38.5 vs. 61.9 ± 31.9 mm, $p < 0.001$).

TABLE 2 Lesion characteristics.

	CTO lesions (*N* = 1806)	AW (*N* = 1309)	ADR (*N* = 497)	*p*
Target vessel				
LAD	652 (36.1%)	516 (39.4%)	136 (27.4%)	**<0.001**
LCX	310 (17.1%)	218 (16.7%)	92 (18.5%)	0.387
RCA	786 (43.5%)	531 (40.5%)	255 (51.3%)	**<0.001**
IMA	14 (0.8%)	9 (0.7%)	5 (1%)	0.697
Side branch	40 (2.2%)	33 (2.5%)	7 (1.4%)	0.209
SVG	4 (0.2%)	2 (0.2%)	2 (0.4%)	0.654
Complexity scores				
J-CTO SCORE	2.1 ± 1,2	2 ± 1.2	2.3 ± 1.2	**<0.001**
CASTLE SCORE	2.4 ± 1.3	2.3 ± 1.3	2.7 ± 1.4	**<0.001**
PROGRESS SCORE	1.4 ± 0.9	1.3 ± 1.0	1.6 ± 0.9	**<0.001**
Mean Lesion length (mm)	33.6 ± 22.9	31.7 ± 20.8	38.9 ± 27.2	**<0.001**
Lesion length>20 (mm)	1114 (6.6%)	780 (59.7%)	334 (67.2%)	**<0.001**
Stump				
Tapered	910 (50.4%)	693 (52.9%)	217 (43.7%)	**<0.001**
Blunt	876 (48.5%)	599 (45.7%)	277 (55.7%)	**<0.001**
Tortuosity (severe)	117 (6.4%)	73 (5.6%)	44 (8.9%)	**0.015**
Previous attempt	1430 (79.1%)	1047 (79.9%)	383 (89.5%)	0.193
CC ≥ 2	812 (44.9%)	627 (47.9%)	185 (37.2%)	**0.001**
Heavy calcifications	466 (25.8%)	316 (24.1%)	150 (30.2%)	**0.01**
In-stent CTO	117 (9.8%)	125 (9.5%)	52 (10.5%)	0.62

Note: Bold values indicate statistically significant values at $p < 0.05$.

Abbreviations: ADR, antegrade dissection re-entry; AW, antegrade wiring; CASTLE, Coronary artery bypass grafting history, Age, Stump anatomy, Tortuosity degree, Length of occlusion and Extent of calcification; CC2, collateral channel Grade 2; CTO, chronic total occlusion; IMA, internal mammary artery; J-CTO, Japanese Multicentre CTO Registry; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; PROGRESS, Prospective Global Registry for the Study of Chronic Total Occlusion; SVG, saphenous vein graft.

TABLE 3 Procedural characteristics and complications.

	CTO lesions (*N* = 1806)	AW (*N* = 1309)	ADR (*N* = 497)	*p*
Technical success	1711 (94.7%)	1262 (96.4%)	449 (90.3%)	**<0.001**
Total procedural time (min)	102.1 ± 58.8	98.4 ± 56.8	111.7 ± 63.1	**<0.001**
Total fluoroscopic time (min)	41.2 ± 29.3	38.4 ± 26.9	48.7 ± 33.8	**<0.001**
Total contrast volume (mL)	310.9 ± 238.8	293.2 ± 177.8	357.2 ± 347.8	**<0.001**
Number of implanted stents	2.39 ± 1,25	2.4 ± 1.2	2.5 ± 1.4	**0.038**
Max stent diameter (mm)	3.17 ± 0.49	3.17 ± 0.48	3.18 ± 0.5	0.778
Total stented length (mm)	63.6 ± 33.9	61.9 ± 31.9	68 ± 38.5	**0.001**
Total stented length/total lesion length	2.66 ± 1.85	2.62 ± 1.73	2.66 ± 1.85	**0.7**

(Continues)

TABLE 3 (Continued)

	CTO lesions (*N* = 1806)	AW (*N* = 1309)	ADR (*N* = 497)	*p*
IVUS-assisted procedure	287 (15.8%)	236 (18%)	51 (10.3%)	**<0.001**
Procedural success	1686 (93.3%)	1250 (95.4%)	436 (87.7%)	**<0.001**
Major complications				
Death	2 (0.1%)	1 (0.1%)	1 (0.2%)	0.41
Q-wave MI	3 (0.1%)	1 (0.1%)	2 (0.4%)	0.382
Non-Q-wave MI	14 (0.7%)	7 (0.5%)	7 (1.4%)	0.111
Clinically driven TLR	6 (0.3%)	3 (0.2%)	3 (0.6%)	0.437
Perforation with tamponade	16 (0.8%)	10 (0.7%)	6 (1.2%)	0.537
Stroke	3 (0.1%)	3 (0.2%)	0%	NS
Other complications				
Minor perforations	33 (1.8%)	19 (1.5%)	14 (2.8%)	0.082
Contrast-induced nephropathy	60 (3.3%)	34 (2.6%)	26 (5.2%)	**0.008**
Dissection of donor artery	9 (0.4%)	3 (0.2%)	4 (0.8%)	0.182
Vascular complications	3 (0.1%)	0 (0%)	3 (0.6%)	NS

Note: Bold values indicate statistically significant values at $p < 0.05$.

Abbreviations: ADR, antegrade dissection re-entry; AW, antegrade wiring; CTO, chronic total occlusion; IVUS, intra-vascular ultrasound; MI, myocardial infarction; TLR, target lesion revascularization.

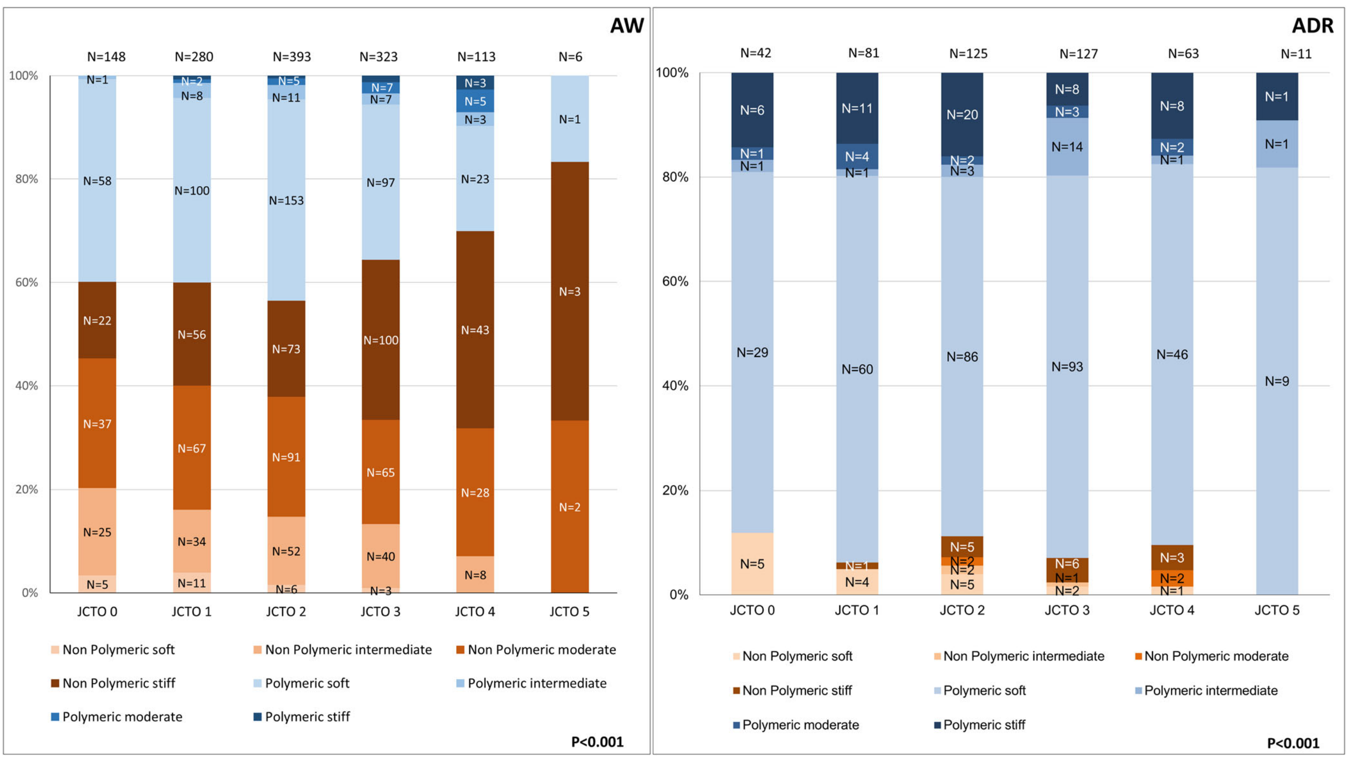


FIGURE 2 Guidewire's type successfully crossing. Proportion of different guidewire types successfully crossing the CTO in each degree of lesion complexity as assessed by the J-CTO Score. ADR, antegrade dissection and re-entry; AW, antegrade wiring; J-CTO, Japanese Multicentre CTO Registry.

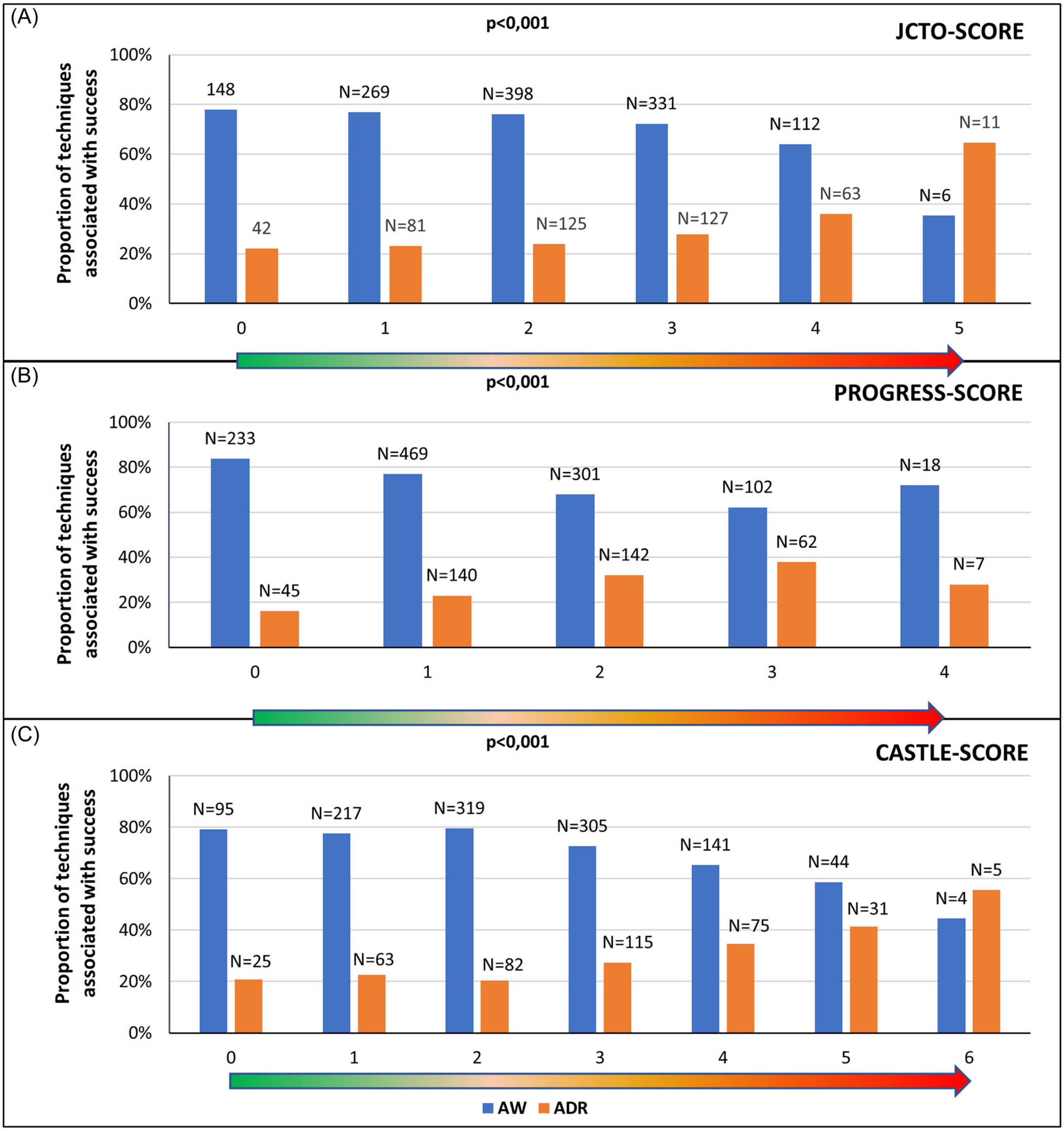
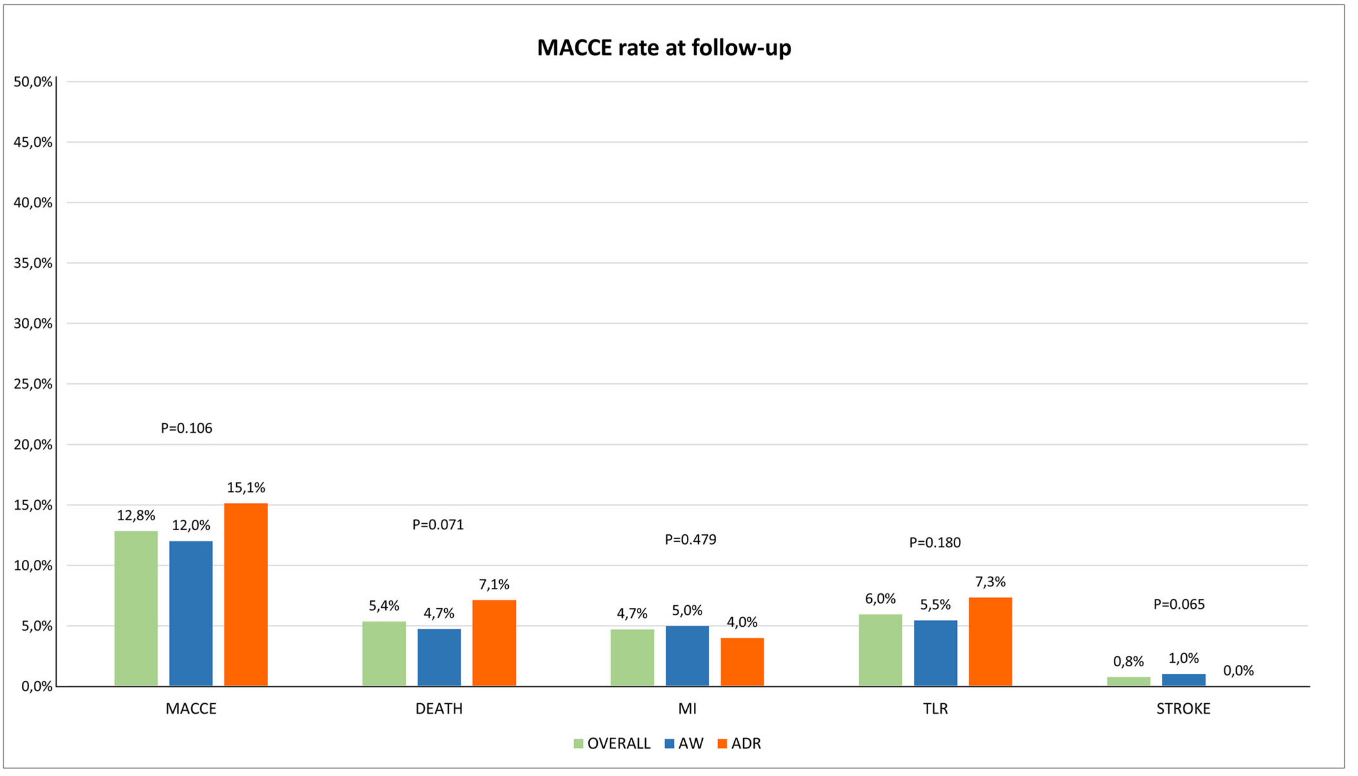


FIGURE 3 Comparison of recanalization techniques associated with technical success. Proportion of techniques associated with success across the entire spectrum of lesion complexity (from easy to very complex) as assessed by (A) J-CTO score (Japanese Multicentre CTO Registry). (B) PROGRESS score (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention). (C) CASTLE score (CABG, Age, Stump anatomy, Tortuosity degree, Length of occlusion and Extent of calcification). ADR, antegrade dissection and re-entry; AW, antegrade wiring.

Major complications were similar in the wire-based ADR group than in the AW group. Among all the other procedural-related complications, only contrast-induced nephropathy occurred more often in the wire-based ADR group than in the AW group (5.2% vs. 2.6%, $p = 0.008$) (Table 3).

3.4 | Clinical follow-up

The mean clinical follow-up period was 27 ± 17.9 months, with a median of 19 months. Figure 4 depicts MACCE of the entire population at follow-up. As compared to AW, Wire-based ADR



CENTRAL ILLUSTRATION 1 (A) Comparison of successful procedures according to lesion complexity as assessed by J-CTO score ≥3 or <3 in AW and wire-based ADR group. (B) Coronary angiogram of very complex (J-CTO ≥ 3) right coronary artery chronic total occlusion. (C) MACCE rates at follow-up in AW and wire-based ADR. (D) Proportion of patients in NYHA classes <I and ≥I at baseline and at follow-up, respectively, in AW and wire-based ADR group. (E) Proportion of patients with CCS scores <2 and ≥2 at baseline and at follow-up, respectively in AW and wire-based ADR group. ADR, antegrade dissection and re-entry; AW, antegrade wiring; CCS, Canadian Cardiovascular Society; MACCE, major adverse cardiac and cerebrovascular events; NYHA, New York Heart Association.

showed similar overall MACCEs rate (15.1% vs. 12%) and similar death rates (7.1% vs. 4.7%), MI (4.0% vs. 5%), TLR (7.3% vs. 5.5%), and stroke (1% vs. 0%).

The logistic regression model identified only low left ventricular ejection fraction (hazard ratio [HR]: 1.59; 95% CI: 1.03–2.5, $p = 0.037$) as an independent predictor of MACCEs at long-term follow-up (Figure 5).

Finally, a significant improvement of angina as assessed by CCS and dyspnea as assessed by NYHA was shown in both groups throughout the duration of the follow-up (Figure 6).

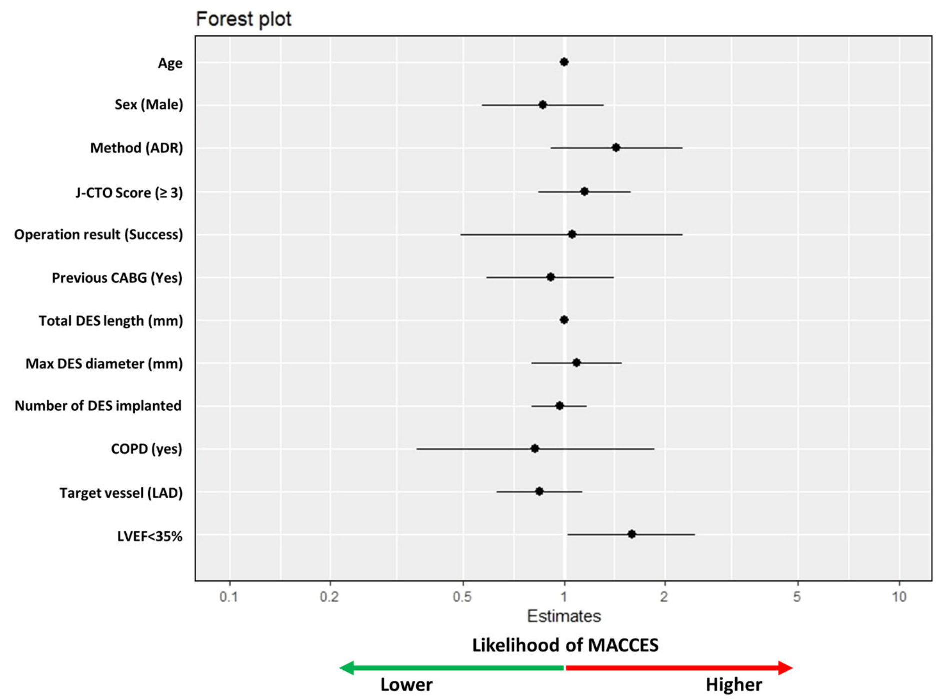
4 | DISCUSSION

The main findings of the present study can be summarized as follows: (1) wire-based ADR technique is performed in most of the cases using new generation polymeric wires and a supporting microcatheter; (2) wire-based ADR proved to have reduced technical success rate as compared to AW; (3) nevertheless, the wire-based ADR technique was used with success more frequently than AW in complex lesions and in the majority of the cases after failure of other strategies; (4) global major procedural complications and MACCEs at long-term follow-up did not differ between wire-based ADR and AW; (5) a significant and similar reduction of angina and dyspnea were observed in both groups consistently at long term follow-up.

4.1 | Wire-based ADR technical features

The rationale for wire-based ADR employment is provided by the understanding of CTO pathophysiology.[23] The human neo-revascularization phenomenon plays a crucial role. It is characterized by a complex three-dimensional network of “longitudinal” and “circumferential” communicating microchannels distributed, respectively, in the intravascular and extravascular spaces. Polymeric wires, for their properties, can move through this complex CTO environment. However, in case of channel interruption, forcing the wire against the occlusion with a support of a low-profile microcatheter, the wire itself might assume the J-loop configuration, crossing the CTO through a path of “less resistance” and re-entering in the true lumen usually close to the occlusion's distal cap.[24–26]

Although we cannot support evidence that the wire behaves always as described above, because of the physical forces at play we believe that, generally, polymeric wire-based ADR is able to achieve a high success rate, especially when large antegrade dissection and hematoma are intentionally avoided. Indeed, differently by the old STAR technique



HR	95% IC	p-value
1,004	0,990-1,019	0,516
0,864	0,570-10311	0,494
1,436	0,912-2,260	0,118
1,149	0,835-1,581	0,393
1,054	0,490-2,270	0,891
0,910	0,587-1,409	0,672
1,002	0,995-1,010	0,527
1,088	0,797-1,486	0,592
0,969	0,802-1,172	0,751
0,820	0,362-1,860	0,636
0,845	0,629-1,135	0,263
1,590	**1,027-2,463**	**0,037**

FIGURE 4 MACCE rates at long-term follow-up. MACCE, Death, MI, TLR, and Stoke rates. ADR, antegrade dissection and re-entry; AW, antegrade wiring; FU, follow-up; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; TLR, target lesion revascularization.

described by Colombo et al.[8] where the intention of knuckling a polymeric stiff wire without microcatheter was performed to track the CTO segment in an extra-plaque fashion, the refined ADR technique is characterized by a more superficial intra-plaque dissection and a target re-entry point close to the end of the CTO body. Both technical aspects are obtained by new polymeric wires supported by a low-profile microcatheter. In our study, a new generation polymeric wire in 90% of the cases was the final guidewire to successfully re-enter the true lumen, either after a dissection operated by the same polymeric wire, or in a step up–step down technique after the use of hydrophilic moderate or stiff wire beforehand (Figure 2).

4.2 | Wire-based ADR technical success

The newest CTO crossing algorithms contemplate ADR techniques as a bailout strategy after AW or retrograde failure, especially in those more complex lesions that represent exactly the case of wire-based ADR adoption in our registry.[4,6,7,27–29]

In our study, wire-based ADR overall technical success was significantly lower than AW (90.3 vs. 96.4%); however, when it was corrected for lesion complexity, the success was significantly higher as compared with AW. Similarly, in the RECHARGE Registry[30] and in the UK Hybrid CTO Registry,[31,32] ADR techniques were primarily used with success in more complex lesions. Even if our analysis was not intended to specifically compare wire-base and device-based ADR techniques, we would underscore that wire-based ADR might be a reasonable cheap technology as compared with other techniques when sophisticated and costly microcatheters, wires, and other dedicated devices are generally employed. Finally, as compared with AW, wire based-ADR procedures were characterized by a longer procedural, fluoroscopic time, and higher total contrast volume employed that could be explained by the higher complexity of the lesion attempted, and by the fact that the ADR technique is used in most of the cases after the failure of a previous time-consuming antegrade or retrograde approach.

4.3 | Procedural complications and long-term outcome after wire-based ADR

Despite the higher complexity of the lesion attempted in wire-based ADR cases, the procedural complication and long-term MACCE rate did not significantly differ between the two groups. Interestingly, the multivariate analysis identified LVEF ≤ 35% only as an independent risk factor of MACCEs. Furthermore, a consistent and similar improvement of angina and dyspnea symptoms was observed in both groups. However, the long-term outcomes of wire-based ADR reported in literature are controversial.[12,22] Rinfret et al.[33] showed that the use of ADR was effective in close to 90% of patients without any negative impact on long-term

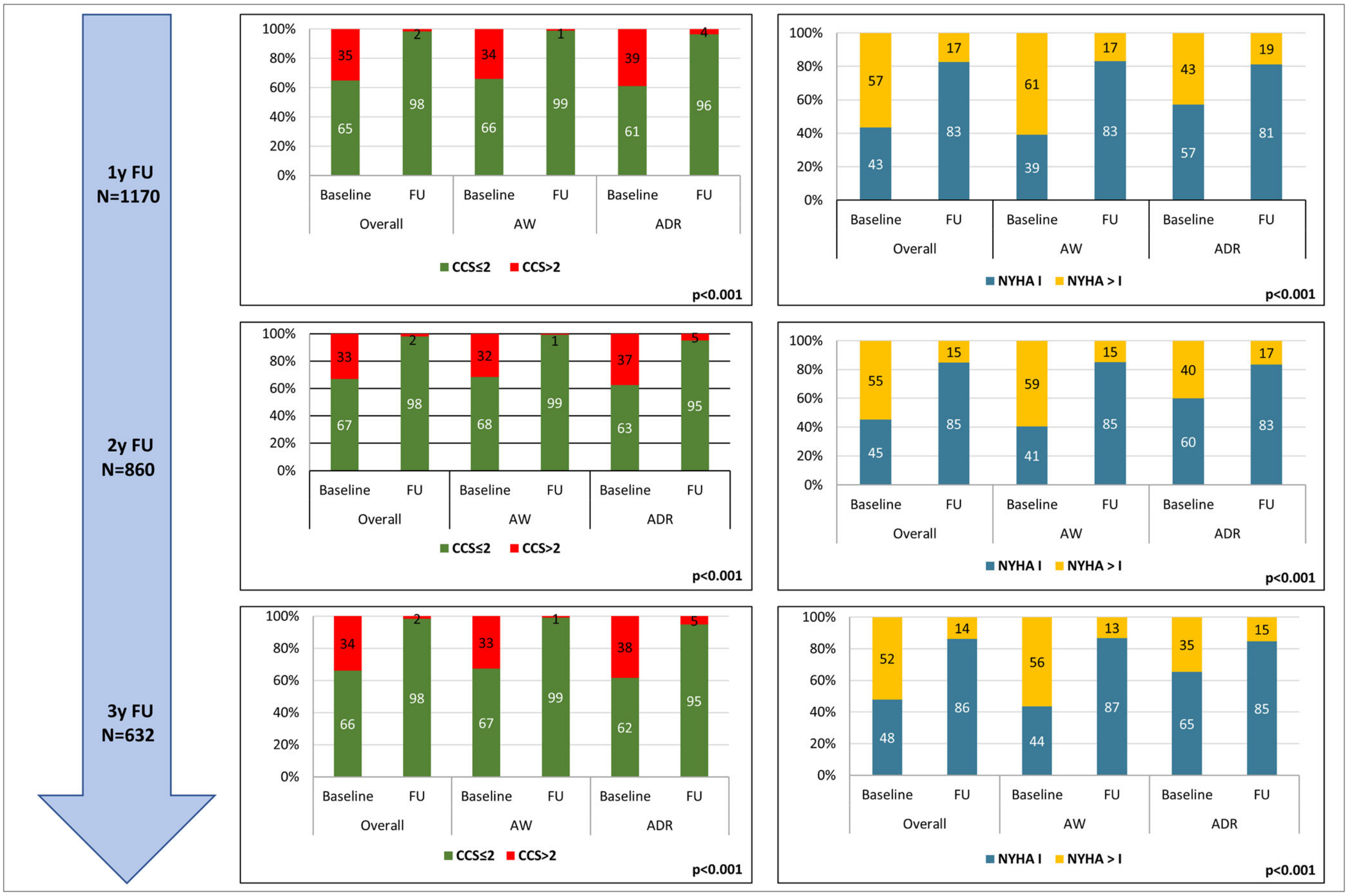


FIGURE 5 COX regression model. Impact of different risk factors for MACCEs occurrence at follow-up. ADR, antegrade dissection and re-entry; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DES, drug-eluting stent; LAD, left anterior descending; LVEF, left ventricular ejection fraction; J-CTO score, Japanese Multicentre CTO Registry.

outcomes. Other studies, where wire-based ADR was employed by soft polymeric wires and low-profile microcatheters, similarly showed a high procedural success rate and low occurrence of acute and long-term adverse events.[11,12] Conversely, other experiences such as those reported by Azzalini et al.,[22] more focused on traditional old wire-based ADR such as the STAR technique, were associated with higher adjusted risk of MACE at long-term follow-up. The authors explained the worse patient outcome by a more aggressive manipulation of the sub-adventitial space and more distal re-entry, especially in cases where standard stiff polymeric wires were employed instead of the Cossboss/Stingray system (Boston Scientific). Finally, in the recently published PROGRESS COMPLICATION SCORE, ADR was shown to be independently associated with higher risk of MACE, death, and pericardiocentesis.[34]

We believe that most of the differences among our study and previous suboptimal experiences of wire-based ADR were possibly related to the inclusion of ADR techniques during an old spam period as opposite to the modern wire-based ADR technique used nowadays, whose results might be more like those achieved by Crossboss/Stingray (Boston Scientific) technique. Indeed, we believe that the concept of "mini-dissection" operated by soft-medium polymer-jacketed wires, or up-escalation to stiff hydrophilic wire followed by re-entry by soft polymeric wire and assisted by a low-profile microcatheter in most of the cases, has opened a new potential for successful re-entry into the CTO occlusion, making nowadays wire-based ADR an innovative and promising CTO PCI technique. Finally, the similar procedural complication rate reported between AW and ADR might be explained by the great operator experience in the ADR technique.

4.4 | Study limitations

This study has several limitations. First, it is not-randomized, and its nature might introduce a case selection bias, which makes it difficult to provide conclusive evidence, although it reflects a "real life" modern era application of the wire-based ADR technique. Second, the sequence of strategies and revascularization techniques were left to the operator's discretion, his personal knowledge and experience, thus results might not be applicable to all CTO operators. Moreover, the operator's greater experience might further explain the reason for the high rate of the overall procedural success and similar complication rate of both techniques. There was no comparison between wire-based ADR and other techniques such as device-based ADR and different strategies as primary or bail-out approach. Despite these limitations, this study reports the procedural technical success and long-term outcome of a wire-based

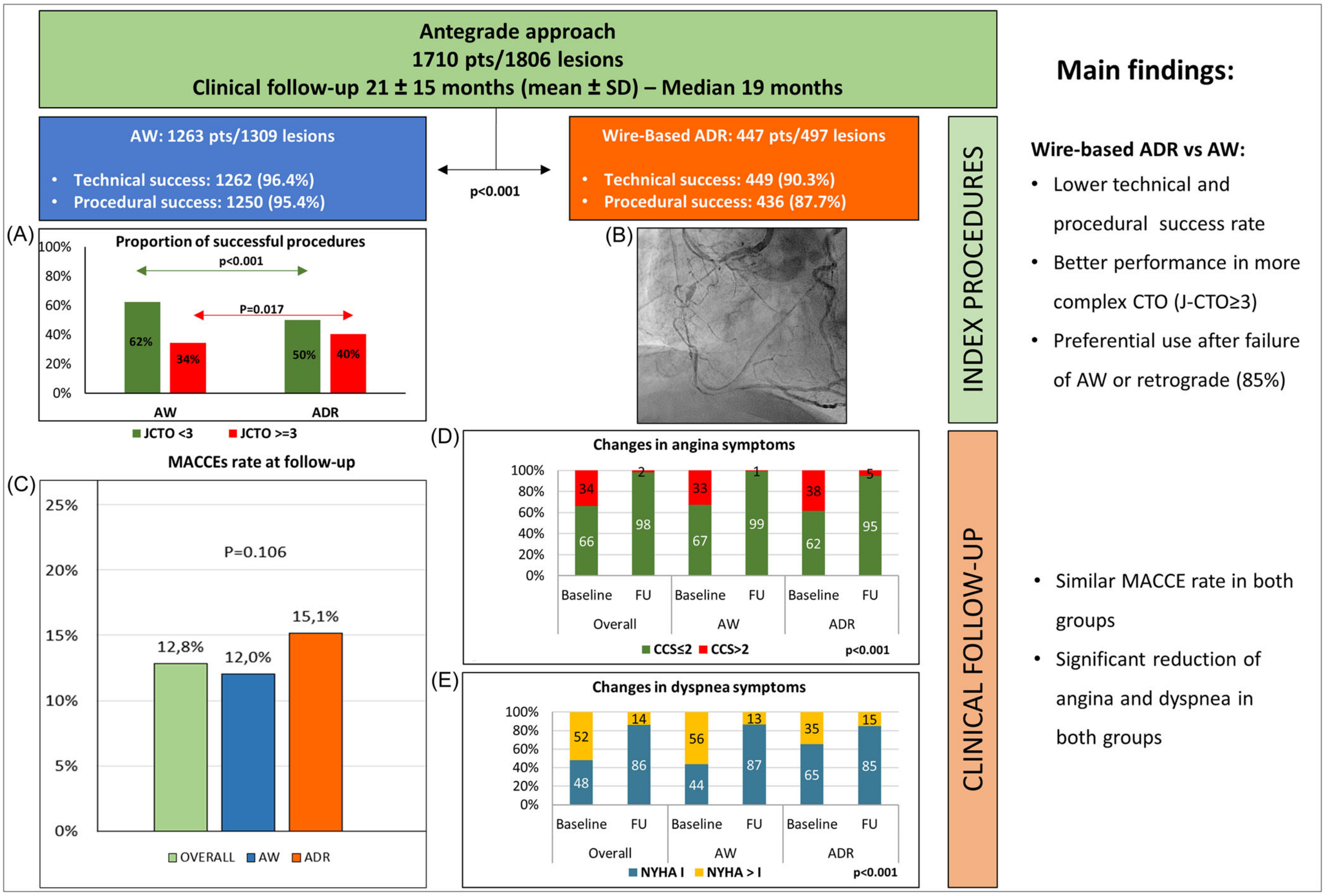


FIGURE 6 Patient's functional status. Patients who underwent AW and ADR showed similar symptoms' improvement (angina and dyspnea) during the follow-up period. ADR, antegrade dissection and re-entry; AW, antegrade wiring; CCS, Canadian Cardiovascular Society; FU, follow-up; NYHA, New York Heart Association.

ADR applied in a consecutive series of complex CTO lesions in a large cohort of patients treated in recent years from prospective European Registry of Chronic Total Occlusions. The exclusion of 768 patients (24% of the entire population) with missing data might represent a potential bias. Finally, the ERCTO does not have core laboratory assessment of the patients' angiograms and there is no independent angiographic and clinical event adjudication that might lead to an overestimation of technical success and conversely, an underestimation of procedural complications. Similarly, symptom improvements at follow-up might have been overestimated. Thus, each center was responsible for the accuracy and completeness of the entered data. Finally, a variability in the way the wire-based ADR technique was employed among the different study's operators may represent a further potential bias despite reflecting a real-life behavior of such procedures.

5 | CONCLUSIONS

This study highlights that the wire-based ADR technique is a reliable alternative strategy for the treatment of most complex CTO lesions that are uncrossable by conventional antegrade strategy, achieving a high procedural success rate and low occurrence of procedural adverse events. At long-term follow-up, the wire-based ADR technique showed similar patient's MACE and similar symptoms improvement to AW techniques.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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