Antegrade Dissection and Reentry as Part of the Hybrid Chronic Total Occlusion Revascularization Strategy

A Subanalysis of the RECHARGE Registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom)

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Background—Development of the CrossBoss and Stingray devices for antegrade dissection and reentry (ADR) of chronic total occlusions has improved historically suboptimal outcomes. However, the outcomes, safety, and failure modes of the technique have to be studied in a larger patient cohort. This preplanned substudy of the RECHARGE registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom) aims to evaluate the value and use of ADR and determine its future position in contemporary chronic total occlusion intervention.

Methods and Results—Patients were selected if an ADR strategy was applied. Outcomes, safety, and failure modes of the technique were assessed. The ADR technique was used in 23% (n=292/1253) of the RECHARGE registry and was mainly applied for complex lesions (Japanese chronic total occlusion score=2.7±1.1). ADR was the primary strategy in 30% (n=88/292), of which 67% were successful. Bail-out ADR strategies were successful in 63% (n=133/210). The Controlled ADR (ie, combined CrossBoss-Stingray) subtype was applied most frequently (32%; n=93/292) and successfully (81%; n=75/93). Overall per-lesion success rate was 78% (n=229/292), after use of additional bail-out strategies. The inability to reach the distal target zone (n=48/100) or to reenter (n=43/100) most commonly led to failure. ADR-associated major events occurred in 3.4% (n=10/292).

Conclusions—Although mostly applied as a bail-out strategy for complex lesions, the frequency, outcomes, and low complication rate of the ADR technique and its subtypes confirm the benefit and value of the technique in hybrid chronic total occlusion percutaneous coronary intervention, especially when antegrade wiring or retrograde approaches are not feasible.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02075372.

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Key Words: antegrade dissection and reentry ■ (coronary) chronic total occlusion ■ hybrid ■ percutaneous coronary intervention ■ registry

Percutaneous coronary intervention (PCI) of chronic total occlusions (CTO) remains a major challenge for interventional cardiologists. A recent registry still confirms that without additional techniques, tools, and dedicated CTO programs, success rates remain low (≈60%).[1]

A retrograde approach, including retrograde wiring and (reverse) controlled antegrade and retrograde subintimal tracking, is an additional strategy that increases the likelihood of success as shown by expert operators.[2–7] However, this technique has an overall failure rate of 20% to 40% and is

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WHAT IS KNOWN

- Antegrade dissection and reentry is a valuable technique for the percutaneous treatment of CTO. Since the first application of subintimal tracking and reentry in 2005, significant improvements have been made including mini-subintimal tracking and reentry, limited antegrade subintimal tracking, and most recently the development of dedicated devices for controlled dissection and reentry.
- However, previous studies on the outcomes and safety of the antegrade dissection and reentry technique are limited in patient numbers, focused on CrossBoss and Stingray only, and provided little explanation for technical failure.

WHAT THE STUDY ADDS

- This substudy assessed the application, outcomes, and safety of the antegrade dissection and reentry technique, including all of its aspects, in a multicenter setting of hybrid operators with different experience levels and including a larger cohort of patients.
- The antegrade dissection and reentry technique and its different subtypes proved to be a frequently applied and valuable technique, allowing the treatment of more patients with chronic total occlusions and further supporting its place in both contemporary and future chronic total occlusions intervention.

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associated with an increased risk of perforations.[8] Moreover, visible interventional collaterals are only present in approximately two third of patients.[9] Therefore, retrograde options may not be available in 30% to 50% of CTO lesions, necessitating the availability of alternative strategies.

Any additional technique, applicable in a safe and reproducible way, may facilitate higher success rates and increased safety in the treatment of complex CTOs. For this reason, subintimal antegrade dissection and reentry (ADR) was developed.

ADR was first applied in peripheral arteries[10] and applied by Colombo in coronary arteries in 2005.[11] Subintimal tracking and reentry (STAR) involves advancing a knuckled guidewire through the subintimal space until it spontaneously reenters the true lumen. The site of reentry is unpredictable, and the risk of myocardial infarction, late target vessel occlusion, and repeat intervention is high.[12] Furthermore, the technique should not be applied in vessels with major side branches (eg, left anterior descending artery), because stenting of the subintimal track can lead to side-branch loss. In current practice, STAR is only applied in bail-out situations.

Mini-STAR[13] and limited antegrade subintimal tracking (LAST)[14] are modifications of STAR, with the aim to limit the dissection length and to reenter in a more targeted fashion, just distal from the CTO using guidewires. Only small numbers of cases with long-term follow-up are reported.[15] In 2012, Whitlow et al[16] reported the use of a novel crossing and reentry system, allowing controlled dissection and reentry. A limited dissection is created with a stiff, metallic, over-the-wire catheter with a 1-mm blunt tip—the CrossBoss catheter (Boston Scientific, Marlborough, MA)—that is advanced through the occlusion by rotating a proximal torque device (fast-spin technique; Figure 1). Reentry is attempted using the Stingray balloon catheter (Boston Scientific), which is advanced within the subintimal space.

The Stingray catheter (ø=2.5 mm/length=10 mm) has a flat shape (ie, wings) and 2 exit ports, 180° opposite to each other (Figure 1). Reentry is performed from one of the exit ports with the Stingray needle, under fluoroscopic guidance. Recently, the CrossBoss device is also used as a stand-alone device to cross in-stent occlusions,[17,18] with the aim to remain within the stent cage.

Both safety of the ADR technique and technical and procedural successes were studied previously.[2,11–14,16,19–24] These reports were limited in patient numbers, focused on the combination of CrossBoss and Stingray alone, while providing no or only a limited explanation for procedural failure. As a preplanned subanalysis of the RECHARGE registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom), our study assessed first the frequency of the ADR technique being used, second the outcome in a larger cohort of patients with the technique being applied by a larger number of operators, and third, the safety of the ADR technique. In addition, a detailed analysis on the different subtypes and failure modes of ADR, when used as part of the hybrid strategy, is reported. The evaluation of the ADR technique, including all of its aspects, within a multicentre setting of operators with different experience levels, will determine both its current and future positions in contemporary CTO-PCI.

Methods

Study Population

Seventeen centers from Belgium, France, the Netherlands, and the United Kingdom prospectively and consecutively collected data between January 2014 and October 2015.[25] All operators are trained in each aspect of CTO-PCI and apply antegrade, retrograde, and ADR techniques. Patients could be included multiple times for a reattempt of the same CTO lesion, a secondary CTO lesion treated at a later stage in time, and/or a second CTO lesion treated at the same procedure. The mean number of annually performed CTO procedures/operator was 64. The study was approved by each institutional review board (according to local regulations), and all patients gave written informed consent.

Study Design

The study design and procedure have been described previously.[25] The first and last author had full access to all study data and take responsibility for the integrity and data analysis. Clinical, angiographic, procedural, and outcome data were collected using a web-based reporting system (OpenClinica Community; LCC, Waltham, MA). This substudy compares patients in which ADR or related techniques have been applied, to those treated with antegrade wire escalation (AWE) and retrograde techniques.

Study Definitions and End Points

A CTO was defined as a lesion of a native coronary artery, which exhibited thrombolysis in myocardial infarction antegrade flow equal to zero, for >3 months. CTO complexity was graded using the Japanese CTO (J-CTO) score or prospective global registry for the study of CTO intervention (PROGRESS) score.[26,27] Easy/intermediate J-CTO lesions and difficult/very difficult J-CTO lesions were combined as less complex and complex lesions, respectively. Patient

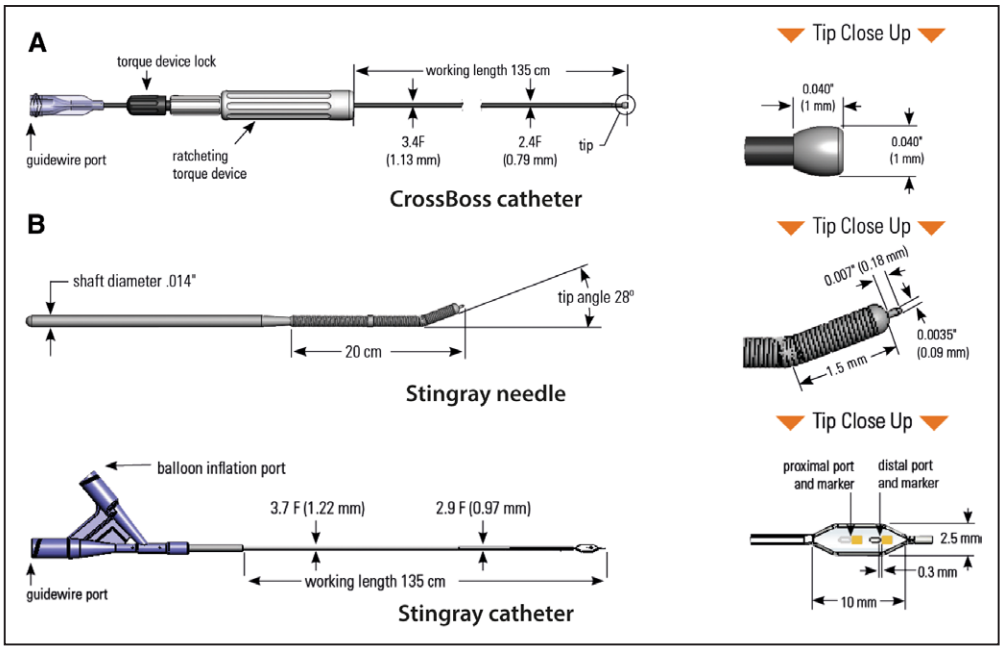

Figure 1. Specifications of the (**A**) CrossBoss catheter and (**B**) Stingray system—Stingray system comprised Stingray catheter and needle. (Image provided courtesy of Boston Scientific. © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.)

and angiographic characteristics, in-hospital major adverse cardiac and cerebrovascular events, and complications have been defined previously. ADR-related in-hospital events and complications were identified.

The population in which there was the intention to apply an ADR technique is divided into 3 groups (Figure 2). Groups A and B reflect those cases in which, respectively, the Stingray catheter or wire-based technology (WBT) were used to perform reentry. In both groups, the dissection plane can be created by the use of CrossBoss, WBT (ie, knuckle) or a combination of both. The use of CrossBoss combined with Stingray is defined as Controlled ADR. If neither CrossBoss nor Stingray were used, ADR was wire based: this includes STAR and LAST. Even though not classifiable as a true ADR technique, stand-alone use of CrossBoss going true-to-true lumen is classified under group C. This includes in-stent crossing.[17,18]

The primary goal of this substudy is to determine the overall value and use of the ADR technique and CrossBoss/Stingray technologies. The efficacy of the CrossBoss and Stingray systems when used as stand-alone devices, combined, as a primary strategy, or when used alongside other techniques is also validated. Additionally, this study aims to evaluate the safety and identify the failure modes of the ADR technology and devices.

Statistical Analyses

Baseline, angiographic, and procedural data were analyzed using descriptive statistics. Numeric values were expressed as mean±SD or median (interquartile range) as appropriate. Categorical variables were expressed as percentages. Normality was assessed using the Shapiro–Wilk statistic. Baseline characteristics were analyzed patient wise. Group comparisons were performed using Pearson χ^2 tests for categorical variables, and the independent Student *t* test, 1-way ANOVA, Mann–Whitney *U* test, or Kruskal–Wallis H test for continuous variables, as appropriate. Lesion-specific data (ie, angiographic characteristics) were analyzed via generalized and general linear mixed models as appropriate, with a random effect for patient (multiple procedures (ie, inclusions) could be performed per patient. All statistical analyses were performed using SPSS Statistics version 22 (IBM SPSS, Inc).

Results

Patient and Lesion Characteristics

Overall, 1253 CTO procedures were included in the RECHARGE registry in 1165 patients. Seventy-six patients were included multiple times, for ≥1 reattempt procedures (n=35), treatment of a second CTO lesion (n=37), or both (n=4). An ADR technique was applied in 24% (n=283/1165) and 23% (n=292/1253) of all patients and procedures, respectively. In 6 procedures, ADR was applied twice, at different stages during the procedure (ie, 298 individual ADR attempts).

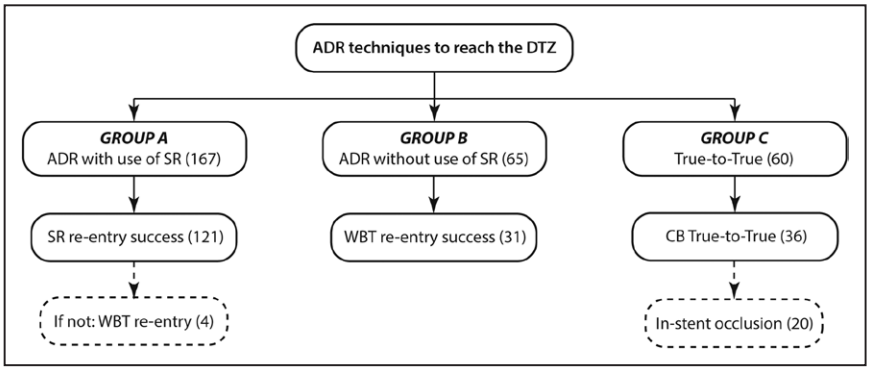

Figure 2. Schematic overview and outcomes of the different antegrade dissection and reentry (ADR) subtypes. CB indicates CrossBoss catheter; DTZ, distal target zone; LAST, limited antegrade subintimal tracking; SR, Stingray system; STAR, subintimal tracking and reentry; and WBT, wire-based technology.

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Demographics were comparable between the ADR and non-ADR patients (Table 1). Angiographically, CTOs treated with the ADR technique had a significantly higher frequency of blunt stump, tortuosity, and long lesion length and were more often in-stent occlusions. In ADR procedures, a significantly higher number of reattempts, proximal cap ambiguity (PCA), diseased distal target zone (DTZ), and proximal cap side branches were present. Overall J-CTO (2.7±1.1 versus 2.1±1.3; *P*<0.001) and PROGRESS (1.4±0.9 versus 1.2±0.9; *P*=0.002) scores were significantly higher in the ADR procedures (Table 2).

Frequency, Outcomes, and Safety of ADR

As stratified by the J-CTO score, the ADR strategy was mainly applied for complex lesions (88%; n=256/292), including 86 difficult and 170 very difficult cases. Less complex lesions (12%; n=36/292) included 3 easy and 33 intermediate cases. Total success rate using ADR was 66% (n=192/292; Table 3). Mean J-CTO score was significantly lower in successful ADR cases (2.7±1.0 versus 2.9±1.1; *P*=0.048). Neither yearly CTO volume[25] (>100 cases/y=67%; 50–100 cases/y=64%; <50 cases/y=65%; *P*=0.818) nor ADR volume (>25% ADR=73%; 20% to 25% ADR=66%; <20% ADR=52%; *P*=0.112) had a significant effect on ADR outcome.

ADR was the primary strategy in 30% (n=88/292), of which 67% (n=59/88) were successful (Table 3). On failure, either the procedure was terminated or subsequent strategies were applied. Application of additional bail-out strategies after primary ADR failure led to 89% (n=77/88) success per lesion. When applied as a secondary strategy (60%; n=174/292), after a failed antegrade wiring (89%) or retrograde strategy (11%), the ADR technique was successful in 64% (n=111/174). If applied as third strategy, success was obtained in 57% (n=17/30). Overall, bail-out ADR strategies (ie, either as secondary or third strategy) were successful in 63% (n=133/210; Table 3). Compared with primary ADR cases, bail-out ADR cases had a higher degree of proximal cap side branches (48% versus 35%), PCA (46% versus 36%), diseased DTZ (43% versus 30%), calcification (66% versus 49%), and a lack of interventional collaterals (41% versus 31%). The average J-CTO and PROGRESS scores were higher in bail-out ADR cases (2.8±1.1 versus 2.7±1.1 and 1.4±0.9 versus 1.1±0.9, respectively). Figure I in the Data Supplement provides an in-depth overview of the ADR outcomes, according to the application stage.

Table 4 shows procedural parameters: compared with stand-alone AWE procedures (J-CTO score=1.7±1.1), the ADR group (J-CTO=2.7±1.1) required more radiation, contrast, time, and materials. On the contrary, these parameters and materials (including stent length) were comparable to retrograde cases (J-CTO score=2.9±1.2).

ADR-related in-hospital major events occurred in 3.4% (n=10/292): 1 inferior ST-segment–elevation myocardial infarction occurred because of a subintimal compression hematoma at the distal right coronary artery bifurcation, resulting in complete absence of antegrade flow (treated conservatively). Diagnostic angiography the next morning showed partial hematoma reabsorption with complete restoration of antegrade flow. In 9 cases, a non–ST-segment–elevation myocardial infarction with clinical sequelae took place: 1 was the result of thrombus formation in a microcatheter located in the non-CTO artery, 1 caused by a distal artery dissection, 3 as a result of significant side-branch loss, 1 because of a subintimal hematoma, and 3 because of a major perforation (wire/microcatheter related, CrossBoss related, or Stingray catheter related). In 2 of 5 perforations, there was no related non–ST-segment–elevation myocardial infarction. Cardiac tamponade was managed either medically (n=3) or with pericardiocentesis (n=2).

Table 1. Demographics of the ADR Subpopulation Compared With the Non-ADR Subpopulation

Demographics	ADR Population (n=283)*	Non-ADR Population (n=882)*	*P* Value
Age, y	66±10	66±10	0.885
Male sex	243 (86)	751 (85)	0.766
Current smoker	76 (27)	183 (21)	0.028†
Hypertension	180 (64)	530 (60)	0.260
Dyslipidemia	186 (66)	593 (68)	0.693
Diabetes mellitus	69 (25)	236 (27)	0.465
Heart failure	22 (8)	77 (9)	0.622
Previous MI	118 (42)	327 (37)	0.150
Previous CABG	49 (17)	145 (17)	0.736
Previous CABG on TV	33 (12)	114 (13)	0.577
Previous PCI	182 (65)	477 (54)	0.002†
Previous stroke	15 (5)	48 (5)	0.937
Peripheral vascular disease	46 (18)	106 (12)	0.006†
Chronic kidney insufficiency	32 (11)	98 (11)	0.903

Values are expressed as mean±SD or n (%). ADR indicates antegrade dissection and reentry; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TV, target vessel.

*Patients included multiple times in both the ADR and non-ADR groups were included once in the ADR group. In all other cases (ie, multiple within-group inclusions), the primary index procedure was included only.

†Statistical significance (*P* value equal to 0.05 or lower).

ADR as Part of the Hybrid Algorithm

A primary ADR strategy is recommended in the presence of a clear proximal cap (by angiography or intravascular ultrasound), a good DTZ, and a long lesion length (≥20 mm). In the ADR procedures, 26% (n=77/292) presented with all 3 characteristics in favor of primary ADR. Forty-four percent (n=34/77) were treated with a primary ADR strategy, of which 79% (n=27/34) was successful. With a different primary technique (66%; n=43), no success was obtained (AWE, n=38; retrograde, n=5), and subsequent strategies were needed. A successful secondary ADR strategy was applied in 64% (n=23/36), after a failed primary AWE strategy.

In case not all characteristics were in favor of primary ADR (n=215), ADR was still applied as first strategy in 54 cases. Most commonly, there was some degree of PCA (n=32), an unhealthy DTZ (n=26) and/or a lesion length <20 mm (n=7). Primary ADR was successful in 61% (n=33/54). Failure was highest in the presence of PCA (67%, n=14) and a diseased DTZ (52%, n=11). In case different primary strategies were applied (n=161), no success was achieved with a

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Table 2. Angiographic Characteristics of the ADR, Compared With the Non-ADR Procedures and According to Outcome

Angiographics	ADR Procedures (n=292)	Non-ADR Procedures (n=961)	*P* Value	ADR Success (n=192)	ADR Failure (n=100)	*P* Value
Normal LVEF (≥50%)	147 (53)	497 (55)	0.597	99 (56)	48 (49)	0.292
CTO target vessel			0.004†			0.323
RCA	204 (70)	555 (58)		127 (66)	77 (77)	
LAD	52 (18)	238 (25)		39 (20)	13 (13)	
CX	35 (12)	165 (17)		25 (13)	10 (10)	
LMCA	1 (0.3)	3 (0.3)		1 (0.5)	0 (0)	
Ostial lesion	17 (6)	81 (9)	0.154	12 (7)	5 (5)	0.673
In-stent occlusion	52 (18)	74 (8)	<0.001†	27 (14)	25 (25)	0.025†
Lesion length ≥20 mm	226 (77)	509 (53)	<0.001†	147 (77)	79 (79)	0.636
Blunt stump	185 (63)	439 (46)	<0.001†	121 (63)	64 (64)	0.867
Calcification	179 (61)	550 (57)	0.220	110 (57)	69 (69)	0.054†
Tortuosity ≥45°	124 (43)	302 (32)	0.001†	78 (41)	46 (46)	0.381
Reattempt	88 (30)	180 (19)	<0.001†	54 (28)	34 (34)	0.302
J-CTO score	2.7±1.1	2.1±1.3	<0.001†	2.7±1.0	2.9±1.1	0.048†
PROGRESS score	1.4±0.9	1.2±0.9	0.002†	1.4±0.9	1.3±0.9	0.711
Proximal cap side branch*	128 (44)	360 (38)	0.055†	79 (41)	49 (49)	0.203
Proximal cap ambiguity	127 (44)	320 (33)	0.002†	86 (45)	41 (41)	0.537
Lack of interventional collaterals	111 (38)	321 (33)	0.149	74 (39)	37 (37)	0.798
Diseased distal landing zone	114 (39)	450 (47)	0.021†	68 (35)	46 (46)	0.082
Distal cap at bifurcation	79 (27)	266 (28)	0.826	44 (23)	35 (35)	0.029†

Values are expressed as mean±SD or n (%). ADR indicates antegrade dissection and reentry; CTO, chronic total occlusion; Cx, circumflex artery; J-CTO, Japanese CTO score; LAD, left anterior descending artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; PROGRESS, prospective global registry for the study of CTO intervention; and RCA, right coronary artery.

*Side branch with diameter >2 mm, within <5 mm of the proximal CTO cap.

†Statistical significance (*P* value equal to 0.05 or lower).

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primary strategy alone. Of these, AWE was the primary strategy in 118 cases, followed by a successful secondary ADR strategy in 68% (n=80/118).

Stepwise Approach to ADR

The initial step in ADR is always to reach the DTZ. This was achieved in 84% (n=244) of all ADR cases. Of these, the CrossBoss catheter was applied in 78% (n=191), either as a stand-alone device or combined with WBT. A stand-alone WBT technology was used in 12% (n=53). To reach the DTZ, proximal cap preparation is often required. For intentional ADR with CrossBoss (with or without WBT), proximal cap preparation was needed in 64% (n=123) cases. This included preparation with guidewire (85%; puncture/knuckle wiring (WBT)), ballooning (24%), deliberate balloon rupture (2%), Carlino (dissection caused by gentle contrast injection within the plaque; 5%) or any of these in combination.[28] The use of WBT in conjunction with CrossBoss was always withheld as proximal cap preparation. Similarly, proximal cap preparation was applied in all stand-alone WBT cases (n=53), as WBT includes knuckle wiring (alone or as part of STAR), puncturing (alone or as part of LAST), or occasional parallel wiring (n=2). In all cases requiring proximal cap preparation (n=176), a blunt proximal cap (62%; n=109/176), calcification (64%; n=112/176), and/or PCA (47%; n=82/176) was present.

In case the DTZ was reached while remaining subintimal, reentry needs to be performed as a second step. In 167 cases, the Stingray system was applied and reached the DTZ in 95% (n=159/167). The Stingray system allowed reentry in 72% (n=121/167). WBT-facilitated reentry was performed in 4 cases, after the Stingray system failed. Significant side branches (ie, diameter ≥2 mm) were lost in 18 patients. The right ventricular branch was lost in 50% (n=9/18) of the cases. As cardiac enzymes were not collected routinely,[25] events related to side-branch loss were assessed clinically. A clinical event took place in 3 cases (2 non–ST-segment–elevation myocardial infarction and 1 subintimal compression hematoma leading to a ST-segment–elevation myocardial infarction). In the other 15 patients, no clinical consequences took place.

Techniques in ADR

Our data show that various technical subtypes are applied to perform both the first (dissection and reaching DTZ) and second (reentry) steps, which differ from controlled ADR. On the basis of the reentry method, 3 main groups could be

Table 3. Procedural Outcomes of the ADR Procedures, According to Lesion Complexity

	Total (n=292)*	Less Complex (n=36)	Complex (n=256)
Primary ADR strategy*	88	12	76
Successful primary ADR strategy	59 (67)	7 (58)	52 (68)
Bail-out ADR strategy*†	210	25	185
Successful bail-out ADR strategy	133 (63)	17 (68)	116 (63)
Overall success using ADR	192 (66)	24 (67)	168 (66)
Overall success†‡	229 (78)	31 (86)	198 (77)

Values are expressed as n or n (%). The Less Complex group includes easy and intermediate J-CTO lesions. The Complex group includes difficult and very difficult J-CTO lesions. ADR indicates antegrade dissection and reentry; CTO, chronic total occlusion; and J-CTO, Japanese CTO score.

*An ADR strategy was applied in 292 cases. In 6 cases, ADR was applied 2 times at different stages during the procedure (=298 individual ADR attempts), because of initial failure to reach the distal target zone (n=1), to reenter/puncture (n=3), or no specific reason at all (n=2). A second ADR attempt was successful in all cases but one, because of a poor runoff.

†Bail-out ADR strategies were applied either as secondary (n=174) or as tertiary strategy (n=30).

‡Overall success including success with subsequent bail-out strategies, after ADR failure.

distinguished (Figure 2): To deliver the Stingray catheter (group A; n=167), a dissection plane was created using CrossBoss (56%; n=93), WBT (14%; n=23), or a combination of both (31%; n=51). Group B included patients for which a wire-based strategy was used to reenter (n=65). Similarly, to prepare for reentry, CrossBoss (23%; n=15), WBT (55%; n=36), or both (22%; n=14) could be applied. Group C included patients where the CrossBoss device went true-to-true (n=60).

In this registry, controlled ADR was applied most frequently (32%; n=93) and was most often successful (81%; n=75/93). Each other subtype (ie, no use of CrossBoss and/or Stingray, and use of WBT—collectively referred to as noncontrolled ADR cases) was applied in a lesser extent. Especially, the use of WBT for dissection and reentry (ie, knuckle, STAR, and LAST) was low. Noncontrolled ADR subtypes were less successful (59%; n=117/199).

Failure Modes

In our study, 2 main reasons of ADR technical failure were identified, both corresponding to the 2 main steps in ADR: the inability to reach the DTZ (n=48/100) or failure to reenter (n=43/100). In the other, a technical device failure (ie, Stingray-related; n=3) or a poor runoff (despite a technically successful ADR strategy; n=7) impeded a successful outcome. In one case, ADR was applied 2 times unsuccessfully, first because of failure to reenter and second because of a poor runoff.

Cases without the ability to reach the DTZ or to perform successful reentry were characterized by a higher degree of several negative angiographic characteristics (Table 2). Noncontrolled ADR subtypes were most frequently applied in failed ADR cases (83% versus 60%; $P<0.001$). Patients treated with noncontrolled ADR subtypes were associated with higher application of proximal cap preparation (83% versus 55%; $P<0.001$), a higher degree of diseased distal landing

Table 4. Procedural Characteristics of the ADR Procedures, Compared With Stand-Alone AWE Cases and Retrograde Procedures, and Classified According to Lesion Complexity

	ADR Procedures (n=292)	AWE Procedures (n=638)	Retrograde Procedures (n=323)	Less Complex (n=36)	Complex (n=256)
Dual catheter injection, %	90	62	95	78	92
Radial access, %*	68	68	70	50	70
Procedure time, min†	119 (90–145)	62 (45–82)	120 (95–156)	112 (83–138)	120 (90–139)
Fluoroscopy time, min†	48 (33–64)	22 (14–33)	56 (41–74)	46 (32–67)	48 (33–64)
Air Kerma dose, Gray†	2.0 (1.4–3.2)	1.2 (0.7–1.8)	1.8 (1.2–2.8)	1.6 (1.1–2.4)	2.1 (1.4–3.3)
DAP dose, Gray*cm^2†	131 (75–203)	68 (40–117)	174 (81–207)	100 (72–221)	136 (78–205)
Contrast volume, mL†	300 (230–380)	200 (150–255)	300 (238–400)	340 (250–450)	300 (220–375)
Guidewires, n†	6.8±3.7	3.0±1.9	8.0±4.1	7.6±4.1	6.7±3.6
Balloons, n†	3.8±2.9	2.8±2.2	4.5±3.4	3.5±2.1	3.8±3.0
Stents, n†,‡	2.8±1.0	2.0±0.9	3.0±1.1	2.6±0.8	2.8±1.0
Stent length, n	87±28	58±30	89±33	83±28	88±28
Microcatheters, n†	1.2±0.7	1.0±0.4	1.5±0.7	1.3±0.9	1.2±0.7

Retrograde procedures included retrograde wiring and retrograde dissection and reentry. Retrograde strategies were applied as stand-alone technique or combined with AWE. The less complex group includes easy and intermediate J-CTO lesions. The complex group includes difficult and very difficult J-CTO lesions. ADR indicates antegrade dissection and reentry; AWE, antegrade wire escalation; CTO, chronic total occlusion; DAP, dose area product; J-CTO, Japanese CTO score; and TIMI, Thrombolysis In Myocardial Infarction.

*Radial access only or combined femoral/radial access.

†Expressed as mean±SD or median (interquartile range).

‡Average number of stents implanted, in case ≥1 stents were implanted during the procedure (n_{ADR}=233; n_{AWE}=596; n_{RETRO}=262). Implanted stents in failed ADR procedures were related to periprocedural complications, the inability to reach TIMI 3 flow, despite stent implantation, or because of overall success with additional bail-out strategies.

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zones (45% versus 27%; *P*=0.004), and a higher J-CTO score (2.8±1.1 versus 2.6±1.0; *P*=0.269), compared with controlled ADR cases (Table 5).

Discussion

In the current CTO practice, ADR is one of the 4 applicable techniques (AWE, ADR, retrograde wire escalation and retrograde dissection, and reentry). ADR is ideally applied when the CTO lesion is long (using AWE, it would be difficult to reach the DTZ and chances to end subintimal or perforate are high) and when there is a good landing zone, not involving a bifurcation (to avoid side-branch loss).[29]

Because the ADR technique requires experience, specific education, training, and, in most cases, dedicated materials (ie, CrossBoss, Stingray system), it is essential to determine its place in contemporary hybrid CTO-PCI. This study sought to determine the value of the ADR technique within the framework of hybrid CTO-PCI, by assessing the real-world application, outcomes, safety, and limitations (ie, failure modes) of the technique.

Our data confirm that ADR is mainly applied in complex CTOs (J-CTO=2.7±1.1), when AWE is futile or as bail-out strategy when AWE or retrograde techniques (or both) have failed. Thus, it extends the range of treatable patients. In RECHARGE, ADR was applied in 23% of the CTO procedures. This corresponds with the anticipated 20% to 25% use overall. In the registries of the United States, the United Kingdom, Italy, and Canada, ADR was applied in 36%, 21%, 19%, and 22%, respectively.[2,5,30,31]

Table 5. Angiographic Characteristics of Procedures Performed With Controlled ADR Versus Noncontrolled ADR Subtypes

	Controlled ADR (n=93)	Noncontrolled ADR (n=199)	*P* Value
Proximal cap preparation performed, %*	55 (n=51/93)	83 (n=125/151)	<0.001†
Angiographic characteristics			
Ostial lesion, %	4 (5)	13 (7)	0.517
In-stent occlusion, %	4 (4)	48 (24)	<0.001†
Lesion length ≥20 mm, %	67 (72)	159 (80)	0.135
Blunt stump, %	58 (62)	127 (64)	0.810
Calcification, %	55 (59)	124 (62)	0.604
Tortuosity ≥45°, %	33 (36)	91 (46)	0.099
Reattempt, %	33 (36)	55 (28)	0.173
J-CTO score*	2.6±1.0	2.8±1.1	0.269
Proximal cap side branch, %	37 (40)	91 (46)	0.340
Proximal cap ambiguity, %	54 (58)	73 (37)	0.001†
Lack of interventional collaterals, %	29 (31)	82 (41)	0.100
Diseased distal landing zone, %	25 (27)	89 (45)	0.004†
Distal cap at bifurcation, %	26 (28)	53 (27)	0.812

Values given as mean±SD or n (%). ADR indicates antegrade dissection and reentry; CTO, chronic total occlusion; DTZ, distal target zone; and J-CTO, Japanese CTO score.

*In case the DTZ was successfully reached. Within controlled ADR cases, the DTZ was reached in 100% (n=93/93). In other ADR subtypes, the DTZ was reached in 76% (n=151/199).

†Statistical significance (*P* value equal to 0.05 or lower).

The isolated technical ADR success rate in our study is 66%. The use of supplementary strategies beyond ADR (within the hybrid algorithm) led to a per-lesion success rate of 78%. These results are in line with those from the United States and the United Kingdom.[2,30] Recently,[31] higher success rates were reported (86%) using ADR, by 4 highly experienced centers. Similar to their findings, however, our data also show that success rates were especially high in controlled ADR (ie, CrossBoss and Stingray systems only; 81%). Our data further demonstrate a higher success when ADR is used as a primary compared with a bail-out strategy, in particular when applied in the presence of favorable hybrid characteristics (79%). Given the low event rates, the safety of the technique is warranted. Furthermore, the incidence and consequences of side-branch's loss on successful reentry was not a clinical issue. These results will most likely be confirmed by the upcoming CrossBoss First trial (NCT02510547).

ADR comprises more than use of CrossBoss and Stingray systems only: many technical variations are applied. The need to adapt the technique or perform additional (preparatory) steps, according to the events, obstacles, and difficulties that are encountered, is indicative of the application of the technology in nonideal and highly complex cases. Proximal cap preparation was often required (72%), and Stingray reentry was not always feasible (28%). Therefore, specific ADR subtypes can be preferred or deliberately chosen. Even with intented controlled ADR, wire-based reentry can also occur inadvertently before Stingray use (commonly accidental mini-STAR while trying to reach the DTZ with a knuckle wire), or much less frequently, can be chosen deliberately (bail-out LAST or mini-STAR). The latter is most likely based on a suboptimal wire position to apply the Stingray technique (ie, driven by the inability to redirect the guidewire in extreme anatomy, the presence of severe calcification, or a [too] large subintimal space). Under these circumstances, STAR or LAST can be attempted as a last resort, if retrograde options are not feasible. Therefore, the Stingray system can be redundant in a variety of scenarios.

It is imperative operators should not be withheld from performing ADR. The treatment of a CTO lesion—which has an indication for primary ADR—that is first treated with an unsuitable AWE strategy, can quickly escalate in an unsuccessful procedure. This will lead to increased use of radiation, contrast, and materials. Although overall procedural parameters of the ADR group were higher—especially compared with stand-alone AWE procedures—ADR was mainly applied as bail-out strategy. This means at least one strategy had been tried previously, resulting in increased procedural parameters to start with.

Although applied in a lower extent compared with AWE or retrograde techniques (80% [n=997] and 34% [n=421], respectively[25]), the successful ADR cases still make up almost 1 out of 5 (18%) successful RECHARGE procedures. Primary ADR applied in lesions with ideal characteristics has a high success rate. Moreover, it remains an additional option when

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antegrade wiring or retrograde strategies fail, because the chances of success are low in these scenarios. Thus, ADR proved to be a valuable technique, allowing the treatment of more patients with CTO.

Study Limitations

The most important limitations of the RECHARGE study have been reported previously.[25] Other limitations are as follows: first, the application of the ADR technique is associated with an initial learning curve and, thus, requires significant training and experience to obtain success rates. In RECHARGE, all operators were certified CrossBoss (Boston Scientific) operators, although differences in experience were present. Moreover, not all centers started inclusion simultaneously, leaving the possibility that experience and thus outcomes may have improved compared with operators that started inclusions earlier in the registry. Although the hybrid algorithm was applied in all cases, the choice to switch to an ADR or other strategy depends on the operator's judgment and could, therefore, have influenced the outcomes with the ADR technique.

Conclusions

Both the efficacy and safety of the ADR technique in a real-world setting of hybrid CTO-PCI has been validated in this substudy. Although applied in a lower extent compared with AWE and retrograde strategies, ADR is still applied in almost 1 out of 4 cases. In ideal settings, the use of the CrossBoss and Stingray systems as a primary strategy results in high success rates (≈80%). As can be expected, unfavorable characteristics, the need of proximal cap preparation, the presence of calcified, tortuous CTO segments, or diseased reentry zones challenge the technique. In these scenarios, ADR is often used as a bail-out strategy. Despite the higher complexity of the technique, both the associated outcomes and limited number of in-hospital complications confirm the benefit of the technique in hybrid CTO-PCI and its additional value. Controlled ADR is the most applied (sub)technique, although the results of this study have shown several subtypes exist, each of them adding to the final outcome of the technique.

Appendix

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Antegrade Dissection and Reentry as Part of the Hybrid Chronic Total Occlusion Revascularization Strategy

A Subanalysis of the RECHARGE Registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom)

Joren Maeremans, MSc; Jo Dens, MD, PhD; James C. Spratt, MD; Alan J. Bagnall, MD, PhD; Wynand Stuijfzand, MD; Alexander Nap, MD, PhD; Pierfrancesco Agostoni, MD, PhD; William Wilson, MD; Colm G. Hanratty, MD; Simon Wilson, MD; Benjamin Faurie, MD; Alexandre Avran, MD; Erwan Bressollette, MD; Mohaned Egred, MD; Paul Knaapen, MD, PhD; Simon Walsh, MD; on behalf of the RECHARGE Investigators*

Background—Development of the CrossBoss and Stingray devices for antegrade dissection and reentry (ADR) of chronic total occlusions has improved historically suboptimal outcomes. However, the outcomes, safety, and failure modes of the technique have to be studied in a larger patient cohort. This preplanned substudy of the RECHARGE registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom) aims to evaluate the value and use of ADR and determine its future position in contemporary chronic total occlusion intervention.

Methods and Results—Patients were selected if an ADR strategy was applied. Outcomes, safety, and failure modes of the technique were assessed. The ADR technique was used in 23% (n=292/1253) of the RECHARGE registry and was mainly applied for complex lesions (Japanese chronic total occlusion score=2.7±1.1). ADR was the primary strategy in 30% (n=88/292), of which 67% were successful. Bail-out ADR strategies were successful in 63% (n=133/210). The Controlled ADR (ie, combined CrossBoss-Stingray) subtype was applied most frequently (32%; n=93/292) and successfully (81%; n=75/93). Overall per-lesion success rate was 78% (n=229/292), after use of additional bail-out strategies. The inability to reach the distal target zone (n=48/100) or to reenter (n=43/100) most commonly led to failure. ADR-associated major events occurred in 3.4% (n=10/292).

Conclusions—Although mostly applied as a bail-out strategy for complex lesions, the frequency, outcomes, and low complication rate of the ADR technique and its subtypes confirm the benefit and value of the technique in hybrid chronic total occlusion percutaneous coronary intervention, especially when antegrade wiring or retrograde approaches are not feasible.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02075372.

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Key Words: antegrade dissection and reentry ■ (coronary) chronic total occlusion ■ hybrid ■ percutaneous coronary intervention ■ registry

Percutaneous coronary intervention (PCI) of chronic total occlusions (CTO) remains a major challenge for interventional cardiologists. A recent registry still confirms that without additional techniques, tools, and dedicated CTO programs, success rates remain low (≈60%).[1]

A retrograde approach, including retrograde wiring and (reverse) controlled antegrade and retrograde subintimal tracking, is an additional strategy that increases the likelihood of success as shown by expert operators.[2–7] However, this technique has an overall failure rate of 20% to 40% and is

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WHAT IS KNOWN

- Antegrade dissection and reentry is a valuable technique for the percutaneous treatment of CTO. Since the first application of subintimal tracking and reentry in 2005, significant improvements have been made including mini-subintimal tracking and reentry, limited antegrade subintimal tracking, and most recently the development of dedicated devices for controlled dissection and reentry.
- However, previous studies on the outcomes and safety of the antegrade dissection and reentry technique are limited in patient numbers, focused on CrossBoss and Stingray only, and provided little explanation for technical failure.

WHAT THE STUDY ADDS

- This substudy assessed the application, outcomes, and safety of the antegrade dissection and reentry technique, including all of its aspects, in a multicenter setting of hybrid operators with different experience levels and including a larger cohort of patients.
- The antegrade dissection and reentry technique and its different subtypes proved to be a frequently applied and valuable technique, allowing the treatment of more patients with chronic total occlusions and further supporting its place in both contemporary and future chronic total occlusions intervention.

associated with an increased risk of perforations.[8] Moreover, visible interventional collaterals are only present in approximately two third of patients.[9] Therefore, retrograde options may not be available in 30% to 50% of CTO lesions, necessitating the availability of alternative strategies.

Any additional technique, applicable in a safe and reproducible way, may facilitate higher success rates and increased safety in the treatment of complex CTOs. For this reason, subintimal antegrade dissection and reentry (ADR) was developed.

ADR was first applied in peripheral arteries[10] and applied by Colombo in coronary arteries in 2005.[11] Subintimal tracking and reentry (STAR) involves advancing a knuckled guidewire through the subintimal space until it spontaneously reenters the true lumen. The site of reentry is unpredictable, and the risk of myocardial infarction, late target vessel occlusion, and repeat intervention is high.[12] Furthermore, the technique should not be applied in vessels with major side branches (eg, left anterior descending artery), because stenting of the subintimal track can lead to side-branch loss. In current practice, STAR is only applied in bail-out situations.

Mini-STAR[13] and limited antegrade subintimal tracking (LAST)[14] are modifications of STAR, with the aim to limit the dissection length and to reenter in a more targeted fashion, just distal from the CTO using guidewires. Only small numbers of cases with long-term follow-up are reported.[15] In 2012, Whitlow et al[16] reported the use of a novel crossing and reentry system, allowing controlled dissection and reentry. A limited dissection is created with a stiff, metallic, over-the-wire catheter with a 1-mm blunt tip—the CrossBoss catheter (Boston Scientific, Marlborough, MA)—that is advanced through the occlusion by rotating a proximal torque device (fast-spin technique; Figure 1). Reentry is attempted using the Stingray balloon catheter (Boston Scientific), which is advanced within the subintimal space.

The Stingray catheter (ø=2.5 mm/length=10 mm) has a flat shape (ie, wings) and 2 exit ports, 180° opposite to each other (Figure 1). Reentry is performed from one of the exit ports with the Stingray needle, under fluoroscopic guidance. Recently, the CrossBoss device is also used as a stand-alone device to cross in-stent occlusions,[17,18] with the aim to remain within the stent cage.

Both safety of the ADR technique and technical and procedural successes were studied previously.[2,11–14,16,19–24] These reports were limited in patient numbers, focused on the combination of CrossBoss and Stingray alone, while providing no or only a limited explanation for procedural failure. As a preplanned subanalysis of the RECHARGE registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom), our study assessed first the frequency of the ADR technique being used, second the outcome in a larger cohort of patients with the technique being applied by a larger number of operators, and third, the safety of the ADR technique. In addition, a detailed analysis on the different subtypes and failure modes of ADR, when used as part of the hybrid strategy, is reported. The evaluation of the ADR technique, including all of its aspects, within a multicentre setting of operators with different experience levels, will determine both its current and future positions in contemporary CTO-PCI.

Methods

Study Population

Seventeen centers from Belgium, France, the Netherlands, and the United Kingdom prospectively and consecutively collected data between January 2014 and October 2015.[25] All operators are trained in each aspect of CTO-PCI and apply antegrade, retrograde, and ADR techniques. Patients could be included multiple times for a reattempt of the same CTO lesion, a secondary CTO lesion treated at a later stage in time, and/or a second CTO lesion treated at the same procedure. The mean number of annually performed CTO procedures/operator was 64. The study was approved by each institutional review board (according to local regulations), and all patients gave written informed consent.

Study Design

The study design and procedure have been described previously.[25] The first and last author had full access to all study data and take responsibility for the integrity and data analysis. Clinical, angiographic, procedural, and outcome data were collected using a web-based reporting system (OpenClinica Community; LCC, Waltham, MA). This substudy compares patients in which ADR or related techniques have been applied, to those treated with antegrade wire escalation (AWE) and retrograde techniques.

Study Definitions and End Points

A CTO was defined as a lesion of a native coronary artery, which exhibited thrombolysis in myocardial infarction antegrade flow equal to zero, for >3 months. CTO complexity was graded using the Japanese CTO (J-CTO) score or prospective global registry for the study of CTO intervention (PROGRESS) score.[26,27] Easy/intermediate J-CTO lesions and difficult/very difficult J-CTO lesions were combined as less complex and complex lesions, respectively. Patient

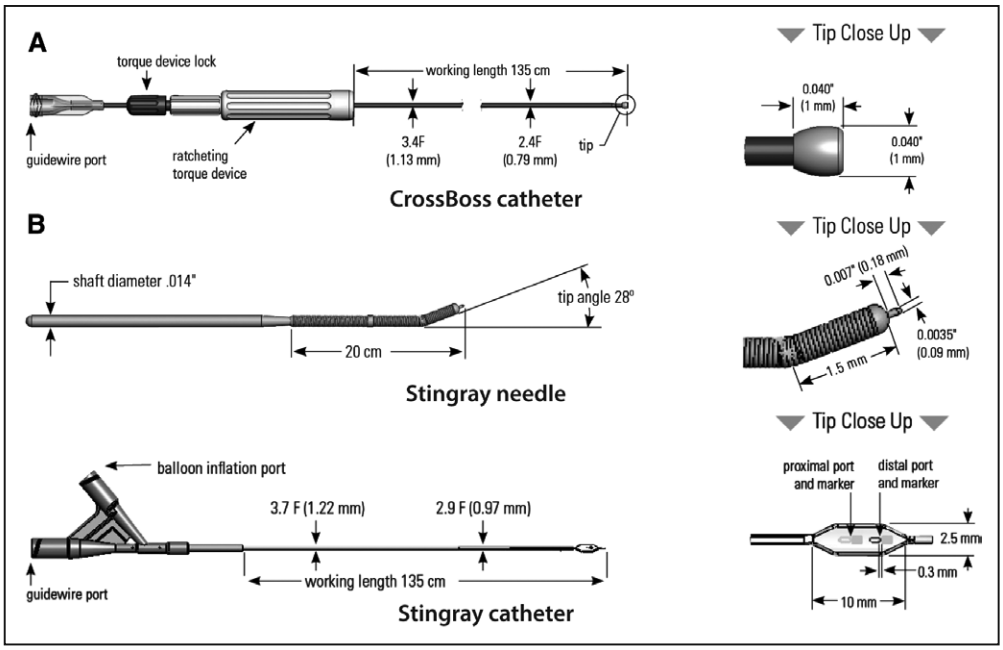

Figure 1. Specifications of the (**A**) CrossBoss catheter and (**B**) Stingray system—Stingray system comprised Stingray catheter and needle. (Image provided courtesy of Boston Scientific. © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.)

and angiographic characteristics, in-hospital major adverse cardiac and cerebrovascular events, and complications have been defined previously. ADR-related in-hospital events and complications were identified.

The population in which there was the intention to apply an ADR technique is divided into 3 groups (Figure 2). Groups A and B reflect those cases in which, respectively, the Stingray catheter or wire-based technology (WBT) were used to perform reentry. In both groups, the dissection plane can be created by the use of CrossBoss, WBT (ie, knuckle) or a combination of both. The use of CrossBoss combined with Stingray is defined as Controlled ADR. If neither CrossBoss nor Stingray were used, ADR was wire based: this includes STAR and LAST. Even though not classifiable as a true ADR technique, stand-alone use of CrossBoss going true-to-true lumen is classified under group C. This includes in-stent crossing.[17,18]

The primary goal of this substudy is to determine the overall value and use of the ADR technique and CrossBoss/Stingray technologies. The efficacy of the CrossBoss and Stingray systems when used as stand-alone devices, combined, as a primary strategy, or when used alongside other techniques is also validated. Additionally, this study aims to evaluate the safety and identify the failure modes of the ADR technology and devices.

Statistical Analyses

Baseline, angiographic, and procedural data were analyzed using descriptive statistics. Numeric values were expressed as mean±SD or median (interquartile range) as appropriate. Categorical variables were expressed as percentages. Normality was assessed using the Shapiro–Wilk statistic. Baseline characteristics were analyzed patient wise. Group comparisons were performed using Pearson χ^2 tests for categorical variables, and the independent Student *t* test, 1-way ANOVA, Mann–Whitney *U* test, or Kruskal–Wallis H test for continuous variables, as appropriate. Lesion-specific data (ie, angiographic characteristics) were analyzed via generalized and general linear mixed models as appropriate, with a random effect for patient (multiple procedures (ie, inclusions) could be performed per patient. All statistical analyses were performed using SPSS Statistics version 22 (IBM SPSS, Inc).

Results

Patient and Lesion Characteristics

Overall, 1253 CTO procedures were included in the RECHARGE registry in 1165 patients. Seventy-six patients were included multiple times, for ≥1 reattempt procedures (n=35), treatment of a second CTO lesion (n=37), or both (n=4). An ADR technique was applied in 24% (n=283/1165) and 23% (n=292/1253) of all patients and procedures, respectively. In 6 procedures, ADR was applied twice, at different stages during the procedure (ie, 298 individual ADR attempts).

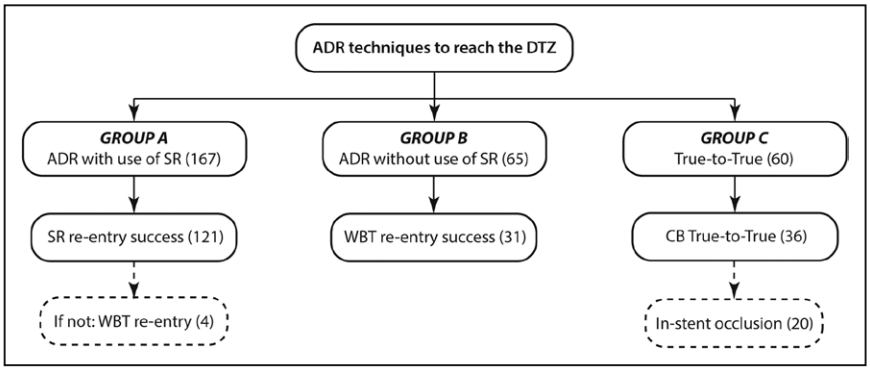

Figure 2. Schematic overview and outcomes of the different antegrade dissection and reentry (ADR) subtypes. CB indicates CrossBoss catheter; DTZ, distal target zone; LAST, limited antegrade subintimal tracking; SR, Stingray system; STAR, subintimal tracking and reentry; and WBT, wire-based technology.

Demographics were comparable between the ADR and non-ADR patients (Table 1). Angiographically, CTOs treated with the ADR technique had a significantly higher frequency of blunt stump, tortuosity, and long lesion length and were more often in-stent occlusions. In ADR procedures, a significantly higher number of reattempts, proximal cap ambiguity (PCA), diseased distal target zone (DTZ), and proximal cap side branches were present. Overall J-CTO (2.7±1.1 versus 2.1±1.3; *P*<0.001) and PROGRESS (1.4±0.9 versus 1.2±0.9; *P*=0.002) scores were significantly higher in the ADR procedures (Table 2).

Frequency, Outcomes, and Safety of ADR

As stratified by the J-CTO score, the ADR strategy was mainly applied for complex lesions (88%; n=256/292), including 86 difficult and 170 very difficult cases. Less complex lesions (12%; n=36/292) included 3 easy and 33 intermediate cases. Total success rate using ADR was 66% (n=192/292; Table 3). Mean J-CTO score was significantly lower in successful ADR cases (2.7±1.0 versus 2.9±1.1; *P*=0.048). Neither yearly CTO volume[25] (>100 cases/y=67%; 50–100 cases/y=64%; <50 cases/y=65%; *P*=0.818) nor ADR volume (>25% ADR=73%; 20% to 25% ADR=66%; <20% ADR=52%; *P*=0.112) had a significant effect on ADR outcome.

ADR was the primary strategy in 30% (n=88/292), of which 67% (n=59/88) were successful (Table 3). On failure, either the procedure was terminated or subsequent strategies were applied. Application of additional bail-out strategies after primary ADR failure led to 89% (n=77/88) success per lesion. When applied as a secondary strategy (60%; n=174/292), after a failed antegrade wiring (89%) or retrograde strategy (11%), the ADR technique was successful in 64% (n=111/174). If applied as third strategy, success was obtained in 57% (n=17/30). Overall, bail-out ADR strategies (ie, either as secondary or third strategy) were successful in 63% (n=133/210; Table 3). Compared with primary ADR cases, bail-out ADR cases had a higher degree of proximal cap side branches (48% versus 35%), PCA (46% versus 36%), diseased DTZ (43% versus 30%), calcification (66% versus 49%), and a lack of interventional collaterals (41% versus 31%). The average J-CTO and PROGRESS scores were higher in bail-out ADR cases (2.8±1.1 versus 2.7±1.1 and 1.4±0.9 versus 1.1±0.9, respectively). Figure I in the Data Supplement provides an in-depth overview of the ADR outcomes, according to the application stage.

Table 4 shows procedural parameters: compared with stand-alone AWE procedures (J-CTO score=1.7±1.1), the ADR group (J-CTO=2.7±1.1) required more radiation, contrast, time, and materials. On the contrary, these parameters and materials (including stent length) were comparable to retrograde cases (J-CTO score=2.9±1.2).

ADR-related in-hospital major events occurred in 3.4% (n=10/292): 1 inferior ST-segment–elevation myocardial infarction occurred because of a subintimal compression hematoma at the distal right coronary artery bifurcation, resulting in complete absence of antegrade flow (treated conservatively). Diagnostic angiography the next morning showed partial hematoma reabsorption with complete restoration of antegrade flow. In 9 cases, a non–ST-segment–elevation myocardial infarction with clinical sequelae took place: 1 was the result of thrombus formation in a microcatheter located in the non-CTO artery, 1 caused by a distal artery dissection, 3 as a result of significant side-branch loss, 1 because of a subintimal hematoma, and 3 because of a major perforation (wire/microcatheter related, CrossBoss related, or Stingray catheter related). In 2 of 5 perforations, there was no related non–ST-segment–elevation myocardial infarction. Cardiac tamponade was managed either medically (n=3) or with pericardiocentesis (n=2).

Table 1. Demographics of the ADR Subpopulation Compared With the Non-ADR Subpopulation

Demographics	ADR Population (n=283)*	Non-ADR Population (n=882)*	*P* Value
Age, y	66±10	66±10	0.885
Male sex	243 (86)	751 (85)	0.766
Current smoker	76 (27)	183 (21)	0.028†
Hypertension	180 (64)	530 (60)	0.260
Dyslipidemia	186 (66)	593 (68)	0.693
Diabetes mellitus	69 (25)	236 (27)	0.465
Heart failure	22 (8)	77 (9)	0.622
Previous MI	118 (42)	327 (37)	0.150
Previous CABG	49 (17)	145 (17)	0.736
Previous CABG on TV	33 (12)	114 (13)	0.577
Previous PCI	182 (65)	477 (54)	0.002†
Previous stroke	15 (5)	48 (5)	0.937
Peripheral vascular disease	46 (18)	106 (12)	0.006†
Chronic kidney insufficiency	32 (11)	98 (11)	0.903

Values are expressed as mean±SD or n (%). ADR indicates antegrade dissection and reentry; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TV, target vessel.

*Patients included multiple times in both the ADR and non-ADR groups were included once in the ADR group. In all other cases (ie, multiple within-group inclusions), the primary index procedure was included only.

†Statistical significance (*P* value equal to 0.05 or lower).

ADR as Part of the Hybrid Algorithm

A primary ADR strategy is recommended in the presence of a clear proximal cap (by angiography or intravascular ultrasound), a good DTZ, and a long lesion length (≥20 mm). In the ADR procedures, 26% (n=77/292) presented with all 3 characteristics in favor of primary ADR. Forty-four percent (n=34/77) were treated with a primary ADR strategy, of which 79% (n=27/34) was successful. With a different primary technique (66%; n=43), no success was obtained (AWE, n=38; retrograde, n=5), and subsequent strategies were needed. A successful secondary ADR strategy was applied in 64% (n=23/36), after a failed primary AWE strategy.

In case not all characteristics were in favor of primary ADR (n=215), ADR was still applied as first strategy in 54 cases. Most commonly, there was some degree of PCA (n=32), an unhealthy DTZ (n=26) and/or a lesion length <20 mm (n=7). Primary ADR was successful in 61% (n=33/54). Failure was highest in the presence of PCA (67%, n=14) and a diseased DTZ (52%, n=11). In case different primary strategies were applied (n=161), no success was achieved with a

Table 2. Angiographic Characteristics of the ADR, Compared With the Non-ADR Procedures and According to Outcome

Angiographics	ADR Procedures (n=292)	Non-ADR Procedures (n=961)	*P* Value	ADR Success (n=192)	ADR Failure (n=100)	*P* Value
Normal LVEF (≥50%)	147 (53)	497 (55)	0.597	99 (56)	48 (49)	0.292
CTO target vessel			0.004†			0.323
RCA	204 (70)	555 (58)		127 (66)	77 (77)	
LAD	52 (18)	238 (25)		39 (20)	13 (13)	
CX	35 (12)	165 (17)		25 (13)	10 (10)	
LMCA	1 (0.3)	3 (0.3)		1 (0.5)	0 (0)	
Ostial lesion	17 (6)	81 (9)	0.154	12 (7)	5 (5)	0.673
In-stent occlusion	52 (18)	74 (8)	<0.001†	27 (14)	25 (25)	0.025†
Lesion length ≥20 mm	226 (77)	509 (53)	<0.001†	147 (77)	79 (79)	0.636
Blunt stump	185 (63)	439 (46)	<0.001†	121 (63)	64 (64)	0.867
Calcification	179 (61)	550 (57)	0.220	110 (57)	69 (69)	0.054†
Tortuosity ≥45°	124 (43)	302 (32)	0.001†	78 (41)	46 (46)	0.381
Reattempt	88 (30)	180 (19)	<0.001†	54 (28)	34 (34)	0.302
J-CTO score	2.7±1.1	2.1±1.3	<0.001†	2.7±1.0	2.9±1.1	0.048†
PROGRESS score	1.4±0.9	1.2±0.9	0.002†	1.4±0.9	1.3±0.9	0.711
Proximal cap side branch*	128 (44)	360 (38)	0.055†	79 (41)	49 (49)	0.203
Proximal cap ambiguity	127 (44)	320 (33)	0.002†	86 (45)	41 (41)	0.537
Lack of interventional collaterals	111 (38)	321 (33)	0.149	74 (39)	37 (37)	0.798
Diseased distal landing zone	114 (39)	450 (47)	0.021†	68 (35)	46 (46)	0.082
Distal cap at bifurcation	79 (27)	266 (28)	0.826	44 (23)	35 (35)	0.029†

Values are expressed as mean±SD or n (%). ADR indicates antegrade dissection and reentry; CTO, chronic total occlusion; Cx, circumflex artery; J-CTO, Japanese CTO score; LAD, left anterior descending artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; PROGRESS, prospective global registry for the study of CTO intervention; and RCA, right coronary artery.

*Side branch with diameter >2 mm, within <5 mm of the proximal CTO cap.

†Statistical significance (*P* value equal to 0.05 or lower).

primary strategy alone. Of these, AWE was the primary strategy in 118 cases, followed by a successful secondary ADR strategy in 68% (n=80/118).

Stepwise Approach to ADR

The initial step in ADR is always to reach the DTZ. This was achieved in 84% (n=244) of all ADR cases. Of these, the CrossBoss catheter was applied in 78% (n=191), either as a stand-alone device or combined with WBT. A stand-alone WBT technology was used in 12% (n=53). To reach the DTZ, proximal cap preparation is often required. For intentional ADR with CrossBoss (with or without WBT), proximal cap preparation was needed in 64% (n=123) cases. This included preparation with guidewire (85%; puncture/knuckle wiring (WBT)), ballooning (24%), deliberate balloon rupture (2%), Carlino (dissection caused by gentle contrast injection within the plaque; 5%) or any of these in combination.[28] The use of WBT in conjunction with CrossBoss was always withheld as proximal cap preparation. Similarly, proximal cap preparation was applied in all stand-alone WBT cases (n=53), as WBT includes knuckle wiring (alone or as part of STAR), puncturing (alone or as part of LAST), or occasional parallel wiring (n=2). In all cases requiring proximal cap preparation (n=176), a blunt proximal cap (62%; n=109/176), calcification (64%; n=112/176), and/or PCA (47%; n=82/176) was present.

In case the DTZ was reached while remaining subintimal, reentry needs to be performed as a second step. In 167 cases, the Stingray system was applied and reached the DTZ in 95% (n=159/167). The Stingray system allowed reentry in 72% (n=121/167). WBT-facilitated reentry was performed in 4 cases, after the Stingray system failed. Significant side branches (ie, diameter ≥2 mm) were lost in 18 patients. The right ventricular branch was lost in 50% (n=9/18) of the cases. As cardiac enzymes were not collected routinely,[25] events related to side-branch loss were assessed clinically. A clinical event took place in 3 cases (2 non–ST-segment–elevation myocardial infarction and 1 subintimal compression hematoma leading to a ST-segment–elevation myocardial infarction). In the other 15 patients, no clinical consequences took place.

Techniques in ADR

Our data show that various technical subtypes are applied to perform both the first (dissection and reaching DTZ) and second (reentry) steps, which differ from controlled ADR. On the basis of the reentry method, 3 main groups could be

Table 3. Procedural Outcomes of the ADR Procedures, According to Lesion Complexity

	Total (n=292)*	Less Complex (n=36)	Complex (n=256)
Primary ADR strategy*	88	12	76
Successful primary ADR strategy	59 (67)	7 (58)	52 (68)
Bail-out ADR strategy*†	210	25	185
Successful bail-out ADR strategy	133 (63)	17 (68)	116 (63)
Overall success using ADR	192 (66)	24 (67)	168 (66)
Overall success†‡	229 (78)	31 (86)	198 (77)

Values are expressed as n or n (%). The Less Complex group includes easy and intermediate J-CTO lesions. The Complex group includes difficult and very difficult J-CTO lesions. ADR indicates antegrade dissection and reentry; CTO, chronic total occlusion; and J-CTO, Japanese CTO score.

*An ADR strategy was applied in 292 cases. In 6 cases, ADR was applied 2 times at different stages during the procedure (=298 individual ADR attempts), because of initial failure to reach the distal target zone (n=1), to reenter/puncture (n=3), or no specific reason at all (n=2). A second ADR attempt was successful in all cases but one, because of a poor runoff.

†Bail-out ADR strategies were applied either as secondary (n=174) or as tertiary strategy (n=30).

‡Overall success including success with subsequent bail-out strategies, after ADR failure.

distinguished (Figure 2): To deliver the Stingray catheter (group A; n=167), a dissection plane was created using CrossBoss (56%; n=93), WBT (14%; n=23), or a combination of both (31%; n=51). Group B included patients for which a wire-based strategy was used to reenter (n=65). Similarly, to prepare for reentry, CrossBoss (23%; n=15), WBT (55%; n=36), or both (22%; n=14) could be applied. Group C included patients where the CrossBoss device went true-to-true (n=60).

In this registry, controlled ADR was applied most frequently (32%; n=93) and was most often successful (81%; n=75/93). Each other subtype (ie, no use of CrossBoss and/or Stingray, and use of WBT—collectively referred to as noncontrolled ADR cases) was applied in a lesser extent. Especially, the use of WBT for dissection and reentry (ie, knuckle, STAR, and LAST) was low. Noncontrolled ADR subtypes were less successful (59%; n=117/199).

Failure Modes

In our study, 2 main reasons of ADR technical failure were identified, both corresponding to the 2 main steps in ADR: the inability to reach the DTZ (n=48/100) or failure to reenter (n=43/100). In the other, a technical device failure (ie, Stingray-related; n=3) or a poor runoff (despite a technically successful ADR strategy; n=7) impeded a successful outcome. In one case, ADR was applied 2 times unsuccessfully, first because of failure to reenter and second because of a poor runoff.

Cases without the ability to reach the DTZ or to perform successful reentry were characterized by a higher degree of several negative angiographic characteristics (Table 2). Noncontrolled ADR subtypes were most frequently applied in failed ADR cases (83% versus 60%; $P<0.001$). Patients treated with noncontrolled ADR subtypes were associated with higher application of proximal cap preparation (83% versus 55%; $P<0.001$), a higher degree of diseased distal landing

Table 4. Procedural Characteristics of the ADR Procedures, Compared With Stand-Alone AWE Cases and Retrograde Procedures, and Classified According to Lesion Complexity

	ADR Procedures (n=292)	AWE Procedures (n=638)	Retrograde Procedures (n=323)	Less Complex (n=36)	Complex (n=256)
Dual catheter injection, %	90	62	95	78	92
Radial access, %*	68	68	70	50	70
Procedure time, min†	119 (90–145)	62 (45–82)	120 (95–156)	112 (83–138)	120 (90–139)
Fluoroscopy time, min†	48 (33–64)	22 (14–33)	56 (41–74)	46 (32–67)	48 (33–64)
Air Kerma dose, Gray†	2.0 (1.4–3.2)	1.2 (0.7–1.8)	1.8 (1.2–2.8)	1.6 (1.1–2.4)	2.1 (1.4–3.3)
DAP dose, Gray*cm^2†	131 (75–203)	68 (40–117)	174 (81–207)	100 (72–221)	136 (78–205)
Contrast volume, mL†	300 (230–380)	200 (150–255)	300 (238–400)	340 (250–450)	300 (220–375)
Guidewires, n†	6.8±3.7	3.0±1.9	8.0±4.1	7.6±4.1	6.7±3.6
Balloons, n†	3.8±2.9	2.8±2.2	4.5±3.4	3.5±2.1	3.8±3.0
Stents, n†,‡	2.8±1.0	2.0±0.9	3.0±1.1	2.6±0.8	2.8±1.0
Stent length, n	87±28	58±30	89±33	83±28	88±28
Microcatheters, n†	1.2±0.7	1.0±0.4	1.5±0.7	1.3±0.9	1.2±0.7

Retrograde procedures included retrograde wiring and retrograde dissection and reentry. Retrograde strategies were applied as stand-alone technique or combined with AWE. The less complex group includes easy and intermediate J-CTO lesions. The complex group includes difficult and very difficult J-CTO lesions. ADR indicates antegrade dissection and reentry; AWE, antegrade wire escalation; CTO, chronic total occlusion; DAP, dose area product; J-CTO, Japanese CTO score; and TIMI, Thrombolysis In Myocardial Infarction.

*Radial access only or combined femoral/radial access.

†Expressed as mean±SD or median (interquartile range).

‡Average number of stents implanted, in case ≥1 stents were implanted during the procedure (n_{ADR}=233; n_{AWE}=596; n_{RETRO}=262). Implanted stents in failed ADR procedures were related to periprocedural complications, the inability to reach TIMI 3 flow, despite stent implantation, or because of overall success with additional bail-out strategies.

zones (45% versus 27%; *P*=0.004), and a higher J-CTO score (2.8±1.1 versus 2.6±1.0; *P*=0.269), compared with controlled ADR cases (Table 5).

Discussion

In the current CTO practice, ADR is one of the 4 applicable techniques (AWE, ADR, retrograde wire escalation and retrograde dissection, and reentry). ADR is ideally applied when the CTO lesion is long (using AWE, it would be difficult to reach the DTZ and chances to end subintimal or perforate are high) and when there is a good landing zone, not involving a bifurcation (to avoid side-branch loss).[29]

Because the ADR technique requires experience, specific education, training, and, in most cases, dedicated materials (ie, CrossBoss, Stingray system), it is essential to determine its place in contemporary hybrid CTO-PCI. This study sought to determine the value of the ADR technique within the framework of hybrid CTO-PCI, by assessing the real-world application, outcomes, safety, and limitations (ie, failure modes) of the technique.

Our data confirm that ADR is mainly applied in complex CTOs (J-CTO=2.7±1.1), when AWE is futile or as bail-out strategy when AWE or retrograde techniques (or both) have failed. Thus, it extends the range of treatable patients. In RECHARGE, ADR was applied in 23% of the CTO procedures. This corresponds with the anticipated 20% to 25% use overall. In the registries of the United States, the United Kingdom, Italy, and Canada, ADR was applied in 36%, 21%, 19%, and 22%, respectively.[2,5,30,31]

Table 5. Angiographic Characteristics of Procedures Performed With Controlled ADR Versus Noncontrolled ADR Subtypes

	Controlled ADR (n=93)	Noncontrolled ADR (n=199)	*P* Value
Proximal cap preparation performed, %*	55 (n=51/93)	83 (n=125/151)	<0.001†
Angiographic characteristics			
Ostial lesion, %	4 (5)	13 (7)	0.517
In-stent occlusion, %	4 (4)	48 (24)	<0.001†
Lesion length ≥20 mm, %	67 (72)	159 (80)	0.135
Blunt stump, %	58 (62)	127 (64)	0.810
Calcification, %	55 (59)	124 (62)	0.604
Tortuosity ≥45°, %	33 (36)	91 (46)	0.099
Reattempt, %	33 (36)	55 (28)	0.173
J-CTO score*	2.6±1.0	2.8±1.1	0.269
Proximal cap side branch, %	37 (40)	91 (46)	0.340
Proximal cap ambiguity, %	54 (58)	73 (37)	0.001†
Lack of interventional collaterals, %	29 (31)	82 (41)	0.100
Diseased distal landing zone, %	25 (27)	89 (45)	0.004†
Distal cap at bifurcation, %	26 (28)	53 (27)	0.812

Values given as mean±SD or n (%). ADR indicates antegrade dissection and reentry; CTO, chronic total occlusion; DTZ, distal target zone; and J-CTO, Japanese CTO score.

*In case the DTZ was successfully reached. Within controlled ADR cases, the DTZ was reached in 100% (n=93/93). In other ADR subtypes, the DTZ was reached in 76% (n=151/199).

†Statistical significance (*P* value equal to 0.05 or lower).

The isolated technical ADR success rate in our study is 66%. The use of supplementary strategies beyond ADR (within the hybrid algorithm) led to a per-lesion success rate of 78%. These results are in line with those from the United States and the United Kingdom.[2,30] Recently,[31] higher success rates were reported (86%) using ADR, by 4 highly experienced centers. Similar to their findings, however, our data also show that success rates were especially high in controlled ADR (ie, CrossBoss and Stingray systems only; 81%). Our data further demonstrate a higher success when ADR is used as a primary compared with a bail-out strategy, in particular when applied in the presence of favorable hybrid characteristics (79%). Given the low event rates, the safety of the technique is warranted. Furthermore, the incidence and consequences of side-branch's loss on successful reentry was not a clinical issue. These results will most likely be confirmed by the upcoming CrossBoss First trial (NCT02510547).

ADR comprises more than use of CrossBoss and Stingray systems only: many technical variations are applied. The need to adapt the technique or perform additional (preparatory) steps, according to the events, obstacles, and difficulties that are encountered, is indicative of the application of the technology in nonideal and highly complex cases. Proximal cap preparation was often required (72%), and Stingray reentry was not always feasible (28%). Therefore, specific ADR subtypes can be preferred or deliberately chosen. Even with intented controlled ADR, wire-based reentry can also occur inadvertently before Stingray use (commonly accidental mini-STAR while trying to reach the DTZ with a knuckle wire), or much less frequently, can be chosen deliberately (bail-out LAST or mini-STAR). The latter is most likely based on a suboptimal wire position to apply the Stingray technique (ie, driven by the inability to redirect the guidewire in extreme anatomy, the presence of severe calcification, or a [too] large subintimal space). Under these circumstances, STAR or LAST can be attempted as a last resort, if retrograde options are not feasible. Therefore, the Stingray system can be redundant in a variety of scenarios.

It is imperative operators should not be withheld from performing ADR. The treatment of a CTO lesion—which has an indication for primary ADR—that is first treated with an unsuitable AWE strategy, can quickly escalate in an unsuccessful procedure. This will lead to increased use of radiation, contrast, and materials. Although overall procedural parameters of the ADR group were higher—especially compared with stand-alone AWE procedures—ADR was mainly applied as bail-out strategy. This means at least one strategy had been tried previously, resulting in increased procedural parameters to start with.

Although applied in a lower extent compared with AWE or retrograde techniques (80% [n=997] and 34% [n=421], respectively[25]), the successful ADR cases still make up almost 1 out of 5 (18%) successful RECHARGE procedures. Primary ADR applied in lesions with ideal characteristics has a high success rate. Moreover, it remains an additional option when

antegrade wiring or retrograde strategies fail, because the chances of success are low in these scenarios. Thus, ADR proved to be a valuable technique, allowing the treatment of more patients with CTO.

Study Limitations

The most important limitations of the RECHARGE study have been reported previously.[25] Other limitations are as follows: first, the application of the ADR technique is associated with an initial learning curve and, thus, requires significant training and experience to obtain success rates. In RECHARGE, all operators were certified CrossBoss (Boston Scientific) operators, although differences in experience were present. Moreover, not all centers started inclusion simultaneously, leaving the possibility that experience and thus outcomes may have improved compared with operators that started inclusions earlier in the registry. Although the hybrid algorithm was applied in all cases, the choice to switch to an ADR or other strategy depends on the operator's judgment and could, therefore, have influenced the outcomes with the ADR technique.

Conclusions

Both the efficacy and safety of the ADR technique in a real-world setting of hybrid CTO-PCI has been validated in this substudy. Although applied in a lower extent compared with AWE and retrograde strategies, ADR is still applied in almost 1 out of 4 cases. In ideal settings, the use of the CrossBoss and Stingray systems as a primary strategy results in high success rates (≈80%). As can be expected, unfavorable characteristics, the need of proximal cap preparation, the presence of calcified, tortuous CTO segments, or diseased reentry zones challenge the technique. In these scenarios, ADR is often used as a bail-out strategy. Despite the higher complexity of the technique, both the associated outcomes and limited number of in-hospital complications confirm the benefit of the technique in hybrid CTO-PCI and its additional value. Controlled ADR is the most applied (sub)technique, although the results of this study have shown several subtypes exist, each of them adding to the final outcome of the technique.

Appendix

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