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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Antegrade dissection & re-entry as part of the hybrid CTO revascularization strategy: a sub-analysis of the RECHARGE Registry

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ABSTRACT

Background Development of the CrossBoss and Stingray devices for antegrade dissection and re-entry (ADR) of chronic total occlusions (CTO) have improved historically suboptimal outcomes. However, the outcomes, safety and failure modes of the technique have to be studied in a larger patient cohort. This pre-planned sub-study of the REgistry of CrossBoss and Hybrid procedures in FrAnce, the NetheRlands, BelGium and UnitEd Kingdom (RECHARGE) aims to evaluate the value and use of ADR and determine its future position in contemporary CTO 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 CTO 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” (i.e. 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 re-enter (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 CTO-PCI, especially when antegrade wiring or retrograde approaches are not feasible.

Clinical Trial Registration Information ClinicalTrials.gov Identifier: NCT02075372 (URL: https://clinicaltrials.gov/ct2/show/NCT02075372?term=recharge&rank=6)

Key Words: Percutaneous coronary intervention, chronic total occlusion, hybrid, antegrade dissection and re-entry

Abbreviations:

ADR: Antegrade dissection and re-entry

AWE: Antegrade wire escalation

CB: CrossBoss

CTO: Chronic total occlusion

DTZ: Distal target zone

J-CTO: Japanese CTO score

LAST: Limited antegrade subintimal tracking

PCA: proximal cap ambiguity

PCI: Percutaneous coronary intervention

PROGRESS: Prospective global registry for the study of chronic total occlusion intervention

SR: Stingray

STAR: Subintimal tracking and re-entry

STEMI: ST-segment elevation myocardial infarction

WBT: Wire-based technology

INTRODUCTION

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 likelihood of success as shown by expert operators[2-7]. However, this technique has an overall failure rate of 20-40%, and is associated with an increased risk of perforations[8]. Moreover, visible "interventional" collaterals are only present in approximately 2/3rd of patients[9]. Therefore, retrograde options may not be available in 30-50% 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 re-entry (STAR) involves advancing a knuckled guidewire through the subintimal space until it spontaneously re-enters the true lumen. The site of re-entry 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 (e.g. left anterior descending artery), since 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 re-enter 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 reported the use of a novel crossing and re-entry system[16], allowing controlled dissection and re-entry. A limited dissection is created with a stiff, metallic, over-the-wire catheter with a 1 mm blunt tip - the

CrossBoss catheter (CB) (Boston Scientific, Marlborough, USA) - that is advanced through the occlusion by rotating a proximal torque device ("fast-spin technique") (Figure 1). Re-entry is attempted using the Stingray (SR) balloon catheter (Boston Scientific), which is advanced within the subintimal space.

The SR catheter (ø=2.5mm/length=10mm) has a flat shape (i.e. wings) and two exit ports, 180° opposite to each other (Figure 1). Re-entry is performed from one of the exit ports with the SR Needle, under fluoroscopic guidance. Recently, the CB 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 the safety of the ADR technique, as well as the technical and procedural success, were studied previously[2, 11-14, 16, 19-24]. These reports were limited in patient numbers, focussed on the combination of CB and SR alone, whilst providing no or only a limited explanation for procedural failure. As a pre-planned sub-analysis of the REgistry of CrossBoss and Hybrid procedures in FrAnce, the NetheRlands, BelGium and UnitEd Kingdom (RECHARGE), our study assessed firstly, the frequency of the ADR technique being used, secondly the outcome in a larger cohort of patients with the technique being applied by a larger number of operators and thirdly, 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 position 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, either for a re-attempt 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, USA). This sub-study compares patients in which ADR or related techniques have been applied, to those treated with AWE and/or retrograde techniques.

Study definitions and endpoints

A CTO was defined as a lesion of a native coronary artery, which exhibited Thrombolysis in Myocardial Infarction antegrade flow equal to zero, for more than 3 months. CTO complexity was graded using the Japanese CTO (J-CTO) or Prospective global registry for the study of chronic total occlusion 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 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 in three groups (Figure 2). Group A and B reflect those cases in which respectively the SR catheter or wire-based technology (WBT) were used to perform re-entry. In both groups, the dissection plane can be created either by use of CB, WBT (i.e. knuckle), or a combination of both. The use of CB combined with SR is defined as “Controlled ADR”. If neither CB or SR were used, ADR was wire-based: this includes STAR and LAST. Even though not classifiable as a true ADR technique, stand-alone use of CB going “true-to-true” lumen, is classified under group C. This includes in-stent crossing[17, 18].

The primary goal of this sub-study is to determine the overall value and use of the ADR technique and CB/SR technologies. The efficacy of the CB and SR 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. Numerical values were expressed as mean ± standard deviation or median (interquartile range) as appropriate. Categorical variables were expressed as percentages. Normality was assessed using the Shapiro-Wilk statistic. Baseline characteristics were analysed patient-wise. Group comparisons were performed using Pearson’s χ^2-tests for categorical variables, and the independent Student’s t-test, one-way analysis of variance, Mann-Whitney U test or Kruskal-Wallis H test for continuous variables, as appropriate. Lesion-specific data (i.e. angiographic characteristics) were analysed via generalized and general linear mixed models as appropriate, with a random effect for patient (multiple procedures (i.e. inclusions) could be performed per patient. All statistical analyses were carried out 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 one or more re-attempt 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 six procedures, ADR was applied twice, at different stages during the procedure (i.e. 298 individual ADR attempts). 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, long lesion length, and were more often in-stent occlusions. In ADR procedures, a significantly higher number of re-attempts, proximal cap ambiguity (PCA), diseased distal target zone (DTZ) and proximal cap side-branches were present. Overall J-CTO (2.7±1.1 vs. 2.1±1.3; p<0.001) and PROGRESS (1.4±0.9 vs. 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 vs. 2.9±1.1; p=0.048). Neither yearly CTO volume[25] ((>100 cases/year=67%; 50-100 cases/year=64%; <50 cases/year=65%; p=0.818), nor ADR volume (>25% ADR=73%; 20-25% 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). Upon 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 (i.e. either as secondary or third strategy) were successful in 63% (n=133/210) (Table 3). Compared to primary ADR cases, bail-out ADR cases had a higher degree of proximal cap side-branches (48% vs. 35%), PCA (46% vs. 36%), diseased DTZ (43% vs. 30%), calcification (66% vs. 49%), and a lack of “interventional” collaterals (41% vs. 31%). The average J-CTO and PROGRESS scores were higher in bail-out ADR cases (2.8±1.1 vs. 2.7±1.1 and 1.4±0.9 vs. 1.1±0.9 respectively). Supplemental Figure 1 provides an in-depth overview of the ADR outcomes, according to the application stage.

Table 4 shows procedural parameters: compared to 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 (incl. 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 (STEMI) occurred due to 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-STEMI 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 due to a subintimal hematoma and 3 due to a major perforation (either wire/microcatheter-, CB-, or SR catheter-related). In 2 of 5 perforations there was no related non-STEMI. Cardiac tamponade was managed either medically (n=3) or with pericardiocentesis (n=2).

ADR as part of the hybrid algorithm

A primary ADR strategy is recommended in the presence of a clear proximal cap (by angiography or IVUS), a good DTZ and a long lesion length (≥20mm). In the ADR procedures, 26% (n=77/292) presented with all three 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) successfully. 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 <20mm (n=7). Primary ADR was successful in 61% (n=33/54). Failure was highest in the presence of PCA (67%, n=14) and/or a diseased DTZ (52%, n=11). In case different primary strategies were applied (n=161), no success was achieved with a 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).

A 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 CB 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). In order to reach the DTZ, proximal cap preparation is often required. For intentional ADR with CB (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 CB 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, re-entry needs to be performed as a second step. In 167 cases, the SR system was applied and reached the DTZ in 95% (n=159/167). The SR system allowed re-entry in 72% (n=121/167). WBT-facilitated re-entry was performed in four cases, after the SR system failed. Significant side-branches (i.e. diameter ≥2mm) 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-STEMI, 1 subintimal compression hematoma leading to a STEMI). In the other 15 patients, no clinical consequences took place.

Techniques in ADR

Our data show various technical subtypes are applied to perform both the first (dissection and reaching DTZ) and second (re-entry) step, and which differ from “Controlled ADR”. Based on the re-entry method, three main groups could be distinguished (Figure 2): To deliver the SR catheter (group A; n=167), a dissection plane was created using CB (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 re-enter (n=65). Similarly, to prepare for re-entry, CB (23%; n=15), WBT (55%; n=36), or both (22%; n=14) could be applied. Group C included patients where the CB 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 (i.e. no use of CB and/or SR, and/or use of WBT - collectively referred to as “non-controlled ADR” cases) was applied in a lesser extent. Especially the use of WBT for dissection and re-entry (i.e. knuckle, STAR, LAST) was low. Non-controlled ADR subtypes were less successful (59%; n=117/199).

Failure modes

In our study, two main reasons of ADR technical failure were identified, both corresponding to the two main steps in ADR: the inability to reach the DTZ (n=48/100) or failure to re-enter (n=43/100). In the other, a technical device failure (i.e. SR-related) (n=3), or a poor run-off (despite a technically successful ADR strategy) (n=7), impeded a successful outcome. In one case, ADR was applied two times unsuccessfully, first due to failure to re-enter, second due to a poor run-off.

Cases without the ability to reach the DTZ or to perform successful re-entry, were characterized by a higher degree of several negative angiographic characteristics (Table 2). Non-controlled ADR subtypes were most frequently applied in failed ADR cases (83% versus 60%, $p<0.001$). Patients treated with non-controlled ADR subtypes were associated with higher application of proximal cap preparation (83% vs. 55%; $p<0.001$), a higher degree of diseased distal landing zones (45% vs. 27%; $p=0.004$), and a higher J-CTO score (2.8±1.1 vs. 2.6±1.0; $p=0.269$), compared to “Controlled ADR” cases (Table 5).

DISCUSSION

In current CTO practice, ADR is one of the four applicable techniques (AWE, ADR, retrograde wire escalation and retrograde dissection and re-entry). 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].

As the ADR technique requires experience, specific education, training, and in most cases dedicated materials (i.e. CB, SR 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 (i.e. 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 and/or retrograde techniques 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 20-25% use overall. In the United States', United Kingdom', Italian', and Canadian' registries, ADR was applied in 36%, 21%, 19% and 22% respectively[2, 5, 30, 31].

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 United Kingdom[2, 30]. Very recently[31], higher success rates were reported (86%) using ADR, by four highly experienced centers. Similar to their findings however, our data also show success rates were especially high in "Controlled ADR" (i.e. CB and SR systems only) (81%). Our data further demonstrate a higher success when ADR is used as a primary compared to 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' loss upon successful re-entry, 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 CB and SR 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 which are encountered, is indicative of the application of the technology in non-ideal and highly complex cases. Proximal cap preparation was often required (72%), and SR re-entry was not always feasible (28%). Therefore, specific ADR subtypes can be preferred or deliberately chosen. Even with intented “Controlled ADR”, wire-based re-entry can also occur inadvertently prior to SR use (commonly accidental mini-STAR whilst 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 SR technique (i.e. driven by the inability to re-direct the guidewire in extreme anatomy, the presence of severe calcification, and/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 SR 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 to AWE or retrograde techniques (80% (n=997), 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, since 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 to 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 sub-study. Although applied in a lower extent compared to AWE and retrograde strategies, ADR is still applied in almost 1 out of 4 cases. In ideal settings, the use of the CB and SR systems and 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 re-entry 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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FIGURE LEGENDS

***Figure 1: Specifications of the (A) CrossBoss catheter and (B) Stingray system** – Stingray system comprised of Stingray catheter and needle (Image provided courtesy of Boston Scientific. ©2016 Boston Scientific Corporation or its affiliates. All rights reserved)*

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

Table 1. Demographics of the ADR subpopulation compared to the non-ADR subpopulation.

Demographics	**ADR population (n=283)***	**Non-ADR population (n=882)***	**p-value**
Age (years)	66 ± 10	66 ± 10	0.885
Male	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

Expressed as mean ± SD or n (%).

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

ADR, antegrade dissection and re-entry; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; TV, target vessel.

Table 2. Angiographic characteristics of the ADR, compared to 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 ≥20mm	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
Re-attempt	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**

Expressed as mean ± SD or n (%).

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

ADR, antegrade dissection and re-entry; CTO, chronic total occlusion; LAD, left anterior descending artery; Cx, circumflex artery; J-CTO, Japanese CTO score; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; PROGRESS, Prospective global registry for the study of CTO intervention; RCA, right coronary artery.

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)

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.

*An ADR strategy was applied in 292 cases. In six cases, ADR was applied two times at different stages during the procedure (= 298 individual ADR attempts), due to initial failure to reach the distal target zone (n=1), to re-enter/puncture (n=3), or no specific reason at all (n=2). A second ADR attempt was successful in all cases but one, due to a poor run-off.

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

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

ADR, antegrade dissection and re-entry; J-CTO, Japanese CTO score.

Table 4. Procedural characteristics of the ADR procedures, compared with stand-alone AWE cases and retrograde procedures, and classified according to lesion complexity. Retrograde procedures included retrograde wiring and/or retrograde dissection and re-entry. Retrograde strategies were applied as stand-alone technique or combined with AWE.

	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

*Expressed as mean ± SD or median, interquartile range.

The Less Complex group includes easy and intermediate J-CTO lesions. The Complex group includes difficult and very difficult J-CTO lesions.

†Radial access only or combined femoral/radial access.

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

AWE, antegrade wire escalation; DAP, dose area product; J-CTO, Japanese CTO score; TIMI, Thrombolysis In Myocardial Infarction.

Table 5. Angiographic characteristics of procedures performed with Controlled ADR versus Non-controlled ADR subtypes.

	Controlled ADR (n=93)	**Non-controlled 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 ≥20mm (%)	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
Re-attempt (%)	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 (%).

* 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).

DTZ, distal target zone. Other abbrevations and definitions as given in Table 2.