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CORONARY ARTERY DISEASE

Editor's Choice

One-Year Outcomes After Successful Chronic Total Occlusion Percutaneous Coronary Intervention: The Impact of Dissection Re-Entry Techniques

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We aimed to determine clinical outcomes 1 year after successful chronic total occlusion (CTO) PCI and, in particular, whether use of dissection and re-entry strategies affects clinical outcomes. Hybrid approaches have increased the procedural success of CTO percutaneous coronary intervention (PCI) but longer-term outcomes are unknown, particularly in relation to dissection and re-entry techniques. Data were collected for consecutive CTO PCIs performed by hybrid-trained operators from 7 United Kingdom (UK) centres between 2012 and 2014. The primary endpoint (death, myocardial infarction, unplanned target vessel revascularization) was measured at 12 months along with angina status. One-year follow up data were available for 96% of successful cases ($n = 805$). In total, 85% of patients had a CCS angina class of 2–4 prior to CTO PCI. Final successful procedural strategy was antegrade wire escalation 48%; antegrade dissection and re-entry (ADR) 21%; retrograde wire escalation 5%; retrograde dissection and re-entry (RDR) 26%. Overall, 47% of CTOs were recanalized using dissection and re-entry strategies. During a mean follow up of 11.5 ± 3.8 months, the primary endpoint occurred in 8.6% ($n = 69$) of patients (10.3% ($n = 39/375$) in DART group and 7.0% ($n = 30/430$) in wire-based cases). The majority of patients (88%) had no or minimal angina (CCS class 0 or 1). ADR and RDR were used more frequently in more complex cases with greater disease burden, however, the only independent predictor of the primary endpoint was lesion length. CTO PCI in complex lesions using the hybrid approach is safe, effective and has a low one-year adverse event rate. The method used to recanalize arteries was not associated with adverse outcomes. © 2017 Wiley Periodicals, Inc.

Key words: revascularization; stent; CrossBoss; stingray; angina; hybrid approach

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INTRODUCTION

Symptomatic patients with chronic total occlusions (CTO) undergo percutaneous coronary intervention (PCI) less commonly than patients with nonocclusive disease [1]. Multiple factors contribute to this referral bias, including concerns regarding potential CTO PCI success, safety and a lack of data demonstrating durability of outcomes. This is especially pertinent in complex CTO lesions, such as those with nontapered (e.g., ambiguous or blunt) proximal caps, tortuosity, calcification, or long occlusion segments where antegrade wire escalation (AWE) or retrograde wire escalation (RWE) techniques are less effective [2]. Antegrade dissection and re-entry (ADR) and retrograde dissection and re-entry (RDR) strategies for CTO PCI have been developed to address many of these technical and clinical limitations.

ADR was first described as the subintimal tracking and re-entry (STAR) technique [3,4]. This involves pushing a folded or "knuckled" (usually jacketed) wire in an antegrade direction through the subintimal space until it re-enters the distal true lumen, which usually occurs at a bifurcation. Long-term outcomes were poor with STAR, with reocclusion rates of up to 50% noted [5,6], most likely related to poor outflow as a result of uncontrolled re-entry into distal small branches [7]. Whilst STAR has been largely abandoned, ADR has evolved as a technique. In contemporary ADR, the dedicated CrossBoss and Stingray system (Boston Scientific, Natick, MA) facilitates safe, controlled antegrade dissection in the subintimal space and targeted re-entry as soon as feasible distal to the occlusion, thus limiting the length of dissection.

RDR techniques have also been introduced into clinical practice. In the controlled antegrade and retrograde tracking (CART) and reverse CART (rCART) techniques [8], the proximal and distal true lumen are connected by a common sub-intimal space within the CTO segment, created by ballooning from a retrograde direction (CART) or antegrade direction (rCART). As with contemporary ADR, the length of the subintimal space created is shorter than typically seen with STAR.

ADR and RDR approaches form an integral part of the hybrid approach to CTO PCI [9] (Fig. 1). This approach advocates an initial employment of wire escalation or dissection and re-entry techniques (DART) based on anatomical considerations, with rapid switching to alternative strategies if there is failure to make progress (Fig. 1). We [2] and others [10–12] have reported success rates of >90% in complex CTO lesions when using the hybrid approach. The long-term outcome of DART is unknown, therefore, we sought to define long-term clinical outcomes of CTO PCI procedures performed according to the "hybrid" algorithm using contemporary ADR and RDR techniques where required. In particular, the influence of stent insertion in the subintimal space was examined to determine if this was associated with adverse outcomes.

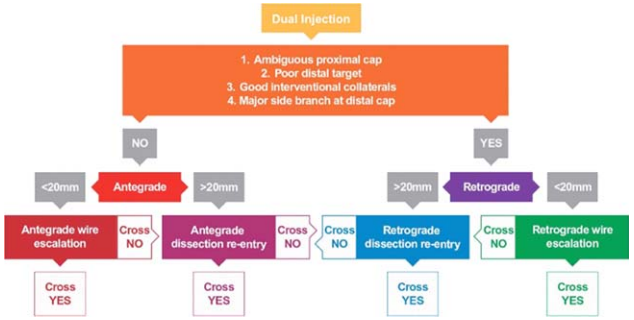

Fig. 1. Hybrid algorithm. [Color figure can be viewed at wileyonlinelibrary.com]

METHODS

Data were collected for consecutive patients undergoing CTO PCI from 7 centres in the United Kingdom performed between January 1, 2012 and March 30, 2014. An anonymised online database for clinical audit was used to collect demographic data, co-morbid conditions, procedural details, and long-term clinical outcomes. Clinical outcomes were collected at hospital discharge, 30-days, and 12 months. Data for clinical events were also collected at the time of a planned review or any repeat readmission. Outcomes for patients not followed up at the performing hospital were collected by chart review or by telephone contact with the patient and/or general practitioner. The operators performed procedural data entry within their respective institutions. The CTO PCI operator did not perform clinical follow-up assessments.

All CTO operators practiced according to the "hybrid" model (Fig. 1) and had performed >300 CTO PCIs in their career. DART were encouraged as a primary approach in complex, long lesions or as bailout techniques if AWE or RWE strategies were unsuccessful. All operators were trained in the use of Crossboss and Stingray devices. Drug-eluting stents were recommended but not mandated. Adherence to guideline-based treatment duration for dual antiplatelet therapy was recommended.

Definitions

Angina status was defined according to the Canadian Cardiovascular Society (CCS) classification [13]. Coronary CTOs were defined as lesions with Thrombolysis in Myocardial Infarction (TIMI) grade flow of 0 for

at least 3 months (angiographically confirmed or estimated clinically from time of symptom onset if prior angiography not available). Lesion complexity was assessed using the J-CTO score (Multi-Centre CTO Registry of Japan: 0 easy; 1 intermediate; 2 difficult; ≥3 very difficult) [14]. Location of the CTO (proximal cap) within the vessel was defined according to the AHA classification [15]. Angiographically visible calcification within the occluded segment was coded as none, mild (spots only), moderate (<50% of vessel circumference), severe (>50% of vessel circumference). Tortuosity within the CTO segment was coded as straight (no bend or <45° single bend), slight (>45°single bend), moderate (2 bends > 45° or 1 bend >90°) or severe (2 bends >90° or 1 bend >120°). Disease proximal and distal to the CTO was classified as absent, mild, moderate, or severe. Occlusion length was estimated by dual injections if proximal and distal caps were defined or from the length of occlusion apparent after guidewire crossing if not clear on initial dual injection.

Technical success was defined as restoration of TIMI 3 antegrade flow with <30% residual diameter stenosis within the treated segment after CTO PCI.

Events during follow-up were evaluated for those with successful CTO PCI and included: death, stroke, stent thrombosis (definite or probable according to Academic Research Consortium guidelines [16], myocardial infarction (MI: chest pain ± ECG changes with typical rise and fall of cardiac biomarkers), target vessel revascularization (TVR) or asymptomatic re-occlusion. TVR was defined as attempted PCI of the previously stented segment/vessel or referral for coronary artery bypass surgery that included the target vessel. The primary outcome of major adverse cardiovascular events (MACE) was defined as the occurrence of death, MI or unplanned TVR.

The primary and final strategies used were recorded, as was any switch in strategy. DART for purposes of this analysis included: primary ADR including limited antegrade subintimal tracking, STAR, and/or Stingray balloon assisted re-entry; primary RDR (synonymous with "rCART"); bailout ADR/RDR after unsuccessful AWE or RWE. DART was also coded if subintimal passage had occurred during an unsuccessful prior attempt (i.e., so-called "investment" procedure) or if 'true to true' Crossboss passage was recorded. The presence of a subintimal tract (SIT) was inferred by selection of a strategy likely to cause a SIT. Use of intravascular ultrasound was only 15% in this cohort and was not mandated to define the presence and length of any SIT. As such, AWE or RWE were considered "no DART," accepting that there may have been inadvertent subintimal wire tracking.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) and were compared using the student-t or Wilcoxan rank-sum tests. Categorical variables are expressed as percentages and were compared using the Chi-Square or the Fisher's exact tests. Data regarding peri-procedural complications is provided for the overall cohort (successful and failed cases) so as to illustrate safety profile for the intention to treat group, whilst outcome data pertains only to those with successful CTO PCI as our focus is the impact of dissection re-entry techniques with stent insertion in the subintimal space upon long-term clinical outcomes. The incidence of clinical events during follow-up was estimated using the Kaplan-Meier method and comparisons between groups made using the log rank test. A multivariable analysis using a Cox regression model was used to determine independent predictors of the primary outcome. Four models were tested using different combinations of predictors, which were selected on the basis of clinical considerations and findings on univariate analysis. In an ancillary analysis, we developed a propensity score model consisting of 22 variables (C statistic = 0.86 and Hosmer-Lemeshow $P = 0.38$); the baseline characteristics were well matched after stratification by the propensity score. We verified the proportional hazard assumption by examining the log-log plot, and by testing for a time-dependent covariate (time × treatment group interaction) in the model. Two sided P values of <0.05 were considered statistically significant. All statistical analyses were performed with SPSS Statistics version 22 (IBM Corporation, Armonk, NY).

RESULTS

Data from 969 patients were collected (Fig. 2). Patients with >1 CTO treated during a single procedure ($n = 40$) were excluded from further analysis. For patients who required more than one CTO PCI procedure to achieve success ($n = 96$), follow-up duration was measured from the first successful procedure. For those patients who had a second CTO in a different vessel treated at a subsequent PCI procedure, only data relating to the first procedure were included. Overall technical success rate (TIMI 3 flow with <30% residual stenosis), including those who required more than one attempt, was 90.3% (839/929). Follow-up data were available for 96% of patients with successful CTO PCI. 805 patients were, therefore, included in this analysis.

Baseline clinical characteristics, lesion characteristics, and procedural details are presented in Tables (I–III) and

stratified by those with and without events during follow up. The mean age was 65.3 ± 10.5 years and 79% were male. Indications for the procedure included: Stable angina 78%, acute coronary syndrome 8%, heart failure 3%, staged post STEMI 3%, staged post NSTEMI 7%. At baseline, 85% of patients had a CCS angina class of 2-4 and 46% had dyspnoea on exertion (NYHA class 2–4). The majority (72%) of patients had pre-catheterisation stress testing and intervention was based upon the presence of symptoms with viability in the affected territory in those without stress testing. The mean (±SD) J-CTO score was 2.4 ± 1.4. Second generation drug-eluting stents were implanted in 98% of patients. The final successful strategy was classified as dissection re-entry in 47% of cases.

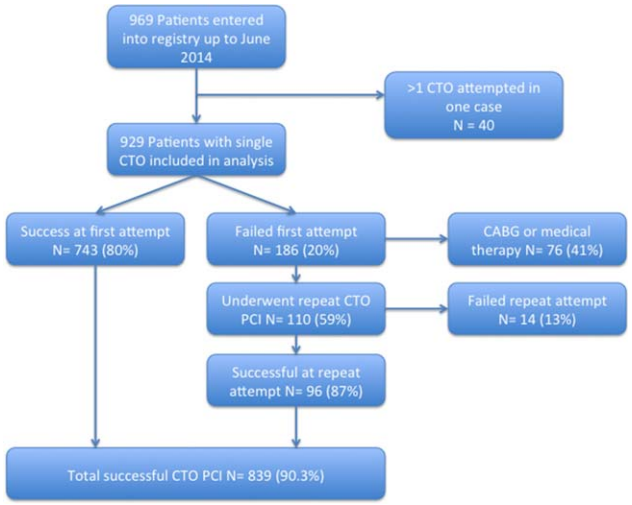

Fig. 2. Patient flow. [Color figure can be viewed at wileyonlinelibrary.com]

Procedural Characteristics and Safety for Overall Group

Procedural characteristics for the overall group ($n = 929$ patients, 1039 procedures, including repeat attempts in 110 patients) were: procedure time 107 ± 51 min, contrast 299 ± 127 ml, X-Ray skin dose 2.3 ± 1.4 Gy, Dose Area Product (DAP) 13226 ± 9547 cGycm^2, fluoroscopy time 40 ± 24 min. CTO lesions requiring DART were significantly more complex than those requiring wire escalation strategies (Table IV); they had a higher mean J-CTO score (3.2 ± 1.2 vs. 1.8 ± 1.3, $P = 0.001$) with longer occlusion lengths (35.9 ± 20.8 mm vs. 18.5 ± 13.1 mm, $P < 0.001$) and longer stent lengths were required (86.8 ± 29.1 mm vs. 62.2 ± 30.3 mm, $P < 0.001$). Previous CABG was more common in the DART group (30% vs. 12%, $P < 0.001$).

All procedural parameters were higher in the DART group compared to the no DART group (procedural time 132 ± 47 vs. 86 ± 43 min, $P < 0.001$; Contrast 335 ± 124 vs. 267 ± 122 ml, $P < 0.001$; Skin dose 2.8 ± 1.3 vs. 1.8 ± 1.2 Gy, $P < 0.001$; DAP 16357 ± 10525 vs. 10,632 ± 7645 cGycm^2, $P < 0.001$; Fluoroscopy time 52 ± 23 vs. 29 ± 19 min, $P < 0.001$).

The mortality rate for the overall group (successful and failed cases) was 0.3% at 30 days. MACE occurred in 1.8% of patients. The respective MACE rates were not significantly different per strategy

TABLE I. Baseline Clinical Characteristics of Successful PCI Group.

Variable	Overall ($n = 805$)	Event ($n = 62$)	No event ($n = 743$)	P value
Age	65.3 ± 10.5	65.6 ± 9.6	65.3 ± 10.5	0.45
Male	79%	84%	79%	0.5
Body mass index	29.1 ± 4.8	29.2 ± 4.8	29.1 ± 4.9	0.71
Hypertension	70%	67%	70%	0.56
Dyslipidemia	68%	70%	68%	0.78
Diabetes Mellitus	27%	35%	26%	0.17
Current smoker	17%	24%	17%	0.20
Heart failure	9%	14%	9%	0.21
LVEF < 55%	33%	40%	33%	0.21
Diseased vessels				
1	52%	44%	53%	0.36
2	28%	32%	28%	
3	20%	24%	19%	
Prior MI	55%	66%	56%	0.11
Prior CABG	21%	23%	21%	0.74
Prior PCI	63%	66%	62%	0.36
Prior failed attempt CTO PCI	27%	31%	27%	0.46
Prior stroke	5%	8%	5%	0.23
Chronic kidney disease	14%	21%	13%	0.08
Chronic obstructive airways disease	8%	9%	7.7%	0.81

LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention.

TABLE II. Baseline Lesion Characteristics of Successful PCI Group

Variable	Overall ($n = 805$)	Event ($n = 62$)	No event ($n = 743$)	P value
J-CTO score	2.4 ± 1.4	3.0 ± 1.2	2.4 ± 1.4	<0.001
J-CTO≥3	49%	71%	47%	<0.001
Target vessel				
Left anterior descending	27%	24%	28%	0.9
Left circumflex	17%	17%	17%	
Right coronary artery	56%	59%	55%	
Calcification				
Any	61%	71%	60%	0.02
Mod-severe	39%	58%	37%	0.002
Tortuosity (mod-severe)	28%	26%	29%	0.07
Tortuosity proximal (moderate-severe)	18%	13%	18%	0.55
Ostial	14%	13%	14%	0.99
Bifurcation involvement	37%	43%	37%	0.34
Lesion length	26.8 ± 19.2	32.0 ± 18.1	26.6 ± 19.3	0.001
Length > 25 mm	41%	62%	40%	0.001
Lesion diameter	3.2 ± 0.4	3.1 ± 0.4	3.2 ± 0.4	0.15
Lesion diameter < 3.0mm	22%	20%	22%	0.63
Disease proximal to CTO				
Any	71%	79%	70%	0.1
Moderate-Severe	43%	58%	42%	0.014
Disease distal to CTO				
Any	84%	91%	84%	0.019
Moderate-severe	65%	78%	64%	0.024
In-stent restenosis	8%	14%	7%	0.12

J-CTO: Japanese Chronic total occlusion.

TABLE III. Procedural Characteristics for Successful PCI Group

Variable	Overall ($n = 805$)	Event ($n = 62$)	No event ($n = 743$)	P value
Final strategy				
AWE	48%	40%	49%	0.11
ADR	21%	18%	21%	
RWE	5%	3%	5%	
RDR	26%	39%	25%	
Final DART	47%	57%	46%	0.14
Any DART	48%	55%	47%	0.29
Any ADR	26%	22%	26%	0.65
Any RDR	28%	40%	27%	0.03
Subintimal tracking	48%	55%	48%	0.29
CrossBoss	19%	16%	19%	0.73
Stingray balloon	14%	3%	13%	0.02
Knuckle	31%	41%	31%	0.11
Number of stents	2.5 ± 1.1	2.6 ± 1.1	2.5 ± 1.1	0.8
Stent length	73.7 ± 32.1	81.2 ± 35.0	73.7 ± 32.2	0.13
Stent length > 50 mm	76%	81%	76%	0.43
Stent length > 75 mm	48%	56%	47%	0.19
Subintimal track length	30 ± 19	32 ± 19.9	29 ± 18.9	0.1
Sub-intimal stent length	19.1 ± 21.2	25.3 ± 21.8	18.4 ± 20.7	0.037
Intravascular ultrasound use	15.9%	21%	16%	0.83

AWE: Antegrade wire escalation; ADR: Antegrade dissection re-entry; RWE: retrograde wire escalation; RDR: retrograde dissection re-entry; DART: dissection and re-entry.

(AWE 1.8%, ADR 0.6%, RWE 2.3%, and RDR 2.9%, $P = 0.34$). Ellis grade 3 perforation requiring pericardiocentesis occurred in 1.6% of patients overall and was not statistically different between strategies (AWE 1.0%; ADR 1.2%, RWE 2.3%, and RDR 2.9%, $P = 0.15$).

One-Year Outcomes for Those with Successful CTO PCI

Mean duration of follow-up was 11.5 ± 3.8 months. The primary endpoint occurred in 8.6% ($n = 69$) of patients. Components of the primary endpoint are described in Table V and sub divided according to

TABLE IV. Differences in Lesion Characteristics According to Final Strategy

	AWE	ADR	RWE	RDR	*P*
Mean JCTO	1.7 ± 1.2	3.2 ± 1.3	2.6 ± 1.2	3.35 ± 1.03	<0.001
JCTO>2	26%	64%	59%	77%	<0.001
Mean lesion length (mm)	17.9 ± 12.6	31.5 ± 18.9	24.8 ± 15.8	39.4 ± 21.8	<0.001
Length > 25 mm	18%	56%	29%	74%	<0.001
Lesion diameter < 3.0 mm	24%	16%	27%	22%	0.16
Disease proximal to CTO (moderate-severe)	45%	38%	38%	55%	0.002
Disease distal to CTO (moderate-severe)	62%	63%	64%	74%	0.04
Calcification (moderate-severe)	31%	43%	39%	50%	<0.001
Bifurcation	34%	31%	43%	45%	0.01
In-stent restenosis	4%	3%	0.4%	0.5%	<0.001
Mean stent length (mm)	60.4 ± 29.9	82.3 ± 28.5	78.0 ± 30.6	89.9 ± 29.3	<0.001
Stent length > 75 mm	30%	61%	54%	70%	<0.001
Subintimal stent length (mm)	0	30.3 ± 21.5	0	28.2 ± 18.3	0.31

AWE: Antegrade wire escalation; ADR: Antegrade dissection re-entry; RWE: Retrograde wire escalation; RDR: Retrograde dissection re-entry; J-CTO: Japanese Chronic total occlusion.

TABLE V. One Year Outcomes According to DART Versus Wire-Based Strategy

Variable	Overall (*n* = 805)	DART (*n* = 375)	Wire based (*n* = 430)	*P* value
Composite endpoint	8.6% (69)	10.3% (39)	7.0% (30)	0.1
Death				
All-cause	2.5% (21)	2.6%	2.3%	0.82
Cardiac	1.0% (8)	1.1%	0.9%	1.0
MI				
All	3.0% (25)	3.7%	1.9%	0.13
Stent thrombosis	1.4% (11)	1.9%	0.9%	0.36
Unscheduled TVR	5.0% (41)	6.1%	3.3%	0.06
Target lesion revascularization	4.5% (37)	5.8%	3.7%	0.19

DART: dissection and re-entry.

whether the final strategy involved DART. A total of 88% of patients had no or minimal angina (CCS class 0 or 1) and 80% described no dyspnoea. Follow-up angiography was performed in 24% of patients, more commonly in the DART group (32 vs. 17%, $P < 0.001$). This was usually scheduled and most frequently to reassess distal vessel run-off and remodelling. Normal angiographic appearances were seen in ~70% of patients. The vessel was occluded in 13% of those who underwent angiography (one third asymptomatic, all managed conservatively), with no difference in frequency of vessel occlusion between DART and wire-based groups.

Predictors of Adverse Events during Follow-Up

Differences between those who had an adverse event and those who did not are described in Tables (I–III). Those with events were more likely to have higher J-CTO scores, longer lesions, greater degrees of calcification, greater disease burden (both proximal and distal to the lesion) and to have had RDR as the final strategy. Freedom from the primary endpoint according to final PCI strategy and lesion length is presented in Fig. 3.

Differences between patients according to final successful strategy are described in Table IV. As expected from the hybrid algorithm, those patients with RDR as the final strategy were more likely to have a J-CTO score >2 (79 vs. 37%, $P < 0.001$), longer occlusion length (>25 mm in 77 vs. 28%, $P < 0.001$), longer stent length (>75 mm in 71 vs. 39%, $P < 0.001$), bifurcation involvement (46 vs. 34%, $P = 0.003$), disease proximal to the CTO (55 vs. 39%, $P < 0.001$), and disease distal to the CTO (72 vs. 62%, $P = 0.02$).

There remained no difference in the primary outcome between DART and no DART groups when the overall cohort was analysed (i.e., inclusion of failed cases). Similarly, there was no difference in the primary outcome if CrossBoss true-to-true passage ($n = 27$) was classified as AWE rather than ADR (DART 10.1% vs. no DART 7.5%, $P = 0.2$).

Multivariable Cox and Propensity Analysis

Multivariable analyses using different combinations of factors predictive of outcome in univariate analysis are presented in Table VI. The only independent predictor of the primary endpoint was occlusion length. In the propensity analysis, a final strategy of DART, compared to no DART, was not independently associated

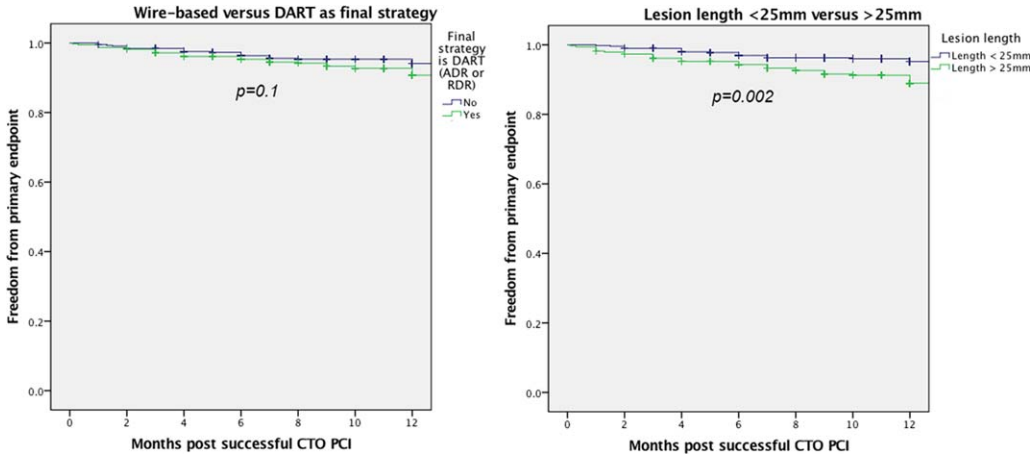

Fig. 3. Survival curves for freedom from the primary endpoint according to strategy (DART vs. no DART) and Lesion length. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE VI. Multivariate Analysis (Cox Regression Models)

	Model 1		Model 2		Model 3		Model 4	
Variable	Odds ratio	*P* value	Odds ratio	*P* value	Odds ratio	*P* value	Odds ratio	*P* value
Final Approach								
AWE	1							
ADR	0.66 (0.3–1.5)	0.32						
RWE	0.68 (0.16–2.9)	0.61						
RDR	1.1 (0.53–2.2)	0.83						
DART (any)			0.74 (0.4–1.4)	0.35				
ADR (any)					0.67 (0.35–1.3)	0.23		
RDR (any)							1.3 (0.67–2.4)	0.47
Lesion length >25 mm	2.5 (1.3–4.8)	0.007	2.9 (1.5–5.6)	0.002	2.6 (1.5–4.8)	0.001	2.3 (1.2–4.3)	0.01
Stent length >50 mm	0.85 (0.4–1.8)	0.85	0.85 (0.4–1.7)	0.65	0.85 (0.41–1.7)	0.66	0.79 (0.39–1.6)	0.52
Disease distal (moderate or severe)	1.6 (0.82–2.9)	0.17	1.67 (0.85–3)	0.15	1.6 (0.83–3.0)	0.17	1.6 (0.86–3.1)	0.16
Bifurcation	1.2 (0.8–2.2)	0.36	1.3 (0.8–2.2)	0.3	1.3 (0.7–2.2)	0.36	1.3 (0.8–2.2)	0.34
Diabetes	1.4 (0.8–2.4)	0.3	1.4 (0.8–2.4)	0.28	1.4 (0.8–2.4)	0.18	1.3 (0.8–2.4)	0.31
In-stent restenosis	1.5 (0.6–3.6)	0.4	1.3 (0.6–3.1)	0.64	1.4 (0.6–3.3)	0.23	1.4 (0.6–3.5)	0.47

Presented as Hazard ratio (95% confidence interval) and *P* value.
AWE: Antegrade wire escalation; ADR: Antegrade dissection re-entry; RWE: retrograde wire escalation; RDR: retrograde dissection re-entry; DART: dissection and re-entry.

with the primary outcome (adjusted HR = 0.77, 95%CI 0.42–1.41, $P = 0.39$).

DISCUSSION

We report very high (>90%) freedom from death, MI and unplanned TVR with durable symptom relief at 12 months in a large cohort of patients with complex CTOs. DART was used frequently (47%) as part of the hybrid approach, particularly in complex lesions, however, the only independent predictor of adverse outcomes was lesion length. Our findings suggest that the majority of patients with complex CTOs, including those with previous bypass grafting, can now expect to achieve successful recanalization of their occluded arteries and have complete or near complete symptom relief out to 1 year.

Adverse Event Rates in Previous CTO PCI Outcome Studies

We report the largest study to date describing longer-term clinical outcomes according to revascularisation strategy after contemporary CTO PCI. Despite the complex cohort recruited, the incidence of adverse events during long-term follow up was favourable with a TLR of 4.5%. Previous reports from CTO cohorts report TLR of 6.3–10.7% [17–19] with second generation DES and 17% with first generation DES [20].

Technical Approaches and Disease Burden/ Complexity

We found no statistically significant difference in MACE at ~12 month follow-up between patients treated with DART versus no-DART approaches on multivariable analysis. Directly comparing strategies as a predictor of outcomes is challenging, particularly as certain adverse anatomical characteristics may favour the use of a particular strategy and in turn prejudice outcomes. Within our database, DART use, particularly RDR, was strongly associated with greater lesion complexity. Higher TLR rates in retrograde cases have been previously reported [21] and were postulated to relate to longer stent length and use in more complex lesions, rather than the retrograde approach per se. Whilst RDR approaches had the highest event rate in our cohort, all baseline characteristics were more unfavourable in this group.

Previous experience with sub-intimal stenting following use of the STAR technique suggested disappointing longer-term outcomes [5,6]. Data regarding outcomes with modern techniques are much more promising, which likely relates to the more favourable distal run-off achievable with targeted and controlled re-entry. Three single-centre North American studies [18,22,23] have demonstrated no difference in adverse clinical events during intermediate-term follow-up between those treated with DART (antegrade or retrograde) versus conventional wire escalation strategies. A sub-analysis of the J PROCTOR registry, which used IVUS to detect subintimal guidewire tracking found greater late lumen loss in the sub-intimal tracking group, however, this did not translate into an increase in clinical events [24]. The majority of events in these studies were related to TVR rather than death or MI. Nonetheless, the duration of follow-up within these reports and in our study is insufficient to exclude an excess of very late stent thrombosis in patients with subintimal stent insertion, thus on-going surveillance is required.

Does the Direction of Dissection Matter?

Both ADR and RDR ("reverse CART") involve dissection and subsequent stenting within the subintimal space. Concern has been expressed that ADR poses a higher risk of subintimal hematoma formation and uncontrolled dissection, which may be associated with unnecessarily longer stent lengths or compression of the distal lumen with consequent undersizing of stents. DART cases in our study were roughly half antegrade and half retrograde, and the length of estimated subintimal stenting was similar in the ADR and RDR groups. There was no signal that those cases completed with ADR (primarily using CrossBoss and Stingray) had higher event rates. Indeed, the ADR event rate closely approximated that of AWE cases, despite higher complexity in the ADR cohort. Whilst there was an excess of events in the patients requiring RDR as the final strategy, this reflected increased lesion complexity and target vessel disease burden. When adjusted for complexity, no independent relationship existed between RDR and adverse outcomes.

Predictors of Adverse Events during Long-Term Follow-Up

The only independent predictor of adverse clinical events in our study was lesion length, The presence of a longer lesion and consequently longer stent length is likely to increase the risk of restenosis. It is intuitive that increased disease burden, as defined by disease proximal and distal to the CTO, would also contribute to an increased risk for TVR, and distal disease may also increase the risk for re-occlusion by contributing to poor runoff. There was a numerical trend in our study for excess events was seen in those who had moderate or severe disease distal to the CTO lesion. This may have implications for case selection, where those vessels with very severe and diffuse distal disease are best managed medically. It is worth acknowledging, however, that it can be difficult to gauge how the distal vessel will behave following recanalization in the presence of flow-mediated positive remodelling [25].

Finally, in the study by Rinfret and colleagues [18], treatment of occlusive in-stent restenosis was independently associated with increased need for TVR. However, occlusive disease within a previously implanted stent was not a predictor of the primary endpoint in our larger study.

Limitations

Whilst this is a large, multicenter study, it is based upon registry data entered by the respective operators. There was no core laboratory for independent review of procedural angiograms, nor independent adjudication of clinical events during follow-up, however, consensus regarding the classification of clinical events was required between at least two authors. Systematic assessment of angina class was not undertaken and definition of procedural complications is potentially subject to observer bias. Follow-up was not 100%, thus the adverse event rate may theoretically be higher. The proportion of cases with DART may have been higher than reported; inadvertent subintimal passage of the wire during AWE or RWE can occur and is generally only detectable by IVUS, which was used in the

minority of cases. Finally, the results of this study may not be reproducible amongst low-volume operators or those who have limited experience of hybrid approaches to CTO lesions.

CONCLUSIONS

CTO PCI in complex lesions using the hybrid approach is safe, has a low 1-year adverse event rate, and produces durable relief from angina. Use of contemporary dissection re-entry techniques did not adversely affect outcomes, with only lesion length predicting a higher incidence of MACE at 1 year.

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