

# Clinical and angiographic outcomes of crossing techniques for coronary chronic total occlusions: the ISAR-CTO registry

Erion Xhepa<sup>1</sup>, MD, PhD; Salvatore Cassese<sup>1</sup>, MD, PhD; Gjin Ndrepepa<sup>1</sup>, MD; Michael Joner<sup>1,2</sup>, MD; Sebastian Kufner<sup>1</sup>, MD; Alp Aytakin<sup>1</sup>, MD; Anna Lena Lahmann<sup>1</sup>, MD; Felix Voll<sup>1</sup>, MD; Michele Fusaro<sup>3</sup>, MD; Susanne Pinieck<sup>1</sup>, RN; Heribert Schunkert<sup>1,2</sup>, MD; Adnan Kastrati<sup>1,2</sup>, MD; Massimiliano Fusaro<sup>1\*</sup>, MD

1. Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; 2. Deutsches Zentrum für Herz- und Kreislauf-Forschung (DZHK) e.V. (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; 3. Department of Diagnostic and Interventional Radiology, Santa Maria di Ca' Foncello Hospital, Treviso, Italy

E. Xhepa and S. Cassese contributed equally to this work and are considered joint first authors.

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## KEYWORDS

- chronic coronary total occlusion
- drug-eluting stent
- in-stent restenosis

## Abstract

**Background:** Clinical and angiographic outcomes following recanalisation of coronary chronic total occlusions (CTO) through contemporary dissection and re-entry techniques (DART) as opposed to intraplaque techniques remain controversial.

**Aims:** The aim of this study was to compare clinical and angiographic outcomes following subintimal and intraplaque CTO recanalisation.

**Methods:** A total of 454 consecutive patients undergoing successful CTO recanalisation (473 vessels) were included. Intraplaque techniques were used in 403 (85.2%) and DART in 70 (14.8%) vessels. Surveillance angiography was scheduled at 6-9 months and clinical follow-up was performed up to 12 months.

**Results:** There were no significant differences in terms of the cumulative incidence of MACE ( $p=0.908$ ) or binary restenosis ( $p=0.320$ ) between the two groups. There was no independent correlation between recanalisation technique and MACE occurrence or in-segment binary restenosis. Target lesion revascularisation (TLR) was performed in 60 (17.5%) and 12 (18.1%) ( $p=0.719$ ) lesions, respectively. The occurrence of occlusive restenosis was low (7 [2.3%] vs 1 [1.6%];  $p=0.824$ ) and comparable between groups.

**Conclusions:** Contemporary DART are associated with similar midterm clinical and angiographic outcomes compared to intraplaque recanalisation. The rate of occlusive restenosis was low and comparable in both groups. Regardless of recanalisation technique, the overall incidences of binary restenosis and TLR following CTO recanalisation remain higher than those reported for non-CTO PCI.

\*Corresponding author: Deutsches Herzzentrum München, Klinik an der Technischen Universität München, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: [fusaro@dhm.mhn.de](mailto:fusaro@dhm.mhn.de)

## Abbreviations

<b>ADR</b>	antegrade dissection and re-entry
<b>AWE</b>	antegrade wire escalation
<b>CTO</b>	chronic total occlusion
<b>DART</b>	dissection and re-entry technique
<b>LASSO</b>	least absolute shrinkage and selection operator
<b>rCART</b>	reverse controlled antegrade and retrograde tracking
<b>RWE</b>	retrograde wire escalation

## Introduction

Chronic total occlusions (CTO) are found in a significant proportion of patients displaying obstructive coronary artery disease (CAD). Historically, CTO percutaneous coronary intervention (PCI) has been associated with lower procedural success and higher major periprocedural complication rates compared to non-CTO PCI<sup>1</sup>. However, recent advances in recanalisation techniques, the introduction of dedicated equipment and the elaboration of systematic algorithmic approaches have significantly improved procedural success and reduced the occurrence of major complications<sup>2,3</sup>.

In particular, the adoption of dissection and re-entry techniques (DART) has played a major role in improving the success rate of CTO PCI<sup>3</sup>. Despite encouraging procedural results, the intermediate- and long-term outcomes of patients treated by means of subintimal as opposed to intraplaque techniques remain a matter of debate. The initial variant of DART, the subintimal tracking and re-entry (STAR) technique, which resulted in an uncontrollable re-entry into the distal lumen, was invariably associated with extensive vascular injury, large intramural haematomas and side branch occlusion as well as prohibitive rates of in-stent restenosis (ISR) and reocclusion<sup>4</sup>. However, DART have evolved over time, aiming at minimising the extent of subintimal dissection and vascular injury. Contrary to initial reports, contemporary DART have shown comparable midterm clinical outcomes to intraplaque crossing techniques<sup>5-10</sup>. However, the majority of studies comparing the outcomes of these recanalisation modalities did not include a systematic angiographic follow-up<sup>5,7,8,10</sup>. The ongoing controversy regarding the use of DART is highlighted by the recent proposal of an alternative CTO crossing algorithm, which restricts upfront adoption of antegrade dissection and re-entry (ADR) techniques even in the presence of long (>20 mm) occlusions, favouring the use of antegrade wire escalation (AWE) instead<sup>11</sup>.

Against this background, the aim of this study was to compare the midterm clinical and angiographic outcomes of intraplaque as opposed to subintimal CTO recanalisation achieved by contemporary DART.

## Methods

### STUDY PATIENTS, ENDPOINTS AND DEFINITIONS

Consecutive patients undergoing successful CTO recanalisation between 2015 and 2018 at the German Heart Centre Munich were included in the Intracoronary Stenting and Angiographic Results – Chronic Total Occlusion (ISAR-CTO) registry. The study complies with the Declaration of Helsinki and the locally appointed

ethics committee approved the study protocol. Informed consent was obtained for all patients prior to each scheduled procedure. Follow-up angiography was scheduled at 6-9 months after successful CTO recanalisation. Target lesion revascularisation (TLR) was performed according to the Academic Research Consortium (ARC) criteria<sup>12</sup> in case of: i)  $\geq 50\%$  diameter stenosis (%DS) with accompanying signs or symptoms of myocardial ischaemia, or ii)  $\geq 70\%$ DS even in the absence of ischaemic signs or symptoms. Clinical follow-up up to 12 months was performed by office visit, phone contact or structured follow-up letter.

Lesion complexity was assessed by means of the J-CTO score. The recanalisation technique was categorised as intraplaque (AWE or retrograde wire escalation [RWE]), or subintimal (ADR or reverse controlled antegrade and retrograde tracking [rCART]). Use of dedicated instruments (CrossBoss™ catheter/Stingray™ LP system; Boston Scientific, Marlborough, MA, USA) was also recorded. Dual antiplatelet therapy was prescribed for at least 12 months following CTO PCI.

The primary endpoint of the study was the cumulative incidence of major adverse cardiac events (MACE), defined as a composite of all-cause death, myocardial infarction (MI) or TLR. The individual components of the primary endpoint were also assessed separately. The secondary endpoint was in-segment binary restenosis at surveillance angiography.

### ANGIOGRAPHIC DATA ACQUISITION AND ANALYSIS

Baseline, post-procedural and follow-up angiograms were recorded and assessed off-line in a core laboratory (ISAResearch Center, Munich, Germany). Details and definitions are provided in **Supplementary Appendix 1**.

### STATISTICAL ANALYSIS

Continuous data are presented as mean $\pm$ SD or median (interquartile range) and categorical data as observed frequencies or proportions (%). The normality of distribution of continuous data was assessed by means of the Shapiro-Wilk test. Data were analysed on a per-patient basis for clinical characteristics and on a per-lesion basis for the remaining calculations. For patient-level data, differences between groups were checked for significance using the Student's t-test or the Mann-Whitney U test for continuous data or the chi-square test (or Fisher's exact test when an expected cell value was <5) for categorical variables. For lesion-level data, differences between groups were checked for statistical significance using generalised estimating equations for non-normally distributed data in order to address intra-patient correlation in the case of patients undergoing multilesion intervention<sup>13</sup>. Clinical outcomes were assessed with the Kaplan-Meier method and hazard ratios (HR) with pertinent 95% confidence intervals (95% CI) were calculated using the univariable Cox proportional hazards model. Independent predictors of MACE occurrence were analysed by means of multivariable Cox proportional hazards models accounting for clustering effect for patients with multilesion intervention, whereas generalised estimating equations were used for the identification of independent

predictors of binary restenosis. The selection of variables for both multivariable models was performed using the least absolute shrinkage and selection operator (LASSO) regression method<sup>14</sup> after entering all clinical, procedural and angiographic parameters as candidates. All tests were two-sided and assessed at a significance level of 5%. Statistical analysis was performed using the R 3.6 Statistical Package (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### BASELINE CLINICAL AND PROCEDURAL CHARACTERISTICS

A total of 473 successful CTO recanalizations (454 patients) were included. CTO recanalization was achieved by means of intraplaque techniques in 403 (85.2%) and DART in 70 (14.8%) lesions.

Baseline clinical and angiographic characteristics are summarised in **Table 1** and **Table 2**. Aside from a significantly higher body mass index in the DART group, clinical characteristics were well balanced between the two groups. The right coronary artery

**Table 1. Baseline clinical characteristics.**

	Intraplaque strategy (n=386)	Subintimal strategy (n=68)	p-value
Number of lesions	1.04±0.20	1.03±0.17	0.602
Age, years	68.0 (60.4-75.8)	66.2 (60.1-72.7)	0.126
Male	331 (85.8)	61 (89.7)	0.494
Current smoker	63 (16.3)	11 (16.2)	>0.999
Body mass index (kg/m <sup>2</sup> )	27.5 (24.9-30.9)	28.7 (26.2-32.7)	0.005
Hypercholesterolaemia	228 (59.1)	35 (51.5)	0.300
Arterial hypertension	341 (88.3)	66 (97.1)	0.050
Diabetes mellitus	126 (32.6)	28 (41.2)	0.218
Insulin therapy	32 (8.3)	12 (17.6)	0.029
Family history	124 (32.1)	20 (29.4)	0.763
Previous myocardial infarction	157 (40.7)	31 (45.6)	0.532
Previous coronary artery bypass grafting	92 (23.8)	22 (32.4)	0.180
Clinical presentation			
Stable angina pectoris or silent ischaemia	329 (85.2)	66 (97.1)	0.080
Unstable angina pectoris	21 (5.4)	1 (1.5)	
Non-ST-segment elevation myocardial infarction	27 (7.0)	1 (1.5)	
ST-segment elevation myocardial infarction	9 (2.3)	0 (0.0)	
Affected vessels			
One vessel	27 (7.0)	5 (7.4)	0.553
Two vessels	66 (17.1)	15 (22.1)	
Three vessels	293 (75.9)	48 (70.6)	
Maximal post-procedural troponin T (ng/ml)	0.04 (0.02-0.11)	0.05 (0.01-0.20)	0.905
Ejection fraction (%)	48.0 (40.0-56.0)	47.0 (38.0-51.0)	0.423
Surveillance angiography available	296 (76.7)	61 (89.7)	0.024
Time interval surveillance angiography, days	196 (177-229)	199 (176-227)	0.834
Data are shown as numbers (%), mean±SD or median (interquartile range).			

**Table 2. Angiographic characteristics and quantitative coronary analysis.**

	Intraplaque strategy (n=403)	Subintimal strategy (n=70)	p-value
Target coronary vessel			
Left main coronary artery	1 (0.3)	1 (1.4)	0.124
Left anterior descending coronary artery	117 (29.0)	14 (20.0)	
Left circumflex coronary artery	114 (28.3)	2 (2.9)	
Right coronary artery	171 (42.4)	53 (75.7)	
In-stent occlusion	84 (20.8)	4 (5.7)	0.005
Vessel tortuosity			
Light	320 (79.4)	39 (55.7)	<0.001
Intermediate	73 (18.1)	22 (31.4)	
Severe	10 (2.5)	9 (12.9)	
Calcification severity			
None/mild	173 (42.9)	14 (20.0)	<0.001
Moderate	142 (35.3)	43 (61.4)	
Severe	88 (21.8)	13 (18.6)	
J-CTO score	1.40±0.82	2.36±1.05	<0.001
J-CTO score categories			
0=easy	34 (8.4)	2 (2.9)	<0.001
1=intermediate	217 (53.8)	13 (18.6)	
2=difficult	113 (28.0)	23 (32.9)	
3=very difficult	39 (9.7)	32 (45.7)	
<b>Quantitative coronary analysis</b>			
Pre-procedure			
Lesion length, mm	33.7±14.4	40.4±19.2	0.016
Reference vessel diameter, mm	2.82±0.45	3.01±0.47	0.002
Post-procedure			
Reference vessel diameter, mm	3.00±0.44	3.24±0.42	<0.001
Minimal lumen diameter, mm	2.53±0.49	2.73±0.44	0.001
% diameter stenosis	15.9±10.0	15.7±7.25	0.838
Data are shown as numbers (%), mean±SD or median (interquartile range).			

was the most common CTO target vessel (47.4%). In-stent CTO was significantly more frequent (20.8% vs 5.7%; p=0.005) in the intraplaque recanalisation group. In line with previous CTO registries<sup>3</sup>, vessel tortuosity and J-CTO score were significantly higher in the subintimal recanalisation group (45.7% of this group having a J-CTO score ≥3).

Procedural characteristics are shown in **Table 3**. An antegrade approach (AWE) was used in 96.8% of the intraplaque strategy group, while RWE was adopted in only 13 (3.2%) lesions of this group. Conversely, in the DART group, an ADR technique was used in 32 (45.7%) and an rCART in 38 (54.3%) lesions; the mode of dissection was wire-based in 29 (90.6%) and CrossBoss-based in 3 (9.4%) lesions, while mode of re-entry was wire-based in 12 (37.5%) and Stingray-based in 20 (62.5%) lesions of the ADR group (**Figure 1**). Finally, a rotablation procedure was performed in 36 (8.9%) and 3 (4.3%) lesions, respectively (p=0.815).

**Table 3. Procedural characteristics.**

	Intraplaque strategy (n=403)	Subintimal strategy (n=70)	p-value
Contrast agent, ml	280 (210-360)	380 (290-470)	<0.001
Dose-area product, Gy·cm <sup>2</sup>	92.6 (54.9-140.5)	134.6 (99.5-209.7)	<0.001
Antegrade	390 (96.8)	32 (45.7)	<0.001
Retrograde	13 (3.2)	38 (54.3)	<0.001
Antegrade wire escalation	390 (96.8)	0 (0.0)	<0.001
Antegrade dissection and re-entry	0 (0.0)	32 (45.7)	<0.001
rCART	0 (0.0)	38 (54.3)	<0.001
Conventional	0 (0.0)	8 (21.1)	
Directed	0 (0.0)	19 (50.0)	
Extended	0 (0.0)	11 (28.9)	
rCART dissection plane preparation			
Antegrade	0 (0.0)	7 (18.4)	<0.001
Retrograde	0 (0.0)	18 (47.4)	
Combined	0 (0.0)	13 (34.2)	
Retrograde true-true	13 (3.2)	0 (0.0)	0.232
CrossBoss	0 (0.0)	3 (4.3)	0.003
Stingray	0 (0.0)	20 (28.6)	<0.001
Rotablation	36 (8.9)	3 (4.3)	0.815
Anchoring balloon	10 (2.5)	11 (15.7)	<0.001
Bifurcation involved and treated	82 (20.3)	18 (25.7)	0.793
Collaterals used	14 (3.5)	36 (51.4)	<0.001
Septal	9 (2.2)	27 (38.6)	<0.001
Epicardial	1 (0.3)	6 (8.6)	<0.001
Vein graft	4 (1.0)	5 (7.1)	0.005
Type of intervention			
PTCA	32 (7.9)	1 (1.4)	0.082
Stent	371 (92.1)	69 (98.6)	
Intravascular imaging	12 (2.9)	2 (2.9)	>0.999
Vessel perforation	5 (1.2)	4 (5.7)	0.031
Nominal balloon, mm	3.30±0.54	3.61±0.47	<0.001
Maximal balloon pressure, atm	16.0 (13.0-18.0)	16.0 (12.0-17.5)	0.529
Maximal stent diameter, mm	3.21±0.48	3.48±0.44	<0.001
Total stented length, mm	45.8±18.9	53.2±22.4	0.011
Stent type			
Durable polymer everolimus-eluting stent	224 (55.6)	43 (61.4)	0.114
Biodegradable polymer everolimus-eluting stent	137 (34.0)	26 (37.1)	
Other drug-eluting stent	10 (2.5)	0 (0.0)	

Data are shown as numbers (%), mean±SD or median (interquartile range). PTCA: percutaneous transluminal coronary angioplasty; rCART: reverse controlled antegrade and retrograde tracking

Maximal stent diameter (3.48±0.44 vs 3.21±0.48 mm; p<0.001) and total stented length (53.2±22.4 vs 45.8±18.9 mm; p=0.011) were significantly higher in the DART group. There were no significant between-group differences in terms of stent type, while vessel perforation occurred more frequently (4 [5.7%] vs 5 [1.2%];

p<0.031) in the DART group. The DART group perforations were localised in an epicardial vessel in three cases, requiring the implantation of single-layer polytetrafluoroethylene-covered stents and needle pericardiocentesis in two patients due to cardiac tamponade, and in a septal perforator in one case, managed conservatively. All patients were alive at 12 months and surveillance angiography was available for all of them; the recanalised vessel was patent in all cases and no TLR was required.

## CLINICAL OUTCOMES

Clinical events for the outcomes of interest are shown in **Table 4**. No significant differences in terms of the cumulative incidence of MACE (**Figure 2**) or the composite of death or MI (**Central illustration, A**) were present between the groups. J-CTO score categories did not impact on the risk of MACE, even when type of recanalisation technique was accounted for (**Supplementary Figure 1, Supplementary Figure 2**).

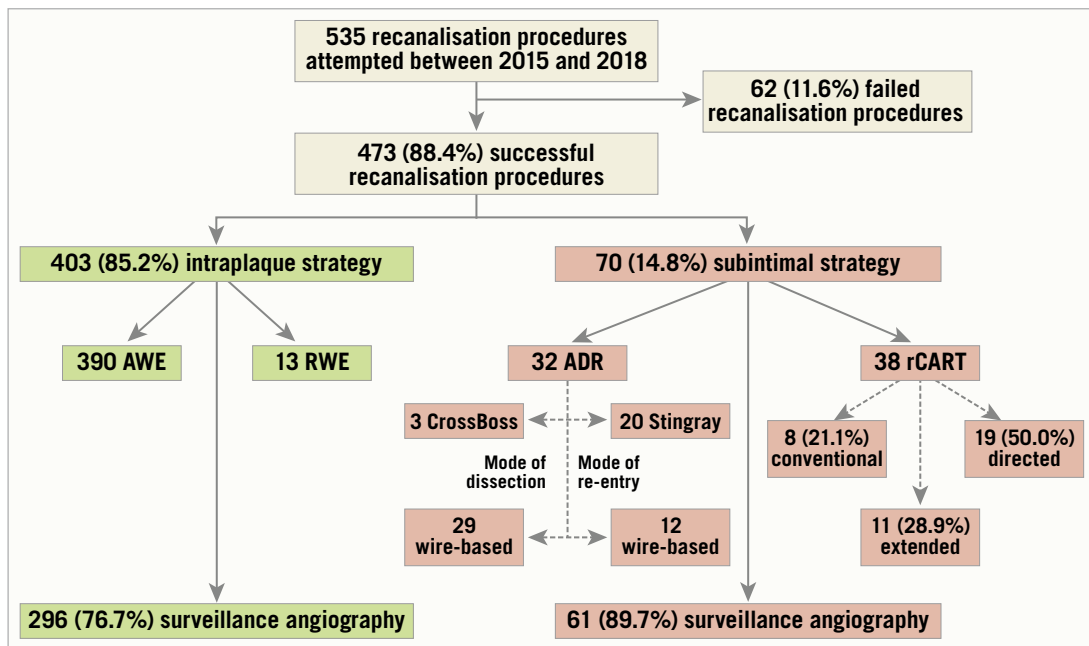
**Table 4. Clinical outcomes and quantitative coronary analysis at surveillance angiography.**

Clinical outcomes	Intraplaque strategy (n=386)	Subintimal strategy (n=68)	Hazard ratio (95% CI)	p-value
Death	10	1	0.55 (0.07-4.28)	0.566
Death or myocardial infarction	12	1	0.46 (0.06-3.50)	0.449
Target lesion revascularisation	60	12	1.12 (0.60-2.08)	0.719
MACE	70	13	1.04 (0.57-1.87)	0.908
Quantitative coronary analysis at surveillance angiography	Intraplaque strategy (n=308)	Subintimal strategy (n=63)	p-value	
Reference vessel diameter, mm	3.01±0.44	3.28±0.42	<0.001	
Minimal lumen diameter (in-stent), mm	2.09±0.80	2.36±0.73	0.010	
Minimal lumen diameter (in-segment), mm	1.79±0.72	2.11±0.76	0.003	
% diameter stenosis (in-stent)	31.1±23.5	28.3±19.8	0.335	
% diameter stenosis (in-segment)	41.2±20.8	36.6±19.7	0.096	
Binary restenosis	90 (29.2)	23 (36.5)	0.320	
Occlusive restenosis	7 (2.3)	1 (1.6)	0.824	

Data are shown as numbers (%), mean±SD or median (interquartile range).

## ANGIOGRAPHIC OUTCOMES AND QUANTITATIVE CORONARY ANALYSIS

Surveillance angiography was available in a significantly higher proportion of patients in the DART group (61 [89.7%] vs 296 [76.7%]; p=0.024), while median clinical follow-up was comparable between the two groups (p=0.834). Preprocedural and post-procedural as well as follow-up QCA results are reported in **Table 2** and **Table 4**, respectively. QCA measured lesion length (40.4±19.2 vs 33.7±14.4 mm; p=0.016) as well as reference vessel diameter (RVD) (3.01±0.47 vs 2.82±0.45 mm; p=0.002) were significantly higher in the DART subgroup.

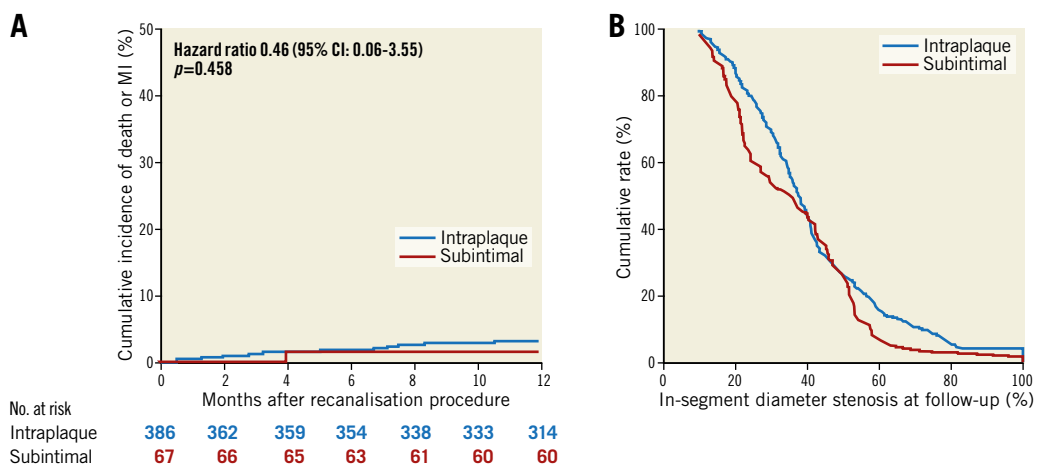


**Figure 1.** Overview of recanalisation procedures. ADR: antegrade dissection and re-entry; AWE: antegrade wire escalation; rCART: reverse controlled antegrade and retrograde tracking; RWE: retrograde wire escalation

QCA of surveillance angiography showed significantly higher RVD ( $3.28\pm 0.42$  vs  $3.01\pm 0.44$  mm;  $p<0.001$ ) as well as minimal lumen diameter (MLD) ( $2.36\pm 0.73$  vs  $2.09\pm 0.80$  mm;  $p=0.010$ ) in the DART group, while no significant differences in terms of in-stent %DS, in-segment %DS (**Central illustration, B**), or binary restenosis were present between the DART and intraplaque groups. TLR was performed in 12 (18.1%) and 60 (17.5%) ( $p=0.719$ ) lesions in the DART and intraplaque groups, respectively; among patients undergoing TLR, only 34 (47.2%) were symptomatic. Importantly, the occurrence of occlusive ISR was low (1 [1.6%] vs 7 [2.3%];  $p=0.824$ ) and not different between the two groups.

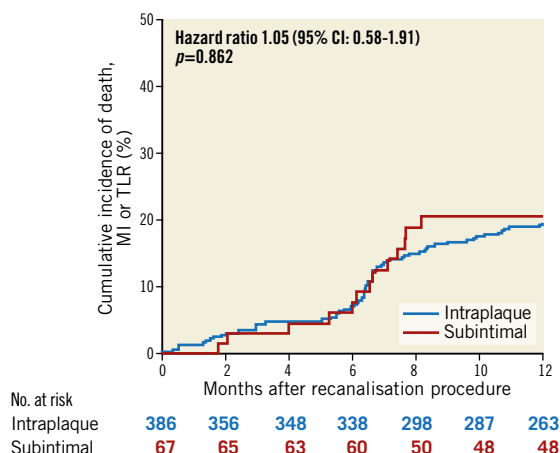
#### PREDICTORS OF MACE AND BINARY RESTENOSIS

Two separate multivariable models were conducted to assess the potential independent role of variables selected by the LASSO regression method regarding the occurrence of MACE and binary restenosis. Baseline clinical, angiographic and procedural characteristics as well as baseline and follow-up QCA, according to MACE occurrence, are summarised in **Supplementary Table 1-Supplementary Table 3**. Besides recanalisation technique (subintimal vs intraplaque), the model for MACE included patient age and sex, previous coronary artery bypass grafting (CABG), presentation with ST-elevation myocardial infarction (STEMI), CAD family history, in-stent CTO and post-procedural %DS as independent variables.



**Central illustration.** Clinical and angiographic outcomes according to CTO recanalisation technique. A) Cumulative incidence of all-cause death or myocardial infarction at 12-month follow-up according to recanalisation technique. B) Cumulative frequency distribution curves for in-segment percent diameter stenosis at angiographic follow-up according to recanalisation technique.





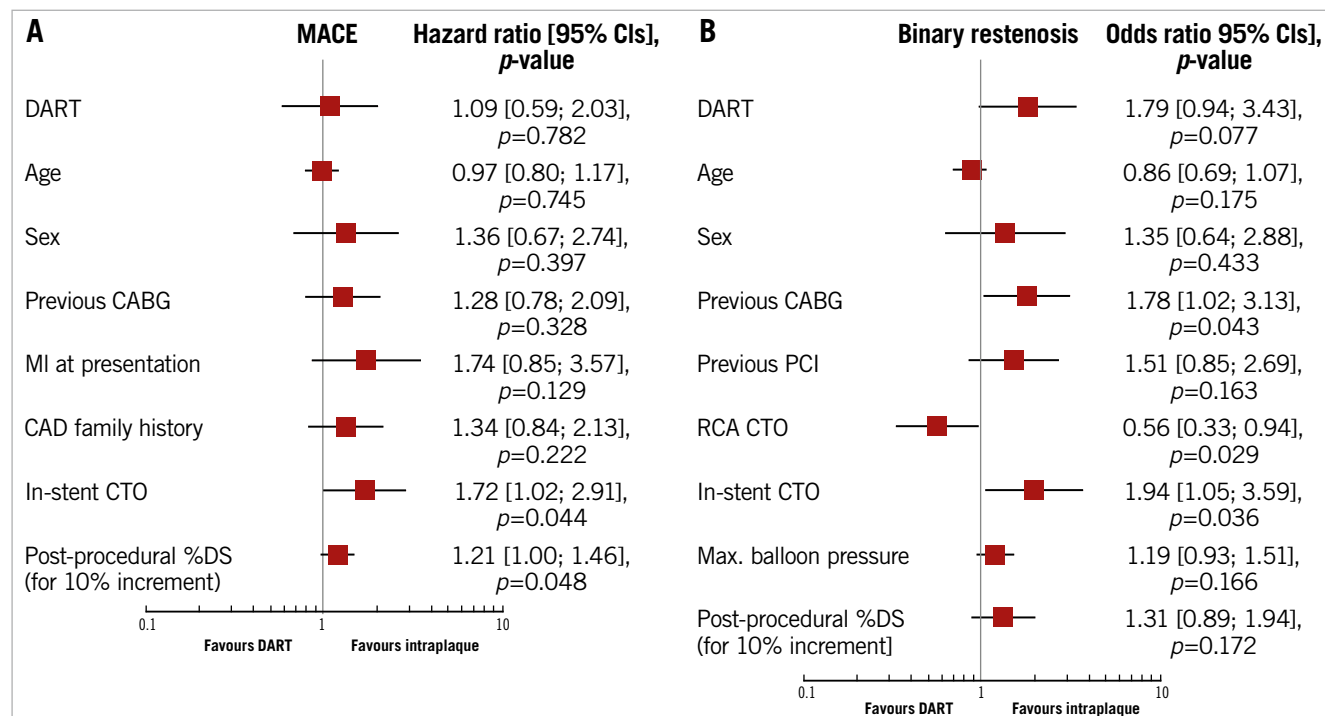
**Figure 2.** Cumulative incidence of major adverse cardiac events at 12-month follow-up according to recanalisation technique.

Among these, in-stent CTO (HR 1.72, 95% CI: 1.02-2.91,  $p=0.044$ ) and post-procedural %DS (HR for 10% increment: 1.21, 95% CI: 1.00-1.46,  $p=0.049$ ) independently correlated with MACE occurrence; all remaining variables, including recanalisation technique, did not independently correlate with MACE at 12-month follow-up ( $p>0.130$  for all variables) (**Figure 3A**). Besides recanalisation technique (subintimal vs intraplaque), the model for binary

restenosis included patient age and sex, previous CABG, previous PCI, right coronary artery (RCA) CTO, in-stent CTO, maximal balloon pressure and post-procedural %DS as independent variables. Among these, in-stent CTO (OR 1.94, 95% CI: 1.05-3.59,  $p=0.036$ ), RCA CTO (OR 0.56, 95% CI: 0.33-0.94,  $p=0.029$ ) and previous CABG (OR 1.78, 95% CI: 1.02-3.13,  $p=0.043$ ) independently correlated with the presence of binary restenosis; all remaining variables, including recanalisation technique, did not independently correlate with the presence of binary restenosis at surveillance angiography ( $p>0.077$  for all variables) (**Figure 3B**).

## Discussion

The main findings of the present study can be summarised as follows: i) use of contemporary DART is associated with similar midterm clinical and angiographic outcomes compared to intraplaque recanalisation techniques; ii) there was no independent correlation between recanalisation technique (subintimal vs intraplaque) and MACE occurrence or in-segment binary restenosis at follow-up; iii) contrary to previous reports applying extensive DART, the rate of occlusive restenosis was low and comparable in both recanalisation strategies; iv) despite similar angiographic outcomes, the overall incidences of binary restenosis and TLR were not negligible in both CTO recanalisation groups; and v) approximately half of the patients undergoing TLR were asymptomatic at the time of angiographic follow-up.



**Figure 3.** Multivariable analysis for predictors of MACE and binary restenosis. A) Plot of hazard ratios associated with MACE. B) Plot of odds ratios associated with binary restenosis. The squares indicate the point estimate and the left and right ends of the lines the 95% CI. 95% CI: 95% confidence interval; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CTO: chronic total occlusion; DART: dissection and re-entry technique; MACE: major adverse cardiac events; MI: myocardial infarction; %DS: percent diameter stenosis; PCI: percutaneous coronary intervention

Increased adoption of DART has revolutionised the field of CTO PCI and played a fundamental role in achieving the high procedural success rates reported in contemporary CTO registries<sup>3</sup>. Despite their indisputable merits in terms of acute procedural success, the intermediate- and long-term outcomes of patients treated by means of subintimal techniques continue to engender significant controversy. Contrary to initial studies<sup>4</sup> applying extensive dissection techniques, recent reports<sup>5-10,15</sup> using limited DART have shown comparable midterm clinical outcomes with intraplaque recanalisation techniques. Although reassuring, these studies<sup>5,7,8,10</sup> did not include a systematic angiographic follow-up; indeed, the number of studies comparing the outcomes of such recanalisation strategies which included surveillance angiography is extremely limited. This is particularly important, since patient clinical status following CTO recanalisation is determined not only by persisting patency of the recanalised vessel, but also by dynamic changes in collateral vessel supply, which, in case of restenosis/reocclusion, can recover to pre-recanalisation levels<sup>16</sup>. The results of the present registry, which, together with the CONSISTENT CTO study<sup>17</sup>, represent the largest data sets comparing contemporary DART and intraplaque recanalisation in terms of both clinical and angiographic outcomes to date, confirm the safety of contemporary DART with a low cumulative incidence of the composite of death and MI up to 12 months following CTO recanalisation with no significant differences between the two recanalisation strategies.

The absence of significant differences in terms of in-stent/in-segment %DS or rates of binary restenosis at surveillance angiography as well as of TLR between the two recanalisation techniques in our study confirms the sustained efficacy of modern DART. Rates of binary restenosis (29.2% and 36.5%) and TLR (17.5% and 18.1%) in our study were lower compared to those reported in the ACE-CTO study (46% and 37%, respectively)<sup>18</sup> and tended to be higher than those reported in the recent CONSISTENT CTO (14.5% as well as 10.9% and 3.7%, respectively)<sup>17</sup> and PRISON IV studies (8.0% and 2.1% as well as 10.5% and 4.0%, respectively)<sup>19</sup>; differences in CTO lesion complexity could explain some of the discrepancies in angiographic outcomes between studies. In view of the high complexity of the lesion subset being recanalised by means of DART in our patient collective (J-CTO score  $\geq 3$  in 45.7% of this subgroup), confirmation of comparable angiographic outcomes between the two groups is a remarkable finding, which confirms the sustained efficacy of contemporary DART.

Despite similar angiographic outcomes, the incidences of binary restenosis and TLR were not negligible in both CTO recanalisation groups. The overall TLR rate in the present study is higher than that reported in studies of non-CTO PCI with surveillance angiography<sup>20</sup>. In the light of the high lesion complexity and lesion length in the present data set, this finding is not unexpected and in line with previous reports following CTO recanalisation procedures<sup>18</sup>. However, contrary to previous studies applying extensive dissection techniques (STAR), the rate of occlusive restenosis following limited DART in our study was extremely low and comparable to intraplaque recanalisation. The low prevalence of

symptoms (47.2%) in the patient subgroup undergoing TLR in our study shows that, in the specific setting of CTO recanalisation, failure to perform a systematic angiographic follow-up may significantly underestimate the occurrence of restenosis/reocclusion.

Finally, another important aspect which may impact significantly on the safety of recanalisation procedures is that of stent healing patterns. Clinical studies using intravascular optical coherence tomography have displayed somewhat conflicting results regarding rates of uncovered and malapposed struts in drug-eluting stents (DES) implanted in CTO lesions<sup>17,21</sup> and the influence of recanalisation technique (intraplaque vs DART) on such intravascular imaging findings. Further investigation will be important in clarifying this issue since both stent coverage and apposition have been linked to the occurrence of stent thrombosis.

### Study limitations

Some limitations should be considered when interpreting the results of the present report. First, despite being one of the largest studies to compare both clinical and angiographic findings of intraplaque as opposed to subintimal CTO recanalisation, this is a single-centre study. Second, no systematic intravascular imaging was performed following initial vessel wiring and the possibility of small subintimal wire trajectories in the intraplaque group cannot be ruled out. Third, since the study period preceded the ARC-2 consensus document, repeat PCI on surveillance angiography was performed according to the initial ARC criteria and physiological evaluation was not used to guide TLR procedures.

### Conclusions

Besides their indisputable role in achieving high procedural success rates, contemporary DART display comparable midterm clinical as well as angiographic outcomes compared to intraplaque recanalisation techniques. Contrary to previous reports applying extensive DART, the rate of occlusive restenosis was low and comparable in both recanalisation strategies. However, irrespective of the recanalisation technique being used, the overall TLR rate following CTO recanalisation remains higher than that reported for non-CTO PCI. This finding, coupled with the absence of symptoms in a considerable proportion of patients undergoing TLR at surveillance angiography, underlines the necessity of a close clinical follow-up and eventually myocardial perfusion imaging as a means of detecting and treating ISR.

### Impact on daily practice

Use of contemporary DART is associated with similar midterm clinical and angiographic outcomes compared to intraplaque recanalisation techniques. Contrary to initial reports applying extensive DART, the rate of occlusive restenosis was low and comparable in both recanalisation strategies. However, regardless of the recanalisation technique being used, the overall incidences of binary restenosis and TLR following CTO recanalisation remain higher than those reported for non-CTO PCI.

## Conflict of interest statement

The authors declare no conflicts of interest related to the present work.

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## Supplementary data

### Supplementary Appendix 1. Methods.

**Supplementary Figure 1.** Cumulative incidence of the combined endpoint of death, myocardial infarction or target lesion revascularisation according to J-CTO categories.

**Supplementary Figure 2.** Risk of MACE at 12 months according to recanalisation technique (DART and intraplaque) stratified by J-CTO score categories.

**Supplementary Table 1.** Baseline clinical characteristics according to MACE occurrence.

**Supplementary Table 2.** Angiographic characteristics and quantitative coronary analysis according to MACE occurrence.

**Supplementary Table 3.** Procedural characteristics according to MACE occurrence.

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## **Supplementary data**

### **Supplementary Appendix 1. Methods**

#### ***Angiographic data acquisition and analysis***

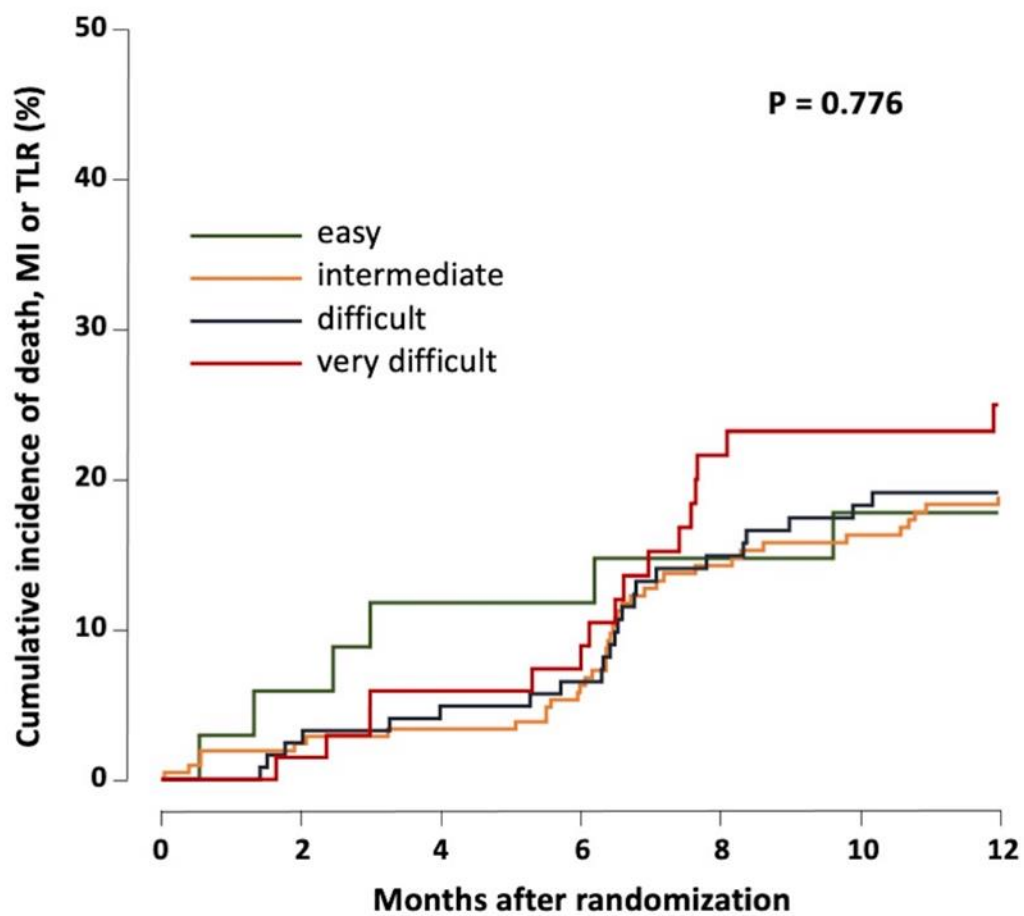
Baseline, post-procedural and follow-up angiograms were recorded and assessed off-line in a core laboratory (ISAResearch Center, Munich, Germany) with an automated edge-detection system (Medis Medical Imaging Systems, Leiden, the Netherlands). Measurements were performed on cineangiograms recorded after intracoronary administration of nitroglycerine. Follow-up QCA measurements were performed using the single worst view projection. The contrast-filled, non-tapered catheter tip was used for calibration. Quantitative analysis was performed on both “in-stent” and “in-segment” areas (including the stented segment as well as both 5 mm margins proximal and distal to the stent). Binary restenosis was defined as % diameter stenosis  $\geq 50\%$  within the target lesion at follow-up angiography.

#### ***Definition of myocardial infarction***

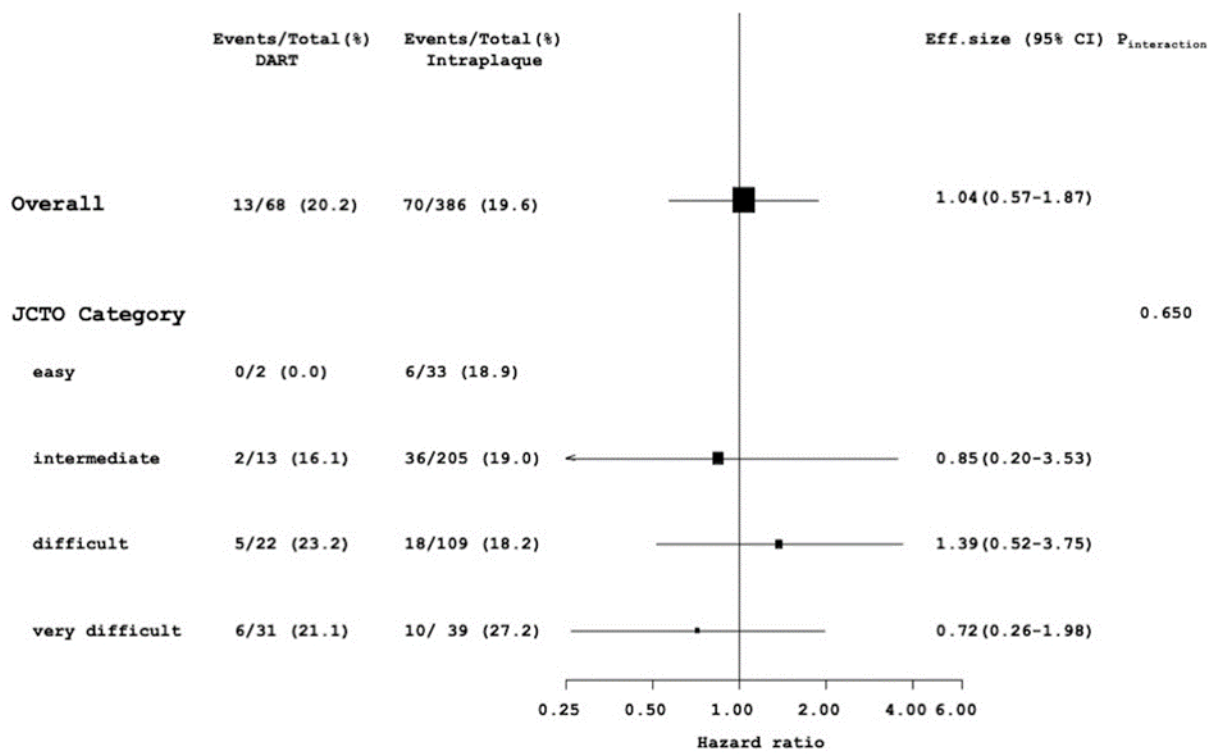
The definition of myocardial infarction used in the present study is adopted from the third universal definition of myocardial infarction. Cardiac troponin was used as the preferred biomarker.

Myocardial infarction diagnosis required the detection of a rise and/or fall in cardiac biomarkers (preferably cardiac troponin) with at least one value above the 99<sup>th</sup> percentile upper reference limit (URL) and with at least one of the following:

- symptoms of ischaemia
- development of pathological Q-waves in the ECG
- new or presumed new ST segment–T-wave changes (ST–T changes) or new left bundle branch block (LBBB)
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality



**Supplementary Figure 1.** Cumulative incidence of the combined endpoint of death, myocardial infarction or target lesion revascularisation according to J-CTO categories.



**Supplementary Figure 2.** Risk of MACE at 12 months according to recanalisation technique (DART and intraplaque) stratified by J-CTO score categories.

**Supplementary Table 1. Baseline clinical characteristics according to MACE occurrence.**

	<b>No MACE n=371</b>	<b>MACE n=83</b>	<b>p-value</b>
Number of lesions	1.04±0.20	1.04±0.19	0.853
Age, years	68.0 (59.8-75.4)	66.7 (62.0-74.0)	0.900
Male	319 (86.0)	73 (88.0)	0.768
Current smoker	61 (16.4)	13 (15.7)	0.992
Body mass index (kg/m <sup>2</sup> )	27.8 (25.3-31.1)	27.5 (24.4-31.4)	0.318
Hypercholesterolaemia	216 (58.2)	47 (56.6)	0.886
Arterial hypertension	331 (89.2)	76 (91.6)	0.663
Diabetes mellitus	124 (33.4)	30 (36.1)	0.730
Insulin therapy	33 (8.9)	11 (13.3)	0.313
CAD family history	110 (29.6)	34 (41.0)	0.061
Previous myocardial infarction	150 (40.4)	38 (45.8)	0.440
Previous coronary artery bypass grafting	87 (23.5)	27 (32.5)	0.113
Clinical presentation			0.246
Stable angina pectoris or silent ischaemia	325 (87.6)	70 (84.3)	
Unstable angina pectoris	18 (4.9)	4 (4.8)	
Non-ST-segment elevation myocardial infarction	23 (6.2)	5 (6.0)	
ST-segment elevation myocardial infarction	5 (1.4)	4 (4.8)	
Affected vessels			0.365
One vessel	29 (7.8)	3 (3.6)	
Two vessels	67 (18.1)	14 (16.9)	
Three vessels	275 (74.1)	66 (79.5)	
Ejection fraction (%)	48.0 (40.0-56.0)	48.0 (38.0-53.0)	0.285
Surveillance angiography available	285 (76.8)	72 (86.7)	0.065
Time interval surveillance angiography, days	197 (178-230)	195 (166-216)	0.109

Data are shown as numbers (%), mean±SD or median (interquartile range).

**Supplementary Table 2. Angiographic characteristics and quantitative coronary analysis according to MACE occurrence.**

	<b>No MACE n=385</b>	<b>MACE n=88</b>	<b>p-value</b>
Target coronary vessel			0.282
Left main coronary artery	1 (0.3)	1 (1.1)	
Left anterior descending coronary artery	103 (26.8)	28 (31.8)	
Left circumflex coronary artery	93 (24.2)	23 (26.1)	
Right coronary artery	188 (48.8)	36 (40.9)	
In-stent occlusion	61 (15.8)	27 (30.7)	0.002
Vessel tortuosity			0.638
Light	293 (76.1)	66 (75.0)	
Intermediate	78 (20.3)	17 (19.3)	
Severe	14 (3.6)	5 (5.7)	
J-CTO score	1.53±0.91	1.61±0.94	0.450
J-CTO score categories			0.823
0=easy	30 (7.8)	6 (6.8)	
1=intermediate	189 (49.1)	41 (46.6)	
2=difficult	111 (28.8)	25 (28.4)	
≥3=very difficult	55 (14.3)	16 (18.2)	
<b>Quantitative coronary analysis</b>			
Pre-procedure			
Lesion length, mm	34.6±15.1	34.1±16.0	0.792
Reference vessel diameter, mm	2.85±0.46	2.85±0.47	0.902
Post-procedure			
Reference vessel diameter, mm	3.04±0.44	3.02±0.49	0.790
Minimal lumen diameter, mm	2.58±0.48	2.45±0.49	0.019
% diameter stenosis	15.1±9.42	19.1±10.1	0.001
Surveillance angiography			



	<b>No MACE n=295</b>	<b>MACE n=76</b>	<b><i>p</i>-value</b>
Reference vessel diameter, mm	3.06±0.43	3.03±0.52	0.609
Minimal lumen diameter (in-stent), mm	2.34±0.66	1.38±0.83	<0.001
Minimal lumen diameter (in-segment), mm	2.00±0.67	1.24±0.69	<0.001
% diameter stenosis (in-stent)	24.2±17.5	55.4±24.4	<0.001
% diameter stenosis (in-segment)	35.5±17.8	59.8±19.4	<0.001
Binary restenosis	53 (18.0)	60 (78.9)	<0.001

Data are shown as numbers (%), mean±SD or median (interquartile range).

**Supplementary Table 3. Procedural characteristics according to MACE occurrence.**

	No MACE n=385	MACE n=88	<i>p</i> -value
Contrast agent	295 (220-390)	300 (220-380)	0.657
Radiation time, min	23.5 (16.2-33.9)	27.2 (18.9-38.9)	0.123
Antegrade	342 (88.8)	80 (90.9)	0.707
Retrograde	43 (11.2)	8 (9.1)	0.707
Antegrade wire escalation	316 (82.1)	74 (84.1)	0.770
Antegrade dissection and re-entry	26 (6.8)	6 (6.8)	>0.999
Reverse controlled antegrade and retrograde tracking	31 (8.1)	7 (8.0)	>0.999
Retrograde true-true	12 (3.1)	1 (1.1)	0.478
CrossBoss	2 (0.5)	1 (1.1)	0.462
Stingray	16 (4.2)	4 (4.6)	0.775
Rotablation	29 (7.5)	10 (11.4)	0.335
Anchoring balloon	19 (4.9)	2 (2.3)	0.393
Bifurcation involved and treated	77 (20.0)	23 (26.1)	0.260
Collaterals used	42 (10.9)	8 (9.1)	0.758
Septal	31 (8.1)	5 (5.7)	0.594
Epicardial	5 (1.3)	2 (2.3)	0.619
Vein graft	8 (2.1)	1 (1.1)	>0.999
Type of intervention			0.003
PTCA	20 (5.2)	13 (14.8)	
Stent	365 (94.8)	75 (85.2)	
Vessel perforation	8 (2.1)	1 (1.1)	>0.999
Nominal balloon, mm	3.35±0.53	3.35±0.56	0.916
Maximal balloon pressure, atm	16.0 (12.8-18.0)	16.0 (12.8-20.0)	0.385
Maximal stent diameter, mm	3.24±0.48	3.32±0.51	0.176
Total stented length, mm	46.4±19.6	49.7±19.7	0.196
Stent type			0.026
Durable polymer everolimus-eluting stent	222 (57.7)	45 (51.1)	
Biodegradable polymer everolimus-eluting stent	134 (34.8)	29 (33.0)	
Other drug-eluting stent	9 (2.3)	1 (1.1)	

Data are shown as numbers (%), mean±SD or median (interquartile range).