New Aspects in Percutaneous Coronary Intervention of Chronic Total Occlusions

Ph.D. Dissertation

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Publications directly related to the subject of the dissertation

I. **Karacsonyi J**, Karatasakis A, Karmpaliotis D, Alaswad K, Yeh RW, Jaffer FA, Wyman MR, Lombardi WL, Grantham JA, Kandzari DE, Lembo N, Moses JW, Kirtane AJ, Parikh MA, Green P, Finn M, Garcia S, Doing A, Patel M, Bahadorani J, Parachini JRM, Resendes E, Rangan BV, Ungi I, Thompson CA, Banerjee S, Brilakis ES. Effect of Previous Failure on Subsequent Procedural Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention (from a Contemporary Multicenter Registry) AMERICAN JOURNAL OF CARDIOLOGY 117:(8) pp. 1267-1271. (2016) IF: 3.398

II. **Karacsonyi J**, Alaswad K, Jaffer FA, Yeh RW, Patel M, Bahadorani J, Karatasakis A, Danek BA, Doing A, Grantham JA, Karmpaliotis D, Moses JW, Kirtane A, Parikh M, Ali Z, Lombardi WL, Kandzari DE, Lembo N, Garcia S, Wyman MR, Alame A, Nguyen-Trong PKJ, Resendes E, Kalsaria P, Rangan BV, Ungi I, Thompson CA, Banerjee S, Brilakis ES. Use of Intravascular Imaging During Chronic Total Occlusion Percutaneous Coronary Intervention: Insights From a Contemporary Multicenter Registry JOURNAL OF THE AMERICAN HEART ASSOCIATION 5:(8) Paper e003890. 13 p. (2016) IF: 4.425

III. **Karacsonyi J**, Karmpaliotis D, Alaswad K, Jaffer FA, Yeh RW, Patel M, Bahadorani J, Doing A, Ali ZA, Karatasakis A, Danek BA, Rangan BV, Alame AJ, Banerjee S, Brilakis ES. Prevalence, indications and management of balloon uncrossable chronic total occlusions: Insights from a contemporary multicenter US registry CATHETERIZATION AND CARDIOVASCULAR INTERVENTIONS 90:(1) pp. 12-20. (2017) IF: 2.602

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The publications marked with "*" were published in 2018, their impact factor is estimated from 2017, as appropriate.

Cumulative impact factor of publications not directly related to the thesis: 148.832

Total impact factor of publications: 159,356

LIST OF ABBREVIATONS

ADR: antegrade dissection and re-entry

BMI: body mass index

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CART: controlled antegrade and retrograde tracking and dissection

CTO: chronic total occlusion

CVD: cerebrovascular disease;

DES: drug eluting stent

FFR: Fractional flow reserve

IMG: imaging

IVUS: intravascular ultrasound

J-CTO score: Japanese chronic total occlusion score

LAD: left anterior descending artery

LCX: left circumflex artery

LVEF: left ventricular ejection fraction

MACE: major adverse cardiac events

MI: myocardial infarction

OCT: optical coherence tomography

OMT: optimal medical therapy

PCI: percutaneous coronary intervention

P-CTO score: Progress chronic total occlusion score

PROGRESS CTO: Prospective Global Registry for the Study of Chronic Total Occlusion Intervention

PVD: peripheral vascular disease

RCA: right coronary artery

TIMI: thrombolysis in myocardial infarction

SUMMARY

Coronary Chronic total occlusions (CTOs) are defined as coronary lesions with Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow of at least 3-month duration. Symptomatic patients with CTOs can be managed in three ways, conservatively with medical therapy, with coronary artery bypass grafting (CABG) or with percutaneous coronary intervention (PCI). CTO PCI can be challenging to perform with variable success rates, depending on operator experience and expertise, but with the development of new techniques and equipment the success rates are getting higher and the complication rates lower. In this dissertation, we focused on three aspects of CTO PCI: (a) the impact of prior failure on the outcomes of CTO PCI, (b) balloon uncrossable lesions and (c) the frequency of use and outcomes of intravascular imaging. We examined the prevalence, clinical and angiographic characteristics, management and procedural outcomes of CTO PCIs in a contemporary, large, multicenter CTO PCI registry.

Prior CTO PCI failure has been associated with lower procedural success rates and is part of the Japanese Chronic Total Occlusion (J-CTO) score that was developed to predict the likelihood of successful guidewire crossing within 30 minutes. We sought to examine the impact of prior failure on the subsequent outcomes CTO PCI. The main finding of our study is that a prior failed CTO PCI attempt is associated with higher angiographic complexity, longer procedural duration and fluoroscopy time, but not with lower success and higher complication rates of subsequent CTO PCI attempts. Balloon uncrossable lesions are lesions that cannot be crossed with a balloon after successful advancement of the guidewire distal to the lesion. These lesions can be challenging to treat, requiring specialized techniques and equipment. In our study, we found that balloon uncrossable CTOs are common, are associated with high rates of technical failure, and require specialized techniques for successful treatment. Intravascular imaging can facilitate CTO PCI. Use of intravascular ultrasound (IVUS) for stent optimization during CTO PCI has been shown to improve long-term outcomes, yet its impact on crossing has received limited study. In our study, we found that intravascular imaging is frequently performed during CTO PCI both for crossing and for stent selection/optimization. Despite its use in more complex lesion subsets, intravascular imaging was associated with similar rates of technical and procedural success for CTO PCI.

1. INTRODUCTION

Chronic total occlusions (CTOs) are defined as a 100% occlusion of a coronary artery exhibiting Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow of at least 3 months of duration (1). If there has been no prior angiogram, it can be difficult to determine the duration of the occlusion, in such cases estimation is based on the first onset of symptoms and/or prior history of myocardial infarction in the target vessel territory.

CTOs are common, they are found in up to approximately one third of the patients undergoing diagnostic coronary angiography with a finding of coronary artery disease. However, the data vary in literature regarding the prevalence of such lesions. In the study population Jeroudi et al. stated that CTOs are highly prevalent, present in 31% of the cases in patients with coronary artery disease (CAD) without prior coronary artery bypass surgery (CABG) (1). Fefer et al. reported an overall CTO prevalence of 18.4% among 1697 patients undergoing non-emergency coronary artery angiography in the Canadian CTO registry (2). The Italian Registry of Chronic Total Occlusion demonstrated an overall CTO prevalence of 13.3% (3). In the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) registry CTO was present in 16.0% of patients with coronary artery disease and 10.9% of all coronary angiographies (4).

Treatment of CTOs should include optimal medical therapy complemented if indicated and possible with revascularization with either CABG or PCI. Revascularization is indicated in patients with angina or other symptoms resulting from ischemia such as dyspnea in spite of optimal medical therapy, and in those with ischemia on non-invasive testing or left ventricular dysfunction. CTO PCI is the preferred revascularization method in case of single vessel disease and post-CABG patients due to the high risk and technical challenges associated with redo cardiac surgery. If the patient has complex, multivessel disease (especially if also diabetic) CABG is generally recommended (5).

Regarding the guidelines, dedicated randomized clinical trials examining the outcomes of patients with CTO allocated to revascularization or conservative therapy are still needed. CTO revascularization based on the 2018 European Society of Cardiology/ European Association of Cardio-Thoracic Surgery guidelines is a Class IIA, level of evidence B recommendation: "Percutaneous revascularization of CTOs should be considered in patients with angina resistant to medical therapy or with a large area of documented ischemia in the territory of the occluded vessel." This has not changed since the previous 2014 guidelines (6).

According to the American College of Cardiology/American Heart Association PCI guidelines published in 2011: “PCI of a CTO in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise” is a Class IIA, level of evidence B recommendation (7).

The clinical decision on whether to perform CTO PCI depends on two things, estimated risk and anticipated benefit resulting from the procedure.

The main benefit of successful CTO PCI is symptomatic improvement. In patients without symptoms performing CTO PCI is generally not recommended except for patients with a large area of ischemia (>10%). Some patients with CTOs might have progressively limited physical activity to prevent symptoms and/or may present with atypical symptoms such as dyspnea rather than angina. Thus an objective evaluation with diagnostic tools is useful to assess patients with limited symptoms, such as treadmill tests, stress tests, 6 minute walking test (8).

Possible benefits of successful CTO PCI include improved quality of life. Patients with medically refractory angina after successful procedures can reduce or eliminate angina and require fewer or no antianginal medication, as well as show improved exercise capacity. (9,10). Two recently published randomized studies have discussed this topic. The DECISION-CTO trial (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion) was presented at the 2017 American College of Cardiology meeting. In this trial 834 patients were randomized to CTO PCI and optimal medical therapy (OMT) or OMT alone. According to the results patients had similar clinical outcomes and quality of life at the median follow-up of 3.1 years in both groups. However, the study had several limitations such as early termination before reaching the target enrollment, high cross-over rates, and mild baseline angina status. In addition to this patients were randomized before revascularization of non-CTO lesions hereby several patients underwent PCI in the OMT group, as well.

The other randomized trial the EuroCTO trial (A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) randomized 396 patients to CTO PCI vs. OMT alone. At 12 months, a greater improvement of Seattle Angina Questionnaire subscales was observed with PCI as compared with OMT for angina frequency and quality of life. There were no periprocedural deaths in the PCI group. Major adverse cardiovascular and cerebrovascular events were similarly low in both groups (11).

For many patients with complex stable CAD CTO PCI is an alternative option. They may either decline CABG for nonmedical reasons or concerns regarding complications of CABG. In addition to this some patients present as poor surgical candidates for example those who require redo CABG or have multiple comorbidities. CTO PCI is preferable over CABG in the following patients: those with single vessel right or circumflex coronary artery CTO and those with prior CABG, especially if the left internal mammary artery graft to the left anterior descending artery is intact (12).

Successful CTO PCI can reduce ischemia in the territories of both the occluded and the donor vessels (13). Fractional flow reserve (FFR) measurement after CTO crossing but before stent implantation showed that the myocardial territories supplied by the CTO are ischemic, even when well developed collaterals are present. In the study by Werner et al resting ischemia was seen in 78% of the patients and with hyperemia significant FFR was observed in all the study patients (14). After successful CTO recanalization the hemodynamic significance of a lesion in the donor vessel of the CTO vessel may decrease. In another study six of nine donor vessel that had baseline ischemia proven by FFR were reduced to nonischemic FFR after successful CTO recanalization (13). In a study examining 301 patients who had myocardial perfusion imaging before and after CTO PCI, a baseline ischemic burden of >12,5% was optimal to detect those patients who will have significant decrease in ischemic burden post CTO PCI (15).

Successful CTO PCI can also improve left ventricular systolic function if the CTO territory is viable (16,17). In patients with systolic heart failure revascularization of the CTO was associated with improvement in left ventricular ejection fraction and improvement in New York Heart Association functional class, angina and brain natriuretic peptide levels (18). However in the recently published EXPLORE trial (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) only the subgroup of the patients with left anterior descending coronary artery CTO had improvement in left ventricular ejection fraction (19).

Several observational studies and meta-analyses demonstrated better long-term survival after successful versus unsuccessful CTO PCI (20,21). A potential beneficial effect of CTO PCI on long-term survival could be attributed to protection from future coronary events in vessels supplying collateral perfusion to the ischemic CTO territory; improved myocardial contractility and reduction in risk for arrhythmias (5). However all of the studies are observational and retrospective, randomized control clinical trials are missing.

CTO revascularization can prevent arrhythmias. In the VACTO study 162 patients with ischemic cardiomyopathy who received an implantable cardioverter defibrillator were examined. Among them 44% had CTO, during median follow-up of 26 months the CTOs were associated with higher rates of ventricular arrhythmias and death suggesting that patients with ischemia related ventricular arrhythmias could benefit from successful CTO PCI (22).

CTO PCI can be challenging to perform with variable success rates, depending on operator experience and expertise (23,24). Prior CTO PCI failure has been associated with lower procedural success rates and is part of the Japanese Chronic Total Occlusion (J-CTO) score that was developed to predict the likelihood of successful guidewire crossing within 30 minutes (25). However, prior CTO PCI failure can be due to multiple factors, such as patient instability, limited local experience, or early cessation of recanalization efforts without exploring alternative CTO crossing options. In the first part of our study we examined a contemporary multicenter registry to determine the impact of prior failed CTO PCI attempts on the outcomes of subsequent procedures.

Balloon uncrossable lesions are lesions that cannot be crossed with a balloon after successful advancement of the guidewire distal to the lesion. CTOs are often balloon uncrossable: in a single center series of CTO PCI the prevalence of balloon uncrossable lesions was 6.4% (26). Balloon uncrossable CTOs can be challenging to treat often requiring multiple techniques focusing on either plaque modification or increasing guide catheter support (26-29). Such techniques include balloon-assisted microdissection (also called grenadoplasty), anchoring techniques, guide catheter extensions, the Threader catheter (combined balloon/microcatheter, Boston Scientific, Natick, Massachusetts), the Tornus catheter (Asahi Intecc, Nagoya, Japan), the Turnpike Spiral and Gold catheters (Vascular Solutions, Minneapolis, Minnesota), the Glider balloon (cut tip balloon, TriReme Medical, Pleasanton, California), laser, atherectomy, or other techniques. In the second section of our study we examined a contemporary, multicenter CTO PCI registry to determine the prevalence of balloon uncrossable lesions, associated treatments and outcomes.

Use of intravascular ultrasound (IVUS) for stent optimization during CTO PCI has been shown to improve long-term outcomes (30-32), yet its impact on crossing in CTO has received limited study (30-38). Intravascular imaging can help resolve proximal cap ambiguity by identifying the position of the main branch (39) and clarify guidewire position during both antegrade and retrograde CTO crossing attempts (40). IVUS can determine optimal balloon sizing for the reverse controlled antegrade and retrograde tracking and dissection (reverse CART) technique (40,41). Moreover, intravascular imaging can facilitate sizing of balloons and stents and optimize stent expansion and stent strut apposition (42). Finally in the third section of our study we examined a large multicenter contemporary CTO PCI registry to determine the frequency of intravascular imaging use during CTO PCI and the associated procedural outcomes.

2. AIMS

1. To examine the impact of prior failure on the outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI).

2. To determine the prevalence of balloon uncrossable lesions associated treatments and outcomes.

3. To determine the frequency of intravascular imaging use during CTO PCI and the associated procedural outcomes.

3. METHODS

3.1 Patient population

In the first part of our analyses we examined the baseline and angiographic characteristics, and clinical outcomes of 1,232 consecutive CTO PCIs performed in 1,213 patients between 2012 and 2015 at 12 US centers. In the second part of the analyses we reviewed the baseline clinical and angiographic characteristics as well as the outcomes of 755 consecutive CTO PCI procedures performed in 734 patients between 2012 and 2016 at 11 US centers. Of the 755 CTO PCI procedures, 37 (4.9%) were excluded because of failure to cross the occlusion with a guidewire. The remaining 718 CTO PCIs performed in 701 patients were included in the final analysis. In the final section of the analyses we analyzed the frequency of use and outcomes of intravascular imaging among 619 CTO PCIs performed between 2012 and 2015 at 7 US centers.

Enrollment was performed during only part of the study period in some centers due to participation in other studies. Data collection was performed both prospectively and retrospectively and was recorded in a dedicated online database (PROGRESS CTO: Prospective Global Registry for the Study of Chronic Total Occlusion Intervention, Clinicaltrials.gov Identifier: NCT02061436).(9,24,43-51) A waiver of informed consent was obtained. The study was approved by the institutional review board of each site.

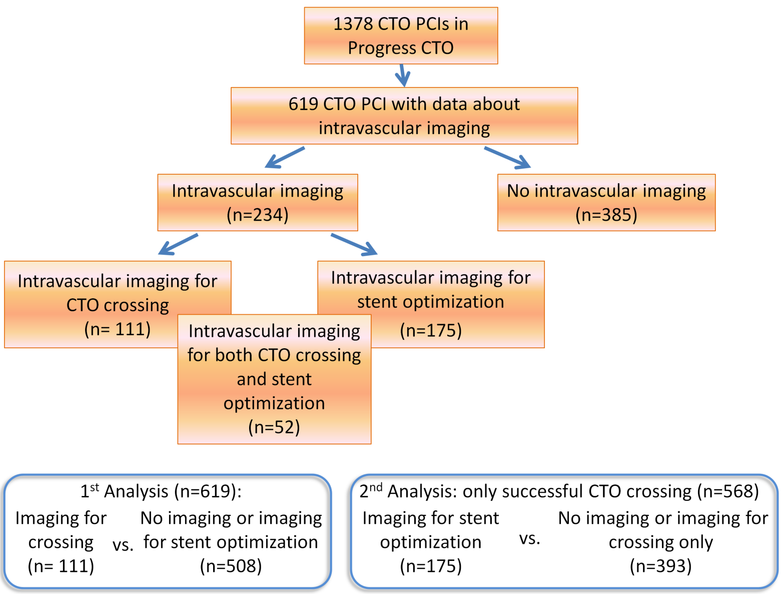
3.2 Definitions

Coronary CTOs were defined as coronary lesions with TIMI grade 0 flow of at least 3-month duration (52). Estimation of the occlusion duration was based on first onset of anginal symptoms, prior history of myocardial infarction in the target vessel territory, or comparison with a prior angiogram. Balloon uncrossable CTOs were defined as lesions that could not be crossed with a balloon despite successful advancement of the guidewire distal to the lesion. Calcification was assessed by angiography as mild (spots), moderate (involving ≤50% of the reference lesion diameter) and severe (involving >50% of the reference lesion diameter). Moderate proximal vessel tortuosity was defined as the presence of at least 2 bends >70 degrees or 1 bend >90 degrees and severe tortuosity as 2 bends >90 degrees or 1 bend >120 degrees in the CTO vessel. The Japanese Chronic Total Occlusion (J-CTO) score was calculated as described by Morino et al (53). The Progress CTO score was calculated as described by Christopoulos et al (49). Technical success was defined as successful CTO revascularization with achievement of <30% residual diameter stenosis within the treated segment and restoration of TIMI grade 3 antegrade flow. Procedural success was defined as achievement of technical success with no in-hospital major adverse cardiac events (MACE). In-hospital MACE included any of the following adverse events prior to hospital discharge: death, myocardial infarction, urgent repeat target vessel revascularization with either PCI or CABG, tamponade requiring either pericardiocentesis or surgery, and stroke. Myocardial infarction was defined using the Third Universal Definition of Myocardial Infarction (54).

3.3 Statistical analysis

In the first section of our study patients were classified in two groups based on whether they had a prior unsuccessful CTO PCI attempt or not. In the second part of the study comparisons were performed between CTO PCI procedures that were successfully crossed with a balloon after guidewire crossing and those that were balloon uncrossable. Finally in the third part of the analyses we did two comparisons regarding intravascular imaging use. The primary comparison of this part of the study was between procedures in which intravascular imaging (intravascular ultrasound and/or optical coherence tomography) was used vs. was not used for crossing the occlusion (**Figure 1**). In a secondary analysis of cases that were successfully crossed with a guidewire, a comparison was made between use vs. no use of intravascular imaging for stent sizing/optimization. The baseline clinical characteristics and the procedural outcomes were analyzed among the patients (606 patients), while the angiographic characteristics were analyzed among procedures (619 procedures).

Figure 1. Flow chart of the intravascular imaging section of the study



Continuous variables were presented as mean ± standard deviation or median (interquartile range) and were compared using the t-test, or Wilcoxon rank-sum test, as appropriate. Categorical data were reported as frequencies or percentages and compared using the chi-square test or Fisher's exact test, as appropriate. All statistical analyses were performed with JMP 11.0 (SAS Institute; Cary, North Carolina). Two-sided p-values <0.05 were considered statistically significant. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Texas Southwestern Medical Center.(55) REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The Redcap system was also supported by CTSA NIH Grant UL 1-RR024982.

4. RESULTS

4.1 Effect of prior failure on outcomes of CTO PCI

In the first section we sought to examine the impact of prior failure on the outcomes of CTO PCI. During the study period 1,213 consecutive patients underwent 1,232 CTO PCI at 12 US centers, in whom the information was available whether they had a prior attempt or not. The baseline patient and angiographic characteristics of the study population are summarized in Table 1. Mean age was 65.5 ± 10 years, 84.8% of the patients were men and 44.2% had diabetes. Nearly all patients had dyslipidemia (94.8 %) and hypertension (90%). Nearly one third of the study population had congestive heart failure (28%) and family history of coronary artery disease (30%), 34% had prior CABG, and 42% had a prior myocardial infarction. Patients with a prior failed CTO PCI attempt had lower rates of congestive heart failure and active smoking, as well as higher ejection fraction and body mass index.

The most common CTO PCI target vessel was the right coronary artery (59%), followed by the left anterior descending artery (22%), and the circumflex artery (19%). The mean J-CTO score was 2.55 ± 1.21. Antegrade wire escalation was the most common successful crossing strategy (41%), followed by retrograde (27%) and antegrade dissection and re-entry (24%). The overall technical and procedural success was 90% and 89%, respectively.

As compared with patients without prior CTO PCI failure, those with prior failed attempts were more likely to have in-stent restenosis, larger target vessel diameter, and were more likely to undergo CTO crossing using the retrograde approach. The distribution of final successful crossing strategy was similar between CTO PCI patients with and without prior CTO PCI failure, although a primary retrograde or antegrade dissection and re-entry approach was more common in patients with prior CTO PCI failure.

Table 1. Baseline clinical and angiographic characteristics of the study patients, classified according to whether they had undergone a prior failed percutaneous coronary intervention attempt in the chronic total occlusion target coronary artery.

Variable	Overall (n=1232)	Prior failed CTO PCI attempt (n=215)	No prior failed CTO PCI attempt (n=1.017)	P
Age (years) [a]	65 ± 10	64.4 ± 11	65.6 ± 9.8	0.177
Men	84.8%	81.4%	85.5%	0.135
BMI (kg/m^2) [a]	30.6 ± 6.3	31.6 ± 6.7	30.3 ± 6.2	0.026
Diabetes Mellitus	44.2%	38.8%	45.3%	0.082
Hypertension	90%	89%	90%	0.692
Dyslipidemia	94.8%	95.2%	94.7%	0.738
Smoking (current)	28%	21%	30%	0.014
LVEF (%) [a]	50 ± 14	53 ± 13	50 ± 14	0.016
Family History of CAD	30 %	34%	29%	0.230
Congestive Heart Failure	28%	19%	30%	0.002
Prior Myocardial Infarction	42%	44%	42%	0.540
Prior CABG	34%	31%	35%	0.221
Prior CVD	11%	8%	11%	0.122
Prior PVD	16%	12%	17%	0.106
Baseline creatinine (mg/dL)[b]	1.0 (0.9,1.2)	1.0 (0.9,1.3)	1.0 (0.9,1.2)	0.891
Angiographic characteristics				
CTO Target coronary artery				
• RCA	59%	58%	58%	0.953
• LAD	22%	23%	22%	
• LCX	19%	19%	19%	

Variable	Overall (n=1232)	Prior failed CTO PCI attempt (n=215)	No prior failed CTO PCI attempt (n=1.017)	P
Successful Crossing Strategy				
• Antegrade wiring	41%	35%	42%	
• Retrograde	27%	26%	27%	0.113
• Antegrade dissection and re-entry	24%	29%	22%	
First Crossing Strategy				
• Antegrade wiring	70%	52%	70%	
• Retrograde	20%	29%	18%	<0.0001
• Antegrade dissection and re-entry	14%	18%	12%	
Retrograde crossing attempt	42.5%	50.2%	40.8%	0.011
J-CTO score [a]	2.55 ± 1.21	3.28 ± 1.29	2.40 ± 1.13	<0.0001
Calcification (moderate/severe)	56.7%	57.4%	56.6%	0.819
Tortuosity (moderate/severe)	34.6%	34.8%	34.5%	0.940
Proximal cap ambiguity	32%	35%	32%	0.423
In-stent restenosis	13.6%	28.4%	10.5%	<0.0001
Interventional Collaterals	59%	60%	59%	0.865
Side branch at the proximal cap	45%	44%	46%	0.765
Blunt/no stump	64%	58%	64%	0.001
Vessel diameter (mm)[b]	2.75 (2.5, 3)	3 (2.5, 3)	2.75 (2.5, 3)	0.014
Occlusion length (mm)[b]	30 (20, 45)	30 (17, 50)	30 (20, 40)	0.485

[a] mean ± standard deviation; [b] median (interquartile range); BMI: body mass index; LVEF: left ventricular ejection fraction; CAD: coronary artery disease CABG: coronary artery bypass grafting; CTO: chronic total occlusion; CVD: cerebrovascular disease; J-CTO score: Japanese chronic total occlusion score; LAD: left anterior descending artery; LCX: left circumflex artery; PVD: peripheral vascular disease; PCI: percutaneous coronary intervention; RCA: right coronary artery.

Technical and procedural success were similarly high among patients with and without prior failed CTO PCI attempts (**Table 2, Figure 2**), whereas the incidence of MACE was numerically higher among prior failed cases (4.2% vs. 2.1%, p=0.067). Mean procedure duration was significantly longer in the group with prior failed CTO PCI attempts (142 vs. 125 min, p=0.026), as was mean fluoroscopy time (55 vs. 45 min, p=0.015), whereas mean air kerma radiation dose (4 vs. 3.39 Gray, p=0.163) and mean contrast volume (260 vs. 260 ml, p=0.893) were similar in the two study groups. Peri-procedural bleeding occurred in 0.9%

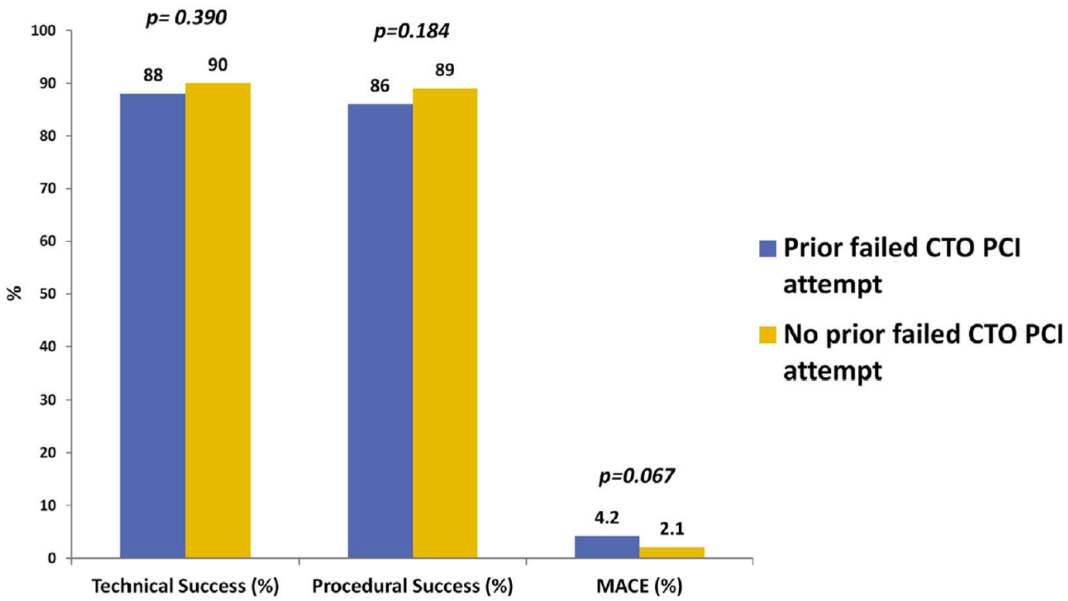
of the overall study population with similar prevalence in both groups (0.9% vs 0.9 %, p=0.949). Peri-procedural bleeding occurred in 11 cases, most of which (10 cases) were access site bleedings, while retroperitoneal bleeding and gastrointestinal bleeding occurred only in one case each.

Table 2. Procedural outcomes of the study patients, classified according to whether they had undergone a prior failed percutaneous coronary intervention attempt in the chronic total occlusion target coronary artery.

Variable	Overall (n=1232)	Prior failed CTO PCI attempt (n=215)	No prior failed CTO PCI attempt (n=1,017)	P
Technical Success	90%	88%	90%	0.390
Procedural Success	89%	86%	89%	0.184
Procedural time (min)[b]	128 (87, 191)	142 (91, 213)	125 (85, 185)	0.026
Fluoroscopy time (min)[b]	47 (28, 76)	55 (33, 82)	45 (27, 74)	0.015
Air kerma radiation dose (Gray)[b]	3.47 (2.03, 5.42)	4.00 (2.20, 5.73)	3.39 (2.00, 5.37)	0.163
Contrast volume[b]	260 (200, 360)	260 (185, 375)	260 (200, 360)	0.893
MACE	2.4%	4.2%	2.1%	0.067
Death	0.4%	0.9%	0.3%	0.183
Acute myocardial infarction	1.1%	2.8%	0.7%	0.006
Repeated PCI	0.3%	0.5%	0.3%	0.690
Stroke	0.3%	0%	0.4%	0.357
Emergency coronary bypass	0%	0%	0%	-
Pericardiocentesis	0.6%	1.4%	0.5%	0.134
Periprocedural bleeding	0.9%	0.9%	0.9%	0.949

[a] mean ± standard deviation; [b] median (interquartile range) CTO: chronic total occlusion; PCI: percutaneous coronary intervention; MACE: major adverse cardiac events;

Figure 2. Impact of prior failure of chronic total occlusion intervention on the outcomes of subsequent chronic total occlusion percutaneous coronary interventions.



4.2 Balloon uncrossable lesions

In the second part of our analyses balloon uncrossable lesions were examined in the study population of the PROGRESS registry. The baseline clinical characteristics of the study patients are shown in **Table 3**. Overall, mean age was 65.6 ± 10 years and 84% of the patients were men. Nearly half of the patients (48%) had diabetes mellitus, 87% had hypertension, 94% had dyslipidemia, 28% had congestive heart failure, 33% had prior CABG, and 46% had a history of myocardial infarction.

The angiographic characteristics of the study CTOs are summarized in **Table 4**. The most common CTO target vessel was the right coronary artery (52%), followed by the left anterior descending artery (25%) and the circumflex (22%). Moderate to severe calcification and moderate to severe tortuosity were present in 55% and 37%, respectively. Overall, technical and procedural rates were 97.6% and 95.9% respectively (as described in the methods section, only cases with successful guidewire crossing were included in this analysis). Antegrade wiring was the successful crossing strategy in 52% of the cases, the retrograde approach in 26% and antegrade dissection and re-entry in 22%.

Table 3. Baseline clinical characteristics of the study patients, classified according to the presence of balloon uncrossable lesions.

Variable	Overall (n=701)	Balloon uncrossable CTOs (n=63)	Balloon crossable CTOs (n=638)	P
Age (years)[a]	65.6 ± 10	67.2 ± 8.2	65.5 ± 10	0.123
Men	84%	84%	83%	0.982
BMI (kg/m2)[a]	30.6 ± 6	30.5 ± 6	30.6 ± 6	0.893
Diabetes Mellitus	48%	54%	47%	0.304
Hypertension	87%	95%	86%	0.054
Dyslipidemia	94%	100%	93%	0.033
Smoking (current)	17%	14%	17%	0.532
LVEF (%)[a]	50 ± 14	49 ± 14	50 ±14	0.635
Family History of CAD	26%	34%	26%	0.193
Congestive Heart Failure	28%	38%	27%	0.072
Prior Myocardial Infarction	46%	52%	45%	0.292
Prior CABG	33%	61%	30%	<0.0001
Prior CVD	11%	20%	10%	0.021
Prior PVD	14%	10%	14%	0.39
Baseline creatinine (mg/dL)[b]	1.0 (0.9,1.3)	1.1 (0.9, 1.3)	1.0 (0.9, 1.3)	0.208

[a] mean ± standard deviation; [b] median (interquartile range) BMI: body mass index; LVEF: left ventricular ejection fraction; CAD: coronary artery disease CABG: coronary artery bypass grafting; CVD: cerebrovascular disease; PVD: peripheral vascular disease.

Balloon uncrossable lesions were encountered in 63 (9%) of the CTO PCI procedures and were more likely to have moderate or severe calcification (82% vs. 52%, p<0.0001), moderate or severe tortuosity (61% vs. 35%, p<0.0001) and higher J-CTO score (2.95 ± 1.32 vs. 2.43 ± 1.23, p=0.005). The final successful crossing strategy in balloon uncrossable lesions tended to be more frequently antegrade wire escalation (65% vs. 51%), while retrograde (22% vs. 26%) and antegrade dissection/re-entry (13% vs. 23%) were less common (p=0.064).

Table 4. Angiographic characteristics of the study lesions, classified according to whether they were balloon uncrossable or not

Variable	Overall (n=718)	Balloon uncrossable CTOs (n=63)	Balloon crossable CTOs (n=655)	P
CTO Target Vessel				
RCA	52%	56%	52%	0.005
LAD	25%	16%	26%	
LCX	22%	26%	22%	
Successful Crossing Strategy				
Antegrade wiring	52%	65%	51%	0.064
Retrograde	26%	22%	26%	
ADR	22%	13%	23%	
First Crossing Strategy				
Antegrade wiring	76%	76%	76%	0.856
Retrograde	16%	14%	16%	
ADR	8%	10%	8%	
Retrograde crossing attempt	38%	32%	38%	0.315
J-CTO score[a]	2.48 ± 1.25	2.95 ± 1.32	2.43 ± 1.23	0.005
Progress-CTO score[a]	1.21 ± 1.02	1.41 ± 1.14	1.19 ± 1.00	0.142
Calcification (moderate/severe)	55%	82%	52%	<0.0001
Tortuosity (moderate/severe)	37%	61%	35%	<0.0001
Proximal cap ambiguity	30%	22%	31%	0.165
In-stent restenosis	16%	25%	15%	0.043
Prior failure to open CTO	19%	30%	18%	0.023
Interventional Collaterals	55%	56%	55%	0.86
Side branch at the proximal cap	49%	47%	49%	0.846
Blunt/no stump, %	56%	52%	57%	0.5
Vessel diameter (mm)[b]	3.0 (2.5, 3.0)	3.0 (2.5, 3.0)	3.0 (2.5, 3.0)	0.827
Occlusion length (mm)[b]	25 (15, 40)	30 (15, 50)	25 (15, 40)	0.162
Number of stents used	2.5 ± 1.2	2.8 ± 1.4	2.5 ± 1.2	0.084

[a] mean ± standard deviation; [b] median (interquartile range); RCA: right coronary artery; LAD: left anterior descending artery; LCX: left circumflex artery; ADR: antegrade dissection and re-entry J-CTO score: Japanese chronic total occlusion score; Progress CTO score: Progress chronic total occlusion score

Procedural outcomes are shown in **Table 5**. and **Figure 3**. Balloon uncrossable lesions were associated with significantly lower technical (90.5% vs. 98.3%, p<0.0001) and procedural (88.9% vs. 96.6%, p=0.004) success rates, but similar incidence of MACE (1.6% vs. 2.2 %, p=0.751). There was no difference between the two groups in the incidence of death, myocardial infarction, emergent PCI, stroke, and pericardiocentesis. In the balloon uncrossable group, one patient had an Ellis type III perforation due to lesion preparation (rotational atherectomy), which was treated with prolonged balloon inflation and a covered stent. Among patients without balloon uncrossable lesions, one patient had an Ellis type II perforation of the right coronary artery of an in-stent restenotic lesion due to the Crossboss catheter exiting through an angulated previously implanted stent; the perforation was successfully treated by a covered stent and pericardiocentesis. Another patient had an Ellis type III perforation of the left anterior descending coronary artery, treated with covered stent, pericardiocentesis and reversal of anticoagulation. Two patients died during CTO PCI due to perforation and tamponade; one death occurred due to multiple organ failure, all the three patients had balloon crossable lesions.

Figure 3. Technical, procedural success and incidence of major adverse cardiac events among study lesions classified according to whether they could be crossed with a balloon or not

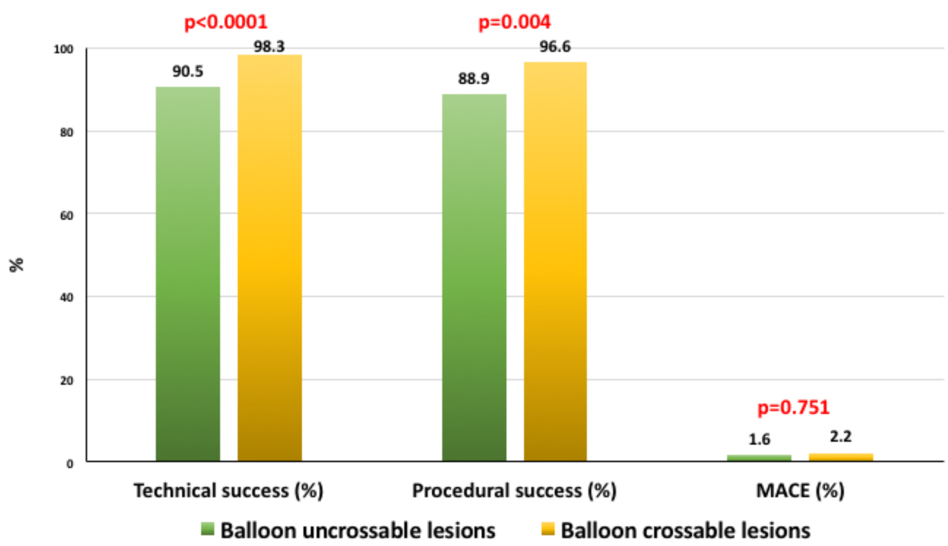


Table 5. Procedural outcomes of the study patients, classified according to whether they had a balloon uncrossable lesion or not.

Variable	Overall	Balloon uncrossable CTOs	Balloon crossable CTOs	P
Technical Success	97.6%	90.5%	98.3%	<0.0001
Procedural Success	95.9%	88.9%	96.6%	0.004
Procedural time (min)[b]	139 (96, 203)	208 (135, 258)	135 (94, 194)	<0.0001
Fluoroscopy time (min)[b]	48 (28, 79)	77 (52, 100)	45 (27, 75)	<0.0001
Air kerma radiation dose (Gray)[b]	3.37 (2.03, 5.00)	3.99 (2.73, 5.38)	3.30 (1.97, 4.78)	0.016
Contrast volume (ml) [b]	265 (200, 350)	275 (210, 350)	260 (200, 350)	0.731
MACE	2.1%	1.6%	2.2%	0.751
Death	0.4%	0%	0.5%	0.585
Acute MI	0.7%	1.6%	0.6%	0.388
Re-PCI	0.1%	0%	0.2%	0.753
Stroke	0.6%	0%	0.6%	0.529
Emergency CABG	0%	0%	0%	-
Pericardiocentesis	0.7%	1.6%	0.6%	0.388

[b] median (interquartile range); MACE: major adverse cardiac events; MI: myocardial infarction; CABG: coronary artery bypass grafting

Median procedure time, fluoroscopy time, air kerma radiation dose and contrast volume were 139 (96, 203) min, 48 (28, 79) min, 3.37 (2.03, 5.00) Gray and 265 (200, 350) ml, respectively. Balloon uncrossable lesions were associated with longer procedure (208 min [135, 258] vs. 135 min [94, 194] min, p<0.0001) and fluoroscopy (77 [52, 100] vs. 45 [27, 75] min, p<0.0001) time, and air kerma radiation dose (3.99 Gray [2.73, 5.38] vs. 3.30 [1.97, 4.78], p=0.016) but similar contrast volume.

Several techniques were used to treat balloon uncrossable lesions (**Table 6**, and **Figures 4, 5 and 6**), such as intentional rupture of a small balloon (called balloon assisted microdissection or grenadoplasty), use of various microcatheters, laser and rotational atherectomy and use of guide catheter extensions and guide anchoring techniques. The most commonly used techniques were grenadoplasty (23%), laser (18%) and rotational atherectomy (16%), followed by use of various microcatheters (**Table 6**, **Figure 4**). Laser atherectomy and grenadoplasty had the highest technical and procedural success rates. In the University of Szeged we applied rotational atherectomy in 2.9% of the CTO PCIs.

Figure 4. Techniques used to treat balloon uncrossable lesions.

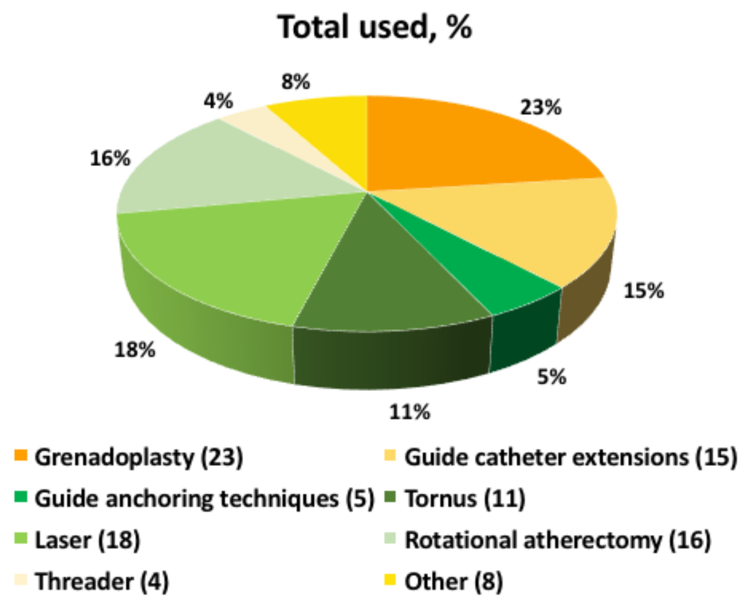


Figure 5. Outcomes of treating balloon uncrossable lesions according to equipment used.

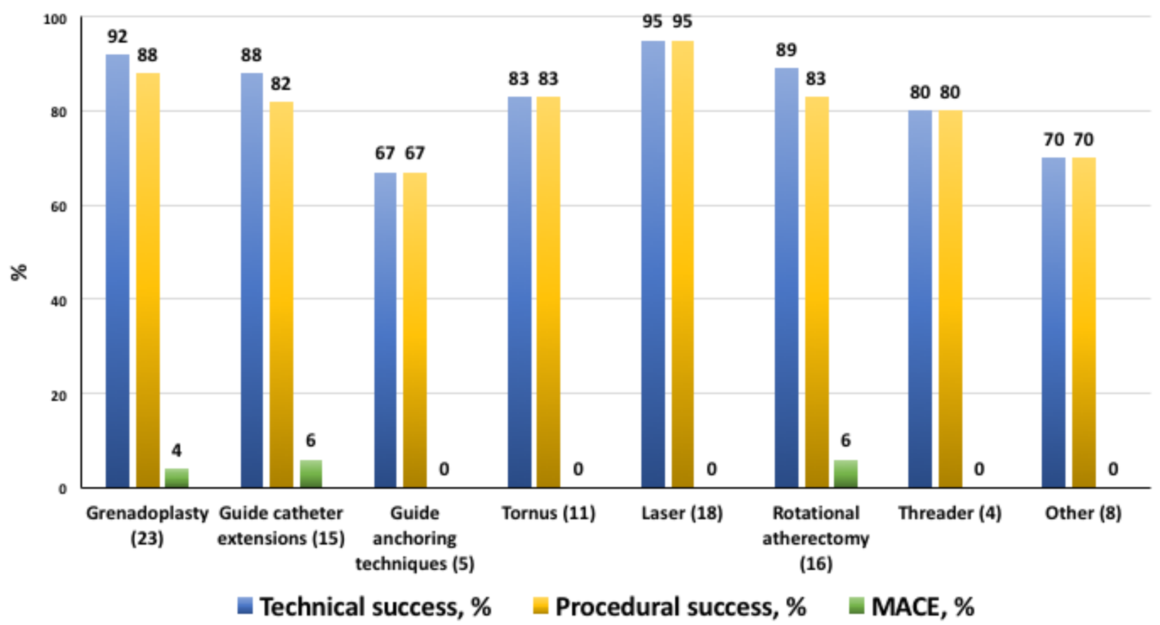
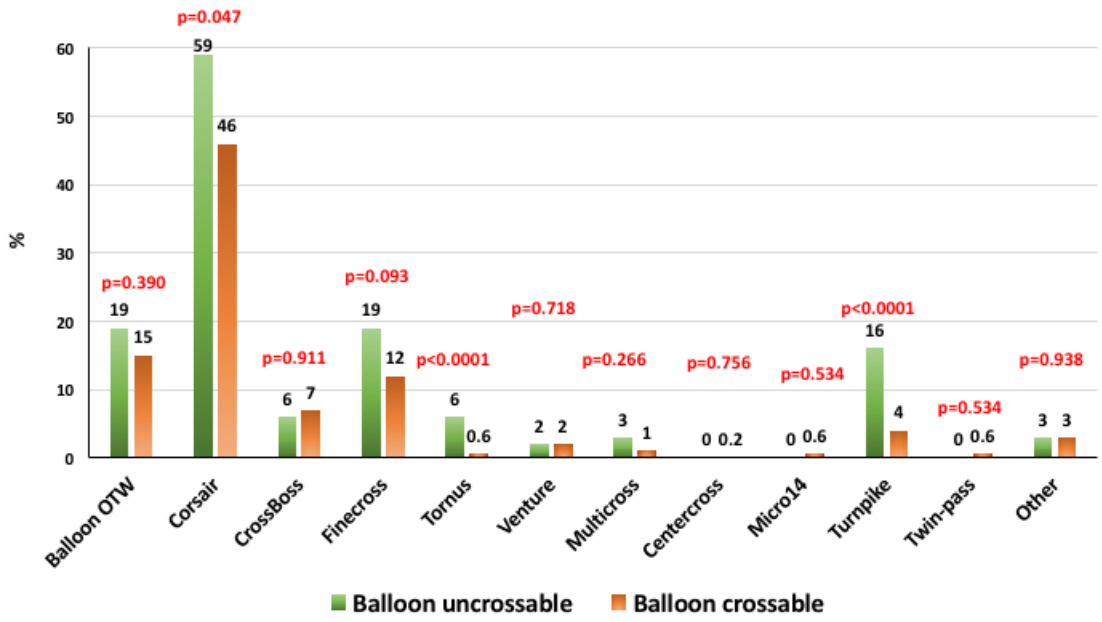


Table 6. Outcomes of the techniques used in balloon uncrossable lesions

Technique	Total used, %	Technical success, %	Procedural success, %	MACE%
Grenadoplasty (n)	23 (26)	92 (24)	88 (23)	4 (1)
Guide catheter extensions (n)	15 (17)	88 (15)	82 (14)	6 (1)
Guide anchoring techniques (n)	5 (6)	67 (4)	67 (4)	0
Tornus (n)	11 (12)	83 (10)	83 (10)	0
Laser (n)	18 (21)	95 (20)	95 (20)	0
Rotational atherectomy (n)	16 (18)	89 (16)	83 (15)	6 (1)
Threader (n)	4 (5)	80 (4)	80 (4)	0
Other (n)	8 (9)	70 (7)	70 (7)	0

MACE: major adverse cardiac events; Other techniques include use of the Threader, Crossboss, other microcatheters (Corsair and Finecross), and microcatheters combined with balloons.

Figure 6. Use of microcatheters among study lesions classified according to whether they could be crossed with a balloon or not



4.3 Intravascular imaging

In the third part of the analyses a total of 619 CTO PCI procedures performed in 606 patients were included. The baseline patient and angiographic characteristics of the study population are summarized in **Table 7**. Mean age was 65.4 ± 10 years and 85% of the patients were men with high prevalence of diabetes (50%), dyslipidemia (92%) and hypertension (88%). Approximately one third had congestive heart failure (33%) or prior CABG (32%).

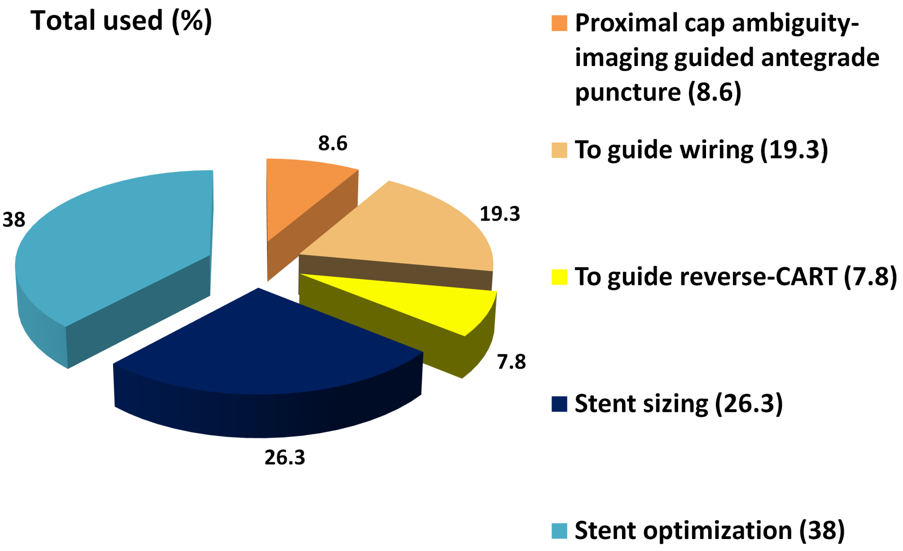
Intravascular imaging was used in 38% of the procedures, as follows: intravascular ultrasound (IVUS) in 36%, optical coherence tomography (OCT) in 3%, and both in 1.45%. The indications for intravascular imaging were to facilitate CTO crossing (overall 35.7%, antegrade in 27.9% and retrograde in 7.8%) and stent sizing (26.3%) or optimization (38.0%) (**Figure 7**). Wide variability was observed in the frequency of intravascular imaging use among various centers (0% to 58%).

Table 7. Baseline clinical characteristics of the study patients, classified according to whether intravascular imaging was used to guide CTO crossing or not.

Variable	Overall (n=606)	Imaging for crossing (n: 111)	No imaging or imaging for stent optimization (n: 495)	P value
Age (years) [a]	65.4 ± 10	65 ± 10	66 ± 10	0.466
Men	85%	91%	84%	0.066
BMI (kg/m^2) [a]	30.6 ± 6	31.7 ± 7	30.4 ± 6	0.058
Diabetes Mellitus	50%	58%	49%	0.069
Hypertension	88%	88%	88%	0.908
Dyslipidemia	92%	94%	92%	0.631
Smoking (current)	23%	77%	77%	0.908
LVEF (%) [a]	51 ± 15	48 ± 15	51 ± 15	0.056
Family History of CAD	24%	24%	24%	0.897
Congestive Heart Failure	33%	37%	32%	0.29
Prior Myocardial Infarction	45%	46%	44%	0.793
Prior CABG	32%	41%	30%	0.024
Prior CVD	11%	8%	12%	0.331
Prior PVD	15%	12%	15%	0.403
Baseline creatinine (mg/dL) [b]	1.0 (0.8,1.2)	1.0 (0.9; 1.3)	1.0 (0.8; 1.2)	0.615

[a] mean ± standard deviation,[b] median (interquartile range)
Imaging for crossing: cases in which intravascular imaging was used for crossing the chronic total occlusion; No imaging or imaging for stent optimization: cases in which intravascular imaging was not used or cases in which intravascular imaging was used for stent optimization; BMI: body mass index; LVEF: left ventricular ejection fraction; CAD: coronary artery disease; CABG: coronary artery bypass grafting; CVD: cerebrovascular disease; PVD: peripheral vascular disease.

Figure 7. Use of intravascular imaging during chronic total occlusion percutaneous coronary intervention (CART: controlled antegrade and retrograde tracking and dissection)



4.3.1 Intravascular imaging for crossing

The baseline clinical and angiographic characteristics of patients who did and those who did not undergo intravascular imaging for crossing were similar (**Table 7** and **8**). The most common CTO PCI target vessel was the right coronary artery (52%), followed by the left anterior descending artery (26%), and the left circumflex (22%). Moderate to severe calcification and moderate to severe tortuosity were present in 53% and 42%, respectively. Procedural outcomes are summarized in **Table 9**. Overall technical and procedural rates were 90.1% and 88.6%, respectively. Antegrade wiring was the successful crossing strategy in 48% of the cases, antegrade dissection and re-entry in 23% and the retrograde approach in 23%.

Table 8. Angiographic characteristics classified according to whether intravascular imaging was used to guide CTO crossing or not.

Variable	Overall (n=619)	Imaging for crossing (n: 111)	No imaging or imaging for stent optimiza-tion (n: 508)	P value
CTO Target Vessel				
RCA	52%	51%	52%	0.861
LAD	26%	28%	26%	
LCX	22%	21%	22%	
Successful Crossing Strategy				
Antegrade wiring	48%	23%	53%	<0.0001
Retrograde	23%	47%	17%	
ADR	23%	25%	23%	
None	6%	5%	7%	
First Crossing Strategy				
Antegrade wiring	78%	78%	78%	0.889
Retrograde	14%	15%	14%	
ADR	8%	6%	8%	
Retrograde crossing attempt	37%	67%	31%	<0.0001
J-CTO score [a]	2.51 ± 1.20	2.86 ± 1.19	2.43 ± 1.19	0.001
Progress CTO score [a]	1.37 ± 1.01	1.64 ± 1.00	1.18 ± 1.02	<0.0001
Calcification (moderate/severe)	53%	60%	51%	0.103
Tortuosity (moderate/severe)	42%	48%	40%	0.126
Proximal cap ambiguity	31%	49%	26%	<0.0001
In-stent restenosis	17%	20%	16%	0.334
Prior failure to open CTO	16%	21%	15%	0.147
Interventional Collaterals	53%	52%	53%	0.794
Side branch at the proximal cap	50%	61%	47%	0.009
Vessel diameter (mm) [b]	2.6 (2.5, 3.0)	2.5 (2.5; 3.0)	2.7 (2.5; 3.0)	0.684
Occlusion length (mm) [b]	30 (19, 45)	30 (22; 50)	30 (18; 40)	0.093
Number of stents used [a]	2.53 ± 1.2	2.78 ± 1.4	2.48 ± 1.19	0.047

[a] mean ± standard deviation; [b] median (interquartile range); Imaging for crossing: cases in which intravascular imaging was used for crossing the chronic total occlusion; No imaging or imaging for stent optimization: cases in which intravascular imaging was not used or cases in which intravascular imaging was used for stent optimization; ADR: antegrade dissection and re-entry.

Intravascular imaging for crossing was used more commonly in lesions with proximal cap ambiguity (49% vs. 26%, p<0.0001), side branch at the proximal cap (61% vs. 47%, p=0.035), and longer occlusion length (30 mm [interquartile range: 22, 50] vs. 28 mm [15, 44], p=0.009) and higher J-CTO (2.86 ± 1.19 vs. 2.43 ± 1.19, p =0.001) and Progress CTO (1.64 ± 1.00 vs. 1.18 ± 1.02, p<0.0001) score. Cases in which intravascular imaging was used for crossing were more likely to succeed using the retrograde approach or antegrade dissection and reentry (47% vs. 17% and 25% vs. 23%), as compared with antegrade wiring (23% vs. 53%, p<0.0001).

Procedural outcomes are summarized in **Table 9** and **Figure 8**. Technical and procedural success were similar in cases in which intravascular imaging was used for crossing (92.8% vs. 89.6%, p=0.302 and 90.1% vs. 88.3%, p=0.588, respectively), whereas the incidence of major adverse events was similarly low in both groups (2.7% vs. 3.2%, p=0.772). Success and complication rates were similar among centers with high vs. low intravascular imaging use (data not shown). There was no significant difference in the incidence of death, myocardial infarction, repeated PCI, stroke, and pericardiocentesis. Mean procedure duration was significantly longer among procedures in which intravascular imaging was used for crossing (192 min [130, 255] vs. 131 min [90, 192], p<0.0001) as was median fluoroscopy time (71 min [44, 93] vs. 39 min [25, 69], p<0.0001), mean air kerma radiation dose (4.98 Gray [3.11, 6.04] vs. 3.42 Gray [2.09, 5.09], p<0.0001), and median contrast volume (310 ml [240, 400] vs. 270 ml [200, 360], p=0.004) as compared with cases in which intravascular imaging was not used.

Figure 8. Technical, procedural success and MACE among study procedures classified according to use of intravascular imaging for crossing

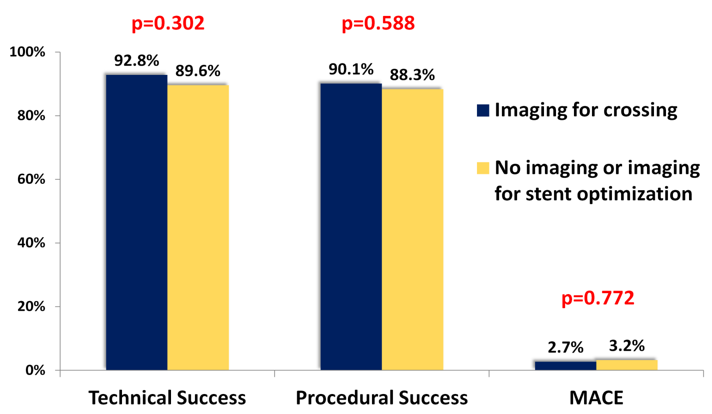


Table 9. Procedural outcomes of the study patients, classified according to whether intravascular imaging was used to guide CTO crossing or not.

Variable	Overall	Imaging for crossing	No imaging or imaging for stent optimization	P value
Technical Success	90.1%	92.8%	89.6%	0.302
Procedural Success	88.6%	90.1%	88.3%	0.588
Procedural time (min) [b]	142 (96, 210)	192 (130; 255)	131 (90; 192)	<0.0001
Fluoroscopy time (min) [b]	45 (27, 75)	71 (44; 93)	39 (25, 69)	<0.0001
Air kerma radiation dose (Gray) [b]	3.59 (2.27, 5.40)	4.98 (3.11; 6.04)	3.42 (2.09; 5.09)	<0.0001
Contrast volume [b]	280 (205, 367)	310 (240; 400)	270 (200; 360)	0.004
MACE	3.1%	2.7%	3.2%	0.772
Death	0.5%	0.0%	0.6%	0.411
Acute Q wave MI	0%	0%	0.0%	-
Acute MI	1.3%	1.8%	1.2%	0.623
Re-PCI	0.3%	0.0%	0.4%	0.502
Stroke	0.4%	0.0%	0.6%	0.411
Emergency CABG	0%	0%	0.0%	-
Pericardiocentesis	0.9%	0.9%	1.0%	0.916

[b] median (interquartile range); Imaging for crossing: cases in which intravascular imaging was used for crossing the chronic total occlusion; No imaging or imaging for stent optimization: cases in which intravascular imaging was not used or cases in which intravascular imaging was used for stent optimization; MACE: major adverse cardiac events; MI: myocardial infarction; CABG: coronary artery bypass grafting

4.3.2 Intravascular imaging for stent sizing and/or optimization

Among CTOs successfully crossed with a guidewire, cases in which imaging was used for stent sizing and optimization were more complex and had higher J-CTO (2.65 ± 1.17 vs. 2.38 ± 1.22, p=0.013) and Progress CTO (1.39 ± 1.09 vs. 1.19 ± 0.98, p= 0.035) scores (**Table 10 and 11**). Cases in which advanced imaging was used were more likely to have moderate/severe calcification (63% vs. 47%, p= 0.001), longer occlusion length (30 mm [20; 50] vs. 28 mm [15; 40], p= 0.030) and be due to in-stent restenosis (23% vs. 14%, p= 0.015) and required longer procedure (162 min [113; 216] vs. 133 min [91; 201], p=0.001) and fluoroscopy (52 min [33; 81] vs. 40 min [26; 73], p=0.014) time with a trend for higher air kerma radiation dose (3.90 Gray [2.48; 5.46] vs. 3.48 Gray [2.13; 5.34], p=0.249) and contrast volume (300 ml [228; 368] vs. 277 ml [200; 370], p=0.106). Use of intravascular imaging was associated with similar technical (97.7% vs. 97.5%, p= 0.854) and procedural (97.1% vs. 95.4%, p= 0.347) success rates and similarly low MACE rates (2.3% vs. 3.1%, p= 0.622) (**Figure 9**). There was a trend toward larger number of stents in procedures where intravascular imaging was used for stent sizing/and/or optimization (2.7 ± 1.3 vs. 2.5± 1.2, p=0.07).

Figure 9. Technical, procedural success and major cardiac adverse events (MACE) according to purpose of intravascular imaging (IMG) techniques

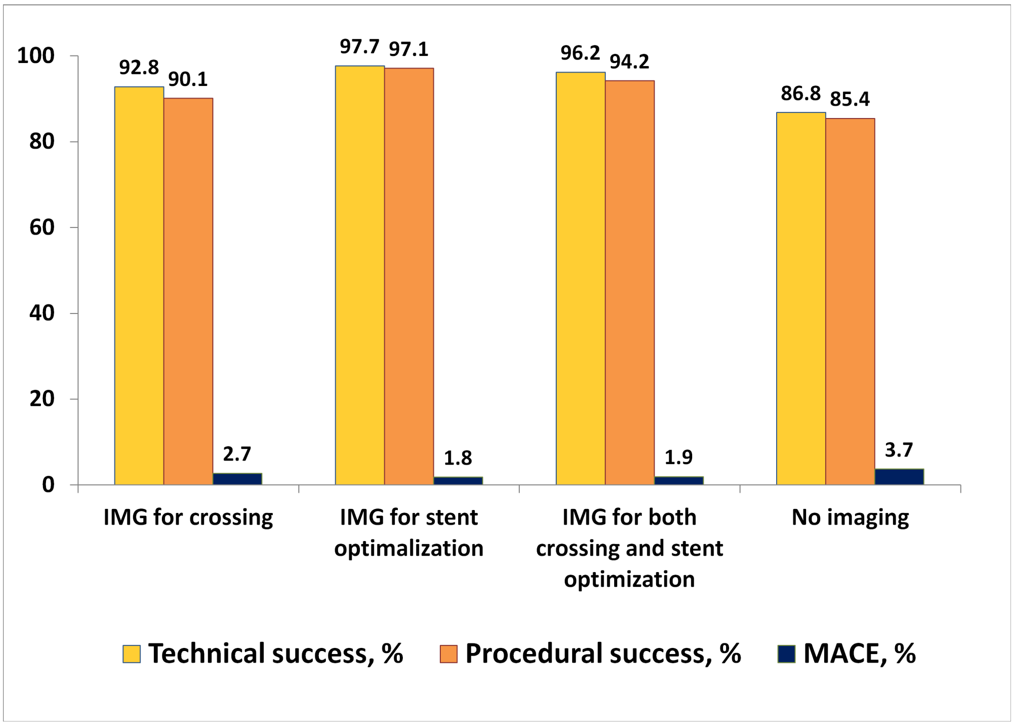


Table 10. Angiographic characteristics classified according to whether intravascular imaging technique was used for stent optimization or not.

Variable	Overall (n=568)	Imaging for stent optimization (n=175)	No imaging or imaging for crossing only (n=393)	P value
CTO Target Vessel				0.137
RCA	51%	49%	52%	
LAD	27%	32%	25%	
LCX	22%	19%	23%	
Successful Crossing Strategy				0.001
Antegrade wiring	51%	42%	55%	
Retrograde	24%	27%	23%	
ADR	25%	31%	22%	
First Crossing Strategy				0.321
Antegrade wiring	78%	77%	79%	
Retrograde	14%	13%	14%	
ADR	8%	10%	7%	
Retrograde crossing attempt	36%	45%	32%	0.003
J-CTO score [a]	2.47 ± 1.21	2.65 ± 1.17	2.38 ± 1.22	0.013
Progress CTO score [a]	1.25 ± 1.02	1.39 ± 1.09	1.19 ± 0.98	0.035
Calcification (moderate/severe)	52%	63%	47%	0.001
Tortuosity (moderate/severe)	41%	42%	40%	0.742
Proximal cap ambiguity	30%	34%	28%	0.155
In-stent restenosis	17%	23%	14%	0.015
Prior failure to open CTO	16%	18%	15%	0.429
Interventional Collaterals	53%	52%	54%	0.648
Side branch at the proximal cap	49%	50%	48%	0.753
Blunt/no stump, %	55%	50%	57%	0.123
Vessel diameter (mm) [b]	2.5 (2.5, 3.0)	2.8 (2.5; 3)	2.5 (2.5; 3)	0.257
Occlusion length (mm) [b]	30 (18, 45)	30 (20; 50)	28 (15; 40)	0.03
Number of stents used	2.5 ± 1.2	2.7 ± 1.3	2.5 ± 1.2	0.076

[a] mean ± standard deviation,[b] median (interquartile range) Imaging for stent optimization: cases in which intravascular imaging was used for stent optimization; No imaging or imaging for crossing only: cases in which intravascular imaging was not used or cases in which intravascular imaging was used only for crossing the chronic total occlusion; ADR: antegrade dissection and re-entry; J-CTO score: Japanese chronic total occlusion score; P-CTO score: Progress chronic total occlusion score, MACE: major adverse cardiac events; MI: myocardial infarction; CABG: coronary artery bypass grafting

Table 11. Angiographic characteristics classified according to whether intravascular imaging technique was used for stent optimization or not

Variable	Overall	Imaging for stent optimization	No imaging or imaging for crossing only	P value
Technical Success	97.5%	97.7%	97.5%	0.854
Procedural Success	95.9%	97.1%	95.4%	0.347
Procedural time (min) [b]	143 (97, 205)	162 (113; 216)	133 (91; 201)	0.001
Fluoroscopy time (min) [b]	44 (27, 75)	52 (33; 81)	40 (26, 73)	0.014
Air kerma radiation dose	3.60 (2.24, 5.37)	3.90 (2.48; 5.46)	3.48 (2.13; 5.34)	0.249
Contrast volume [b]	282 (205, 369)	300 (228; 368)	277 (200; 370)	0.106
MACE	2.9%	2.3%	3.1%	0.622
Death	0.4%	0.0%	0.5%	0.347
Acute Q wave MI	0%	0%	0.0%	
Acute MI	1.3%	0.6%	1.6%	0.346
Re-PCI	0.4%	0.0%	0.5%	0.347
Stroke	0.7%	0.6%	0.8%	0.808
Emergency CABG	0%	0%	0.0%	
Pericardiocentesis	0.7%	1.2%	0.5%	0.398

[b] median (interquartile range) Imaging for stent optimization: cases in which intravascular imaging was used for stent optimization; No imaging or imaging for crossing only: cases in which intravascular imaging was not used or cases in which intravascular imaging was used only for crossing the chronic total occlusion; MACE: major adverse cardiac events; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft

5. DISCUSSION

5.1 Effect of prior failure

In the first section of our study the main finding is that a prior failed CTO PCI attempt is associated with higher angiographic complexity, longer procedural duration and fluoroscopy time, but not with the lower success and higher complication rates of subsequent CTO PCI attempts.

Few studies have examined the impact of prior failed CTO PCI attempt on subsequent procedural outcomes. Morino et al. created a five point scoring system combining five baseline clinical and angiographic parameters to assess the difficulty of CTO crossing,(25) that was assessed in four subsequent studies (9,25,45,56). These five parameters are blunt stump, presence of calcification, within the lesion bending>45°, occlusion length ≥ 20 mm, and prior attempt at CTO PCI. One point was given for each of the parameters, which were associated with lower probability of successful guidewire crossing within 30 minutes. Nombela-Franco et al. validated the J-CTO score in an independent contemporary cohort, and found that all J-CTO score variables except prior failed attempt had significant univariate association with successful guidewire crossing within 30 minutes (57). Our findings also support a limited role of prior failure in predicting subsequent CTO PCI success. Indeed, prior failure was not included in the recently developed Progress-CTO risk score that is associated with technical success and includes four variables (proximal cap ambiguity, presence of interventional collaterals, moderate/severe tortuosity, and circumflex target vessel) (58).

There are multiple potential explanations for the lack of impact of prior failure on CTO PCI outcomes. First, initial failure could be related to limited experience and expertise or lack of equipment at the treating center. Second, it could have been due to a complication. Third, at times a failure can predispose to subsequent success by allowing recanalization of the occlusion after angioplasty of a subintimal dissection plane (investment procedure) (59). The higher incidence of MI in prior failed cases may be related to more frequent use of the retrograde approach in these patients.

5.2 Balloon uncrossable lesions

In the second section of our study examining the balloon uncrossable CTOs the main findings are that (a) balloon uncrossable lesions are common in CTO PCI, being encountered in approximately 9% of occlusions that are successfully crossed with a guidewire; (b) often require use of multiple treatment modalities; and (c) are associated with lower technical and procedural success rates.

The prevalence of balloon uncrossable CTOs has received limited study. Patel et al. reported 24 balloon uncrossable CTOs among 373 consecutive CTO PCIs (6.4%, 95% confidence intervals 4.2% to 9.4%) in a single center study (26). Kovacic et al. demonstrated that a Guideliner guide catheter extension was used in 28 balloon uncrossable CTO PCIs among 372 procedures (7.5%) and was successful in delivering a small balloon in 85.7% (29). Fernandez et al. reported that excimer laser coronary atherectomy (ELCA) was used in 58 of 6,882 consecutive PCIs (0.84%) performed at a single center over a four-year period. Of those 58 cases 36 were due to failure of the balloon to cross the lesion, of which 16 were in CTOs (0.23% of all PCIs). Procedural success with ELCA was 87.5% (60). Pagnotta et al. reported failure to cross a CTO with a balloon in 7% of all CTOs that are successfully crossed with guidewire; rotational atherectomy was successful in 95.5% of these cases (61). The prevalence of balloon uncrossable CTOs was higher in our study (9%), likely because it systematically collected this information rather than relying on chart review.

As anticipated, balloon uncrossable lesions were more likely to have complex angiographic characteristics, such as severe calcification and tortuosity (62), that can hinder advancement of equipment through the occlusion. Moreover, failure to cross with a balloon tended to be more common when crossing was achieved using antegrade wire escalation. This is not surprising given that the subintimal space provides less resistance as compared with intimal planes, and highlights a potential advantage of dissection/re-entry strategies in those lesions. Indeed dissection and re-entry has been used as an advanced technique for treating balloon uncrossable lesions when other attempts failed (63-65). An increased frequency of balloon uncrossable lesions may be a potential downside of the higher antegrade wiring escalation crossing success that can be achieved with the recently introduced highly torquable composite core guidewires (66). In our analysis prevalence of tortuous lesions were significantly higher among balloon uncrossable lesions. Pre-procedural CTA with modern high-resolution scanners may provide incremental information about the occlusion, which might enhance procedural planning and outcomes (67).

Several techniques are currently available to treat balloon uncrossable lesions, both simple and more advanced. Those techniques can be categorized into those that modify the lesion and those that increase guide catheter support (39). Simpler techniques are attempted first, such as using a new, small (1.2 to 1.5 mm) balloon that can sometimes be ruptured intentionally to modify the plaque [balloon assisted microdissection or grenadoplasty] (26). Alternatively, the Threader (Boston Scientific), the Glider (TriReme Medical) and various microcatheters can be used, such as the Tornus (Asahi Intecc), Turnpike Spiral and Gold (Vascular Solutions), Corsair and Caravel (Asahi Intecc), and Micro 14 (Roxwood Medical). The Tornus catheter (Asahi Intecc) is rotated in a counterclockwise direction to advance and in a clockwise direction for withdrawal (27,28), paying attention to avoid over-rotation that could result in catheter deformation and possibly entrapment. Another advanced lesion modification technique is the "see-saw balloon-wire cutting technique": the lesion is crossed by two guidewires over which two short and low profile balloons are alternatively advanced and inflated at high pressure producing a cutting effect to crush the proximal fibrous cap in multiple positions. This technique was successful in 17 of 21 patients (81%) in one series (68). A dedicated new device utilizing a similar concept is the BLIMP Scoring Balloon Catheter (IMDS) providing: (a) ultralow balloon crossing profile, (b) high burst pressure (c) combined with scoring properties of the guidewire back-loaded from the tip.

Enhanced support can be achieved by using guide catheter extensions (29) or anchoring techniques. Those techniques can be used simultaneously with a lesion modifying technique (69), further enhancing the likelihood for success.

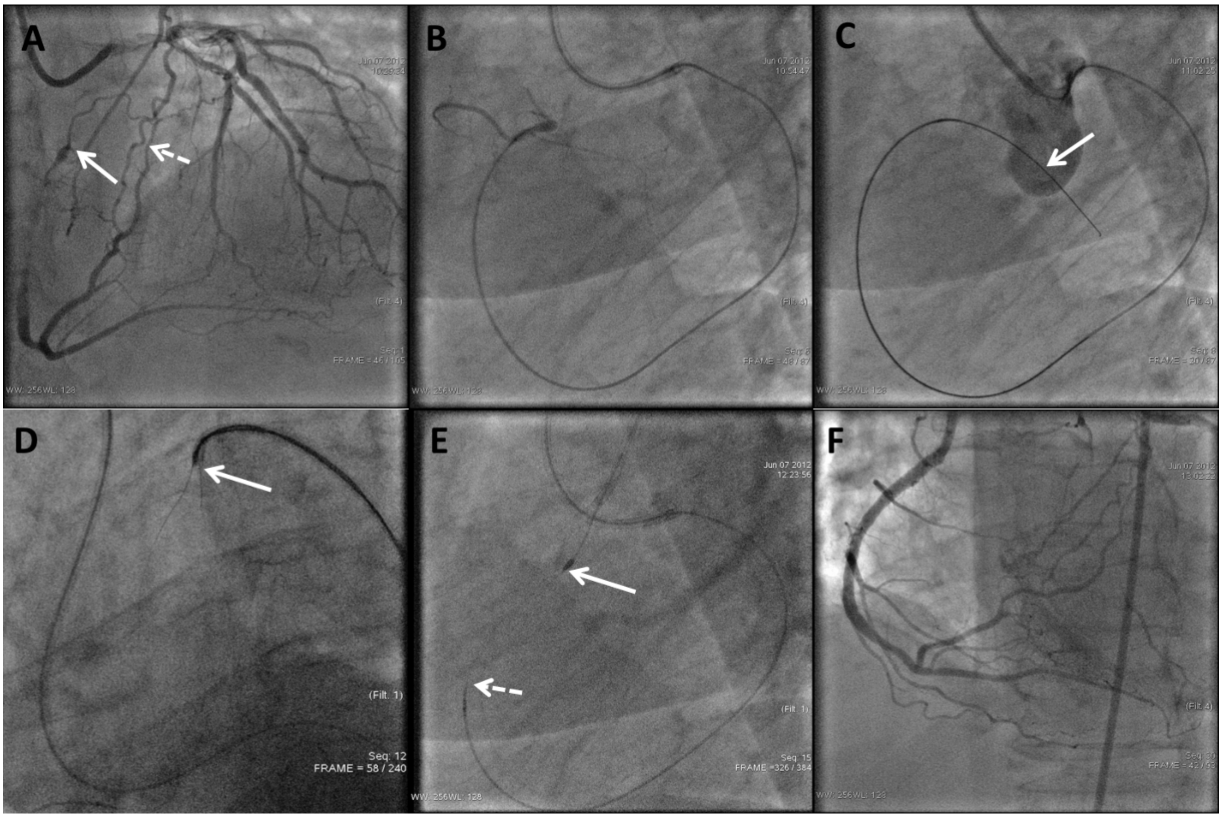
More advanced treatment strategies for balloon uncrossable lesions include laser and rotational atherectomy, that were among the most successful techniques in our analysis. Laser is particularly well suited for treating such lesions as it can be used over any standard 0.014 inch guidewire, but has limited availability. Laser is proven to reach high success rates in balloon resistant coronary lesions in the LEONARDO (early outcome of high energy Laser (Excimer) facilitated coronary angioplasty ON hARD and complex calcified and ballOn-resistant coronary lesions) study (70). In LEONARDO 80 patients with 100 lesions were treated with laser for various indications, such as calcification, balloon failure, and CTO). The laser was successful in 93.7% of the lesions and 93.7% in cases with balloon failure (70). Sapontis et al. reported use of excimer laser atherectomy to successfully treat a balloon resistant lesion, impenetrable proximal fibrous cap, in-stent restenosis and difficult device tracking within the subintimal space (71). Rotational atherectomy is highly effective for facilitating lesion crossing, but requires exchange of the guidewire for a specialized guidewire, possibly resulting in failure to re-cross the lesion. The use of rational atherectomy is demonstrated in two cases in **Figure 10. and 11.** In the first case rotational atherectomy was used successfully for the antegrade recanalization of a balloon uncrossable chronic total occlusion. While in the second case a retrograde wired ostial chronic total occlusion was successfully passed antegrade by using a rotational atherectomy device. Both cases resulted in successful recanalization without any procedural complications, demonstrating the usefulness of rotational atherectomy as an important tool in percutaneous intervention of calcified chronic total occlusions with high success and low complication rates. However, the disadvantage of rotational atherectomy compared to the laser is the compulsory use of the dedicated rotawire. Based on our own experience this limitation can be solved by a microcatheter pushed to the proximal cap and switching the CTO crossing wire to dedicated rotawire.

If all else fails, subintimal strategies can be used for balloon uncrossable lesions, by advancing a knuckled guidewire or a CrossBoss catheter through the subintimal space across the occlusion, followed by: (a) modification of the lesion by subintimal balloon inflation (64); (b) distal anchoring by inflating a balloon distal to the occlusion (63) that facilitates intimal balloon crossing; or (c) by re-entry into the distal true lumen followed by stenting of the subintimal space (72).

Given the high prevalence and significant impact of balloon uncrossable lesions in reducing procedural success, having a clear understanding and local availability of equipment and techniques to treat balloon uncrossable lesions is critical.

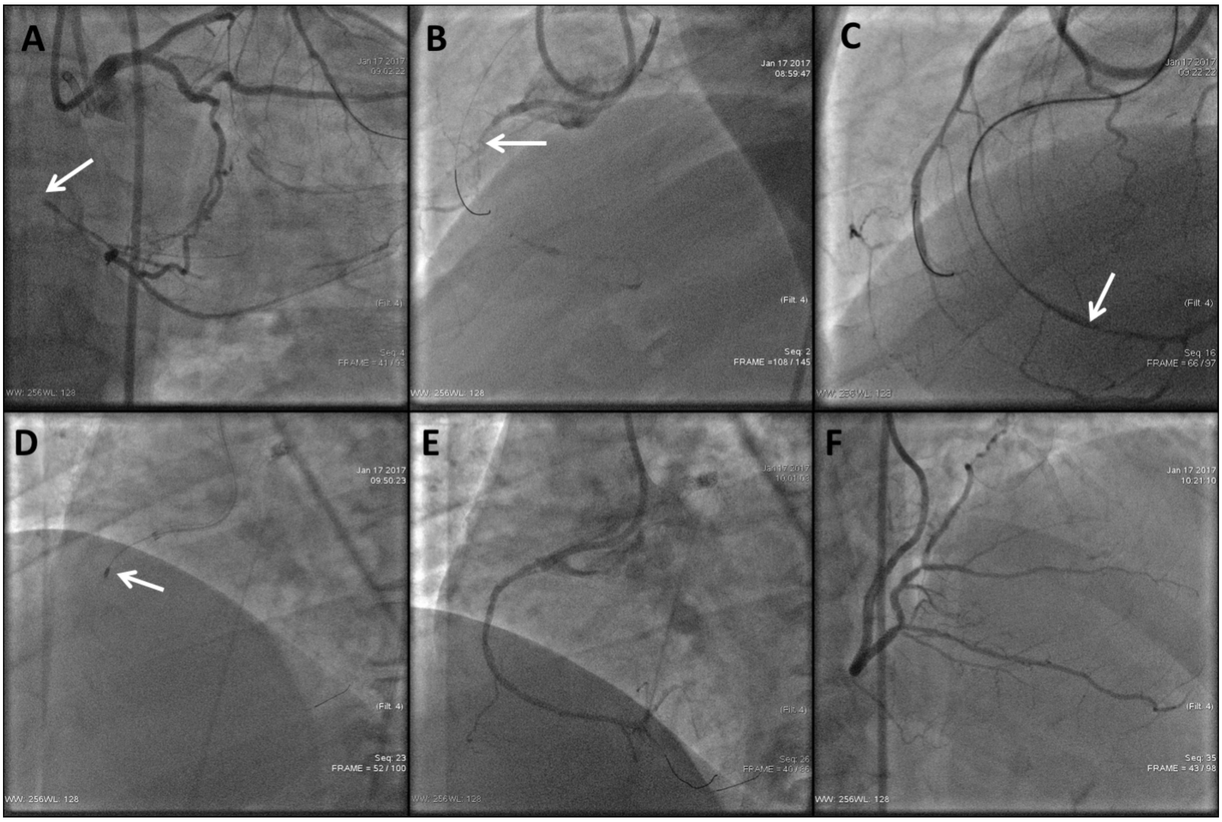
In our analysis pericardiocentesis due to perforation occurred similarly in the balloon uncrossable group and the balloon crossable lesions (1.6% vs. 0.6%, p=0.388). In the study of Kovacic et al. in which the Guideliner (Vascular Solutions) was used, distal guidewire perforation occurred in only one of 28 CTO PCIs, with no pericardial effusion (29). The complication rates of rotational atherectomy and the Tornus catheter were similar in the study by Pagnotta et al. (73) and by Fang et al. (6% Tornus vs. 5% rotational atherectomy) (74). In the Amsterdam-Rotterdam (AMRO) trial there was no difference in major complications between laser and balloon angioplasty (75). No complications were reported in the LEONARDO study of laser atherectomy (70). However, additional studies are needed to assess the complication rates of the various techniques that can be used to treat balloon uncrossable lesions.

Figure 10. Ostial right coronary artery CTO PCI with successful retrograde crossing and plaque modification with rotational atherectomy.



Panel A: Retrograde contrast injection demonstrating aorto-ostial RCA CTO (white arrow). The broken line points to the epicardial collateral from the left circumflex. Panel B: Contrast injection from the microcatheter proves the successful collateral crossing through the epicardial collateral. Panel C: Crossing the lesion with a Confianza Pro 12 guidewire (white arrow). Panel D: Switched to Whisper LS and snaring the guidewire with an AndreSnare (white arrow). Panel E: Switching the guidewire with a microcatheter to a Rotawire ES 330 mm, successful antegrade rotational atherectomy with a 1.5 mm RotaLink Exchangable Burr (white arrow). Panel F: Final result after stent implantation

Figure 11. Right coronary artery antegrade CTO PCI with rotational atherectomy.



Panel A: Retrograde contrast injection demonstrating the distal cap of the CTO (white arrow). Panel B: Same projection, antegrade contrast injection. Panel C: Gaia 2nd guidewire (white arrow) crossed to the distal true lumen. Panel D: Successful rotational atherectomy with a 1,5 mm-es RotaLink Exchangable Burr (white arrow) after switching the guidewire to RotaWire Floppy. Panel E: Control angiography after rotational atherectomy and further lesion preparation with balloon dilations. Panel F: Final result after stent implantation.

5.3 Intravascular imaging in CTO PCI

The main findings of the third section of our study are that intravascular imaging is frequently performed during CTO PCI both for crossing and for stent selection/optimization. Intravascular imaging was used in more complex occlusions and was associated with similarly high success rates, but longer procedure time and higher radiation dose.

5.3.1 Frequency of intravascular imaging use in CTO PCI

In our study intravascular imaging was used in 38% of CTO PCI cases, which is similar to 39% utilization in the Multicenter Korean CTO Registry (30). Okamura et al. reported use of IVUS in 47.5% of patients in their study about complications during retrograde approach in the Japanese Multicenter CTO Registry IVUS (76). In contrast, in the European Registry of Chronic Total Occlusion, IVUS use was significantly lower (2.9% overall (77) and 9.2% in retrograde cases (78), suggesting that imaging use may be low even among experienced operators and centers. Habara et al (79) compared CTO PCI outcomes according to operator experience: when using the antegrade approach after retrograde failure, the success rate of IVUS –guided techniques was significantly higher in higher volume centers than lower volume centers (13.3% vs. 3.3%; p=0.018). Therefore, IVUS guidance for antegrade crossing require high operator skill and experience (80). Moreover, the cost of catheters and the additional time required for obtaining and interpreting the images is also likely affecting the use intravascular imaging and may explain the wide variability in its use for CTO (and non-CTO) PCI.

5.3.2 Selection of intravascular imaging modality for CTO PCI

IVUS was the intravascular imaging modality used in most CTO PCIs, as in contrast to OCT, does not require flushing of the blood column within the arterial lumen and has higher penetration depth. OCT performed before stenting could also cause subintimal hematoma due to the need for guide flushing. OCT however offers superior resolution compared to IVUS and has been used in CTO PCI to determine guidewire position and stent optimization after deployment. The ALSTER OCT-CTO (AskLepios ST. GEoRg's Hospital-Optical Coherence Tomography for follow-up of Chronic Total Occlusions) registry reported significantly higher rate of uncovered and malapposed stent struts in CTOs as compared to non-occlusive lesions (81). These findings may favor prolonged administration of dual antiplatelet therapy, in an attempt to reduce the risk for stent thrombosis (82).

Solid-state, phased array catheters (Eagle-Eye, Volcano) are preferred over rotational IVUS systems, because the imaging transducer is closer to the tip of the IVUS catheter. A short-tip solid-state IVUS catheter (Eagle Eye Short Tip, Volcano) is advantageous for imaging in CTO PCI, as it minimizes the extent of distal advancement required for distal imaging and may be more deliverable (39).

5.3.3 Imaging for CTO crossing

Intravascular imaging can assist CTO crossing by: (a) identifying the proximal cap in cases with proximal cap ambiguity, for example by imaging through a side branch adjacent to the occlusion (33); (b) confirming whether the antegrade guidewire has engaged the occlusion and navigating the antegrade guidewire to the true lumen in case of dissection (83) (34); (c) confirming that the retrograde guidewire has entered the proximal true lumen before externalization; and (d) determining the appropriate balloon size for the CART and reverse CART techniques (39,40). Moreover, use of IVUS could assist re-entry into the distal true lumen after subintimal crossing (83) and reduce the need for fluoroscopy and contrast injection (34). In our study 3 characteristics of CTOs were associated with IVUS utilization during crossing: side branch at proximal cap (61% vs. 47%, $p=0.009$), proximal cap ambiguity (49% vs. 26%, $p<0.001$) and blunt/no stump (68% vs. 55%, 0.009).

Park et al reported that IVUS-guided wiring technique was useful and safe for antegrade recanalization of 31 stumpless CTOs. The IVUS catheter was advanced into the side branch to identify the CTO entry point, while another stiffer guidewire was directed under IVUS guidance to the occlusion entry point and penetrated the proximal cap. In case of subintimal position of the guidewire IVUS was also used to redirect the wire into the true lumen. However this technique has two potential limitations: firstly, IVUS cannot provide information on the course of the vessel distal to the occlusion (dual injection can be used to visualize the entire course of the vessel distal to the occlusion); secondly, IVUS-guided wiring cannot be applied in cases without appropriate side branches (for example with smaller vessel diameter than the IVUS catheters) (33).

IVUS may be particularly useful for the retrograde approach to CTO crossing, as retrograde cases are often more complex than antegrade-only cases due to difficulties crossing the collateral and/or crossing the occlusion and externalizing the guidewire. Indeed, IVUS was used in 67% of retrograde vs. 31% of antegrade-only cases in our study ($p<0.0001$). IVUS can clarify the location of guidewires and guide balloon size selection when performing reverse CART. Dai et al. showed that IVUS-guided reverse CART approach is efficient and safe for revascularization of complex CTOs. They overlapped an antegrade and a retrograde guidewire within the occlusion and inflated a small balloon (1.2–1.5 mm) to create an antegrade subintimal or intimal dissection. The IVUS catheter was then advanced into the dissection plane to guide crossing of the occlusion (40).

5.3.4 Imaging for stent optimization

Intravascular imaging can assist with optimizing stent diameter and length selection, and further ensure that optimal expansion has occurred (39). Two randomized-controlled trials have compared IVUS-guidance vs. angiographic guidance for stent optimization after CTO PCI. Kim et al randomized 402 patients to IVUS-guidance vs. angiographic guidance and found that IVUS guidance reduced the subsequent incidence of MACE (32). Similarly, Tian et al. in the AIR-CTO (Angiographic and clinical comparisons of intravascular ultrasound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions) study randomized 230 patients to IVUS or angiographic guidance and found that IVUS-guidance was associated with lower in-stent late lumen loss at one-year angiographic and IVUS follow-up, leading to less frequent restenosis and lower rates of stent thrombosis (31). These findings are in agreement with the findings of the IVUS-XPL (The Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) study that randomized 1400 patients to undergo IVUS-guided or angiography-guided everolimus-eluting stent implantation in non-CTO long lesions and resulted in a significantly lower rate of 12-month MACE, primarily driven by lower risk for target lesion revascularization (84). Use of intravascular imaging (either IVUS or OCT) can help identify and treat stent underexpansion that is an important risk factor for both restenosis (35) and stent thrombosis. Use of intravascular imaging may be of particular importance in long and calcified CTOs. In our study we observed a trend toward higher number of stents in procedures guided by IVUS. This could be related to higher lesion complexity among imaged lesions, but could also indicate increased detection of dissection flaps, gaps between stents, or untreated residual coronary disease that might have not been apparent during diagnostic angiography.

5.3.5 Intravascular imaging and contrast use

Mariani et al in the MOZART (Minimizing cOntrast utilization With IVUS Guidance in CoRonary angioplasTy) trial found that IVUS as a primary imaging tool to guide PCI was safe and markedly reduced the volume of iodine contrast as compared with angiography-guided PCI (85). Dai et al suggested that IVUS guided reverse controlled antegrade and retrograde tracking technique could reduce the contrast volume (40). However, in our study contrast volume was higher among cases in which intravascular imaging was used for crossing, likely reflecting the higher complexity of such cases.

5.4 Study limitations

Our study has potential limitations. First, PROGRESS CTO is an observational registry without adjudication of clinical events by an independent events committee. Second, quantitative coronary angiographic analysis was not performed and therefore assessment of angiographic characteristics was susceptible to operator-related bias. Third, the experience of the operator who performed the initial failed procedure is not known. Forth, procedures were performed by centers with significant expertise in CTO PCI, hence, our findings may not be generalizable to less experienced centers and operators. Fifth, the time interval between the prior failed attempt and the subsequent CTO PCI and the reason for failure was not collected. Sixth, use of intravascular imaging was performed at the discretion of the operator, with high variability between centers.

6. CONCLUSIONS

1. Prior failed CTO PCI attempt is associated with higher angiographic complexity, longer procedural duration and fluoroscopy time, but not with the lower success and higher complication rates of subsequent CTO PCI attempts.

2. Balloon uncrossable lesions: (a) are commonly encountered during CTO PCI, especially in more complex occlusions; (b) often require advanced treatment strategies; and (c) are associated with lower technical success rate, emphasizing the importance of advanced training in order to develop expertise in treating these challenging lesions.

3. Intravascular imaging is frequently performed during CTO PCI both for crossing and for stent selection/optimization. Even though intravascular imaging was used in more complex lesions, it was associated with similar rates of technical and procedural success, but higher use of radiation and longer procedure time.

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