Differences in patients and lesion and procedure characteristics depending on the age of the coronary chronic total occlusion

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Abstract

Introduction: Whether duration of chronic total occlusion (CTO) affects lesion and procedural characteristics remains largely unknown.

Aim: To investigate whether CTO duration influences lesion characteristics and revascularization success.

Material and methods: EuroCTO Registry data on patients who had CTO percutaneous coronary intervention between January 2015 and April 2017 were analyzed. Three groups were created based on occlusion age: 3 to 6 months (n = 1415), 7 to 12 months (n = 973), > 12 months (n = 1656).

Results: Patients with greater CTO duration were older (63.0 (56.0–70.0); 63.0 (56.0–71.0); 66.0 (59.0–73.0) years respectively; $p < 0.001$), had more 3-vessel disease (32.2%; 30.9%; 46.1% respectively; $p < 0.001$) and more frequent prior coronary artery bypass grafting (8.2%; 9.9%; 29.4% respectively; $p < 0.001$). In multivariate analysis, occlusion duration was associated with moderate/severe calcification (OR = 1.52; 95% CI: 1.28–1.80; $p < 0.001$), lesion length > 20 mm (OR 1.77; 95% CI 1.49–2.10; $p < 0.001$), and collateral circulation Werner type 2 (OR = 1.20; 95% CI: 1.01–1.43; $p = 0.041$). The CTO duration was associated with lower procedural success (OR for success 0.60; 95% CI: 0.46–0.79; $p < 0.001$). In multivariate analysis in-hospital adverse events did not differ according to duration of CTO.

Conclusions: Coronary artery CTO duration is associated with greater extent of calcification, lesion length, development of collateral circulation and, most importantly, with lower procedural success.

Key words: chronic total occlusion, lesion characteristics, percutaneous coronary intervention.

Summary

In our study, longer chronic total occlusion (CTO) duration was associated with longer procedure time, greater volume of dye used and lower revascularization success. However, it did not influence the in-hospital adverse event rate. This should be taken into account when planning procedures of CTO older than 12 months. Moreover, in our study longer CTO duration was associated with lower procedural success.

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Introduction

Chronic total occlusion (CTO) is present in about 16% to 30% of patients undergoing coronary angiography [1–3]. Despite the increased experience due to the growth of the number of the performed procedures and the introduction of new techniques and equipment, CTO still remains one of the most demanding procedures in interventional cardiology. Using large registry databases, differences in outcomes and revascularization success in patients with CTO were published during the past years [4–9]. However, as determining age of the CTO may be very challenging, most of them did not include this factor in the analysis. There are several reports describing how and whether CTO duration may affect lesion and procedural characteristics [10–14].

However, none of those studies focused on such a large cohort of patients treated in recent years, and therefore benefiting the most from the latest developments in the field of CTO.

Material and methods

The European Registry of CTOs (ERCTO) is a prospective real-world monitored based registry involving over 100 centers across Europe including patients treated with CTO percutanous coronary intervention (PCI) [6].

For the purpose of our study we included patients admitted to the hospitals between January 2015 and the end of April 2017. The treatment indication for CTO was symptomatic myocardial ischemia and/or evidence of reversible myocardial ischemia by perfusion imaging or stress testing. Registry data from both members and associates of the Euro CTO Club were included. Only patients with certain or likely CTO duration were included in the analysis. Out of 10699 patients in the database recruited during the selected period of time, 5933 patients were excluded due to undetermined age of the occlusion. Out of the remaining 4766 patients we excluded 287 patients with an additional acute coronary syndrome and 435 patients with insufficient further data regarding the occlusion characteristics. In the end, a total of 4044 patients were included in the data analysis (Figure 1). Patients were divided into 3 groups according to age of the CTO: 1) 3–6 months; 2) 7–12 months; 3) over 12 months.

Coronary CTO was defined as angiographic evidence of total occlusions with thrombolysis in myocardial infarction (TIMI) flow grade of 0 and estimated duration of at least 3 months. The length of coronary occlusions was estimated from angiographic projections. Degree of calcification was estimated visually on fluoroscopy. Moderate and severe calcifications were defined as calcium extending for less than half or equal/greater than half of the total CTO segment, respectively. The assessment of collateral connections was made according to the Werner classification (CC) [15]. Occlusion duration in the ERCTO was divided into 3 levels of certainty (certain and angiographically confirmed; likely and clinically confirmed; undetermined), as suggested by the Euro CTO Club consensus document [16]. Procedural success was defined as angiographic success (final residual stenosis < 30% by visual estimation and TIMI flow grade of 3 after CTO recanalization). In-hospital adverse events (AEs) were defined as the composite of non-Q-wave and Q-wave myocardial infarction (MI), coronary perforation requiring intervention, recurrent angina requiring urgent repeat revascularization with PCI or coronary bypass surgery, major bleeding, stent thrombosis, stroke, and death. The complexity of CTO lesion was assessed through the J-CTO (Multicenter CTO Registry in Japan) score and the clinical and lesion-related (CL) score [17, 18].

Statistical analysis

Categorical variables are presented as counts and percentages (%). The median (25^{th}–75^{th} percentiles) is reported for continuous data. Fisher's exact test or χ^2 test was used for categorical variables, and the Mann-Whitney *U* test was used to compare continuous variables. Multivariable logistic regression analyses were performed to determine the independent predictors for lesion and procedural characteristics. Univariate analysis was performed for all variables in the study, then the variables with $p < 0.05$ were included in the multivariable models for adjusted analysis. Statistical analyses were performed with R 3.4.

Results

A total of 4044 of patients were included in the main analysis. Patients with the longest CTO duration as compared to patients with CTO duration 3–6 months were

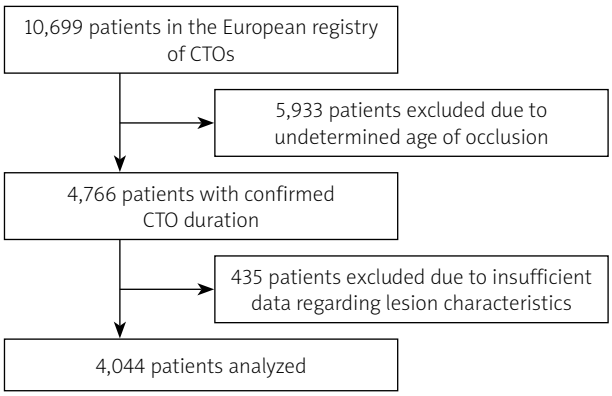

Figure 1. Flow chart. Out of 10699 patients in the database recruited during the selected period of time, 5933 patients were excluded due to undetermined age of the occlusion. Out of the remaining 4766 patients we excluded 287 patients with an additional acute coronary syndrome and 435 patients with insufficient further data regarding the occlusion characteristics. In the end a total of 4044 patients were included in the data analysis

significantly older (63.0 (56.0–70.0) vs. 66.0 (59.0–73.0) years) and had higher prevalence of peripheral artery disease (8.8% vs. 12.4%) (Table I). The group with the longest CTO duration had higher incidence of myocardial infarction (MI) and prior coronary artery bypass grafting (CABG) as compared to other groups. Lesion and pro-

Table I. Clinical characteristics of patients depending on the chronic total occlusion age

Parameter	3–6 months (*n* = 1415)	7–12 months (*n* = 973)	> 12 months (*n* = 1656)	Overall *p*-value
Age [years]	63.0 (56.0–70.0)	63.0 (56.0–71.0)	66.0 (59.0–73.0)	< 0.001
Gender (male), *n* (%)	1197 (84.7)	812 (83.5)	1440 (87.0)	0.030
BMI [kg/m^2]	27.8 (25.3–31.1)	27.8 (25.3–31.1)	28.3 (25.6–31.1)	0.077
Hypertension, *n* (%)	1097 (77.5)	787 (80.9)	1369 (82.7)	0.002
Diabetes, *n* (%)	426 (31.8)	288 (31.6)	539 (35.4)	0.062
Hypercholesterolemia, *n* (%)	1137 (80.4)	762 (78.3)	1317 (79.5)	0.479
Smokers, *n* (%)	334 (25.0)	220 (24.1)	299 (19.6)	0.001
PAD, *n* (%)	124 (8.8)	98 (10.1)	206 (12.4)	0.004
Previous MI, *n* (%)	557 (40.0)	394 (41.1)	818 (51.2)	< 0.001
Previous CABG, *n* (%)	116 (8.2)	96 (9.9)	486 (29.4)	< 0.001
Previous PCI, *n* (%)	682 (48.2)	481 (49.4)	913 (55.2)	< 0.001
GFR [ml/min/1.73 m^2]	91.2 (70.4–111.3)	91.2 (71.6–112.2)	84.0 (66.7–108.2)	< 0.001
Left ventricular EF < 35, *n* (%)	78 (5.5)	49 (5.1)	120 (7.3)	0.039
3-vessel disease, *n* (%)	449 (32.2)	294 (30.9)	749 (46.1)	< 0.001

Values are median (25th–75th percentile) or n (%). BMI – body mass index, CABG – coronary artery bypass grafting, EF – ejection fraction, GFR – glomerular filtration rate, MI – myocardial infarction, PAD – peripheral artery disease, PCI – percutaneous coronary intervention.

Table II. Lesion characteristics depending on the chronic total occlusion age

Parameter	3–6 months (*n* = 1415)	7–12 months (*n* = 973)	> 12 months (*n* = 1656)	Overall *p*-value
CTO artery				0.001
RCA, *n* (%)	773 (54.7)	545 (56.0)	998 (60.3)	
LM, *n* (%)	6 (0.4)	5 (0.5)	19 (1.1)	
LAD, *n* (%)	393 (27.8)	250 (25.7)	342 (20.7)	
Cx, *n* (%)	235 (16.6)	168 (17.3)	288 (17.4)	
CTO in bypass, *n* (%)	5 (0.4)	5 (0.5)	8 (0.5)	
Ostial CTO, *n* (%)	154 (10.9)	102 (10.5)	254 (15.4)	< 0.001
Vessel diameter [mm]	3.0 (2.5–3.0)	3.0 (2.7–3.0)	3.0 (2.7–3.0)	0.006
CTO length [mm]	20.0 (15.0–30.0)	25.0 (15.0–30.0)	28.0 (20.0–40.0)	< 0.001
Collateral circulation type 2, *n* (%)	333 (24.7)	274 (29.5)	474 (30.1)	0.002
Proximal tortuosity, *n* (%)	271 (19.4)	162 (16.9)	332 (20.6)	0.073
In CTO bend, *n* (%)	388 (27.5)	330 (34.2)	614 (37.3)	< 0.001
Moderate and severe calcification, *n* (%)	486 (34.4)	370 (38.3)	851 (51.6)	< 0.001
Blunt stump, *n* (%)	610 (43.3)	405 (41.7)	734 (44.5)	0.366
Severe distal disease, *n* (%)	475 (34.5)	353 (38.0)	783 (48.8)	< 0.001

Values are median (25th–75th percentile) or n (%). CTO – chronic total occlusion, Cx – circumflex artery, LAD – left anterior descending artery, LM – left main artery, RCA – right coronary artery.

Table III. Procedural characteristics depending on the chronic total occlusion age

Parameter	3–6 months (*n* = 1415)	7–12 months (*n* = 973)	> 12 months (*n* = 1656)	Overall *p*-value
One or more previous attempts, *n* (%)	470 (33.2%)	319 (32.8%)	563 (34.0%)	0.789
Retrograde approach, *n* (%)	342 (24.2%)	237 (24.4%)	638 (38.5%)	< 0.001
Procedural failure, *n* (%)	112 (7.9%)	109 (11.2%)	273 (16.5%)	< 0.001
AE, *n* (%)	29 (2.0%)	24 (2.5%)	60 (3.6%)	0.024
Procedure time	85.0 (57.0–120.0)	90.0 (63.0–127.0)	120.0 (77.0–162.0)	< 0.001
Fluoroscopy time	31.5 (19.0–53.0)	32.5 (20.0–52.0)	45.0 (27.0–70.0)	< 0.001
Dye used	237.0 (170.0–330.0)	250.0 (170.0–350.0)	250.0 (190.0–350.0)	< 0.001

Values are median (25th–75th percentile) or n (%). AE – adverse events.

cedural characteristics also differed between patients with different age of the CTO (Tables II, III). Patients with the longest CTO duration as compared to patients with CTO duration 3–6 months had longer occlusions (28.0 (20.0–40.0) vs. 20.0 (15.0–30.0) mm), more calcified lesions (calcification moderate or severe; 51.6% vs. 34.4%), better collateral circulation (30.1% vs. 24.7% for CC2) and more advanced coronary artery disease distal to CTO (48.8% vs. 34.5%). The revascularization success rate was the highest in the patients with CTO duration 3–6 months as compared to the patients with the oldest CTO (92.1% vs. 83.5%), and the retrograde approach was less common in those lesions (24.2% vs. 38.5%). Intravascular ultrasound was used more frequently in the older occlusions (15.7% vs. 9.5%). Incidence of in-hospital AEs increased from 2.0% in the group with the shortest CTO duration to 3.6% in the group with the longest CTO duration (Table III). Time of the procedure and dye volume increased significantly with increased CTO duration, reaching up to 120 min and 250 ml of dye used in the last group (Table III). The J-CTO score as well as the CL score were higher in older lesions (Figure 2).

In multivariate analysis (univariate analysis is presented in Table IV) we found that CTO duration was an

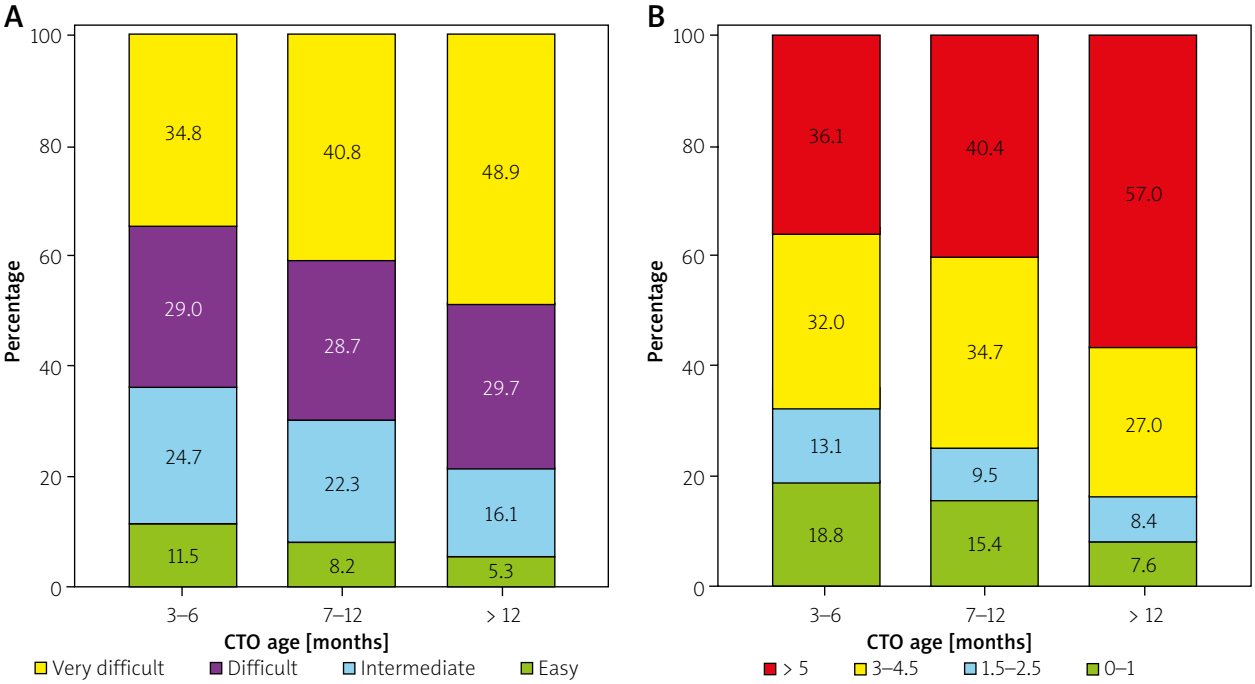

Figure 2. Differences in J-CTO score (**A**) and CL score (**B**) depending on the chronic total occlusion age. Differences in J-CTO score between patients with different chronic total occlusion (CTO) duration were significant (3968 patients; $p < 0.001$). J-CTO score of 3 or more increased with increase of the lesion age. In the CL score only patients with a first attempt were included in the analysis (2692 patients). Differences in CL score depending on the occlusion duration were significant ($p < 0.001$) and prevalence of a CL score of more than 5 points increased with the lesion age

independent predictor of lesion length, severity of calcification, better developed collateral circulation and procedure failure, but it did not influence the AE rate (Table V). Full multivariate analysis is presented in Table VI.

Differences between patients with undetermined age of the occlusion and known occlusion duration are presented in the Supplement (Table VII). As expected, patients with determined age of occlusion had previous MI and CABG more frequently (37.5% vs. 44.8% and 8.1% vs. 17.3% respectively). The procedural failure rate was similar in both groups (11.9% vs. 12.2%). Interestingly, incidence of AEs was higher in the group with undetermined age of the occlusion (3.7% vs. 2.8%).

Discussion

Our study, performed on a large cohort of patients, demonstrated that: 1) longer duration of CTO is associated with longer procedure and fluoroscopy time, and greater amount of dye used; 2) longer duration of CTO is a predictor of greater calcification, longer lesions and more developed collateral circulation; 3) age of the CTO influences the procedure success, but not in-hospital AEs.

Procedure duration

As observed in previous studies, patients with longer CTO duration had longer procedure and fluoroscopy time, as well as a greater amount of dye used [10]. These results should be taken into account when planning a procedure with known age of the CTO.

Calcification

In our study occlusion duration of over 12 months was an independent predictor of calcification. In more advanced coronary artery disease (CAD), elevated lipid content and inflammatory mediators induce osteogenic differentiation of vascular smooth muscle cells in the intima – usually calcific deposits are found more frequently and in greater amounts among more advanced lesions and in elderly individuals [19]. These observations were confirmed in the CTO histopathology study where older lesion age was associated with a greater fibrocalcific component [20]. Comparable to our results, Danek *et al.* recently observed a difference of 16% in moderate/severe calcification between patients with a CTO duration shorter than 5 and longer than 36.3 months [10]. Moreover, as previously reported, CABG in medical history was also associated with higher prevalence of calcification in CTO lesions [21]. Importantly, calcification is regarded as one of the predictors of failure when performing PCI of CTO – both the CL score proposed by Alessandrino *et al.* and the J-CTO score include calcification in their scoring systems [17, 18].

Collateral circulation

We observed that occlusion duration longer than 6 months was a predictor of development of collaterals in CC grade 2 proposed by Werner *et al.* [15]. Time of recruitment of collaterals in CTO is still debatable, ranging from several weeks to months [22]. Collateral flow plays several major roles in CTO. First, well-developed collaterals have the capacity to prevent myocardial necrosis and may preserve myocardial viability [22]. Second, collaterals are used during the retrograde approach and thus poorly developed collaterals were found to be an independent predictor of technical failure in CTO PCI [5, 23].

Lesion length

In contrast to the study of Danek *et al.*, we found that CTO length increased with age of the CTO [10]. In our study, even occlusion duration longer than 6 months was an independent predictor of CTO length over 20 mm. One could speculate that with the novel techniques including the hybrid approach and retrograde revascularization lesion length may be less important in assessing complexity of the CTO procedures as shown in the PROGRESS CTO score and ORA score [5, 23]. In contrast, Ellis *et al.* showed in their recent study assessing predictors of a successful hybrid approach that procedure failure is correlated with occlusion length over 10 mm [7]. Besides that, longer lesions may still influence the duration of the procedure [17].

Procedural success

Currently several different angiographic scoring systems assessing predictors of failure and success in CTO PCI are available, but none of them has ever included the duration of CTO in their analysis [24–26]. On the other hand, CTO duration as predictor of revascularization failure has been described in computed tomography studies [13, 14]. Given the results of those studies and our current study, it is plausible to say that duration of CTO may have an influence on procedural success and PCI of CTO should not be postponed, although this observation merits further research. Nevertheless, it should be underlined that in our study the exact age of CTO lesions could only be determined in less than 50% of the cases; thus implementing CTO duration in future scoring systems may be challenging. Lastly, some of the studies did not find a correlation between CTO duration and procedural success; however, the number of patients included in the analysis was also significantly lower [27].

Adverse events

A weighted meta-analysis by Patel *et al.* with 18061 patients included from 65 studies revealed low rates of AEs in patients undergoing CTO PCI [2]. In our study rates of AEs were comparable, with 0.4% deaths and 0.7% MI

Table IV. Univariate analysis for lesion characteristics

Parameter	Moderate/severe calcification (*n* = 2320)	Mild/no calcification (*n* = 1701)	*P*-value
Age [years]	63.0 (55.0–70.0)	66.0 (59.0–74.0)	< 0.001
Gender (male), *n* (%)	1961 (84.6)	1472 (86.3)	0.139
BMI [kg/m^2]	27.8 (25.4–31.1)	28.1 (25.5–31.2)	0.135
Hypertension, *n* (%)	1808 (77.9)	1435 (84.1)	< 0.001
Hypercholesterolemia, *n* (%)	1819 (78.4)	1385 (81.1)	0.037
Diabetes, *n* (%)	640 (29.5)	609 (38.4)	< 0.001
Smoker, *n* (%)	544 (25.1)	305 (19.2)	< 0.001
PAD, *n* (%)	187 (8.1)	239 (14.0)	< 0.001
COPD, *n* (%)	85 (3.7)	110 (6.4)	< 0.001
Prior stroke, *n* (%)	64 (2.8)	45 (2.6)	
Previous MI, *n* (%)	1047 (45.9)	714 (43.2)	0.1
Previous CABG, *n* (%)	269 (11.6)	426 (25.0)	< 0.001
Previous PCI, *n* (%)	1144 (49.3)	922 (54.0)	0.004
GFR [ml/min/1.73 m^2]	91.2 (71.5–113.6)	84.2 (65.5–107.2)	< 0.001
Left ventricular EF < 35%, *n* (%)	143 (6.2)	103 (6.1)	0.91
Number of diseased vessels, *n* (%):			< 0.001
1-vessel disease	823 (36.2)	392 (23.3)	
2-vessel disease	736 (32.4)	514 (30.6)	
3-vessel disease	715 (31.4)	773 (46.0)	
CTO artery, *n* (%):			< 0.001
RCA	1248 (53.9)	1061 (62.2)	
LAD	597 (25.8)	383 (22.4)	
Cx	451 (19.5)	235 (13.8)	
LM	3 (0.1)	27 (1.6)	
CTO in bypass	17 (0.7)	1 (0.1)	
CTO in side branch	78 (3.4)	34 (2.0)	0.012
Ostial CTO	227 (9.8)	281 (16.5)	< 0.001
Occlusion duration, *n* (%):			< 0.001
3–6 months	486 (28.5)	925 (39.9)	
7–12 months	370 (21.7)	596 (25.7)	
Over 12 months	851 (49.9)	799 (34.4)	
Parameter	**CC2 (*n* = 2772)**	**CC0/CC1 (*n* = 1081)**	***P*-value**
Age [years]	64.0 (57.0–72.0)	64.0 (57.0–72.0)	0.917
Gender (male), *n* (%)	2331 (84.2)	951 (88.0)	0.003
BMI [kg/m^2]	28.1 (25.4–31.1)	27.8 (25.4–31.1)	0.372
Hypertension, *n* (%)	2236 (80.7)	864 (79.9)	0.636
Hypercholesterolemia, *n* (%)	2206 (79.6)	859 (79.5)	0.97
Diabetes, *n* (%)	878 (33.7)	308 (30.7)	0.087
Smoker, *n* (%)	592 (22.7)	231 (23.0)	0.9
PAD, *n* (%)	282 (10.2)	127 (11.7)	0.171
COPD, *n* (%)	133 (4.8)	57 (5.3)	0.597
Prior stroke, *n* (%)	71 (2.6)	34 (3.1)	0.373
Previous MI, *n* (%)	1214 (44.8)	464 (44.1)	0.743
Previous CABG, *n* (%)	448 (16.2)	214 (19.8)	0.008
Previous PCI, *n* (%)	1428 (51.5)	550 (50.9)	0.742
GFR [ml/min/1.73 m^2]	89.0 (68.8–110.7)	89.1 (69.8–111.3)	0.5
Left ventricular EF < 35%, *n* (%)	182 (6.6)	48 (4.5)	0.018

Table IV. Cont.

Parameter	CC2 (*n* = 2772)	CC0/CC1 (*n* = 1081)	*P*-value
Number of diseased vessels, *n* (%):			< 0.001
1-vessel disease	790 (28.9)	372 (35.4)	
2-vessel disease	873 (32.0)	323 (30.7)	
3-vessel disease	1067 (39.1)	357 (33.9)	
CTO artery, *n* (%):			< 0.001
RCA	1555 (56.2)	681 (63.0)	
LAD	666 (24.1)	261 (24.1)	
Cx	521 (18.8)	126 (11.7)	
LM	14 (0.5)	12 (1.1)	
CTO in bypass	12 (0.4)	1 (0.1)	
CTO in side branch	96 (3.5)	10 (0.9)	< 0.001
Ostial CTO	330 (11.9)	163 (15.2)	0.008
Occlusion duration, *n* (%):			0.003
3–6 months	333 (30.8)	1013 (36.5)	
7–12 months	274 (25.3)	656 (23.7)	
Over 12 months	474 (43.8)	1103 (39.8)	
Parameter	**Lesion length < 20 mm (*n* = 1167)**	**Lesion length > 20 mm (*n* = 2832)**	***P*-value**
Age [years]	65.0 (58.0–73.0)	64.0 (57.0–71.0)	0.015
Gender (male), *n* (%)	973 (83.4)	2438 (86.1)	0.034
BMI [kg/m^2]	27.8 (25.3–30.8)	28.0 (25.5–31.2)	0.032
Hypertension, *n* (%)	930 (79.7)	2287 (80.8)	0.467
Hypercholesterolemia, *n* (%)	944 (80.9)	2237 (79.0)	0.19
Diabetes, *n* (%)	356 (32.3)	885 (33.7)	0.45
Smoker, *n* (%)	233 (21.2)	614 (23.4)	0.155
PAD, *n* (%)	100 (8.6)	322 (11.4)	0.01
COPD, *n* (%)	51 (4.4)	144 (5.1)	0.383
Prior stroke, *n* (%)	32 (2.7)	78 (2.8)	1
Previous MI, *n* (%)	471 (41.2)	1282 (46.4)	0.003
Previous CABG, *n* (%)	163 (14.0)	524 (18.5)	0.001
Previous PCI, *n* (%)	551 (47.2)	1497 (52.9)	0.001
GFR [ml/min/1.73 m^2]	87.0 (68.5–108.2)	89.2 (69.1–111.4)	0.159
Left ventricular EF < 35%, *n* (%)	68 (5.9)	178 (6.3)	0.629
Number of diseased vessels, *n* (%):			0.044
1-vessel disease	372 (32.6)	838 (30.1)	
2-vessel disease	376 (32.9)	867 (31.2)	
3-vessel disease	394 (34.5)	1078 (38.7)	
CTO artery, *n* (%):			< 0.001
RCA	538 (46.2)	1747 (61.7)	
LAD	349 (30.0)	629 (22.2)	
Cx	263 (22.6)	421 (14.9)	
LM	12 (1.0)	18 (0.6)	
CTO in bypass	2 (0.2)	16 (0.6)	
CTO in side branch	59 (5.1)	51 (1.8)	< 0.001
Ostial CTO	110 (9.4)	389 (13.8)	< 0.001
Occlusion duration, *n* (%):			< 0.001
3–6 months	514 (44.0)	890 (31.4)	
7–12 months	277 (23.7)	687 (24.3)	
Over 12 months	376 (32.2)	1255 (44.3)	

Table IV. Cont.

Parameter	Procedure success – not successful (*n* = 494)	Procedure success – successful (*n* = 3550)	*P*-value
Age [years]	66.0 (60.0–73.0)	64.0 (57.0–72.0)	< 0.001
Gender (male), *n* (%)	423 (85.8)	3026 (85.3)	0.804
BMI [kg/m^2]	28.4 (26.0–31.6)	27.9 (25.4–31.1)	0.014
Hypertension, *n* (%)	410 (83.0)	2843 (80.1)	0.142
Hypercholesterolemia, *n* (%)	386 (78.1)	2830 (79.7)	0.45
Diabetes, *n* (%)	181 (39.4)	1072 (32.4)	0.003
Smoker, *n* (%)	92 (20.0)	761 (23.0)	0.179
PAD, *n* (%)	80 (16.2)	348 (9.8)	< 0.001
COPD, *n* (%)	40 (8.1)	156 (4.4)	0.001
Prior stroke, *n* (%)	22 (4.5)	88 (2.5)	0.017
Previous MI, *n* (%)	234 (49.0)	1535 (44.3)	0.059
Previous CABG, *n* (%)	115 (23.3)	583 (16.4)	< 0.001
Previous PCI, *n* (%)	299 (60.5)	1777 (50.1)	< 0.001
GFR [ml/min/1.73 m^2]	84.7 (66.4–106.9)	89.1 (69.4–111.0)	0.016
Left ventricular EF < 35%, *n* (%)	34 (7.0)	213 (6.0)	0.488
Number of diseased vessels, *n* (%):			0.213
1-vessel disease	136 (28.2)	1086 (31.2)	
2-vessel disease	148 (30.7)	1106 (31.7)	
3-vessel disease	198 (41.1)	1294 (37.1)	
CTO artery, *n* (%):			0.02
RCA	316 (64.0)	2000 (56.4)	
LAD	102 (20.6)	883 (24.9)	
Cx	74 (15.0)	617 (17.4)	
LM	1 (0.2)	29 (0.8)	
CTO in bypass	1 (0.2)	17 (0.5)	
CTO in side branch	10 (2.0)	102 (2.9)	0.35
Ostial CTO	97 (19.7)	413 (11.7)	< 0.001
In stent CTO	31 (6.3)	367 (10.3)	0.006
Bifurcation, *n* (%)	130 (26.3)	992 (27.9)	0.482
Vessel diameter [mm]	3.0 (2.8–3.0)	3.0 (2.5–3.0)	0.839
CTO length [mm]	30.0 (20.0–40.0)	25.0 (15.0–35.0)	< 0.001
Collateral circulation type 2, *n* (%)	118 (25.1)	963 (28.5)	0.135
Proximal tortuosity, *n* (%)	134 (27.7)	631 (18.1)	< 0.001
In CTO bend, *n* (%)	254 (52.4)	1078 (30.5)	< 0.001
Moderate and severe calcification, *n* (%)	307 (62.8)	1400 (39.6)	< 0.001
Blunt stump, *n* (%)	243 (49.4)	1506 (42.6)	0.005
Side branch 3 mm proximal to CTO, *n* (%)	133 (26.9)	943 (26.6)	0.908
Visible distal opacification, *n* (%)	143 (29.2)	1652 (46.7)	< 0.001
Severe distal disease, *n* (%)	251 (53.0)	1360 (39.6)	< 0.001
One or more previous attempts, *n* (%)	185 (37.4)	1167 (32.9)	0.049
Retrograde approach, *n* (%)	207 (41.9)	1010 (28.5)	< 0.001
AE, *n* (%)	24 (4.9)	89 (2.5)	0.005
Occlusion duration, *n* (%):			< 0.001
3–6 months	112 (22.7)	1303 (36.7)	
7–12 months	109 (22.1)	864 (24.3)	
Over 12 months	273 (55.3)	1383 (39.0)	
Parameter	**Non-AE (*n* = 3931)**	**AE (*n* = 113)**	***P*-value**
Age [years]	64.0 (57.0–72.0)	66.0 (59.0–73.0)	0.056
Gender (male), n (%)	3363 (85.6)	86 (76.1)	0.007

Table IV. Cont.

Parameter	Non-AE (*n* = 3931)	AE (*n* = 113)	*P*-value
BMI [kg/m^2]	28.0 (25.5–31.1)	27.7 (24.8–31.1)	0.275
Hypertension, *n* (%)	3154 (80.2)	99 (87.6)	0.067
Hypercholesterolemia, *n* (%)	3119 (79.3)	97 (85.8)	0.117
Diabetes, *n* (%)	1220 (33.3)	33 (31.7)	0.825
Smoker, *n* (%)	834 (22.7)	19 (18.3)	0.339
PAD, *n* (%)	407 (10.4)	21 (18.6)	0.008
COPD, *n* (%)	186 (4.7)	10 (8.8)	0.074
Prior stroke, *n* (%)	103 (2.6)	7 (6.2)	0.033
Previous MI, *n* (%)	1709 (44.6)	60 (53.6)	0.073
Previous CABG, *n* (%)	674 (17.2)	24 (21.2)	0.314
Previous PCI, *n* (%)	2017 (51.3)	59 (52.2)	0.927
GFR [ml/min/1.73 m^2]	89.0 (69.0–110.8)	81.2 (67.3–101.7)	0.013
Left ventricular EF < 35%, *n* (%)	235 (6.0)	12 (10.6)	0.07
Number of diseased vessels, *n* (%):			0.683
1-vessel disease	1192 (30.9)	30 (27.0)	
2-vessel disease	1217 (31.6)	37 (33.3)	
3-vessel disease	1448 (37.5)	44 (39.6)	
CTO artery, n (%):			0.707
RCA	2254 (57.4)	62 (54.9)	
LAD	956 (24.3)	29 (25.7)	
Cx	670 (17.1)	21 (18.6)	
LM	30 (0.8)	0 (0.0)	
CTO in bypass	17 (0.4)	1 (0.9)	
CTO in side branch	108 (2.8)	4 (3.5)	0.555
Ostial CTO, *n* (%)	494 (12.6)	16 (14.2)	0.728
In stent CTO, *n* (%)	391 (9.9)	7 (6.2)	0.246
Bifurcation, *n* (%)	1085 (27.6)	37 (32.7)	0.273
Vessel diameter [mm]	3.0 (2.5–3.0)	3.0 (2.5–3.0)	0.805
CTO length [mm]	25.0 (15.0–35.0)	30.0 (18.0–40.0)	0.136
Collateral circulation type 2, *n* (%)	1043 (27.9)	38 (33.9)	0.195
Proximal tortuosity, *n* (%)	750 (19.5)	15 (13.4)	0.138
In CTO bend, *n* (%)	1285 (32.9)	47 (41.6)	0.067
Moderate and severe calcification, *n* (%)	1658 (42.4)	49 (43.4)	0.908
Blunt stump, *n* (%)	1702 (43.5)	47 (41.6)	0.765
Side branch 3 mm proximal to CTO, *n* (%)	1041 (26.5)	35 (31.0)	0.338
Visible distal opacification, *n* (%)	1743 (44.6)	52 (46.0)	0.834
Severe distal disease, *n* (%)	1567 (41.3)	44 (38.9)	0.69
One or more previous attempts, *n* (%)	1315 (33.5)	37 (32.7)	0.955
Retrograde approach, *n* (%)	1165 (29.6)	52 (46.0)	< 0.001
Procedural failure, *n* (%)	470 (12.0)	24 (21.2)	0.005
Occlusion duration, *n* (%):			0.024
3–6 months	1386 (35.3)	29 (25.7)	
7–12 months	949 (24.1)	24 (21.2)	
Over 12 months	1596 (40.6)	60 (53.1)	

Values are median (25th – 75th percentile) or n (%). AE – adverse events, BMI – body mass index, CABG – coronary artery bypass grafting, COPD – chronic obstructive pulmonary disease, CTO – chronic total occlusion, Cx – circumflex artery, EF – ejection fraction, GFR – glomerular filtration rate, LAD – left anterior descending artery, LM – left main artery, MI – myocardial infarction, PAD – peripheral artery disease, PCI – percutaneous coronary intervention, RCA – right coronary artery. For calcification, lesion length and collateral circulation only clinical predictors were included in the analysis. For procedural success and AE clinical, lesion characteristics and retrograde approach were included in the analysis.

Table V. Predictors for lesion characteristics and adverse events – multivariate analysis

Variable	OR	95% CI lower bound	95% CI upper bound	*P*-value
Calcification (moderate or severe):				
Occlusion duration 7–12 months	1.14	0.95	1.38	0.165
Occlusion duration > 12 months	1.52	1.28	1.8	< 0.001
Collateral circulation type 2:				
Occlusion duration 7–12 months	1.26	1.03	1.53	0.021
Occlusion duration > 12 months	1.2	1.01	1.43	0.041
Lesion length 20 mm:				
Occlusion duration 7–12 months	1.43	1.19	1.72	< 0.001
Occlusion duration > 12 months	1.77	1.49	2.1	< 0.001
Procedural success:				
Occlusion duration 7–12 months	0.78	0.57	1.06	0.116
Occlusion duration > 12 months	0.6	0.46	0.79	< 0.001
AE:				
Occlusion duration 7–12 months	1.17	0.67	2.03	0.578
Occlusion duration > 12 months	1.56	0.98	2.47	0.06

Only results for occlusion duration (as compared to occlusion duration 3–6 months) are presented in the table. Full multivariate analysis is presented in Table VI. AE – adverse events, CI – confidence interval, CTO – chronic total occlusion, OR – odds ratio. Number of patients included in the analysis (n): calcification (moderate or severe), n = 3589; collateral circulation type 2, n = 3739; Lesion length 20 mm, n = 3815; AE, n = 4037.

during the hospitalization period. A recent study showed that complications during PCI of CTO were more frequent in females [28]. In concordance with that observation, female gender was one of two AE predictors in our study. Not surprisingly, the retrograde approach was the other predictor of AEs as this approach is considered as more complex when compared to the antegrade approach [6, 29]. However, it should be noted that the retrograde approach is often used in very advanced lesions where the antegrade approach is not feasible or ended with failure. Importantly, although patients with the longest CTO duration had higher incidence of AEs as compared to the patients with the shortest CTO duration, the age of the CTO was not an independent predictor of AEs. Barlis *et al.* in their study compared AEs in patients with undetermined and known occlusion duration [30]. In long-term follow-up they found that undetermined occlusion duration was a predictor of AEs. In contrast to our study they did not find any differences in in-hospital outcomes between groups with known and unknown occlusion duration. However, their study was limited by the sample size.

Limitations

First, our study is limited by its observational design. Second, angiography-dependent and clinical outcomes were not independently adjudicated. Third, data regarding patients and lesion and procedural characteristics were missing in some cases. Moreover, only in half of the patients could CTO age be assessed. Out of 10 699 patients, 4044 (37.8%) were included in the final analysis, which could have involved selection bias. Further, patients excluded from the study differed from those included in important lesion characteristics such as lesion location, number of previous attempts and severity of coronary artery disease. Lastly, the exact age of the CTO is often unclear. Hence, it is often very challenging to determine the exact age of the CTO.

Conclusions

Longer CTO duration is associated with greater prevalence of calcification, longer lesions, and better developed collateral circulation. Most importantly, in our study longer CTO duration was associated with lower revascularization success by PCI. However, it did not affect the rate of in-hospital AEs. Our results should be taken into account when planning procedures of CTO older than 12 months.

Conflict of interest

The authors declare no conflict of interest.

Table VI. Full multivariate analysis

Parameter	OR	95% CI lower bound	95% CI upper bound	*P*-value
Calcification (moderate or severe):				
Age	1.03	1.02	1.04	< 0.001
Gender (male)	1.31	1.06	1.61	0.011
BMI	1.02	1	1.03	0.038
Occlusion duration 7–12 months[1]	1.14	0.95	1.38	0.165
Occlusion duration over 12 months[1]	1.52	1.28	1.8	< 0.001
Hypertension	1.13	0.94	1.37	0.201
Hypercholesterolemia	1.21	1.01	1.45	0.038
Diabetes	1.21	1.03	1.41	0.017
Smoker	0.86	0.72	1.03	0.107
PAD	1.4	1.11	1.76	0.005
COPD	1.64	1.19	2.27	0.003
Previous CABG	1.58	1.28	1.96	< 0.001
Previous PCI	1.14	0.98	1.31	0.084
CKD class 4	2.45	1.4	4.31	0.002
2-vessel CAD disease	1.46	1.21	1.75	< 0.001
3- vessel CAD disease	1.82	1.51	2.2	< 0.001
CTO in bypass[2]	0.02	0	0.16	< 0.001
CTO in LAD[2]	0.85	0.72	1.01	0.068
CTO in Cx[2]	0.51	0.41	0.63	< 0.001
CTO in LM[2]	5.31	1.21	23.17	0.027
CTO in side branch	0.41	0.26	0.66	< 0.001
Ostial CTO	2.07	1.66	2.6	< 0.001
Collateral circulation 2:				
Age	1	1	1.01	0.472
Gender (male)	1.47	1.18	1.83	0.001
BMI	0.99	0.98	1.01	0.394
Occlusion duration 7–12 months[1]	1.26	1.03	1.53	0.021
Occlusion duration over 12 months[1]	1.2	1.01	1.43	0.041
Previous CABG	1.46	1.17	1.82	0.001
Left ventricular EF < 35%	0.67	0.48	0.94	0.022
2-vessel CAD disease	0.79	0.66	0.94	0.01
3-vessel CAD disease	0.66	0.54	0.8	< 0.001
CTO in bypass[2]	0.14	0.02	1.08	0.059
CTO in LAD[2]	0.88	0.74	1.05	0.154
CTO in Cx[2]	0.57	0.46	0.72	< 0.001
CTO in LM[2]	1.45	0.65	3.23	0.362
CTO in side branch	0.31	0.16	0.6	0.001
Ostial CTO	1.49	1.2	1.85	< 0.001
Lesion length > 20 mm:				
Age	0.99	0.98	1	0.019
Gender (male)	1.19	0.97	1.45	0.087
BMI	1.02	1	1.03	0.05
Occlusion duration 7–12 months[1]	1.43	1.19	1.72	< 0.001
Occlusion duration over 12 months[1]	1.77	1.49	2.1	< 0.001
PAD	1.27	0.99	1.64	0.059
Previous MI	1.12	0.96	1.3	0.146
Previous CABG	1.17	0.93	1.48	0.183

Table VI. Cont.

Parameter	OR	95% CI lower bound	95% CI upper bound	*P*-value
Previous PCI	1.19	1.03	1.38	0.022
2-vessel CAD disease	1.03	0.86	1.23	0.749
3-vessel CAD disease	1.17	0.96	1.42	0.112
CTO in bypass[2]	1.71	0.38	7.79	0.488
CTO in LAD[2]	0.6	0.51	0.71	< 0.001
CTO in Cx[2]	0.52	0.43	0.64	< 0.001
CTO in LM[2]	0.27	0.12	0.61	0.002
CTO in side branch	0.32	0.21	0.48	< 0.001
Ostial CTO	1.85	1.44	2.37	< 0.001
Procedural success:				
Age	0.99	0.97	1	0.015
Gender (male)	1	0.73	1.37	0.997
BMI	0.98	0.96	1.01	0.132
Occlusion duration 7–12 months[1]	0.78	0.57	1.06	0.116
Occlusion duration over 12 months[1]	0.6	0.46	0.79	< 0.001
Diabetes	0.89	0.71	1.12	0.314
PAD	0.7	0.51	0.95	0.024
COPD	0.61	0.4	0.93	0.022
Prior stroke	0.65	0.37	1.12	0.122
Previous CABG	1.01	0.76	1.34	0.956
Previous PCI	0.61	0.49	0.77	< 0.001
CTO in bypass[2]	2.99	0.37	24.24	0.305
CTO in LAD[2]	0.99	0.75	1.3	0.917
CTO in Cx[2]	1.27	0.92	1.76	0.148
CTO in LM[2]	6.48	0.83	50.51	0.075
Ostial CTO	0.58	0.43	0.78	< 0.001
In stent CTO	1.9	1.23	2.93	0.004
Lesion length > 20 mm	0.61	0.46	0.83	0.001
Proximal tortuosity	0.85	0.66	1.11	0.239
In CTO bend	0.57	0.46	0.71	< 0.001
Moderate/severe calcification	0.55	0.43	0.7	< 0.001
Blunt stump	0.79	0.63	0.98	0.034
Visible distal opacification	1.77	1.39	2.24	< 0.001
Severe distal disease	0.99	0.79	1.26	0.965
One or more previous attempts	0.87	0.69	1.09	0.231
AE:				
Age	1.01	0.99	1.03	0.313
Gender (male)	0.52	0.33	0.81	0.004
BMI	0.98	0.94	1.03	0.44
Occlusion duration 7–12 months[1]	1.17	0.67	2.03	0.578
Occlusion duration over 12 months[1]	1.56	0.98	2.47	0.06
PAD	1.67	1.02	2.76	0.043
Prior stroke	2.09	0.93	4.73	0.075
Retrograde approach	1.93	1.31	2.83	0.001

AE – adverse events, BMI – body mass index, CABG – coronary artery bypass grafting, CAD – coronary artery disease, CI – confidence interval, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease, CTO – chronic total occlusion, Cx – circumflex artery, EF – ejection fraction, LAD – left anterior descending artery, LM – left main artery, OR – odds ratio, PAD – peripheral artery disease, PCI – percutaneous coronary intervention. [1]As compared to occlusion duration 3–6 months; [2]as compared to right coronary artery. For calcification, lesion length and collateral circulation only clinical predictors were included in the analysis. For procedural success and AE clinical, lesion characteristics and retrograde approach were included in the analysis. Number of patients included in the analysis (n): calcification (moderate or severe), n = 3589; collateral circulation type 2, n = 3739; lesion length 20 mm, n = 3815; procedural success, n = 3513; AE, n = 4037.

Table VII. Comparison between patients with undetermined age of the occlusion and known occlusion duration

Parameter	Undetermined age of the occlusion (*n* = 5033)	Known occlusion duration (*n* = 4044)	*P*-value
Age [years]	64.0 (57.0–72.0)	64.0 (57.0–72.0)	0.862
Gender (male), *n* (%)	4246 (84.4)	3449 (85.3)	0.239
BMI [kg/m^2]	27.7 (25.1–30.7)	28.0 (25.4–31.1)	< 0.001
Hypertension, *n* (%)	3824 (76.0)	3253 (80.4)	< 0.001
Hypercholesterolemia, *n* (%)	3548 (70.5)	3216 (79.5)	< 0.001
Diabetes, *n* (%)	1546 (32.9)	1253 (33.2)	0.78
Smoker, *n* (%)	1367 (29.1)	853 (22.6)	< 0.001
PAD, *n* (%)	594 (11.8)	428 (10.6)	0.073
COPD, *n* (%)	262 (5.2)	196 (4.8)	0.466
Prior stroke, *n* (%)	147 (2.9)	110 (2.7)	0.611
Previous MI, *n* (%)	1807 (37.5)	1769 (44.8)	< 0.001
Previous CABG, *n* (%)	406 (8.1)	698 (17.3)	< 0.001
Previous PCI, *n* (%)	2492 (49.5)	2076 (51.3)	0.086
GFR [ml/min/1.73 m^2]	86.9 (67.0–109.4)	88.6 (68.9–110.7)	0.006
Left ventricular EF < 35%, *n* (%)	412 (8.2)	247 (6.1)	< 0.001
Number of diseased vessels, *n* (%):			< 0.001
1-vessel disease	1677 (34.4)	1222 (30.8)	
2-vessel disease	1654 (33.9)	1254 (31.6)	
3-vessel disease	1549 (31.7)	1492 (37.6)	
CTO artery, *n* (%):			< 0.001
RCA	2746 (54.7)	2316 (57.3)	
LAD	1338 (26.6)	985 (24.4)	
Cx	914 (18.2)	691 (17.1)	
LM	13 (0.3)	30 (0.7)	
CTO in bypass	12 (0.2)	18 (0.4)	
CTO in side branch	110 (2.2)	112 (2.8)	0.086
Ostial CTO	463 (9.2)	510 (12.6)	< 0.001
In-stent CTO	369 (7.3)	398 (9.8)	< 0.001
Bifurcation	1275 (25.3)	1122 (27.7)	0.01
Vessel diameter [mm]	3.0 (2.5–3.0)	3.0 (2.5–3.0)	0.136
CTO length [mm]	25.0 (15.0–35.0)	25.0 (15.0–35.0)	0.225
Collateral circulation type 2, *n* (%)	1443 (31.5)	1081 (28.1)	0.001
Proximal tortuosity, *n* (%)	941 (19.0)	765 (19.3)	0.714
In CTO bend, *n* (%)	1550 (31.0)	1332 (33.2)	0.034
Moderate and severe calcification, *n* (%)	2182 (43.5)	1707 (42.4)	0.294
Blunt stump, *n* (%)	2043 (40.7)	1749 (43.4)	0.01
Visible distal opacification, *n* (%)	2043 (41.0)	1795 (44.6)	0.001
Severe distal disease, *n* (%)	1721 (38.5)	1611 (41.2)	0.013
One or more previous attempts, *n* (%)	1115 (22.2)	1352 (33.4)	< 0.001
Retrograde approach, *n* (%)	1411 (28.0)	1217 (30.1)	0.033
Procedural failure, *n* (%)	597 (11.9)	494 (12.2)	0.629
AE, *n* (%)	185 (3.7)	113 (2.8)	0.019
Radial access, *n* (%)	2324 (46.2)	1290 (31.9)	< 0.001
Rotablation, *n* (%)	122 (12.4)	100 (2.5)	0.881
IVUS, *n* (%)	653 (13.0)	503 (12.4)	0.446
Procedure time	90.0 (60.0–129.0)	100.0 (63.0–144.0)	< 0.001
Fluoroscopy time	33.0 (19.0–55.0)	37.0 (22.0–60.8)	< 0.001
Dye used	236.0 (170.0–320.0)	250.0 (180.0–350.0)	< 0.001

Values are median (25th–75th percentile) or n (%). AE – adverse events, BMI – body mass index, CABG – coronary artery bypass grafting, COPD – chronic obstructive pulmonary disease, CTO – chronic total occlusion, Cx – circumflex artery, EF – ejection fraction, GFR – glomerular filtration rate, LAD – left anterior descending artery, LM – left main artery, MI – myocardial infarction, PAD – peripheral artery disease, PCI – percutaneous coronary intervention, RCA – right coronary artery. Out of 5933 patients with undetermined age of the occlusion, 900 were excluded due to insufficient data regarding the occlusion characteristics. In the end a total of 4044 patients with known occlusion duration and 5033 patients with undetermined age of the occlusion were included in the data analysis.

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