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Rīga Stradiņš University

Artis Kalniņš

Comparison of Treatment Methods for Coronary Heart Disease in Patients with Chronic Total Coronary Artery Occlusions

Summary of the Doctoral Thesis for obtaining a doctoral degree (*Ph.D.*)

Sector – Clinical Medicine
Sub-Sector – Cardiology

Riga, 2021

Artis Kalniņš

ORCID 0000-0001-8906-0111

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The Doctoral Thesis was developed at Riga East Clinical University Hospital, Latvia

Supervisors of the Doctoral Thesis:

Dr. med., Professor **Aivars Lejnieks**,
Rīga Stradiņš University, Latvia

Dr. med., Professor **Andrejs Ērglis**,
University of Latvia

Official Reviewers:

Dr. med., Professor **Oskars Kalējs**,
P. Stradiņš Clinical University Hospital,
Rīga Stradiņš University, Latvia

Dr. med., **Ainārs Rudzītis**,
P. Stradiņš Clinical University Hospital,
University of Latvia

Ph.D., Professor **Sergey Furkalo**,
National Institute of Surgery and Transplantology NAMS,
Kiev, Ukraine

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Secretary of the Promotion Council:

Dr. med., Associated Professor **Ilze Konrāde**

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Abbreviations used in the Thesis

ACC	American College of Cardiology
ADR	antegrade dissection re-entry
AHA	American Heart Association
BASE	balloon assisted subintimal entry
BMI	body mass index
BMS	bare metal stent
CABG	coronary arteries bypass grafting
CART	controlled antegrade and retrograde tracking
CASTLE score	score: CABG history, Age (≥ 70yrs), Stump anatomy (blunt or invisible), Tortuosity degree (severe or unseen), Length of occlusion (≥ 20 mm) and Extent of calcification (severe)
CC	collateral connection
CFI	collateral flow index
CHD	coronary heart disease
CI	confidence interval
CL	score: The Clinical and Lesion related score
CTO	chronic total occlusion
DECISION CTO	trial: Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion,
DES	drug eluting stent
ECG	electrocardiogram
ESC	European Society of Cardiology
FFR	fractional flow reserve
hMBP	hyperaemic myocardial blood flow
IVUS	intra vascular ultrasound
23J-CTO	score: Multicentre Chronic Total Occlusion (CTO) Registry in Japan

LAD	left anterior descending artery
LCX	left circumflex artery
LIMA	left internal mammary artery
LM	left main
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events
MI	myocardial infarction
MSCT	multi-slice computer tomography
NS	not significant
OAT	trial: Occluded Artery Trial
PCI	percutaneous coronary intervention
POBA	plain old balloon angioplasty
PROGRESS CTO	score: Prospective Global Registry for the study of Chronic Total Occlusion Intervention
RCA	right coronary artery
RDR	retrograde dissection re-entry
REVASC	trial: Recovery of Left Ventricular Function in Coronary Chronic Total Occlusion
SAQ	Seattle Angina Questionnaire
STAR	subintimal tracking and re-entry
SYNTAX	trial: The SYNergy between PCI with TAXus and cardiac surgery
TIMI	thrombolysis in myocardial infarction

Introduction

Cardiovascular diseases are the leading cause of death worldwide. Almost 18 million deaths each year are due to atherosclerosis (Roth et al., 2017), however cardiovascular mortality rates across the world are very different. In North America and Western / Northern Europe, they are significantly lower than in Eastern Europe, Asia and Africa. In France, for example, the age-standardized mortality rate in 2017 was around 86 per 100.000 population; In Eastern Europe as a whole, this figure was about 5 times higher – 400–500 per 100.000 inhabitants. In Latvia, cardiovascular diseases have been the most common cause of death for many years and it significantly exceeds such causes as malignancies or externally caused causes of death (Latvian Health Care Statistics Yearbook, 2018). The largest share of cardiovascular mortality is due to coronary heart disease (CHD), which, despite the reduction in mortality achieved in many countries around the world and also in Latvia, is still the main cause of premature death.

One of the treatment methods for CHD is percutaneous coronary intervention (PCI). Method is a relatively new and was founded by Andreas Gruntzig, who performed the first coronary balloon angioplasty (POBA) in 1977. In the following years new PCI technologies rapidly developed, balloon angioplasty was followed by the era of stent implantation, which began with conventional metal stents (BMS). The first coronary angioplasty with stent implantation was performed in 1987 by Ulrich Sigwart (Roubin, 2014). In 2002, drug eluting stents (DES) entered in clinical practice, which is considered to be one of the greatest advances in the field of PCI. The use of DES significantly reduced the restenosis often caused by conventional metal stents. However, difficulties in invasive treatment are still caused by anatomically complex lesions – long, calcified stenoses, chronic total occlusions, bifurcations lesions, small artery disease, etc. One of the biggest challenges in the interventional cardiology still remains chronic total coronary artery occlusions. CTOs are relatively common, approximately 30% of patients with angiographically significant coronary artery disease have at least one CTO (Christofferson et al., 2005). Treatment of these kind of lesions are difficult, because the procedures are technically complex, material and time consuming, the percentage of successful coronary angioplasties is relatively low, but at the same time the potential risk of possible complications is increased (Shahet al., 2011). Patients with CTO are usually older, have more comorbidities and worse left ventricular contractility. (Christofferson et al. 2005; Fefer et al., 2012; Jeroudi et al., 2014).

The first balloon angioplasty for a chronically occluded coronary artery was performed in 1984 (Stein et al., 1984). When performing procedures with the traditional antegrade method, the number of successful procedures usually does not exceed 65–70% (Ruocco et al., 1992; Ivanhoe et al., 1992). Using the retrograde method, the number of successful CTO PCIs in centres with extensive experience in applying this method reaches 80–100% (Karmpaliotis, 2012). Since the first report on the retrograde CTO opening through a vein shunt was published in 1990 (Kahn et al., 1990), this method has evolved significantly. Over the past 5 years, many new materials (wires, balloons, microcatheters) have been introduce in practice, as well as new techniques specifically designed to improve CTO retrograde recanalization results (Surmely, 2006; Saito, 2009; Kimura, 2009; Tomasello, 2014). A meta-analysis of several retrospective registries has found that successful CTO recanalization reduces the incidence of angina, improves left ventricular function, increases survival, and reduces the risk of fatal arrhythmias (Joyal, 2010). Although data from several registries show a reduction in mortality in the successful CTO PCI group, however benefit from invasive recanalization of CTO compared with drug therapy or compared with aortocoronary bypass grafting has not been proved in randomized studies (Nombela-Franco, 2012).

The first successful retrograde CTO angioplasty in Latvia was performed in 2007 at Gailezers Hospital (Kalnins et al., 2013). A register of these procedures and patients has been established at Gailezers Hospital since 2007. In 2008, the European Occlusion Club (Euro CTO Club) was founded to gather up-to-date information on CTO invasive treatments and to allow the invasive cardiologists to exchange experience. Since Euro CTO Club foundation, Latvian cardiologists have actively been involved in its work, and since 2011 most of the CTO PCI procedures performed in Latvia have been entered in the Euro CTO Club database.

There is no doubt that for some CTO patients, revascularization or recanalization does not alter the long-term prognosis and may even worsen it for some patients, especially when performing technically complex procedures with a high risk of complications. Today, when the anatomical complexity of CTO is no longer an obstacle to PCI, it is important to identify both patients, who are expected to have benefit and those who may will not have improvement.

Keywords: field of science – clinical medicine, sub-field – internal medicine; interventional cardiology, coronary heart disease, percutaneous coronary interventions, chronic total coronary artery occlusions.

Objective of the Thesis

1. To compare long-term survival results in patients after successful and unsuccessful percutaneous coronary interventions for chronic total coronary artery occlusion.

2. To compare the long-term results of procedures performed by antegrade and retrograde percutaneous coronary intervention techniques in patients with chronic total coronary artery occlusion and to clarify all anatomical, morphological and functional aspects when chronic total coronary artery occlusion can be initiated with retrograde percutaneous coronary intervention.
3. To evaluate the multifactor effect of chronic total coronary artery occlusion complexity on the outcome and survival of percutaneous coronary intervention.
4. To explore and evaluate results of percutaneous coronary interventions for chronic total coronary artery occlusions for different groups of patients:
   - with and without diabetes,
   - until and after the age of 65,
   - men and women,
   - with and without previous coronary artery bypass graft surgery.

Aim of the Thesis

The aim of the study is to compare the long-term results of invasive treatment methods for patients with coronary heart disease and chronic total coronary artery occlusions.

Hypotheses of the Thesis

1. Successful invasive recanalization of chronic total coronary artery occlusions, regardless of its complexity and regardless of the percutaneous coronary intervention technique used, is an effective

method for treating chronic total coronary artery occlusions and improves patient survival.

2. Use of the retrograde method improves the results of percutaneous coronary intervention for chronic total coronary artery occlusion, does not worsen the long-term prognosis and in some cases can be used as the primary strategy of percutaneous coronary intervention.

Scientific Novelty of the Study

According to statistics, 5–10% of all percutaneous coronary interventions are performed for chronic total occlusions. In Latvia, the long-term results of such operations have not been studied and their results and usefulness have been assessed contradictory in the scientific literature.

Approbation of the Thesis

The approbation of the Thesis was carried out on 28 June, 2021 at the meeting of the Department of Internal Diseases of Rīga Stradiņš University.

1 Materials and methods

The scientific work was performed at the Clinic of Cardiovascular Diseases in Riga East Clinical University Hospital. In 2007, a registry of invasive treatment of chronic total coronary artery occlusions was established. During 10 years, until 31 December 2016, 551 patients were included in the registry. Consent form for the PCI procedure, approved by the hospital administration, had been signed by all patients.

1.1 Description of patients and procedure included in the registry

1.1.1 Demographic and clinical characteristics

Detailed demographic, clinical and medical history was collected for all patients included in the registry:

- age (years),
- gender (male, female),
- height (cm) and weight (kg), BMI,
- smoking (never, ex, current),
- diabetes (no diabetes, insulin dependent diabetes, non-insulin dependent diabetes),
- dyslipidaemia (no or yes),
- chronic obstructive pulmonary disease (COPD) (no or yes),
- arterial hypertension (no or yes),
- prior stroke (no or yes),
- peripheral arterial disease (no or yes),
- previous myocardial infarction (no or yes),
- previous CABG (no or yes),

- previous PCI (no or yes, additional information, if PCI was performed for CTO vessel),
- angina pectoris (no or yes),
- dyspnoea (no or yes),
- ECG (normal, non-Q waves, Q waves, not evaluable),
- Echo findings (ejection fraction, presence or absence of hypo or akinesia),
- proof of ischemia (not done, negative, positive, uncertain),
- evidence of myocardial viability (no Q waves on ECG, PET, MRI, myocardial scintigraphy).

1.1.2 Assessment of coronary anatomy

- number of diseased coronary arteries (1, 2 or 3),
- CTO artery (LAD, LCX, RCA, other),
- CTO location (ostial, proximal, middle, distal),
- number of segments involved (one or more),
- bifurcation involvement (no or yes),
- CTO duration in months (undetermined, clinically confirmed, angiographically confirmed),
- how CTO duration was calculated (angiographically, clinically, undetermined),
- tortuosity (none, mild, moderate, severe),
- calcification (none, mild, moderate, severe),
- visual estimation vessel diameter (mm),
- visual estimation CTO length (mm),
- stump assessment (tapered, blunt, no stump),
- distal opacification (good, faint, no visible),

- distal vessel disease (no, minimal, severe),
- collaterals (septal, epicardial, ipsilateral),
- collateral circulation (CC0, CC1, CC2, CC3),
- previous CTO PCI attempts (no or yes),
- CTO complexity score assessment (J-CTO, Progress, CL, CASTLE).

1.1.3 Description of percutaneous coronary intervention

The registry contains detailed information of the CTO PCI procedure and devices:

- PCI procedure date,
- planed and actual approach (primarily antegrade, primarily retrograde, ante – retrograde, retro- antegrade),
- guiding catheter size (Fr),
- contralateral injections (no or yes),
- microcatheters and dedicated devices usage,
- total number of used coronary wires,
- wire brand name for collateral passage and for CTO crossing,
- total number of used balloons and brand name of balloon for CTO crossing,
- total number of implanted stents, stents sizes,
- final stenosis, final runoff (TIMI 0, TIMI 1, TIMI 2, TIMI 3),
- operation success (successful, unsuccessful),
- total time of the procedure (minutes),
- radiation exposure time (minutes),
- dose area product (Gr), cumulative Air Kerma,
- amount of contrast entered (ml),

- complications,
- biochemical and blood tests result within 48 hours after the procedure.

1.1.4 Results of percutaneous coronary intervention

In registry had listed all information of the technical results and clinical outcomes of the procedures during the intra hospital period. In 2019, patients were surveyed by obtaining data from the Centre for Disease Prevention and Control, as well as from the National Health Service. Was obtained information about the patients who died, the date of death and the causes of death.

1.1.5 CTO assessment (scoring)

All CTO lesions were evaluated according to 4 different CTO complexity scoring systems, which are based on angiography and clinical data – J-CTO score, Progress score, CL score, CASTLE score.

1.2 Subgroups of patients included in the register

Several subgroups of patients were established in the registry to evaluate the outcomes and trends of invasive treatment of chronic total coronary artery occlusion:

1. Groups of patients with successful and unsuccessful CTO PCI result.

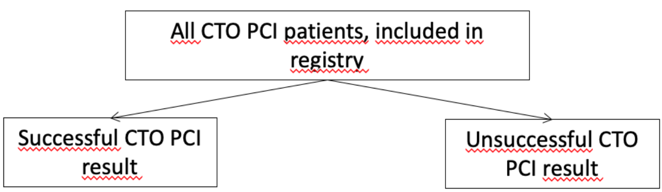


Figure 1.1 **Distribution of CTO PCI patients by procedure result**

2. Groups of patients treated with antegrade only and treated with the retrograde method.

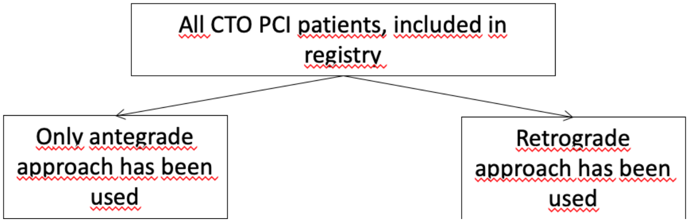


Figure 1.2 **Distribution of CTO PCI patients depending to the used approach**

3. Separate groups of patients with low, medium and high score evaluation, evaluating according to 4 different scales.

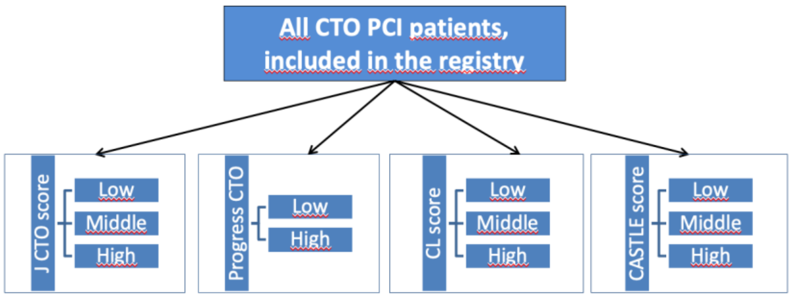


Figure 1.3 **Distribution of CTO PCI patients into subgroups depending on assessment by 4 different CTO scoring systems**

4. Separately were analysed different patient subgroups: men and women, patients before and after the age of 65, patients with and without diabetes, patients who had previous undergone coronary artery bypass graft surgery, and patients who had no history of such surgery.

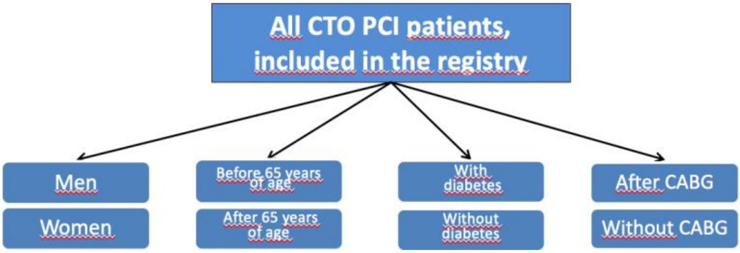


Figure 1.4 **Distribution of CTO PCI patients into subgroups according gender, age, presence of diabetes and previous CABG**

1.3 Statistical analysis

Statistical processing of data was performed using computer programs SPSS and Microsoft Office Excel. For the characterization of patient parameters, the generally accepted descriptive statistical methods were used – summary tables together with bar graphs or histograms. The arithmetic mean and standard deviation (SD) of the central trend were evaluated. The proportions in the subgroups were compared with the Chi-square test, the arithmetic means – with the two-tailed t-test, the variables that did not correspond to the normal distribution – with the Mann-Whitney U test.

Survival analysis was performed by the Kaplan-Meier method and by Cox regression. The observation period began on the day of the procedure and ended on the day of death or 31 December 2019. The percentage of patients who survived and the standard error of the mean (SE) at certain time points after the procedure were calculated. A log-rank test was used to compare Kaplan-Meier survival curves between subgroups. In Cox regression, the effects of several factors on survival were assessed by comparing them. The assumption of proportionality of risk of death was verified by visual assessment of log-log curves and no significant deviations from proportionality were observed. The association of factors with survival in the Cox regression model was expressed using the hazard ratio (HR). The association of CTO complexity with the success or failure of the procedure was only assessed with ROC curves by calculating the area under the curve (AUC) with 95% CI. A p value of <0 .05 was considered statistically significant.

2 Results

From January 1, 2007 to December 31, 2016, 551 patients were included in the CTO registry in RAKUS Gaiļezers Hospital, for whom CTO PCIs were performed. The mean age of the patients was 63.5 (+ / – 10.4) years and 80% of the patients were male. 4.5% had previous history of coronary artery bypass graft surgery (CABG) and 52.5% had a previous PCI. 20% of patients had diabetes and 72.6% had documented previous myocardial infarction (Table 2.1).

Patients were divided into two groups according to the result of the CTO PCI procedure – the successful group (N = 454) and the unsuccessful group (N = 97). Patients were also divided into two groups according to the applied technique – antegrade only approach group (N = 368) and retrograde approach group (N = 183). All patients were assessed by 4 different CTO scoring systems and according assessment, cases was divided into low, middle and high complexity subgroups. In parallel patients was divided into groups according gender, age, presence of diabetes and presence of previous CABG.

All patients received aspirin and a P2Y12 receptor inhibitor (clopidogrel) prior to the procedure. Each patient received 5,000 units of heparin at the beginning of the procedure. An additional 2,500 units were injected every hour. Activated clotting time (ACT) was not controlled. Glycoprotein 2B3A receptor blockers were not used in any of the procedures.

J-CTO, PROGRESS CTO, CL, and CASTLE scores were calculated retrospectively based on coronary angiography and medical records.

The primary end points were the result of the procedure (success) and the mortality of all causes.

CTO was defined as complete occlusion of the coronary artery (TIMI flow 0) lasting at least 3 months. The duration of occlusion was assessed based on the history (previous myocardial infarction, first onset of angina symptoms) or based on previous angiographic data. If one CTO was attempted to be opened in two or more separate procedures during the registration period, only the last procedure was included in the registry. If a patient with two or more CTOs underwent multiple CTO PCI attempts during the registration period and results was different (one procedure for one CTO was successful, the other for another CTO was not), the patient was excluded from the registry. There were 12 such patients during the study period.

A successful procedure was defined as complete restoration of antegrade blood flow (TIMI 3) with residual stenosis no more than 10%.

2.1 Comparison of successful and unsuccessful procedures

454 of the 551 registered CTO PCI procedures were successful. The number of successful procedures during 10 years has increased from 74% in 2007 up to 84% in 2016 (Figure 2.1).

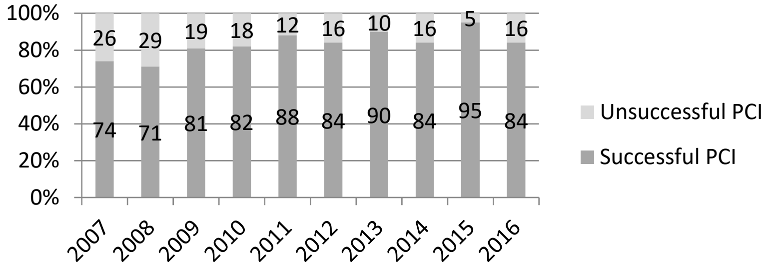


Figure 2.1 **Distribution of successful and unsuccessful CTO PCI procedures 2007–2016**

In the groups of successful and unsuccessful cases, no significant differences were found between the initial characteristics (Table 2.1). In the group of unsuccessful procedures, the percentage of patients after documented myocardial infarction and after coronary artery bypass graft surgery was higher, but statistically insignificant, and there were statistically significantly more patients after previous PCI.

Table 2.1

Characteristics of CTO PCI patients

Factors	All cases (n = 551)	Successful cases (n = 454)	Unsuccessful cases (n = 97)	p value
Average age (± SD)	63.5 (10.4)	63.3 (10.5)	64.3 (9.9)	0.394
Men, n (%)	441 (80.0%)	364 (80.2%)	77 (79.4%)	0.859
Smokers: • never • ex-smoker • current	 309 (56.1%) 173 (31.4%) 69 (12.5%)	 248 (54.6%) 146 (32.2%) 60 (13.2%)	 61 (62.9%) 27 (27.8%) 9 (9.3%)	0.296
Hypertension	461 (83.7%)	383 (84.4%)	78 (80.4%)	0.340
Dyslipidaemia	390 (70.8%)	329 (72.5%)	61 (62.9%)	0.060
Diabetes	110 (20.0%)	95 (20.9%)	15 (15.5%)	0.222
Previous MI	400 (72.6%)	323 (71.1%)	77 (79.4%)	0.099
Previous CABG	45 (8.2%)	35 (7.7%)	10 (10.3%)	0.396
Previous PCI	289 (52.5%)	229 (50.4%)	60 (61.9%)	0.041

Comparing the anatomical features of successful and unsuccessful CTO PCI cases, no association was found between the success of the procedure and the localization of CTO in the left anterior descending, left circumflex or right coronary artery. The mean diameters of the occluded coronary artery did not differ in both groups; however, the mean CTO length was longer in the unsuccessful cases group. Comparing the complexity of CTO lesions, significantly higher scores were found in the group of unsuccessful cases (Table 2.2).

Table 2.2

Successful and unsuccessful CTO PCI. Comparison of anatomical features

Variable	All cases (n = 551)	Successful cases (n = 454)	Unsuccessful cases (n = 97)	p value
CTO vessel: • LAD • LCX • RCA • Other	 176 (32.0%) 48 (8.7%) 320 (58.0%) 7 (1.3%)	 149 (32.7%) 39 (8.5%) 259 (57.1%) 7 (1.7%)	 28 (28.9%) 9 (9.3%) 60 (61.9%) 0 (0%)	0.507
Average CTO length (± SD), mm	22.5 (10.1)	22.0 (9.8)	24.7 (11.0)	0.025
Average CTO vessel diameter (± SD), mm	3.2 (0.3)	3.2 (0.4)	3.3 (0.3)	0.172
Average J CTO score (± SD)	1.8 (1.2)	1.7 (1.2)	2.5 (1.0)	< 0.001
Average PROGRESS score (± SD)	0.9 (0.8)	0.8 (0.8)	1.1 (0.7)	< 0.001
Average CL score (± SD)	3.2 (1.4)	3.1(1.4)	3.7 (1.3)	< 0.001
Average CASTLE score (± SD)	1.8 (1.0)	1.7 (1.0)	2.2 (1.0)	< 0.001

The median follow-up was 7.5 years (IQR 4.6–10.1 years); the minimum and maximum observation periods were 0.03 years and 13.0 years, respectively. Comparing the survival of patients – the percentage of patients who are alive after a certain period of time, statistically better survival was found in the successful cases group (p = 0.033) (Figure 2.2).

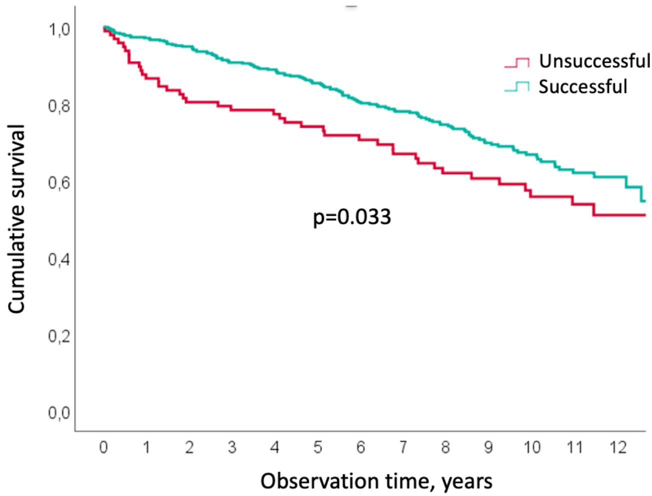


Figure 2.2 **Survival after CTO PCI depending on the outcome of the procedure**

Analysing the mortality dynamics at 1, 3, 5 and 10 years, the largest reduction in mortality after successful procedures was observed within 3 years after the procedure, when 9.3% of patients died in the successful PCI group and 21.6% in the unsuccessful PCI group (Table 2.3).

Table 2.3

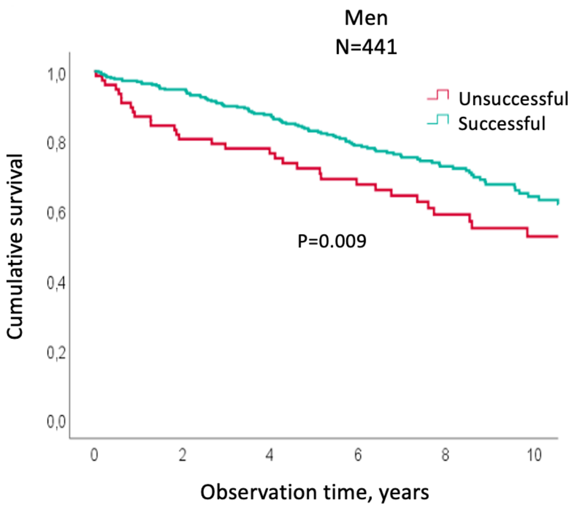
Survival after successful and unsuccessful CTO PCI. Results after 1, 3, 5 and 10 years

Result of CTO PCI	**Dead / All**	**Survival% (SE) after specific time period after the procedure**			
		1 year	**3 years**	**5 years**	**10 years**
Successful	128 / 454	97.1 (0,8)	90.7 (1.4)	85.4 (1.7)	66.7 (2.7)
Unsuccessful	41 / 97	86.6 (3.5)	78.4 (4.2)	74.0 (4.5)	55.7 (5.5)

2.2 Survival after successful and unsuccessful procedures in different patient groups

2.2.1 Men and women

Comparing patients by gender, a statistically significant relationship between successful procedure and survival was found in men (Long-rank p = 0.009). In women, on the other hand, there were practically no differences between the long-term results (Long-rank p = 0.761) (Figure 2.3). The possible explanation – the small total number of women in the study – 110.



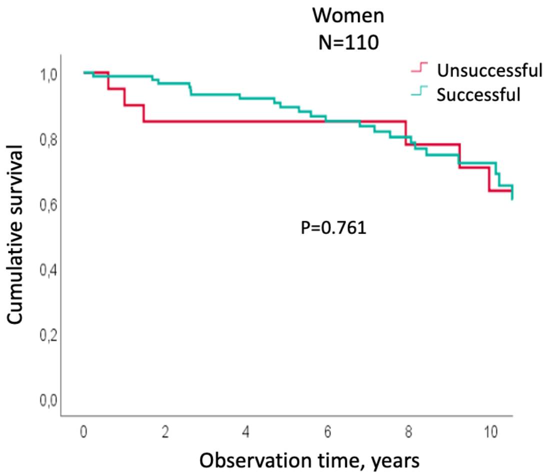


Figure 2.3 **Survival after successful and unsuccessful CTO PCI for men and women**

2.2.2 Patients before and after 65 years of age

Comparing the long-term outcomes of successful and unsuccessful procedures in patients under 65 years of age and after 65 years, the survival curve was better in both age groups for successful procedures, however, these differences were not statistically significant in either age groups (Figure 2.4).

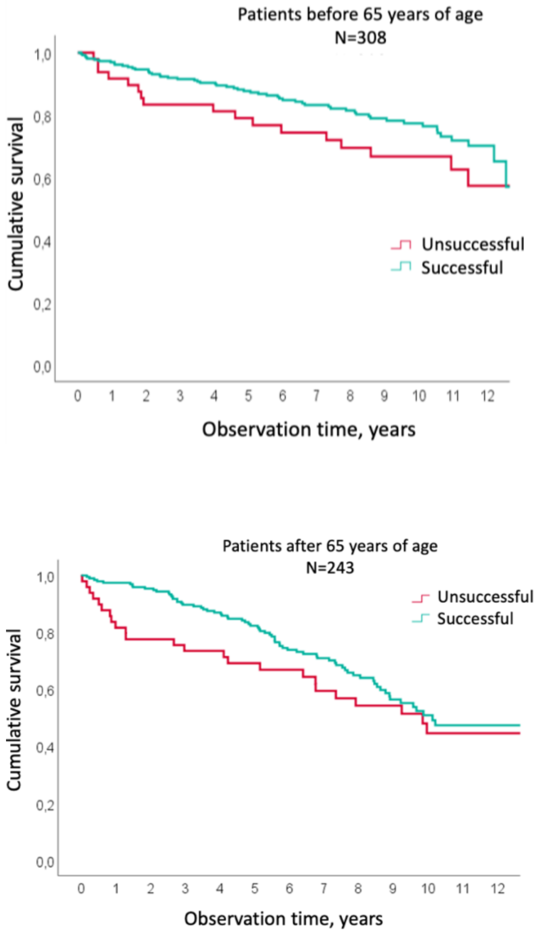


Figure 2.4 **Survival after successful and unsuccessful CTO PCI for patients before and after 65 years of age**

2.2.3 Patients with and without diabetes

Comparing patients with and without diabetes, a similar association of procedure success with survival was observed in both groups (Figure 2.5).

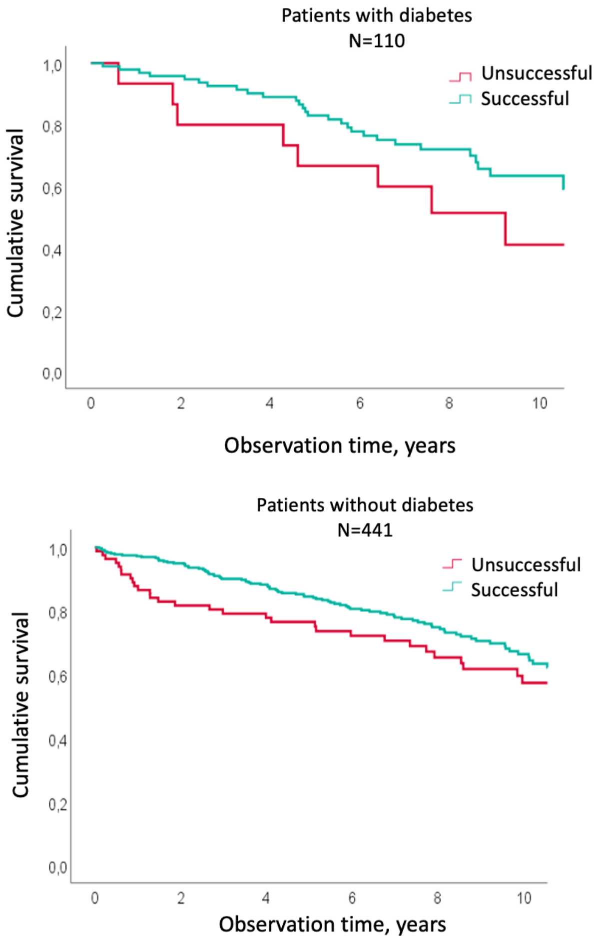


Figure 2.5 **Survival after successful and unsuccessful CTO PCI for patients with and without diabetes**

Using the Cox regression method and analysing survival depending on the success of the procedure, the patient's age, gender and the presence or absence of diabetes and comparing these factors, was found that mortality increases with age ($p < 0.001$, HR 1.05, which means that the risk of death increases of age every year by 5%) and mortality was 1.6-fold higher in men than in women (p = 0.023). The association of diabetes with a higher risk of death (HR 1.34) was not statistically significant (Table 2.4). In the case of a failed procedure, the risk of death was 46% higher, and the relationship between survival and the outcome of the procedure before and after mapping was the same. Thus, the relationship between success of the procedure and survival did not depend on the other factors included in the model. When patients were not commensurate by age, mortality was 18% higher in men that is non-statistically reliable, but after both sexes mapping by age, mortality, was 57% higher in men.

Table 2.4

Relationship between survival and procedure outcome, patient age, gender, diabetes. Cox regression model

Factors	**Without mapping**			**With mapping**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age:						
Increase by 1 year	1.04	1.02–1.06	< 0.001	1.05	1.03–1.06	< 0.001
Gender:						
male vs. female	1.18	0.81–1.73	0.384	1.57	1.06–2.32	0.023
Procedure:						
unsuccessful vs. successful	1.47	1.03 –2.09	0.034	1.47	1.03–2.09	0.033
Diabetes:						
yes vs. no	1.23	0.87–1.75	0.248	1.34	0.94–1.90	0.108

2.2.4 Patients with and without a history of coronary artery bypass grafting

45 of all 551 patients included in the registry, had a history of coronary artery bypass grafting (CABG). The mean age of patients after CABG was 64.82 years (63.35 years in the non-CABG group) and 75.56% were male. Of all CTO in this patient group, 7 was localized in LAD, 6 in LCX and 33 in RCA. In 50% of cases, a retrograde approach was used. The number of successful procedures in patient group after CABG was 78.3%.

Patients with a history of CABG had a higher incidence of both diabetes mellitus (33.3% vs. 18.8%, p = 0.019) and previous myocardial infarction (86.7% vs. 71.3%) compared to patients without previous CABG (p = 0.027). Comparing the technical aspects of the CTO PCI procedure and the applied methods, the retrograde approach for patients after CABG was significantly more often used (Table 2.5).

Survival rates in patients with a history of CABG were found to be worse than in patients without CABG (Figure 2.6) (Tables 2.5 and 2.6).

Table 2.5

Comparison of CTO PCI patients with and without a history of CABG

Factors	All (n = 551)	Without CABG (n = 506)	After CABG (n = 45)	p value
Age (±SD)	63.5 (10.4)	63.4 (10.4)	64.8 (10.7)	0.363
Men, n (%)	441 (80.0%)	407 (80.4%)	34 (75.6%)	0.433
Smokers: • never • ex • current	 309 (56.1%) 173 (31.4%) 69 (12.5%)	 286 (56.5%) 158 (31.2%) 62 (12.3%)	 23 (51.1%) 15 (33.3%) 7 (15.6%)	0.728
Hypertension n (%)	461 (83.7%)	419 (82.8%)	42 (93.3%)	0.067
Dyslipidaemia	390 (70.8%)	354 (70.0%)	36 (80.0%)	0.156
Diabetes	110 (20.0%)	95 (18.8%)	15 (33.3%)	0.019
Previous MI	400 (72.6%)	361 (71.3%)	39 (86.7%)	0.027
Previous PCI	289 (52.5%)	260 (51.4%)	29 (64.4%)	0.093
Success rate	454 (82.4%)	419 (82.8%)	35 (77.8%)	0.396
Usage of retrograde approach	183 (33.2%)	160 (31.6%)	23 (51.1%)	0.008

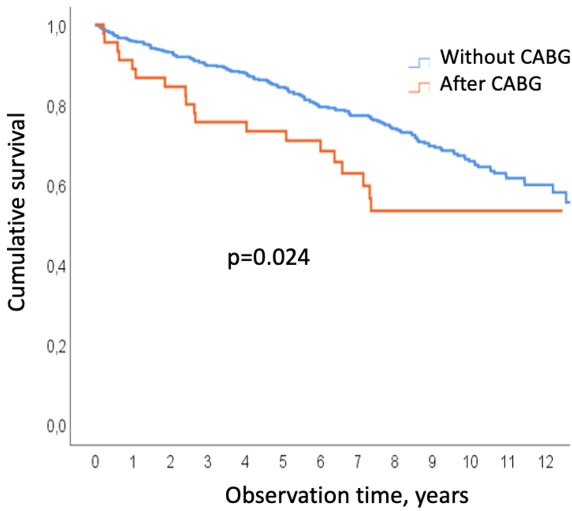


Figure 2.6 **Comparison of survival after CTO PCI for patients with and without a history of CABG**

Table 2.6

Survival after CTO PCI for patients with and without a history of CABG

Previous CABG	**PCI result**	**No of patients Dead / Total**	**Survival %**			
			1 year	**3 years**	**5 years**	**10 years**
Yes	Successful	14 / 35	94.3 (3.9)	82.9 (6.4)	79.9 (6.8)	53.9 (9.4)
	Unsuccessful	5 / 10	70.0 (14.5)	50.0 (15.8)	50.0 (15.8)	50.0 (15.8)
No	Successful	114 / 419	97.4 (0.8)	91.4 (1.4)	85.8 (1.7)	68.0 (2.8)
	Unsuccessful	36 / 87	88.5 (3.4)	81.6 (4.2)	76.8 (4.6)	56.8 (5.8)

2.3 Causes of death

During observation time died 169 patients. The leading cause of death was cardiovascular diseases (IK-I99 codes from ICD-10), from of which died 118 (69.8%) patients, from of which, in turn, 87 had coronary heart disease (I20 – I25 codes from ICD-10) and in 18 cases cerebrovascular disease (IK-I69 codes from ICD-10). The second most common group of underlying causes of death was malignancy (C00 – C97 codes from ICD-10), of which 31 patients had died (18.3% of deaths).

Analysing the relationship between the outcome of the procedure and mortality depending on the cause of death, the group of unsuccessful procedures tended to have higher mortality from any cardiovascular cause, however, the difference did not reach the level of statistical significance (p = 0.060) (Figure 2.7). Comparing deaths from CHD and deaths from malignancies, no statistically significant long-term differences were found between the groups of successful and unsuccessful procedures (Figures 2.8 and 2.9).

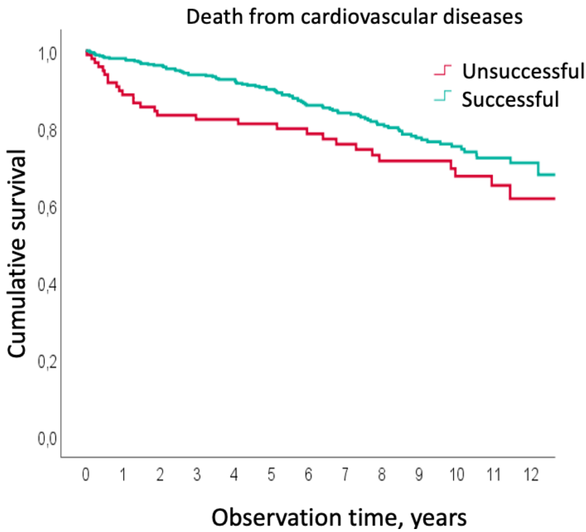


Figure 2.7 **Mortality from any cardiovascular cause in groups of successful and unsuccessful CTO PCI procedures**

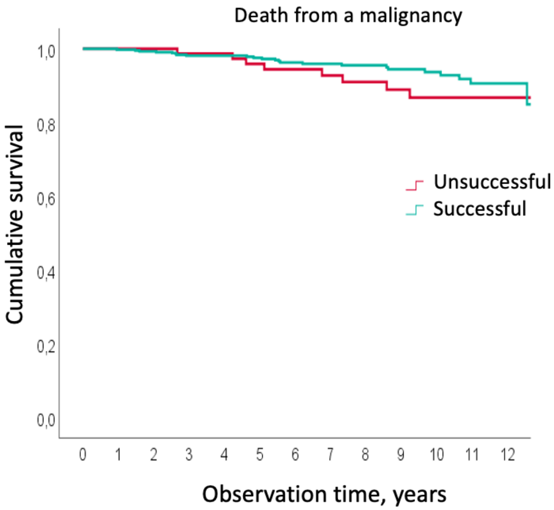


Figure 2.8 **Mortality from malignant neoplasms in groups of successful and unsuccessful CTO PCI procedures**

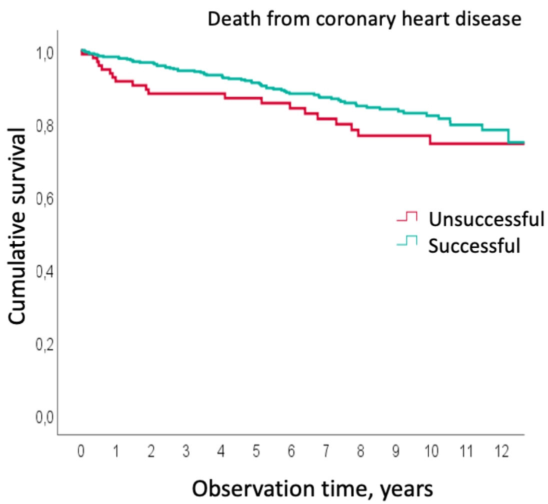


Figure 2.9 **Mortality from CHD in groups of successful and unsuccessful CTO PCI procedures**

2.4 Usage of antegrade and retrograde approach

The use of the retrograde approach has increased from 13% of cases in 2007 up to 51% of cases in 2013 and then again decreased to 40–46% in 2015–2016g. (Figure 2.10). In total, out of 551 patients included in the register, the retrograde approach was applied to 183 (33.39%) patients (Table 2.7).

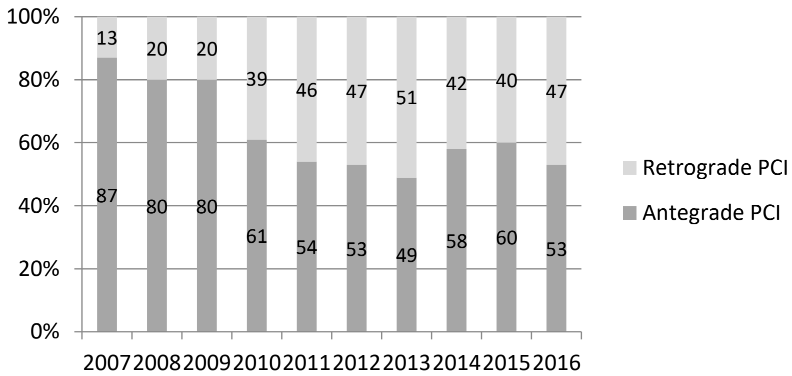


Figure 2.10. **Retrograde and antegrade approach only usage in CTO PCI cases 2007–2016**

Table 2.7

Number of retrograde CTO PCI 2007–2016

Year	All CTO PCI	Retrograde CTO PCI	Retrograde CTO PCI%
2007	69	9	13.0
2008	100	20	20.0
2009	59	12	20.3
2010	65	25	38.5
2011	50	23	46.0
2012	51	24	47.1
2013	34	17	50.0
2014	42	17	40.5

Table 2.7 continued

Year	All CTO PCI	Retrograde CTO PCI	Retrograde CTO PCI%
2015	42	16	38.1
2016	39	20	51.3
Total:	551	183	33.2

No more frequent use of retrograde method was found in relation to patients age, gender, history of infarction. Retrograde approach was more often used for patients after CABG ($p = 0.008$), after previous PCI ($p < 0.001$), as well as in patients who had repeated CTO attempt ($p < 0.001$). This approach also was more often used for patients with more complex CTO lesions (with higher scores on all 4 scoring systems) ($p < 0.001$) (Table 2.8).

Two strategies for retrograde approach were applied: retrograde as primary strategy, including second stage repeat procedures after previous antegrade failure and retrograde immediately after antegrade failure in one session.

Out of all 183 retrograde CTO PCI, in 151 (83%) cases the retrograde method was applied immediately after an unsuccessful attempt to cross the occlusion antegrade and 92 (60.5%) procedures were successful. In 32 (17%) cases, the procedure was initiated primary retrograde, of which in 9 cases it was done due to previous unsuccessful antegrade attempt had been performed, 13 (59%) and 5 (55%) procedures were successful, respectively (Table 2.9).

Comparing two different strategies for performing retrograde CTO PCI procedures, was found that primary retrograde approach was more often used for patients with more complex anatomy, especially in cases with ambiguous proximal cap. The length of the occluded segment didn't play a role in the choice of primary or secondary retrograde strategy, as this indicator does not differ in the two groups (Table 2.10).

Table 2.8

Correlation of retrograde method application with various factors

Correlation	Spearman r	p value
Retr vs. gender	–0.073	0.086
Retr vs. age	0.012	0.786
Retr vs. previous MI	0.026	0.548
Retr vs. diabetes	–0.061	0.158
Retr vs. previous CABG	0.113	< 0.001
Retr vs. previous PCI	0.225	< 0.001
Retr vs. previous attempt	0.227	< 0.001
Retr vs. final result	–0.179	< 0.001
Retr vs. J-CTO score	0.331	< 0.001
Retr vs. PROGRESS score	0.176	< 0.001
Retr vs. CASTLE score	0.265	< 0.001
Retr vs. CL score	0.315	< 0.001
Retr vs. stent length	0.074	0.084

Table 2.9

Strategies of applying retrograde method and their success

Factors	**Retrograde immediately after failed anterograde**	**Retrograde as primary strategy**	**Retrograde after previous failed anterograde**
All procedures (successful / unsuccessful)	151 (92 / 59)	23 (13 / 10)	9 (5 / 4)
Success rate (%)	61	57	55

Table 2.10

CTO complexity parameters for primary and secondary retrograde approaches

Complexity parameter	Retrograde immediately after failed anterograde (n = 151)	Retrograde as primary strategy (n = 32)
CTO ostial location (n, %)	16 (11%)	8 (25%)
Ambiguous proximal cap (n, %)	41(27%)	14 (44%)
CTO length > 20 mm (n, %)	80 (53%)	16 (50%)
Previous failed anterograde attempt (n, %)	27 (18%)	9 (28%)

2.5 Relationship between CTO complexity and long-term outcome

For all 551 patients, enrolled in the study, retrospectively were calculated CTO complexity by 4 different scoring systems: J-CTO, PROGRESS, CASLTE and CL. Depending on the number of points collected, patients were divided into low, medium and high complexity groups. The distribution of patients was uneven, with the majority of patients in the low and medium complexity groups (Table 2.11).

Table 2.11

Distribution of patients by disease severity according to different scoring systems

<table>
<tr><th colspan="2">J-CTO</th><th colspan="2">PROGRESS</th><th colspan="2">CASTLE</th><th colspan="2">CL*</th></tr>
<tr><th>Score</th><th>N</th><th>Score</th><th>N</th><th>Score</th><th>N</th><th>Score</th><th>N</th></tr>
<tr><td>0</td><td>82</td><td>0</td><td>182</td><td>0</td><td>62</td><td rowspan="6">0–1
1.5–2.5
>2.5</td><td rowspan="6">71
146
334</td></tr>
<tr><td>1</td><td>165</td><td>1</td><td>255</td><td>1</td><td>146</td></tr>
<tr><td>2</td><td>165</td><td>2</td><td>105</td><td>2</td><td>202</td></tr>
<tr><td>3</td><td>111</td><td>3</td><td>9</td><td>3</td><td>118</td></tr>
<tr><td>4</td><td>28</td><td rowspan="2">4</td><td rowspan="2">0</td><td>4</td><td>22</td></tr>
<tr><td>5</td><td>0</td><td>5</td><td>1</td></tr>
</table>

* Due to the complex scoring, 16 different results are possible on the CL scale, so patients are divided into 3 groups

Comparing the CTO complexity with the results of the procedure, was found that as the level of complexity increased, the number of successful procedures significantly decreased in all scoring systems (Figure 2.11), however less significant correlation was found in the PROGRESS CTO score (Tables 2.12 and 2.13). All four scoring systems had moderate predictive power (AUC for J-CTO 0.714, $p < 0.001$; AUC PROGRESS for CTO 0.605, $p < 0.001$; AUC CL for 0.624, $p < 0.001$; AUC CASTLE for 0.641, $p < 0.001$), but assessment by J CTO was more accurate than others (Figure 2.11).

Table 2.12

Distribution of patients according to the degree of CTO complexity and its correlation with the outcome of the procedure

<table>
<tr><th>Level of complexity
(score value)</th><th>Quantity</th><th>Successful
procedures, n (%)</th><th>p value</th></tr>
<tr><td colspan="4">J-CTO</td></tr>
<tr><td>Low (0; 1)</td><td>247</td><td>229 (92.7%)</td><td rowspan="3">< 0.001</td></tr>
<tr><td>Middle (2)</td><td>165</td><td>136 (82.4%)</td></tr>
<tr><td>High (3; 4; 5)</td><td>139</td><td>89 (64.0%)</td></tr>
<tr><td colspan="4">PROGRESS</td></tr>
<tr><td>Low (0; 1)</td><td>437</td><td>369 (84.4%)</td><td rowspan="2">0.014</td></tr>
<tr><td>High (2; 3; 4)</td><td>114</td><td>85 (74.6%)</td></tr>
</table>

Table 2.12 continued

Level of complexity (score value)	Quantity	Successful procedures, n (%)	p value
CASTLE			
Low (0; 1)	208	188 (90.4%)	< 0.001
Middle (2; 3)	320	250 (78.1%)	
High (4;5;6)	23	16 (69.6%)	
CL			
Low (0–1)	71	68 (95.8%)	< 0.001
Middle (1.5–2.5)	146	126 (86.3%)	
High (> 2.5)	334	260 (77.8%)	

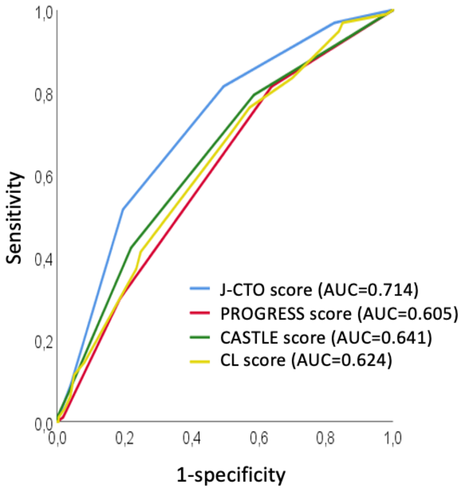


Figure 2.11 **ROC curves: predictability of a successful procedure according to different CTO scoring systems'**

Table 2.13

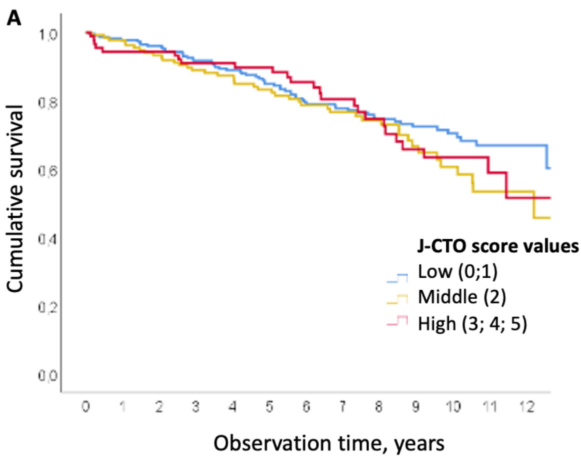
ROC curves: predictability of a successful procedure according to different CTO scoring systems

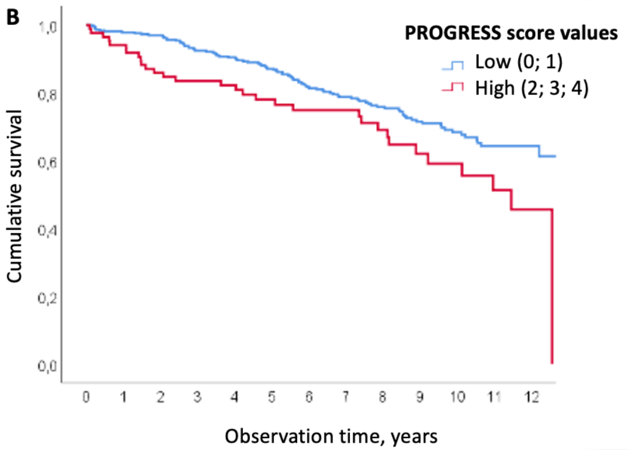
Scoring system	AUC*	95% CI	p value
J-CTO	0.714	0.660–0.768	< 0.001
PROGRESS	0.605	0.546–0.665	0.001
CASTLE	0.641	0.581–0.701	< 0.001
CL	0.624	0.565–0.683	< 0.001

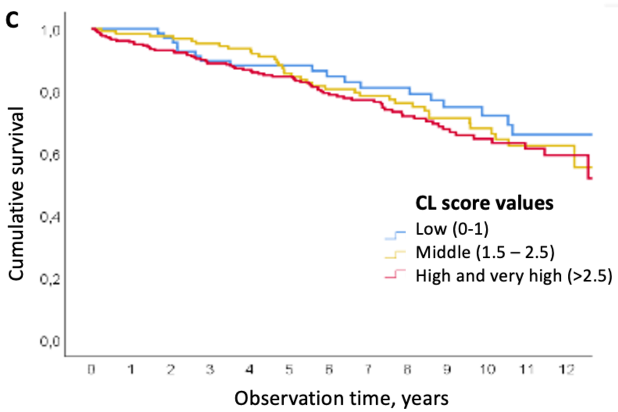
*AUC – area under curve

The complexity of CTO, measured by PROGRESS and CASTLE scores, showed association with all-cause mortality (Figure 2.12), however, after 5 years, significant association with events was found only for the PROGRESS indicator (Table 2.14). Mortality was 64% higher in patients with a high PROGRESS score than in patients with a low score (HR 1.64; 95% CI 1.09–2.46); and for patients with high and moderate CASTLE scores were 2.6-fold (HR 2.64; 95% CI 1.11–6.27) and twice (HR 2.05; 95% CI 1.39–3.02), respectively, higher than in patients with low scores. Mapping by gender and in case of J CTO and PROGRESS scores also by age (because age is not included in these scores) did not affect the results (Table 2.15).

Further comparison of CASTLE score results with age slightly reduced the strength of the association: mortality hazard ratio (HR) for patients with a high score was 1.83 (95% CI 0.75–4.50; p = 0.185) and for patients with a medium score of 1.63 (95% CI). CI 1.09–2.45; p = 0.017) compared to the group with the lowest score, suggesting that older age partially contributed to this association. In case of PROGRESS score, the age adjustment did not affect the calculations.




B
PROGRESS score values
Low (0; 1)
High (2; 3; 4)
Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
0
1
2
3
4
5
6
7
8
9
10
11
12
Observation time, years


C
CL score values
Low (0-1)
Middle (1.5 – 2.5)
High and very high (>2.5)
Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
0
1
2
3
4
5
6
7
8
9
10
11
12
Observation time, years

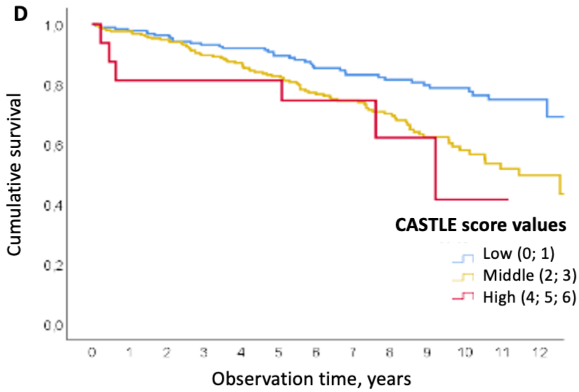


Figure 2.12 **Survival after successful CTO PCI procedures depending on CTO complexity, assessed using different scoring systems**

A – JCTO score; B – PROGRESS score; C – CL score; D – CASTLE score.

Table 2.14

Relationship between CTO complexity and 5-year survival, according to different scoring systems for patients after successful procedures

CTO complexity (score values)	5 years survival, %	95% CI, %	p value
J-CTO			
Low (0; 1)	83.5	78.4–88.6	> 0.05
Middle (2)	81.9	75.2–88.6	
High (3; 4; 5)	89.5	83.0–96.0	
PROGRESS			
Low (0; 1)	86.3	82.6–90.0	0.028
High (2; 3; 4)	74.6	64.8–84.4	
CASTLE			
Low (0; 1)	88.0	83.1–92.9	> 0.05
Middle (2; 3)	81.9	77.0–86.8	
High (4; 5; 6)	74.5	52.9–96.1	
CL			
Low (0–1)	86.3	78.1–94.5	> 0.05
Middle (1.5–2.5)	84.0	77.1–90.9	
High (>2.5)	83.7	79.0–88.4	

Table 2.15

Relationship between CTO complexity and survival throughout the observation period according to different scoring systems by complexity of procedures

Scoring system and score value	No of patients dead / total	Without mapping			Mapped by gender and age*		
		HR	95% CI	p value	HR	95% CI	p value
J-CTO							
Low	60 / 229	Ref.	–	–	Ref.	–	–
Middle	43 / 136	1.33	0.90–1.97	0.151	1.34	0.91–1.99	0.142
High	25 / 89	1.18	0.74–1.88	0.490	1.12	0.70–1.79	0.641
PROGRESS							
Low	97 / 369	Ref.	–	–	Ref.	–	–
High	31 / 85	1.64	1.09–2.46	0.017	1.69	1.12–2.55	0.012
CASTLE							
Low	37 / 188	Ref.	–	–	Ref.	–	–
Middle	85 / 250	2.05	1.39–3.02	< 0.001	2.05	1.39–3.03	< 0.001
High	6 / 16	2.64	1.11–6.27	0.028	2.66	1.12–6.33	0.027
CL							
Low	18 / 68	Ref.	–	–	Ref.	–	–
Middle	36 / 126	1.16	0.66–2.04	0.606	1.16	0.66–2.05	0.605
High	74 / 260	1.33	0.80–2.24	0.275	1.33	0.79–2.24	0.281

* CASTLE and CL – only proportional to gender, as age is already included in the scale.

2.6 Complications

No serious vascular access site complications were observed for any patients enrolled in the study. Also, none of the patients had complications related to contrast administration and radiation. Renal function after procedures was controlled only for patients with known renal impairment.

Cardiac complications associated with the PCI procedure were observed in 29 patients, representing 5.25%. Two aortic dissections were reported, both of which were treated conservatively. In three cases occurred material entrapment. Coronary artery perforations occurred in 19 cases, leading to cardiac tamponade in 5 cases. All tamponade cases were successfully treated with pericardial drainage and subsequent insertion of coil into the perforated blood vessel. No deaths were observed in the intra-hospital stay period in any of patients.

More perforations were found in cases, where retrograde approach was used (perforations 5.46% vs. 2.44%) (Table 2.16).

Comparing the cumulative survival of patients after successful CTO PCI procedures, no significant difference was found between patients who was treated used only the antegrade approach and those who was treated used retrograde approach. Also, comparing the cumulative survival of patients after unsuccessful CTO PCI, no differences were found depending on the antegrade or retrograde approach, suggesting that the highest number of perforations in the retrograde method group does not affect patient long-term survival (Figure 2.13 and Figure 2.14).

Table 2.16

CTO PCI complications

Complications	**All cases (n = 551)**	**Antegrade approach (n = 368)**	**Retrograde approach (n = 183)**	**P value**
Aortic dissection	2 (0.36%)	1 (0.27%)	1 (0.54%)	–
Equipment lost and entrapment	3 (0.54%)	2 (0.54%)	1 (0.54%)	–
Perforations, including cardiac tamponade	19 (3.44%) 5 (0.90%)	9 (2.44%) 1(0.27%)	10 (5.46%) 4 (2.18%)	p = 0.07 p = 0.03
Intrahospital death	0	0	0	–

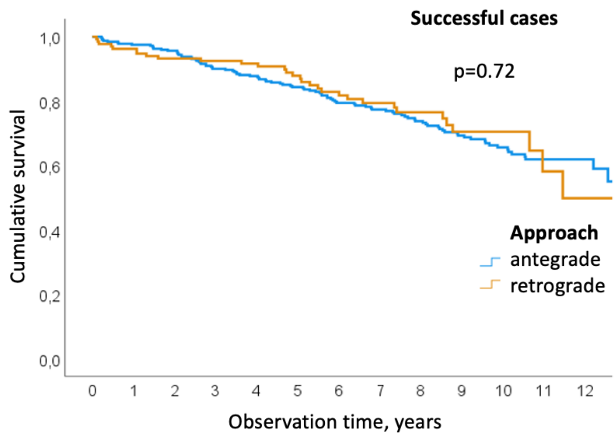


Figure 2.13 **Comparison of cumulative survival after successful CTO PCI procedures performed using retrograde or antegrade only approach**

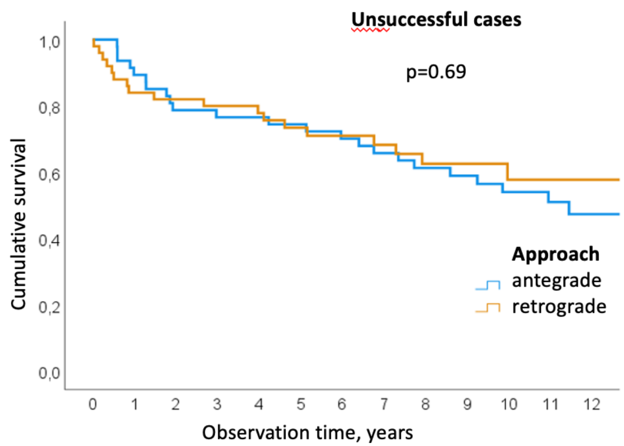


Figure 2.14 **Comparison of cumulative survival after unsuccessful CTO PCI procedures performed using retrograde or antegrade only approach**

3 Discussion

This retrospective study has analysed a group of 551 patients who underwent CTO PCI procedures at a single centre during the 10 years. 454 procedures were successful. The number of successful procedures has increased from 73.9% in 2007 to 84.4% in 2016. The increase in successful procedures correlates with the increase in the use of the retrograde approach, which increased from 13% in 2007 to 47% in 2016. A meta-analysis of 26 studies published in 2014 on the use of the retrograde method showed similar trends (El Sabbagh, 2014).

The study confirmed that patients had better survival after a successful CTO PCI compared to a failed CTO PCI. Several randomized comparative studies have shown the beneficial effects of CTO recanalization on symptoms, quality of life, and left ventricular function (Joyal et al., 2010: Christakopoulos et al., 2015), however its effect on long-term prognosis remains unclear (Christakopoulos et al., 2015; Joyal et al., 2010; Lee et al., 2016; Henriques et al., 2016). In a DECISION-CTO study, for example, all types of death, MI, stroke and any revascularization after 3 years observational period were similar for the PCI and optimal medical treatment group and for the optimal medical therapy only group (20.6% vs. 19.6%) (Lee, 2019). It should be noted, however, that only medically treated group in this study was relative, because for patients in this group it was allowed to perform PCI for non-CTO lesions and the average number of stents implanted per patient in each group, was not significantly different.

Relatively recently published ISCHEMIA trial results induced a wide-ranging discussion. Although ISCHEMIA was not CTO trial, it included patients with proven ischemia, and this study also failed to demonstrate that revascularization provided clinical benefit in addition to optimal medical therapy.

On the other hand, the efficacy of CTO PCI for reducing symptoms has been confirmed in a Euro CTO study that showed a better effect of PCI and optimal medical therapy on the incidence and quality of life of angina compared to optimal medical therapy only (Werner et al., 2018), for that reason CTO PCI in most of centres are performed generally for symptomatic patients and refusal to do CTO PCI is often justified by the lack of randomized data that successful CTO PCI could improve long-term outcome.

Analysing 460 patients who was included in the Syntax study with at least one CTO and comparing 10-year outcomes in patients after successful and unsuccessful CTO revascularizations, was not find any differences in mortality, regardless of whether the patient underwent PCI or CABG (Table 3.1) (Kawashima et al., 2021)

Table 3.1

10-year mortality for CTO patients after invasive recanalization and surgical revascularization (Kawashima, 2021)

	Successful	Unsuccessful	HR	95% CI
PCI	29.9%	29.4%	0.99	0.47–2.08
CABG	28.0%	21.4%	0.66	0.28–1.53

The study has not found that localization of CTO would affect mortality. Comparing CTO only in the left anterior descending and CTO in the left circumflex artery, mortality did not differ between successful and unsuccessful recanalized or revascularized patients (34.5% vs. 26.9%; adjusted HR 0.90; 95% CI 0.31–2, 56). Comparing PCI and CABG, PCI success rates were lower than with CABG (43.5% vs. 60.5%; $p < 0.001$) (Kawashima, 2021).

It should be noted that the number of successful CTO revascularizations and recanalizations in the Syntax study was very small, with only 49% successful CTO PCI procedures and 68% successful surgical recanalization (Farooq, 2013), which is insufficient to assess the long-term benefits of successful revascularization or recanalization.

In another analysis of 2,659 CTO patients in China, they were followed for 5 years (Guan, 2021). In difference to the traditional patient division into two groups – after successful and after unsuccessful procedures, in this study patients were divided into three groups:

- Optimal recanalization (58.7%): Reperfusion of CTO and side branches (if any) with TIMI 3 flow rate.
- Suboptimal recanalization (15.0%): CTO reperfusion with TIMI 1–2 flow and / or residual stenosis > 30% and / or large occluded side branches.
- Unsuccessful procedures (26.3%): The balloon catheter couldn't cross CTO during the procedure.

Successful CTO recanalization over five years was not associated with a reduced risk of cardiac death or myocardial infarction compared to unsuccessful procedures but was significantly higher in those who had suboptimal result (10.1%) compared to those with optimal recanalization (6.5%; $p = 0.02$) and those who failed the procedures (6.3%; $p = 0.03$). During the follow-up period periprocedural myocardial infarction and re-revascularization also were more common in the suboptimal recanalization group. Main reason of myocardial infarction in the suboptimal group was side branch occlusions.

The study concludes that one of the most important measures that could increase the number of successful and optimal CTO PCI is careful pre-procedure planning using one of the CTO scoring systems or multi slice computed tomography coronary angiography. The study also confirms that, in the absence of optimal CTO recanalization, the decision to discontinue the procedure may be the best option in cases where procedure continuing and stenting may lead to a suboptimal angiographic result. It should be noted that the study report did not include information of the procedure effect on the patient's symptoms (angina class) (Guan, 2021).

In our study, a separate, suboptimal CTO revascularization group was not distinguished. However, the small number of serious complications is an indirect indication of a relatively moderate strategy for performing CTO PCI. This may have avoided sub-optimal result procedures inclusion in the successful procedure group, which in turn could reduce survival in the successful procedure group.

Recently was published a meta-analysis of 25 studies, involving a total of 19,806 patients with stable CHD. In all studies was comparing revascularization plus medical versus only medical therapy and analysing both cardiac mortality and spontaneous myocardial infarction and their association with cardiac death. Three of the 25 studies were CTO studies, but patients with CTO were also included in the majority of other. A meta-analysis conclusively shows lower cardiac mortality and a lower number of spontaneous myocardial infarctions in the group of revascularized patients (Navarese et al., 2021). In our study, cases of spontaneous myocardial infarctions during the observation period were not counted, but was analysed total cardiovascular mortality. Our study showed significantly higher overall ($p = 0.033$) and cardiovascular mortality ($p = 0.06$) in the failed CTO PCI group, while the number of deaths due to oncological causes did not differ between the two groups. In total, we can assume that the meta-analysis data of 25 studies are in line with the results of our study.

So far, the studies comparing the long-term results of invasive plus optimal medical treatment versus only optimal medical treatment strategies, have mostly considered the overall mortality. This is probably one of the reasons why the benefits of invasive treatment strategy have not been evaluated and proven up to now. It is clear that the number of non-cardiac deaths is increasing every year, and in the case of prolonged follow-up, mortality will inevitably approach 100%, regardless of treatment. In our study, we compared patients up to and after the age of 65 years. Patients under the age of 65 had a 49% higher overall mortality after failed CTO PCI procedures, and patients over the age of 65 had a 32% higher mortality after unsuccessful procedures. This is logical, because in the case of long-term observation time, as was the case in our study, older patients die more, regardless of the outcome of the procedure. A more accurate indicator of the long-term outcome of invasive treatment is likely to be cardiac death or the incidence of recurrent spontaneous myocardial infarction.

The retrograde approach in our study was used for 183 patients, of which in 31 cases it was the primary strategy. The percentage of successful procedures was the same both, when the retrograde method was used immediately after unsuccessful antegrade attempt and when it was used as the first strategy, which shows that the decision to start procedure immediately retrograde in these cases was correct. Comparing the anatomical complexity for retrograde CTO PCI patients, it can be seen that in cases, when procedure was started primary retrograde, was a more ambiguous proximal cup, was more ostial CTOs, and more frequent was done previous unsuccessful CTO PCI attempts. On the other hand, such indicator of complexity as the length of the occluded segment does not differ between the two groups, which means that it did not serve the choice of starting the procedure with retrograde approach.

Although higher number of the most serious complications – perforations – was found in the retrograde approach group, long-term survival in this patient group was not affected. To be objective, we compared survival both between successful antegrade and successful retrograde procedures, and between unsuccessful antegrade and unsuccessful retrograde procedures.

In unsuccessful group, the survival was better even for the retrograde patients. That means, that timely complications diagnostic and successful treatment can reduce the patient's risk to a minimum.

Recently, the data from a CTO patient registry in Netherlands including 212 patients was published. All patients had undergone the PET scans for detecting the myocardial ischaemia before and 3 months after the procedure. The mean age of the patients was 62 years and 84% of them were male. 16% of patients were asymptomatic, 41% had a retained left ventricular ejection fraction, but 59% had a slight EF reduction (EF above 40%). After a median follow-up of 2.8 years, mortality was 8% and 2% of patients had experienced non-fatal myocardial infarction. Better survival was observed in patients with improved perfusion and no residual ischemia ($p = 0.04$; HR 0.34; 95% CI 0.13–0.93). Better survival was also observed in patients who achieved an increase in hyperaemic myocardial blood flow (hMBF) above the population mean after CTO PCI ($p < 0.01$; HR 0.16; 95% CI 0.05–0.54) (Schumacher et al., 2021). Although this was not a randomized study but a registry, it demonstrates that long-term benefits can be obtained by performing a technically perfect procedure in a centre with extensive experience in performing CTO PCI in properly selected patients.

An explanation for why some of the registries show a benefit from CTO PCI while randomized trials do not, could be their scope. In randomized, multi-centre studies, there are inevitably risks of both patient selection and different data interpretations, as well as differences in the quality of revascularisation procedures.

In our study, ischemia tests were not performed neither before, nor after the CTO PCI procedure, and the main indication for PCI was symptoms. In Netherlands study, 16% of patients were asymptomatic, but qualitative ischemia tests showed that almost all CTO patients (93%) had inducible ischemia. This calls into question the usefulness of ischemia tests for CTO patients with single artery disease if symptoms exist and myocardial contractility is preserved.

Despite good angiographic results, 50% of patients in the Netherlands study of successful CTO PCI still had residual ischemia, and there are currently no precise methods to predict which patient will benefit from the CTO PCI procedure and which will not. The answer is most likely to be found in the assessment of the complexity of the CTO.

The first CTO complexity scoring system, the J CTO score, was developed to predict the possibility of crossing the CTO with a string and thus to predict the technical outcome of the procedure (Joyal, 2010). Procedures with higher CTO scores are more technically complex and have a lower level of success. More complex procedures, in turn, are associated with the use of more aggressive techniques, higher material consumption, longer procedure duration, higher radiation and contrast consumption, as well as a higher risk of complications.

Our study evaluated whether technically complex CTO angioplasty affects long-term outcomes. It is no secret that the cause of a failed CTO PCI and / or the reason for terminating the procedure are often complications. In order to objectively assess whether invasive treatment of technically complex CTO actually affects patient survival, only the results of successful procedures of varying complexity were compared.

No differences in long-term results were found between procedures of varying complexity when analysing cases with the J CTO and CL scoring systems. At the same time, when analysing cases with PROGERESS CTO and CASTLE, more complex patients had a statistically worse long-term prognosis. Some of the CTO complexity indicators are included in several scoring systems, but some are unique. The PROGRESS CTO scoring system differs from the others because it is based only on 4 anatomical criteria, including the absence of collaterals for retrograde approach and CTO localization in the left circumflex coronary artery, which are not included in any other scoring system as complexity criteria. These two factors certainly complicate the procedure, as the prognostic value of the PROGRESS CTO scale did not differ significantly from other scales – a high number of PROGRESS CTO scores correlated with a lower number of successful procedures. On the other hand, correlation, compared to other scoring systems was lower and that indicating a lower prognostic value of these two factors. The importance of CTO LCX localization as an indicator of complexity was not confirmed by trials or observation studies. However, long-term outcomes were significantly worse in patients with higher PROGRESS CTO scores than in those with low scores. Comparing different scoring systems according to the maximum possible number of difficulty points, for PROGRESS it is the smallest – maximum only 4 points, thus the distribution of the patients is not as wide as in other scores and the value of each individual difficulty point increases. Chronic total occlusions in the left circumflex coronary artery are less common than in the left anterior descending or right coronary artery. There are no studies that suggest a worse prognosis in patients with LCX CTO. The presence or absence of collaterals for angioplasty, in turn, is a very important factor that is included in all CTO crossing algorithms. The absence of usable collaterals allows only the use of antegrade CTO crossing techniques. This, in turn, can increase the risk of side branch closure and periprocedural myocardial infarction in more complex cases, which, according to the above-mentioned study in China, may lead to a suboptimal outcome and worsen the long-term outcome of the procedure.

The CASTLE score differs in that it includes the patient's age and a history of coronary artery bypass graft surgery as factors of complexity. Age and aging are known as independent risk factor for cardiovascular events (Stahli, 2018).

The previous CABG in patient anamnesis, in turn, can be assessed as a set of potential several, important risk factors, as CTO patients with a history of CABG are both older and more likely have had a myocardial infarction, as well as more often have undergone previous PCI. Although the majority of CTO patients (60%) do not have previously documented MI (Fefer et al., 2012), more than 90% of CTO patients can detect scar tissue in the CTO zone (Schumacher et al., 2021). CTO after a myocardial infarction is known to be an independent risk factor for ventricular arrhythmias, which increases the occurrence of ventricular arrhythmias 2 – 3 times even after radiofrequency ablation (Di Marko et al., 2017, 2019). Patients with CTO and implanted defibrillator-cardioverter for primary or secondary prevention of sudden cardiac death have more frequent device discharges than patients with ischemic cardiomyopathy and without CTO (Fefer et al., 2012). The necrotic zone and scar tissue are likely to serve as causative factor of ventricular arrhythmia (Di Marko et al., 2017, 2019). This all may lead to poorer long-term results for patients with a higher CASTLE score.

A little bit unexpected finding of our study turned out to be the comparison of long-term CTO PCI results after successful and unsuccessful procedures for men and women. No significant differences in survival were found between the groups of successful and unsuccessful procedures for women. However, looking careful to other registers we can see that similar results have been obtained in other studies. According to various observations, CTO is less common in women and the proportion of women in CTO PCI registers usually varies between 10 and 20%. A study, done in the United States and Korea from

1998 until 2007, included 1791 CTO PCI patients and only 14% of patients were female. Comparing successful and unsuccessful procedures, during the 2.9-year observation period, there were significantly less major cardiovascular events in successful procedures group for both men and women (men 13.1% vs. 24.4% ($p < 0.01$), women 12.3 versus 15.5% ($p = 0.04$)), however, a much larger decrease in events was observed in the male group ($p < 0.01$) (Claessen, 2012).

In similar study in China, published in 2019 was included only 1702 patients and 23.5% were female. In this study, half of the patients received only optimal medical therapy and the other half underwent CTO PCI. Patients were divided into 3 groups: optimal medical treatment only, patients after successful CTO PCI, patients after unsuccessful CTO PCI. The optimal medical treatment group was compared with the successful CTO PCI group. There were no significant differences between the medical treatment and successful CTO PCI groups in the female group in terms of cardiac death (medical treatment against successful PCI: 6.8% vs. 3.9%, $p = 0.287$) and major cardiovascular events (20.9% vs. 21.3%, $p = 0.810$). In the male group, cardiac deaths (MT versus successful PCI: 6.6% vs. 3.8%, $p = 0.066$) were similar in both groups, but the rate of major cardiovascular events (30.0% vs. 18.5%, $p < 0.001$) was significantly higher in the medical therapy only group (Guo et al., 2019).

The average age of the women in our study and in both studies mentioned above was higher than that of the men. This confirms the previously known fact about the protective effect of oestrogen on the development of atherosclerosis in women before menopause and the subsequent development of atherosclerosis. Older age, on the other hand, reduces the differences between successful and unsuccessful CTO PCI patient groups with a long follow up time.

46 (8.35%) of the patients included in the study had CABG medical history in anamnesis. Compared to other CTO PCI registries, where the number of CABG patients ranges from 7.5% in Japan (Muramatsu et al., 2014) to 37% in North America (Dautov, 2016), this percentage is not high, which can be explained by the historical relationship between PCI and CABG performance in Latvia, where it is 7–8 : 1. There were no statistically significant differences in clinical characteristics between patients with and without a history of CABG, however analysed parameters showed that bypass patients were generally older and sicker, they more often had cardiovascular diseases risk factors – hypertension and dyslipidaemia, and more often they had myocardial infarction and previous PCI in history. For these patients a retrograde approach was used more frequently. The number of successful procedures was lower, and the long-term survival after successful CTO PCI procedures was worse. This could allow to consider CTO patients post CABG as high-risk patients. However, percentage of post CABG patients in our study was low, thus not allowing for an objective and complete analysis of this group of patients.

Conclusions

1. Successful revascularization of CTO, compared to unsuccessful, improves patient survival.
2. The use of the retrograde method improves the results of procedures and does not worsen the prognosis. The retrograde method should be considered as the primary strategy in cases where the CTO localized ostially and/or proximal entrance is unclear.
3. CTO complexity, determined using the J CTO, PROGRESS CTO, CL, and CASTLE scales, directly correlates with CTO PCI outcome, but does not affect patient survival.
4. CTO revascularization provides better survival for men than for women. The presence or absence of diabetes does not affect the long-term results of CTO PCI. For patients under 65 years of age, survival after a successful PCI procedure is not related to the patient's age but to the outcome of the procedure. Patients with a history of CTO and coronary artery bypass graft surgery should be considered as patients with increased complexity of CTO PCI.

Hypotheses

The hypothesis “successful invasive recanalization of chronic total coronary artery occlusions, regardless of its complexity and regardless of the percutaneous coronary intervention technique used, is an effective method of treating chronic total coronary artery occlusions and improves patient survival” was confirmed in the study. Patients had statistically significantly better survival after successful CTO PCI procedures than after unsuccessful CTO PCI procedures.

The hypothesis "application of retrograde method improves the results of percutaneous coronary intervention of chronic total coronary artery occlusion, does not worsen long-term prognosis and in some cases can be used as the primary strategy of percutaneous coronary intervention" was also confirmed in the study. A correlation has been found between the application of the retrograde method and the increase in the number of successful procedures. No deterioration in survival was observed in retrograde patients. Success in the case of primary retrograde CTO PCI was found to be similar to that in the retrograde method immediately after an unsuccessful antegrade attempt.

Possible practical application of the results

Based on the results of the work, has been confirmed the importance of successful CTO PCI for improving patient survival. Has been proved the importance of using of retrograde method to improve the results of CTO revascularization. The introduction of the retrograde method in clinical practice throughout Latvia has been promoted. Has been demonstrated the importance of assessing the complexity of the CTO to predict both the outcome and the long-term results of the procedure.

Publications

Scientific publications in international peer-reviewed journals:

1. Kalnins, A., Strele, I., Lejnieks, A. 2019. Comparison among Different Scoring Systems in Predicting Procedural Success and Long-Term Outcomes after Percutaneous Coronary Intervention in Patients with Chronic Total Coronary Artery Occlusions. *Medicina (Kaunas, Lithuania)*. 55(8), 494. https://doi.org/10.3390/medicina55080494.

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1. Kalnins, A., Strele, I., Lejnieks, A., Lukstins, G. 2013. Chronic total coronary artery occlusion recanalization with percutaneous coronary intervention using anterograde and retrograde approach – Riga EAST Clinical University Hospital Experience. *Acta Chirurgica Latviensis.* Volume 13 (1) de Gruyter – Dec 1, 2013.

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1. Kalniņš, A., Strēle, I., Lejnieks, A., Kurcalte, I., Strēlnieks, A. RSU Scientific Conference 2013. Oral report. Comparison of invasive treatment methods for chronic total coronary artery occlusion. Abstracts of the scientific conference (Riga, March 21–22, 2013). Rīga Stradiņš University. – Riga, 2013. p.105.
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