Analysis of a Canadian Database of Patients with Chronic Total Occlusion – Percutaneous Coronary Intervention

Israth Jahan, BSc

Faculty of Medicine and Health Sciences

Department of Epidemiology, Biostatistics, and Occupational Health

McGill University, Montreal

May 2023

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree.

of Master of Science

Abstract

Background: Chronic total occlusions (CTOs) are complete blockages of coronary arteries observed in roughly one out of every 5 patients with coronary artery disease (CAD). Percutaneous coronary intervention (PCI) is a minimally invasive procedure used to treat CAD. However, its chances of success were initially reported to be lower in patients with CTO. Recent improvements in technology and techniques have improved these chances. Furthermore, centres with higher volumes tend to report better outcomes. The available evidence to date is largely drawn from registry studies in the United States and Japan. Given the potential for variation in patient characteristics, practice patterns and outcomes across settings, there is a need to examine the Canadian experience in CTO PCI.

Objectives:

1) To characterize patients undergoing CTO PCI in Canada
2) To estimate the impact of previously reported risk factors for procedural success and complications in this population.
3) To examine characteristics of patients receiving antegrade vs. retrograde CTO PCI
4) To estimate the impact of risk factors for procedural success and complications among subjects who received antegrade vs. retrograde CTO PCI

Methods: This thesis reports on the first analysis of the Canadian CTO PCI registry (CCTOP), the first multicentre Canadian cohort of patients who underwent CTO-PCI in one of six major participating tertiary care centres during 2014 to 2019. A review of the literature is provided, including registry studies from other jurisdictions. Descriptive statistics were used to summarize demographic and clinical characteristics of patients, and characteristics of CTO-PCI procedures applied in CCTOP. The outcomes of interest included short-term procedural success of CTO-

PCI, defined as technical success without major complication within 30 days and complications. Logistic regression and classification and regression tree (CART) models were used to estimate the association between each risk factors for procedural success.

Results: A total 1194 consecutive patients were examined among whom 549 underwent antegrade-only (46 %) and 525 underwent retrograde (44%) CTO-PCI procedures. Procedural success was high overall (n=928, 88%). It was higher for antegrade vs. retrograde procedures as expected (91% vs. 81%). Important predictors of an unsuccessful CTO-PCI included presence of a prior Coronary Artery Bypass Graft (CABG) procedure (OR, 0.46, [95% CI, 0.22,0.94]), severely reduced Left Ventricular Ejection Fraction (LVEF) (OR, 0.29, [95% CI, 0.10,0.88]), collateral that were not crossed(OR, 0.10, [95% CI, 0.04,0.29]), ambiguity in the proximal cap(OR, 0.50, [95% CI, 0.25,0.99]). Classification and Regression Trees (CART) analysis did not identify any interactions between the risk factors studied.

Conclusions: This analysis demonstrates that the Canadian experience with CTO-PCI is comparable to other major centres worldwide in terms of the high overall success and low risk of complications. Further, it shows that retrograde procedures can be attempted with a high level of success for certain groups of patients.

Résumé

Contexte: Les occlusions chroniques totales (OTC) sont des blocages complets des artères coronaires observés chez environ un patient sur cinq souffrant de coronaropathie. L'intervention coronarienne percutanée (ICP) est une procédure peu invasive utilisée pour traiter la maladie coronarienne. Cependant, ses chances de succès ont été initialement rapportées comme étant plus faibles chez les patients atteints de CTO. Des améliorations récentes de la technologie et des techniques ont permis d'augmenter ces chances. En outre, les centres ayant des volumes plus importants tendent à rapporter de meilleurs résultats. Les données disponibles à ce jour proviennent en grande partie d'études de registres réalisées aux États-Unis et au Japon. Étant donné que les caractéristiques des patients, les modes de pratique et les résultats peuvent varier d'un endroit à l'autre, il est nécessaire d'examiner l'expérience canadienne en matière d'ICP des OTC.

Objectifs :

1) Caractériser les patients subissant une ICP CTO au Canada

2) Estimer l'impact des facteurs de risque déjà signalés pour le succès de l'intervention et les complications dans cette population.

3) Examiner les caractéristiques des patients subissant une ICP CTO antérograde ou rétrograde.

4) Estimer l'impact des facteurs de risque pour le succès de l'intervention et les complications chez les sujets ayant subi une ICP de la CTO antérograde par rapport à ceux ayant subi une ICP de la CTO rétrograde.

Méthodes : Cette thèse rend compte de la première analyse du registre canadien des ICP CTO (CCTOP), première cohorte canadienne multicentrique de patients ayant subi une ICP CTO dans l'un des six principaux centres de soins tertiaires participants entre 2014 et 2019. Une revue de la littérature est fournie, y compris des études de registres d'autres juridictions. Des statistiques descriptives ont été utilisées pour résumer les caractéristiques démographiques et cliniques des patients, ainsi que les caractéristiques des procédures de CTO-PCI appliquées dans le CCTOP. Les résultats d'intérêt comprenaient le succès procédural à court terme de l'ICP-CTO, défini comme le succès technique sans complication majeure dans les 30 jours et les complications. Des modèles de régression logistique et d'arbre de classification et de régression (CART) ont été utilisés pour identifier les facteurs de risque de réussite de la procédure.

Résultats : Au total, 1194 patients consécutifs ont été examinés, dont 549 ont subi une intervention de CTO-PCI antégrade uniquement (46 %) et 525 une intervention de CTO-PCI rétrograde (44 %). Le succès de la procédure a été globalement élevé (n=928, 88%). Comme prévu, il était plus élevé pour les procédures antérogrades que pour les procédures rétrogrades (91 % contre 81 %). Les principaux facteurs prédictifs d'un échec de la CTO-PCI étaient la présence d'un pontage aorto-coronarien (PAC) antérieur (OR, 0,46, [IC 95 %, 0,22,0,94]), une fraction d'éjection du ventricule gauche (FEVG) sévèrement réduite (OR, 0. 29, [95% CI, 0.10,0.88]), collatérales non franchies (OR, 0.10, [95% CI, 0.04,0.29]), ambiguïté de la coiffe proximale (OR, 0.50, [95% CI, 0.25,0.99]). L'analyse par arbres de classification et de régression (CART) n'a pas permis d'identifier d'interactions entre les facteurs de risque étudiés.

Conclusions : Cette analyse démontre que l'expérience canadienne en matière d'ICP-CTO est comparable à celle d'autres grands centres dans le monde en termes de succès global élevé et de faible risque de complications. De plus, elle montre que les procédures rétrogrades peuvent être tentées avec un haut niveau de succès pour certains groupes de patients.

Acknowledgments

Throughout the writing of this thesis, I have received a great amount of support and assistance.

I would first like to thank my supervisor, Dr. Nandini Dendukuri, to offer me the opportunity to develop this thesis. Her constant positive guidance and care has motivated me throughout my journey academically and made me feel confident in my abilities.

I would also like to thank Dr. Stephane Rinfret, my co-supervisor, for believing in me and providing his valuable advice and feedback and allowing me to part of a research paper which was published in a high impact journal.

I would like to thank the members of the Research Institute, based at McGill University Health Centre (RI-MUHC) for providing the necessary administrative support.

Finally, I would like to thank all the people that helped me with my move to Montreal. And my family for supporting me mentally from a distance during these difficult times of the pandemic.

List of Abbreviations

ADR	Antegrade Dissection/Re-Entry
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CART	Classification and Regression Trees
CC	Collateral Channel
CCTOP	Canadian CTO PCI
CHUM	Centre Hospitalier de l'Université de Montréal
CTO	Chronic Total Occlusion
DECISION-CTO	Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion
EXPLORE	Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction
ERCTO	The European Registry of CTOs
EURO-CTO	European CTO
IUCPQ	Institut Universitaire de Cardiologie et de Pneumologie de Québec
J-CTO	Japanese CTO
LM	Left Main
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACCE	Major Adverse Cardiac and Cerebrovascular Event
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MLP	Multi-Layer Perceptron
MUHC	McGill University Health Centre
OM	Obtuse Marginal
OPEN-CTO	Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures

PCI	Percutaneous Coronary Intervention
PRISON IV	Hybrid Sirolimus-eluting Versus Everolimus-eluting Stents for Total Coronary Occlusions
PROGRESS CTO	Prospective Global Registry for the Study of Chronic Total Occlusion
RECHARGE	REgistry of Crossboss and Hybrid procedures in FrAnce, the NetheRlands, BelGium and UnitEd Kingdom
TIMI	Thrombolysis in Myocardial Infarction
VGH	Vancouver General Hospital

List of Figures

List of Tables and Boxes

Table of Contents

Chapter 1 Introduction

Coronary artery disease (CAD) or ischemic heart disease is the second most common cause of death in Canada in terms of public health burden (1). It is the most common type of heart disease and occurs when the arteries of the heart are either narrowed or obstructed (2).

1.1 Chronic total occlusion

One of the complications that arise from CAD is Chronic Total Occlusion (CTO) (3). Although there are numerous definitions of CTO, the two main characteristics are: an obstruction without forward flow through the lesion and a suspected or recorded period of this obstruction lasting more than three months (4).

The prevalence of CTO among CAD patients is around 18% to 50% (5). Usually, patients with CTO have collateralization i.e., alternate circulation around the obstructed vessel, providing flow to the resting heart, but insufficient blood flow to the myocardial bed on higher demand, resulting in symptoms of ischemia and angina. As time passes, the thrombosed segments begin to compact with fibrous tissue and calcify, which makes it difficult to treat (6). Though experts believe CTO diagnosis requires that the condition be present for at least three months, it is often challenging to determine the starting time of the occlusion (7).

1.2 Percutaneous coronary intervention

Percutaneous Coronary Intervention (PCI), previously known as coronary angioplasty, is a treatment for coronary artery disease. It is a non-surgical procedure to facilitate blood flow to the heart (8). PCI is carried out to unblock the buildup of atherosclerotic plaque or to widen or open narrowed coronary arteries. During the procedure, a catheter is inserted into, either from the common femoral or the radial artery and is used to inject contrast dye into the coronary arteries. This step is referred to as cardiac catheterization with coronary angiography. The catheter is then passed through the arteries into the heart, where the coronary artery is constricted, using a specific form of X-ray called fluoroscopy. A balloon is first advanced into the lesion, inflated to open the blockage, followed with placement of a stent. A stent is crimped on a balloon; once the balloon is inflated, the stent is left apposed to the wall of the artery, alleviating the blockage. The balloon is deflated and withdrawn. The stent remains in place in the artery, keeping it open (9).

PCI serves to relieve symptoms caused by chronic coronary heart disease or to reduce the damage to the heart due to myocardial infarction. PCI is offered to patients when medical therapy is not adequate to mitigate the symptoms or in the improvement of long-term outcomes, and when Coronary Artery Bypass Graft (CABG) surgery is considered too invasive because of single vessel disease (7) or because of prior CABG, for example. It has also emerged as an effective alternative to CABG for patients with lower-risk 3-vessel illness and patients with left main trunk disease.

1.3 CTO PCI

PCI for CTO treatment (or CTO PCI) has been reported to be less successful than PCI for the broader group of CAD patients who do not have CTO, due to the complexity (6). Compared to regular PCI, where a guidewire is easily inserted through a non-occlusive lesion, CTO PCI starts with crossing of the totally blocked artery with guidewires aimed to connect into the collateralized segment through or around the plaque. While success rates were traditionally around 50-60% despite the selection of easier and more favorable cases, current techniques involving the retrograde approach and dissection-reentry have raised the success rate to 85-90% in experienced centers despite treatment of very difficult cases. Although PCI is most commonly used in CTO patients to relieve angina, it also enhances the function of the left ventricle (6).

1.3.1 Antegrade and retrograde CTO PCI

Different techniques for performing CTO PCI can be distinguished. The choice between the technique depends on several angiographic characteristics (see Box 1). Further, a previous procedural failure would also be indicative of the need for an alternative technique.

- ***Lesion length:*** The length of the occlusion
- ***Anatomy of proximal and distal cap:*** Shape of the proximal and distal ends of the occlusion, which may be blunt, tapered or ambiguous
- ***Tortuosity:*** The extent to which the blood vessel is twisted
- ***Calcification***: Presence of calcium build up in the occlusion
- ***Distal landing zone:*** The quality of the blood vessel in terms of plaque build-up beyond the distal cap
- ***Presence of interventional collaterals:*** Presence of smaller blood vessels that can provide alternative circulation around the obstructed blood vessel

Box 1.1: Angiographic features affecting choice of CTO PCI technique and success. (10)

The major crossing techniques that may be used during a CTO PCI procedure are: antegrade wiring, antegrade dissection/re-entry (ADR), the retrograde approach and hybrid approach. They are described below:

- ***Antegrade wiring,*** formerly called antegrade wire escalation, is the preferred technique for treating CTO among patients for a less complex CTO as described by a low rating on the J-CTO score (11, 12). The initial step often uses the antegrade wiring algorithm, which includes crossing the proximal cap while remaining within the actual plaque at all times. It is the most regularly implemented strategy and the most technically simple method of crossing. This technique is based on the intention to cross from the proximal true lumen to the distal true lumen with an intra-plaque course of the wire. While wires need to escalate in strength in the process crossing, it is often required to stick wires to softer ones once the proximal cap has been punctured, often referred as de-escalation. Therefore, the term Antegrade Wiring has been recommended (4). Because of its relative technical simplicity compared to other techniques, antegrade wiring is often used by low and intermediate volume operators. However, it is a skill that is required by even the most seasoned operators (14).
- ***Antegrade Dissection Reentry (ADR):*** Antegrade dissection re-entry involves an antegrade PCI where the guidewire is intentionally or inadvertently inserted into the subintimal or extraplaque space with subsequent re-entry into the distal true lumen (13). If the proximal cap is unambiguous and a good quality vessel with an estimated occlusion length of ≥20 mm, ADR is the strategy that is preferred (14-16). It is also normally utilized after the failure of the previous crossing technique (14, 17).

- ***Retrograde approach:*** The retrograde approach involves advancement of the guidewire through the distal cap via bypass grafts or collateral vessels (18). Initially the retrograde approach would be used after the failure of an antegrade CTO PCI attempt (19). Nevertheless, with time and experience, retrograde CTO PCI has also been progressively utilized as the first strategy in patients tough to operate with an antegrade approach, for example those with ostial or long (>30 mm) occlusions, occlusions without a stump, occlusions with large side branches at the proximal or distal cap, occlusions with severe tortuosity or calcification and small or poorly visualized distal vessels (20-22).
- ***Hybrid approach:*** The hybrid approach is a careful, efficient and effective approach that focuses on success, efficiency and risk. (15). With the hybrid approach, the goal is to test all possible crossing strategies in the same sitting, including antegrade wiring (23), antegrade dissection re-entry (17, 24-26) and the retrograde approach, if appropriate collateral exists.

For the purposes of this thesis, if the lesion crossing was attempted from the distal cap, after delivery of a guidewire through a collateral vessel or bypass graft supplying the target vessel distal to the lesion, the procedure is defined as "retrograde". Otherwise, the classification of the procedure is "antegrade only".

A study comparing the clinical, angiographic, technical and procedural characteristics of CTO PCI outcomes between the "early era" (2012-2016) and the "current era" (2017-2019) (32) found that 87% used antegrade wire escalation, 34% used retrograde and 28% used antegrade dissection re-entry (ADR) as the first crossing strategy overall, from 2012 - 2019 (32). Antegrade wire escalation was higher in the current era (92%) than the early era (83%). Retrograde and

ADR was higher in the early era (39% and 32%) than the current era (29% and 23%). There were similar trends for the final crossing strategy.

1.3.2 CTO PCI usage

Given the complexity of CTO PCI, it has been traditionally associated with a higher risk for the patient in terms of procedural success and complications. Over the last four decades, CTO-PCI practice has evolved using new devices and techniques, though the fundamental principles remain the same. In recent years, technical and procedural success rates improved as a result along with quality-of-life metrics in patients (27, 28).

Registry studies in the United States and Japan have gathered evidence about the usage and outcomes following CTO PCI and provide most of the observational evidence on CTO PCI. The generalizability of this evidence to other settings, including the Canadian context is limited by several factors. One important factor is differences in healthcare systems and insurance coverage between the three countries. In Canada, healthcare is publicly funded and administered by the provinces, while in the United States and Japan, healthcare is delivered through a mix of public and private insurance systems (29). Differences in healthcare provider training and experience, as well as differences in procedural techniques and equipment, may also impact the generalizability of CTO PCI data across countries (30).

1.3.3 CTO PCI in Canada

CTO PCI has been in use in Canada since the 1990s, with varied levels of success (31). The first retrograde CTO PCI performed in Quebec has stimulated the learning of modern CTO PCI across Canada (31). Most Canadian studies published to so far have been single-operator studies. Given the growing number of CTO PCIs performed in Canada and the number of centres where they are performed, and the potential benefits, risks and costs associated with the procedure, it is important to assess outcomes in Canadian patients and to confirm the importance of previously reported factors predicting procedural success.

1.4 Objectives

This thesis will examine the analysis of the Canadian CTO PCI (CCTOP) registry, a multi-centre Canadian cohort of patients who received CTO-PCI in 6 major tertiary centres. The specific objectives of this thesis are:

1) To characterize patients undergoing CTO PCI in Canada
2) To examine characteristics of patients receiving antegrade vs. retrograde CTO PCI.
3) To estimate the association of previously reported predictors of a successful outcome (procedural success, defined as technical success without major complication) in this cohort in the short term.
4) To estimate the association of previously reported predictors of a successful outcome (procedural success, defined as technical success without major complication) in this cohort in the short term within strata defined by CTO PCI technique.

The variable of interest for this thesis, that is, antegrade vs retrograde, cannot be randomized, as there are too many anatomic and procedural variables involved in the decision to proceed one way. This thesis will be organized in 4 chapters. Chapter 2 will review the literature on outcomes following CTO PCI as well as the literature on some relevant statistical methods. Chapter 3 will cover the statistical methods used to answer the objectives of the thesis. Chapter 4 will present the corresponding results. Chapter 5 will present a discussion of the findings and future directions for research.

Chapter 2 Literature review

This chapter reviews the literature on Chronic Total Occlusion (CTO) and on Percutaneous Coronary Intervention in patients with Chronic Total Occlusion (CTO-PCI). It covers the frequency of use of CTO-PCI over the years and challenges faced, the chances of success, factors associated with success and the risk of complications. It also discusses reports based on large cohorts from different countries.

Cohorts reporting on predictors of successful CTO-PCI generally have a small sample size and may benefit from the use of alternative statistical modeling methods than the widely used logistic regression. One such statistical methodology, called Classification and Regression Trees (CART), is reviewed at the end of the chapter.

2.1 Epidemiology of chronic total occlusion (CTO)

There is limited data in the literature on the prevalence of patients recognized as having CTO during the coronary angiography diagnostic procedure, their clinical characteristics and decisions made regarding their treatment. In 1993, Kahn conducted a retrospective study of coronary angiograms on a sample of 287 CAD patients and reported that the prevalence of CTO, characterized by 50% diameter stenosis (narrowing) was 35% (34). A retrospective registry analysis of 8004 patients was done by Christofferson *et al*. in the Veteran Administration Hospital of Seattle, a single institution, from 1990 to 2000. It was found that the prevalence of CTO was 52% with at least 1 coronary stenosis (70% diameter stenosis).

The first Canadian CTO registry on PCI was constructed by Strauss *et al*. starting from a larger study consisting of data from around 15,000 patients who underwent coronary angiography from April 2008 to July 2009 at 3 Canadian centers, aimed at describing prevalence and management of the disease. The prevalence of CTO among these patients with coronary artery disease of

(>50% stenosis in ≥ 1 coronary artery) was 18.4%. Most patients experienced angina and the CTO management was mainly done through medical therapy (64%), i.e. without revascularization, 26% went through CABG and 30% had a PCI. (35).

Azzalini *et al*. confirmed, from a large single-center experience, the incidence of CTO in the CAD population to be 20% (36) in non-CABG patients. All patients were catheterized in 2014 from January to October with a coronary CTO.

Pereg *et al.* concluded that it is common for CABG patients to develop a new CTO within the first postoperative year of the bypassed native coronary artery (37). The participants were patients enrolled in the multicentre radial artery patency study from November 1996 to January 2001 with a 1-year follow-up angiography. After examining both pre- and postoperative angiograms, it was found that more than 40% of post-CABG patients at one year had developed a new CTO (37).

Across different studies, the mean age of the patients with CTO has been reported to be around 60 – 70 years and the percentage of males among these patients to be 70 – 80 % (34-36, 38). Common comorbidities associated with CTO include diabetes mellitus, hypertension, and hyperlipidemia (6).

2.2 Risk of failed attempts, poor outcomes, and complications during percutaneous coronary intervention for chronic total occlusion (CTO PCI)

As mentioned in the introduction, the treatment of CTO with PCI is associated with worse outcomes than among patients undergoing non-CTO PCI. The main difficulty arises because of the inability to cross the lesion with a guidewire. The inability to cross the lesion with a balloon after successful guidewire crossing (“balloon-uncrossable” CTOs) is the second most frequent reason for technical failure in recanalizing CTOs (i.e. re-establishing blood flow) (39). Due to long procedure duration, there is a potential for radiation dermal injury and contrast-induced renal dysfunction. There is also a risk for vessel perforation, that may result in tamponade. Disruptions of collateral flow to the vessel distal of the occlusion due to collateral vessel damage or donor vessel complication can lead to significant ischemia and periprocedural infarction.

2.3 Frequency of CTO PCI and characteristics of patients receiving it

The percentage of patients receiving CTO PCI has been reported to be 9 – 30% of patients with a CTO (35, 36, 38, 40). From the national inpatient sample, the largest in-patient care database in the United States, with records of 109,094 hospitalizations for single-vessel coronary CTO PCI from 2008 to 2014, the incidence of single-vessel coronary CTO PCI with stable CAD increased by 9% from 2465 per 100,000 PCI procedures in 2008 to 2688 per 100,000 PCI procedures in 2014 with an overall in-hospital mortality of 0.5% (40). In this database, the mean age of the patients' undergoing CTO PCI was 67 years with a greater percentage of males (73.6%) and the percentage with single-vessel coronary CTO being 26.4%. The comorbidities most frequently associated with hospitalizations for single-vessel coronary CTO PCI were hypertension (78.9%) and diabetes (36.9%) (40). A meta-analysis reported that 14–23.7% of the patients were represented by females (41).

In a Canadian study with 3 study sites, 30% of all patients with a CTO underwent PCI of which only 10% were targeted to treat the CTO itself, with success rate of 70% (35).

2.4 Definition of successful CTO PCI and associated factors

According to the most recent research in 2021, Ybarra *et al*. recommended the following definitions of success with establishment of common end points specific to CTO PCI

Crossing Success: This end point is described as angiographic or intravascular imaging affirmation associated with guide wire (or related device) positioning in the true lumen of the principal vessel beyond the occluded segment. Settlement of guide wire directly into the distal true lumen (if done in the antegrade direction) or in the proximal true lumen (if done in the retrograde direction) is usually considered a CTO crossing success. Guide wire arrangement on the distal cap of the CTO from the retrograde direction by means of a collateral is reported as a crossing success only after the wire has effectively surpassed into the true lumen proximal towards the CTO.

Technical success: The TIMI (thrombolysis in myocardial infarction) flow grading system is classified into a scoring system from 0-3 based the flow of coronary blood during coronary angiography (42). The TIMI flow grading system consist of the following:

- TIMI 0 flow (no perfusion-complete occlusion) – No onward flow beyond the coronary blockage.
- TIMI 1 flow (penetration without perfusion) - With an inadequate filling of the distal coronary bed, there is weak forward flow beyond the blockage.
- TIMI 2 flow (partial reperfusion) - retarded forward flow with entire filling of the distal coronary bed.
- TIMI 3 flow (full perfusion) - fills the distal coronary bed with normal blood flow.

Technical success is outlined as accomplishment of thrombolysis in myocardial infarction (TIMI) grade 2 or higher antegrade flow in all ≥2.5-mm distal branches with <30% residual stenosis of the focused CTO lesion at termination of the procedure, as determined by quantitative coronary angiography performed by an independent core laboratory. This is said that technical success was complete. This was occasionally referred to as angiographic success with correspondence to former studies. While it is acknowledged that TIMI grade 2 flow may impart a more unfavorable prognosis in certain operations such as subintimal tracking and reentry, TIMI grade 3 flow is typically difficult to produce when competing collateral flow is present. When TIMI grade 2 or greater antegrade flow with <30% residual stenosis into at least 1 but not all ≥2.5-mm distal side branches are attained, it is termed as partial technical success.

Procedural Success: Procedural success, like in previous non-CTO trials, is described as technical success without in-hospital major adverse cardiovascular event (major adverse cardiac event (MACE); death, myocardial infarction (MI), or even clinically driven focus on target vessel revascularization). If technical success was complete, procedural success may be subclassified as complete. Similarly, if technical success was partial, procedural success may be subclassified as partial (4).

Most studies on CTO PCI have reported on procedural success hence, the "success" mentioned in this thesis refers to procedural success.

According to a single-center multi-decade review carried out between 1979 and 1989, the procedural success rate for CTO PCI was 51% (43). The success rate increased to around 70% once coronary stents were used, from 1990 to 2006 during the stent era, and this rate was persistent across many studies (7, 43-45).The multicenter PROGRESS CTO registry study conducted in the United States, Europe and Russia during 2012-2017, with a diverse group of patients and operators, and including new techniques such as the retrograde approach and antegrade dissection and reentry reported acute technical and procedural success rates of 87% and 85%, respectively (13).

Over the past ten years, the technical success rate for CTO PCI improved with the establishment of advanced specialized techniques (46). Additionally, Stone mentions that improvements in outcomes of CTO PCI in the past 30 years were due to equipment, commencement of a new approach accompanied by drug-eluting stents, the selective use of atherectomy, intravascular imaging, and optimal pharmacotherapy (47).

Improvements in success rates has also been attributed to the development of advanced materials and teachable methods such as retrograde wiring and antegrade or retrograde dissection and re-entry techniques (48). Luo *et al*. and Rolf *et al*. had similar results when they reported that there is a higher success rate when a coronary computed tomography angiography is performed before PCI of CTO lesions (49). Clinical characteristics of the patient may also affect success. For example, increasing rates of acute renal failure were associated with a significantly higher odds of unsuccessful CTO PCI around 166% (40), due to inability to complete the procedure without an increased risk of acute renal failure with additional contrast. A study where CTO PCI were performed by Japanese specialists also conducted a multivariate analysis where prior CABG, prior PCI and diabetes have a higher odds of CTO PCI failure of 1.47, 1.28 and 1.12 respectively (50).

Once the clinical indication has been determined, the operator must have a pragmatic estimate of the probability of procedural success which will be reviewed with the patient and play an important role in medical decision-making. The complexity of the procedure is mainly decided by structural features of the CTO, the structure of the coronary body and clinical factors. Several scores have been proposed in the past 10 years in order to incorporate these factors and conduct a correct objective assessment related with procedural CTO issues (51). In this thesis the J-CTO score will be used in the analyses (52) .

The J-CTO score was developed as a tool to classify case complexity and procedure success rates from the JCTO (Multicenter CTO Registry of Japan) registry cohort. A total of 5 independent variable were identified, each given 1 point if present, to determine the difficulty level. They were categorized as 4 groups: easy (J-CTO score of 0), intermediate (score of 1), difficult (score of 2), and very difficult (score of ≥ 3). The independent variables were given each a score of 1 if the occlusion length was greater 20mm, if a bending of greater than 45° was detected within the CTO segment, if the occluded segment ended with a funnel-shaped form or "blunt", if it was a second attempt from a previously failed attempt, or if any calcification was present in the CTO segment (53). Nombela-Franco et al. have validated the J-CTO score in an independent cohort. Their study revealed that the J-CTO score is reliable and helpful for estimating the duration of the entire process, the radiation dosage, and the amount of contrast that will be used (54).

According to a multicenter study conducted in the United States from may 2012 to may 2016 at 15 CTO PCI centers, elderly people are independently associated with reduced technical success in CTO PCI and increased in-hospital MACE (55). A systematic review and meta-analysis by Mannem *et al.* from nine different studies with 30,830 CTO subject concluded that gender is neither an independent risk factor for MACE nor a successful procedure for CTO patients who have undergone PCI (41). In contrast to patients with normal renal function, chronic kidney disease is associated with a lower success rate after CTO-PCI and a higher risk of acute and long-term complications as stated by Moroni *et al*. from a systematic review of eight studies with

8439 patients. Their analysis showed that chronic kidney disease was associated with higher technical (relative risk [RR] = 1.44, 95% confidence interval [CI] 1.14–1.82, p =.002) and procedural (risk ratio-RR = 1.40, 95% CI 1.00–1.96, p = .05) failure, higher in-hospital mortality (RR = 4.96, 95% CI 2.49–9.87p < 001) (56). Patients with diabetes address a subset of high-risk patients. Patients with diabetes suffer from more widespread and complex atherosclerosis than those without diabetes, and have a higher incidence of CTO lesions, multivessel disease, and diffuse CAD, small vessel disease and calcification of coronary arteries (57). A systematic review containing 16 studies, which included two randomized controlled trials, and 14 observational studies determined that non-diabetic patients undergoing CTO-PCI have lower all-cause mortality and MACE than diabetic patients. During the longest follow up, all-cause mortality (OR 0.54 [95% CI 0.37–0.80],p< 0.0001) and MACE (OR 0.82 [95% CI0.72–0.93],p< 0.00001) were significantly lower in non-DM CTO patients (57). A meta analysis of 7 studies comprising of 11099 patients found results that showed that compared to non CABG patients, prior CABG patients were associated with lower technical success (82.3% versus 87.8%; OR, 0.60; 95% CI, 0.53–0.68;P<.00001;I2=0%) and procedural success (80.4% versus 86.2%; OR, 0.61; 95% CI, 0.53–0.70;P<.00001;I2=10%) (58). The meta-analysis of 34 studies have shown that a successful CTO reopening improves overall absolute LVEF points of 4.44% and improves survival (OR: 0.52) (59).

2.5 Complications associated with CTO PCI

The in-hospital major adverse events (MACE) following CTO PCI include death, myocardial infarction (MI), recurrent symptoms which required urgent repeat revascularization of target vessel with PCI or CABG surgery, tamponade which requires either pericardiocentesis or surgery and stroke (13). In the PROGRESS-CTO study, the in-hospital major complication rate was 3% (13). An experienced CTO PCI center in Japan reported in-hospital complication rates of 0.5% for death, 3% for myocardial infarction, 0.2% for emergency CABG, and 0.6% for tamponade. The complication rates for less experienced centers can be higher (7). It was found from a meta-analysis done in 2013 that perforation and contrast nephropathy were the most commonly observed complications (60). The complication rates are higher in patients with unsuccessful PCIs and the success rates are lower for further PCIs. Hence, the number of attempts for CTOs should be minimum to achieve a successful PCI (49). Myocardial infarction rate will strongly depend on the definition used; most registries did not collect troponin systematically, and therefore, only clinically overt post PCI MI with symptoms, Q-wave and confirmed elevation of troponins when drawn are included.

2.6 Benefits of CTO PCI

If the risk to benefit ratio is beneficial, a CTO PCI should be carried out (15). Possible benefits of CTO PCI are relief of angina (61), better exercise (62), improved left ventricular (LV) function (7, 41, 63), improvement in tolerating a subsequent acute coronary syndrome (64), lowering the requirement of CABG (65) and improved survival (7, 41, 66, 67).

Six observational studies in a meta-analysis compared recurrent angina events among patients undergoing successful vs. unsuccessful CTO PCI. Over a 6-year follow up, there was a notable reduction in recurrent angina among the patients who had undergone a successful intervention compared to patients whose PCI was unsuccessful (odds ratio, 0.45; 95% confidence interval, 0.30 to 0.67) (66). Two studies using cardiac magnetic resonance imaging showed improvements in LV end-systolic volume, LV end-diastolic volume and fractional shortening 5 months later among patients with LV dysfunction who went through successful CTO PCI. Thirteen observational studies in a meta-analysis comparing mortality rates between patients with successful vs. unsuccessful CTO PCI found that successful CTO PCI was associated with reduced mortality (14.3% versus 17.5%; odds ratio, 0.56; 95% confidence interval, 0.43 to 0.72) (7). A study was performed on CTO PCI patients with refractory angina symptoms from the OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures) registry which had 12 US centers. The Seattle angina questionnaire was used to measure improvement in angina. The Seattle angina questionnaire is a questionnaire with 19 items with a 4-week recall period that calculates 5 domains of health status of patients with CAD. The domains were seattle angina questionnaire angina frequency, angina stability, quality of life (seattle angina questionnaire quality of life), physical limitation and treatment satisfaction.

Technical success was achieved in 120 (81.1%) at the initial attempt and major adverse cardiac and cerebral events occurred in 10 (6.8%). There were no procedural deaths. Through 1-year follow-up, patients with successful CTO PCI had significantly larger degree of improvement of Seattle angina questionnaire angina frequency and Seattle angina questionnaire summary score (35.0±26.8 versus 18.8±28.9, $P<0.01$; 34.2±19.4 versus 22.5±20.8, $P<0.01$) in comparison to unsuccessful CTO PCI.(68). Since CTO programs in hospitals are associated with significant expenditure due to the training of personal and equipment, CTO PCI should preferably be performed on patients who would get maximum benefit from the process (41). A peculiar risk of PCI in CTOs is that it is difficult to execute complete revascularization. Worse clinical outcomes are often related to incomplete revascularization (7).

2.7 Comparison of CTO PCI to alternatives

Treatment options for patients with CTO depend on the severity of symptoms and ischemia and the severity of the associated coronary artery disease (CAD) (7). It has been recommended that patients with stable CAD should go for antianginal therapy and therapies to encourage vascular health. Revascularization is considered for symptomatic patients or those who have a large burden of ischemia, on maximized medical therapy. When the revascularization approach is chosen, CTO PCI will be offered when the extent of CAD is limited, or CABG when CAD is more extensive (7).

CTO patients are referred for PCI when medical treatment is insufficient to control symptoms or to improve of long-term outcomes (7). Only an estimated 12% of CTO patients go through PCI as their treatment (69). Randomized trials comparing PCI and CABG suggest that CABG is the preferred treatment option for patients with complex coronary artery disease, particularly those with diabetes, as long as they are suitable surgical candidates. On the other hand, for most patients with a single vessel CTO and for those with a history of CABG, PCI is generally preferred due to the higher risk of redo CABG. To ensure the best outcome, CTO PCI should be performed by experienced operators and centers that can achieve high success rates and are equipped to manage any complications that may arise (4).

It was reported that the Canadian Multicenter CTO Registry had a higher percentage of patients received CABG (17.5%) compared to PCI (10.7%) for coronary revascularization. CABG showed a stronger link to improved long-term outcomes than PCI, which was due to patient selection. The healthier and less frail patients were more likely to undergo CABG (70). The rest are rather managed with bypass surgery or continue with medical therapy and/or exercise regimens. There are limitations in both revascularization methods. Since bypass surgery is more invasive in comparison to percutaneous revascularization, the amount of time spent in hospital and recovery is more. It is also correlated with certain morbidity which includes strokes and persistent cognitive dysfunction. CTO patients who go through medical therapy have a restricted lifestyle and the treatment is often not effective (69). There are also additional technical challenges with bypass surgery for CTO vessels, which are under perfused and small. As a result, one study showed that up to 4 out of 5 saphenous vein grafts placed on CTO vessels are occluded one year after the surgery (71).

2.8 Overview of experience with CTO PCI around the world

Registry studies: Advances in the rates of successful CTO PCI procedures were achieved over the years thanks to the international alliances between the United States, Japan, and Europe. The multicenter PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) registry collected data on 3,122 CTO PCI procedures performed in 3,055 patients between 2012 and 2017 from 20 centers in the United States and Europe and had an acute technical success rate of 87% (47). Similar results on technical success rate were reported from other multicenter studies with highly skilled operators. The U.S. based OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures) registry reported an 86% success rate (72), the European RECHARGE (REgistry of Crossboss and Hybrid procedures in FrAnce, the NetheRlands, BelGium and UnitEd Kingdom) registry reported 86% procedural success rate (48) and the J-CTO (Japanese multicenter CTO) registry reported an 89% success rate (73).

Randomized Controlled Trials (RCTs): Randomized controlled trials have been viewed to have the highest level of evidence in the hierarchies of research methods (74). The number of randomized trials executed for the evaluation of the safety and efficacy of CTO PCI is limited due to the challenges in carrying out a trial of an invasive intervention (4). These trials require a large sample to assess outcomes. While recruiting patients, some may have a lot of symptoms and would like to still be managed medically. It may be difficult to justify assigning patients to a control group randomized controlled trials cannot be generalizable because the selection criteria are often very strict, which does not apply to the general population. If a patient comes to the doctor for assessment, they proceed with patient accordingly. Megaly et al. says that there were significant differences in patient characteristics between those undergoing chronic total occlusion (CTO) revascularization in clinical trials and those in real-world registries. Patients enrolled in clinical trials tended to be younger, have fewer comorbidities, and had a lower prevalence of previous myocardial infarction, heart failure, or peripheral artery disease. In contrast, patients in real-world registries were older, had more comorbidities, and had a higher prevalence of previous myocardial infarction, heart failure, or peripheral artery disease. The authors also found that patients in clinical trials had higher success rates and lower rates of major adverse cardiovascular events compared to those in real-world registries (33).

The EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) trial was an investigator-initiated, prospective, multicenter, international, randomized, 2-arm trial with blinded evaluation of endpoints with centres from Europe and North America. It included 304 patients who underwent initial PCI for acute ST-elevation myocardial infarction and had a contemporaneous CTO in a non-infarct related artery. Patients were randomly assigned to further undergo CTO

PCI within 1 week of the index operation or no extra CTO PCI between 2007 and 2015. A total of 148 patients were assigned randomly to receive CTO PCI treatment in the trial, while 154 patients were randomly assigned to receive no-CTO PCI treatment. At a 4-month follow-up, no difference was seen in terms of LVEF (CTO PCI 44.1%±12.2% vs. no CTO PCI 44.8%±11.9%), and MACE rates were higher in the CTO PCI arm than the no CTO PCI arm, but low overall (5.4% vs 2.6). The study only comprised patients with post ST-elevation myocardial infarction, therefore more research into clinical outcomes following CTO PCI in other situations is required (75). Authors concluded that it was possible and safe to do another CTO PCI within one week of the first ST-elevation myocardial infarction PCI. While they uncovered that there were no overall advantage for CTO PCI in patients with ST-elevation myocardial infarction and contemporaneous CTO in terms of left ventricular ejection fraction (LVEF) or left ventricular end diastolic volume (76), clinical outcomes of patients who had CTO PCI was improved.

The European CTO (EURO-CTO) was a prospective, multicentre, open-label, and controlled clinical trial which compared the quality of life of patients having CTO PCI to optimal medical treatment with a 2:1 randomization ratio at 12-month follow-up and clinical endpoints at 3-year follow-up recruited from 28 European centres. It enrolled 396 patients from 2012 to 2015. The European Quality of Life–5 Dimensions instrument was used to assess general health and the self-assessment questionnaire was used to assess the disease-specific health status. Angina stability and quality of life was higher in PCI group than optimal medical treatment group at follow-up, 55.9% (51.2–60.5) vs 57.8% (54.4–61.2) and 70.5% (65.4–75.6) vs 77.1% (73.3–80.9) respectively (77). They determined that in individuals with stable angina and a CTO, percutaneous coronary intervention improves their health significantly more than Optical Medical Therapy alone.

The DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion) trial was an open-label, multicenter, randomized controlled trial that consisted of 19 sites in the Asian countries of Korea, India, Indonesia, Thailand, and Taiwan from 2010 to 2016 with 834 patients that were randomly assigned to the CTO-PCI (n=417) or no CTO-PCI (n=398) strategy. It had a 5-year follow-up measuring cardiac mortality and myocardial infarction in patients randomized to optimal medical treatment or CTO PCI. The outcomes of death, MI, stroke, revascularization, or any combined secondary outcomes did not differ between the CTO-PCI and no CTO-PCI groups (78). The authors settled to believe that CTO-PCI was a viable option with a high success rate. The trial was limited by low power for clinical end goals and high crossover rates across groups, although there was no change in the incidence of significant adverse cardiovascular events with CTO-PCI versus no CTO-PCI.

2.9 CTO PCI in Canada

Canadian cardiologists have assumed a main part internationally in the advancement of methods and instruments. By the late 1980s, numerous medical centers throughout the country had acquired significant expertise in balloon angioplasty after the introduction of Simpson's over-the-wire balloon systems. Research presented at the science sessions of the Canadian Cardiovascular Society in 1992 showed that plain old balloon angioplasty for CTOs resulted in severe recoil and frequent re-occlusion within 24 hours (79). Around the years of 1980s and 1990s, Canadian performance and failure rates have not been recorded. The Total Occlusion Study of Canada trial contributed to bridge this gap as did other observational research (79, 80). In Quebec City in 2011, the first Canadian antegrade dissection re-entry case by means of the CrossBoss and StingRay system was done (81). The first Canadian CTO registry was published in 2012 by

Strauss and collaborators, who gathered data from 3 Canadian centres (35). Strauss *et al.* reported that among patients with CAD, 18.2% of them had CTOs from this registry (70).

The inclusion of only three institutions might be related to the high diversity in treatment allocation seen between sites. This variability may have been decreased if the sample size had been bigger. Another drawback was the absence of reliable documentation of viability or ischemia in the region given by the CTO, as well as whether this information was connected to the choice to act in the CTO. Nonetheless, this investigation identified current frequency, clinical features, and therapy allocation in three high-volume Canadian hospitals. The outcomes following antegrade and retrograde CTO PCI in Canada remains unknown. This thesis will therefore focus on this topic.

2.10 Review of observational studies of CTO PCI patients

Comparison of antegrade and retrograde approaches: A total of twelve observational studies that compared the outcomes of retrograde vs antegrade CTO approaches between 2000 and 2019 were included in a meta-analysis (82). There were three studies that included patients from North America (83-85), four from Europe (86-89), and five from Asia (50, 90-93). A total of 10240 patients enrolled from 2005 to 2016. The primary approach was retrograde in two of the 12 studies (50, 89). In two other studies retrograde was used after the failure of an antegrade approach (87, 88). It was reported that retrograde CTO PCI was associated with a lower procedural success rate in comparison to antegrade CTO PCI (80.9% vs. 87.4%; OR for procedural failure 2.16, 95% CI 1.71–2.73), longer duration (mean difference 61.52 min, 95% CI 50.57–72.48 min), longer fluoroscopy time (mean difference 32.33 min, 95% CI 23.45–41.22 min), and higher contrast volume (mean difference 76.73 mL; 95% CI 50.9–96.55 mL). There was no difference in long term mortality when comparing the two CTO PCI approaches. However, association with higher risk of myocardial infarction (MI) was more apparent in the retrograde approach I (5.6% vs. 2.6%; OR 2.07, 95% CI: 1.10–3.88).

CTO Registry studies: The following sub-sections cover studies from 4 major CTO registries – The European Registry of CTOs (ERCTO), PROGRESS CTO, OPEN CTO, RECHARGE CTO – and summarize the results of studies based on each of them.

Table 2.1 Observational studies based on the 4 major CTO registries.

Author & year published	**Study period**	**N patients**	**Inclusion/ exclusion**	**N retrograde**	**Outcomes**	**Method used for association**	**Limitations**	**Predictors of successful outcome**
ERCTO								
Galassi *et al.*, (2015) (2)	Jan 2008 to Dec 2102	8600	All patients undergoing retrograde or antegrade CTO PCI, no exclusion criteria	1395 (16%)	Overall procedural success rate was 75.3%. 108 (6.8%) of the retrograde group had procedural complications, and long-term clinical follow-up was available in 931 (66.7%) of the retrograde patients	Logistic regression was used to identify factors for procedural failure. The multivariate cox regression analysis identified female (hazard ratio [HR]: 2.06; 95% CI [1.33,3.18] p=0.001), prior PCI (HR: 1.73; 95% CI [1.16, 2.60], p= 0.011), low left ventricular ejection fraction (HR: 2.43; 95% CI [1.22, 4.83] p=0.011), J-CTO score ≥ 3 (HR: 2.08; 95% CI [1.32, 3.27] p=0.002),and procedural failure (HR: 2.48; 95% CI [1.72, 3.57]; p<0.001) as independent predictors of MACCEs at long-term follow-up	Operators were experienced and highly skilled, not applicable to less experienced in real world. Clinical follow-up was missing in approximately one-third of the initial cohort and the follow-up period was not homogeneous between patients	Univariate and multivariate prognostic analyses showed that low experience and lesion complexity (measured by J-CTO score negatively affected the final outcome (p<0.0001). Age (per 10-year increase) was also found to be an independent prognostic factor at multivariate analysis (OR: 1.19; 95% CI [1.03, 1.34], p=0.02)
Konstantinidis *et al.*, (2018) (3).	Jan 2008 to Jun 2015	17 626	All patients undergoing CTO PCI, no exclusion criteria	10.1% in 2008 to 29.9% in 2014	Procedural success rate increased over time, from 79.7% in 2008 to 89.3% in 2015. In-hospital mortality was low, ranging from 0.4% to 0.1%.	Not available	ADR was available after 2013 in the database, there it was underreported. All patients were treated by experienced CTO operators, therefore the data presented reflect their practice and cannot be generalized for nondedicated European centers	Not available

Myat, A., *et al*. (2022) (4)	Jan 2018 to Dec 2019	7047	All patients undergoing CTO PCI, no exclusion criteria	2364	Procedural success was achieved in 1,820 (77.0%) of retrograde cases. Higher success rates observed in CTOs with shorter length, less calcification, and less tortuosity, and in patients with lower score. Operator experience was a significant predictor of procedural success, with higher success rates observed in procedures performed by more experienced operators.	The forest plot of independently predictive variables, and their subcategorization, after multivariable logistic regression and backward elimination shows that most significant independent predictor variables that offered the greatest chance of retrograde success were in lower levels of lesion calcification ($p < 0.0001$), higher level of distal vessel opacification ($p < 0.0001$), lower proximal target vessel tortuosity ($p = 0.001$), werner collateral connection classification CC1 ($p < 0.0001$) or CC2 ($p < 0.0001$),9 and an operator in the top tertile of procedure volume conducting the CTO PCI ($p = 0.002$)	independent adjudication with review of the angiogram was performed in fewer than 10% of cases, exposing the analysis to possible underreporting and publication bias.	Less calcification with good distal vessel opacification, little or absent proximal vessel tortuosity, and visible collateral connections, along with high-volume operator status, were all independently predictive of angiographically successful retrograde CTO PCI
PROGRESS CTO								
Nikolakopoulos *et al.*, (2020) (5)	2016 to 2019	2936	inclusion and exclusion criteria not specified	935 (32%)	Patterns in equipment utilization. The guidewires most commonly used for retrograde techniques were the Sion (44%), the Pilot 200 (27%) and the Fielder FC (26%).	Not available	The total number of guidewires and the different guidewire types used but not the actual number of guidewires per type of guidewire or the sequence of guidewire use. Procedures were performed by experienced operators and may not apply to centers with limited experience	Not available
Nikolakopoulos *et al.*, (2020) (6).	May 2012 to Aug 2019	1572	Patients with follow-up data	47% with prior CABG, 28% with no prior CABG	Patients with prior CABG patients have more comorbidities, lower procedural success, and higher incidence of subsequent MACE. Median follow-up was 110 days. The retrograde technique was successful more often in the prior	Cox proportional hazards model to assess the relationship of baseline angiographic and procedural characteristics with the composite endpoint of death, myocardial infarction, and coronary revascularization. At 1-year follow-up, the composite endpoint of death, myocardial infarction, and	Potential selection bias. Confounders could exist beyond the multivariable analysis, as the operators might choose a more aggressive approach in prior CABG patients. There was no core laboratory review of angiograms or	Not available

					CABG group vs the non-prior CABG group (27.4% vs 17.1%; P<.001).	revascularization was higher in prior CABG patients (21.79% vs 12.73%; hazard ratio, 1.76; 95% CI [1.27, 2.45]; P<.001).	independent outcomes adjudication. All procedures were performed by experienced operators, limiting extrapolation to low-volume, non-expert operators. Not all patients had follow-up data available.	
Xenogiannis *et al.*, (2020)	Jan 2012 to Nov 2019	1612	Patients with follow-up data. Patients who underwent more than 1 CTO PCI during the same procedure with discordant outcome for each lesion were excluded	550 (34%)	The study found that successful CTO-PCI is associated with angina improvement and lower incidence of MACE during follow-up. CTO-PCI was successful in 1387 patients (86%). Compared with failed CTO-PCI, successful CTO-PCI patients were less likely to have history of heart failure (33% vs 41%; P=.02), prior MI (49% vs 62%; P<.01), or prior coronary revascularization (63% vs 71% [P=.03] for PCI and 30% vs 40% [P<.01] for coronary artery bypass graft surgery)	Cox proportional hazards analysis showed that diabetes mellitus (hazard ratio [HR], 1.65; 95% CI [1.17,2.34] and the PROGRESS-CTO complications score (HR, 1.20; 95% CI, [1.09,1.31]) were independently associated with higher incidence of the composite endpoint. In contrast, technical success was not independently associated with MACE (HR, 0.66; 95% CI [0.44,1.03]).	Lower incidence of MACE did not hold up on multivariable analysis and should therefore be interpreted cautiously. Follow-up was not available in all patients. The procedures were performed in dedicated, high-volume CTO centers by experienced operators, limiting extrapolation to less-experienced operators and lower-volume centers. Symptom improvement was not evaluated by a standardized questionnaire.	Not available
Christopoulos *et al.*, (2015) (7)	Jan 2011 to Jul 2014	650	patients included in the PROGRESS who underwent CTO PCI at 6 experienced centers in the United States	44%	The study demonstrates that compared with low, high J-CTO scores are associated with lower technical and procedural CTO PCI success rates; longer fluoroscopy and total procedure time, higher patient dose, and higher contrast administration; more frequent use of the retrograde approach; and higher MACE. The multivariable analysis, the J-CTO score components were not	Association of the J-CTO score with technical success and procedure time was assessed in univariable logistic and linear regression. Odds ratios or regression coefficients with their respective 95% confidence intervals were calculated for a 1-point increase of the J-CTO score. On univariable analysis, a 1-point increase in J-CTO score was associated with a 2-fold increase in the odds of technical failure (OR: 2.04, 95% CI [1.52, 2.80], P<0.001).	Procedural success (technical success in the absence of MACE) and lesion crossing within 30 minutes were not evaluated. It is unknown whether the findings will apply to lower-volume operators or operators trained in antegrade-only techniques, especially given the higher need for retrograde techniques among high J-CTO strata.	High J-CTO score is associated with lower technical and procedural success.

					directly linked to clinical outcomes. Technical and procedural success was 93.0% and 91.5% overall.		Although every possible effort was made to eliminate operator-related bias, such bias is still possible.	
Tajti *et al.*, (2019) (8)	May 2012 to May 2018	3418 patients, 1101 of whom (32%) had prior CABG	patients included in the PROGRESS from 19 United States, 1 European, and 1 Russian centers.	37.3%	CTO-PCI in prior CABG patients has lower technical and procedural success rates as compared with CTO-PCI in patients without prior CABG; requires more frequently use of antegrade dissection/re-entry and the retrograde approach. CTO PCIs using the retrograde approach (n=587) had significantly lower technical (79% versus 89%; P<0.001) and procedural success (76% versus 85%; P<0.001).	Multivariable analysis showed that history of prior CABG was not associated with technical success (adjusted relative risk of 0.99; 95% CI [0.95,1.05]; P=0.952) or the incidence of in-hospital MACE (adjusted RR=0.74; 95% CI [0.46,1.20]; P=0.227)	The study did not have core laboratory assessment of the study angiograms, or independent clinical event adjudication. Some sites enrolled patients during part of the study period that may lead to selection bias. Study procedures were performed in dedicated, high volume CTO centers by experienced operators, limiting the extrapolation to less experienced operators, and lower volume centers.	Adequate distal landing zone (adjusted RR = 1.04; 95% CI [0.97,1.11]; P=0.278), Circumflex CTO target vessel (adjusted RR = 1.02; 95% CI [0.98,1.06]; P=0.343), Interventional collaterals (adjusted RR = 1.10; 95% CI [1.07,1.14]; P<0.001), and Radial access used(adjusted RR = 1.03; 95% CI [0.99,1.06]; P=0.066) were associated technical success.
Martinez-Parachini *et al.*, (2017) (9)	May 2012 to Sep 2015	1308	patients included in the PROGRESS who underwent CTO PCI at 11 experienced centers in the United States	27.7% patients with diabetes and 30% without diabetes	diabetes was highly prevalent among people undergoing CTO PCI and similar success and complication rates were found in people with diabetes as compared with people without diabetes. Technical (90.7 vs 90.3%; P = 0.8) and procedural (89.3 vs 89.1%; P = 0.9) success was similar in participants with and without diabetes mellitus.	Not available	Only procedural outcomes without long-term follow-up were reported, which might be worse among people with diabetes because of higher risk of in-stent restenosis. There was no clinical event adjudication by a clinical events committee. All procedures were performed at centres experienced in CTO contemporary crossing techniques and strategies. The results of the study may not be generalizable to settings with limited experience in CTO PCI.	Not available

OPEN CTO								
Salisbury *et al.*, (2017) (10)	Jan 2014 to Jul 2015	1000	Patients above 18 included in the OPEN CTO registry who underwent CTO PCI at one of the 12 centers in the United States	144 (14.4%) patients with diabetes and 177 (17.7%) patients without diabetes	lower rates of technical success of CTO PCI among diabetic patients reflected the impact of prior CABG on the difficulty of CTO PCI. CTO PCI was performed in patients with and without diabetes experienced large, clinically meaningful improvements in health status after CTO PCI	Crude rates of technical success were lower in patients with diabetes than those without (83.5% vs. 88.1%; p¼0.04). After adjusting for clinical and angiographic characteristics, it was no longer statistically significant when adjusted for potential clinical and angiographic confounders (relative risk [RR]: 0.96, 95% CI [0.91, 1.01] ; p = 0.12)	The results may not be generalizable to all care settings as the lower success rates were observed in the complex lesions often found in diabetic patients when treated by less experienced CTO operators. There could be unmeasured confounding in the results.	Not available
Salisbury *et al.*, (2019) (11)	Jan 2014 to Jul 2015	964	Patients above 18 included in the OPEN CTO registry who underwent CTO PCI at one of the 12 centers in the United States	292	Mean costs for the index hospitalization were \$17,048 ± 9,904. Complications accounted for \$911 per patient in hospital costs. Patients with complications had higher mean hospital costs (by \$8,603) and length od stay (by 1.5 days) than patients without complications.	Not available	OPEN-CTO did not mandate routine post-PCI collection of cardiac biomarkers or serum creatinine values. There is a possibility of underestimation of the true incidence of complication in the study population. Some of the cost estimates have wide confidence intervals, and it is possible that some rare, but costly, complications were not identified in the study.	Not available
Pershad *et al.*, (2019) (12)	1 year after CTO-PCI	1000	All patients scheduled for a CTO PCI by an experienced CTO operator familiar with the hybrid strategy at each participating hospital were screened for possible inclusion	257 out of 804 among men, 64 out of 196 among women, total 321 (32.1%)	There were no sex differences in outcomes after the treatment at 1 year. There were no differences in technical success, procedural success or MACCE rates between men and women. At 1 year, women derived the same marked benefit in the coronary disease specific health status outcomes as men.	Multivariate conditional logistic regression modeling for predictors of procedural success revealed that younger age (OR= 0.955, 95% CI [0.55,1.50]; p = 0.0214), lower J-CTO score (OR= 0.764, 95% CI [0.61,0.94]; p = 0.0128), and absence of prior CABG (OR= 0.580, 95% CI[0.38,0.86]; p = 0.0076), were predictors of procedural success.	The operators in this registry were high volume, experienced operators. These results cannot be extrapolated to less experienced and lower-volume CTO operators. Biomarkers, hemoglobin, and creatinine measurements were self-reported by the participating institutions and might therefore been	Young, low J-CTO score and absence of prior CABG were predictors of procedural success.

							underestimated in this registry.	
Kalra *et al.*, (2021) (13)	Jan 2014 to Jul 2015	885	All patients undergoing planned PCI for a CTO. Among 1000 patients enrolled in the OPEN CTO registry, 115 patients had multiple CTO lesions treated during the hospitalization and were excluded from analysis	454 (51%)	Patients undergoing retrograde CTO PCI had more comorbidities and greater lesion complexity compared with patients undergoing antegrade-only CTO PCI. Retrograde CTO PCI was associated with a lower rate of technical (82.4% vs 94.2%) and procedural success (74.7% vs 91.9%) and higher risk of in-hospital MACCE (10.8% vs 3.2%), due to a higher rate of procedure-related complications. Retrograde CTO PCI resulted in similar improvement in disease-specific health status and quality of life compared with antegrade-only CTO PCI at 1 year.	The multivariable mixed effect regression model, with adjustment showed that retrograde CTO PCI (Relative Risk = 2.73, 95%CI [1.45,5.13]; p <.01) and older age (RR = 1.60, 95%CI [1.23,2.08]; p <.01) were an independent predictors of in-hospital MACCE.	Results obtained may not be generalizable to low-volume centers, where complication rates may be higher than those reported. Given the lack of randomization and limited number of adverse outcomes, the effect of unmeasured confounders cannot be excluded	Not available
RECHARGE CTO								
Maeremans *et al.*, (2016) (14)	Jan 2014 to Oct 2015	1177	consecutive patients treated for CTO PCI were prospectively included in the RECHARGE registry by CTO operators in 17 European centers, including Belgium, France, the Netherlands,	207 (17%)	The study demonstrates that hybrid techniques for CTO-PCI as applied by dedicated CTO operators with a variety of experience have high success rates. The mean number of annually performed CTO procedures per operator was 64, and 32% of the operators performed fewer than 50 procedures/year. Overall procedure success was 86% and major in-	Not available	Not all centers started inclusion at the same time, and experience among some operators could have increased in the meantime, influencing outcomes. Because pre- and post-procedural laboratory tests were only available in a minority of the patients, especially the number of	Not available

			and the United Kingdom		hospital complications occurred in 2.6%. Antegrade wire escalation was the preferred primary strategy in 77% of the patients.		periprocedural myocardial infarctions were underreported.	
Maeremans et al., (2018) (15)	Jan 2014 to Oct 2015	1067		268 (25%)	The use of the hybrid algorithm with contemporary techniques by moderate to highly experienced operators for CTO-PCI is safe and associated with a low 1-year event rate. Overall technical success was 86% and MACE was 8.7% at 1 year after discharge. The presence of peripheral vascular disease increased the risk for MACE by a factor of 2 (adjusted hazard ratio, 1.97; P<.01)	Cox regression analysis was done and showed that peripheral artery disease was a negative predictor for MACE (adjusted hazard ratio = 1.97; 95% CI [1.21, 3.21]; P<.01).	The study may be susceptible to the effects of unidentified confounders. Clinical events during follow-up were operator reported, and there was no central independent adjudication of these events. Not all centers provided follow-up, and follow-up was not 100%	Not available

ERCTO: The European Registry of CTOs (ERCTO) is a prospective registry from 55 centres around Europe containing data on patients undergoing CTO from January 2008. The retrograde strategy as the first approach was more successful than after a failed antegrade approach (82.2% vs 53.1%) (94) . In successful cases, the retrograde crossing technique was controlled antegrade retrograde tracking (13.9%), reverse controlled antegrade retrograde tracking (16%), touching wires (22%), or simple retrograde wire crossing (31.2%). 0.8% of the patients experienced in-hospital major adverse cardiac and cerebrovascular event (MACCEs) in the retrograde CTO cohort, compared with 0.5% of patients in the anterograde group (94). From 2008 to 2014, the retrograde approach rate increased from 10.1% to 29.9% (P value for trend <0.001) (95). Among the failed CTOs, the retrograde approach was higher at 35.9%. As retrograde approach was more accessible in Europe in 2008, there was a steep increase from 2.6% in 2008 to 39.2% in 2014 to 2015. The antegrade dissection reentry (ADR) strategy increased slightly throughout the study period reaching a peak of 5.5% from 2014 to 2015 (95).

PROGRESS CTO: The PROGRESS CTO registry includes patients from the United States, Europe Union, and Russia. It began in 2012 and is scheduled to stop recruiting patients in 2022. In 2020, Xenogiannis and his collaborators conducted a study comparing patients with vs without peripheral artery disease at the time of reviving CTO PCI by contrasting clinical angiographic characteristics and procedural outcomes (96) . They concluded that there is lower procedural success among patients undergoing CTO-PCI with peripheral artery disease. These patients have more comorbidities and complex lesions (96). Nikolakopoulos *et al*. examined the usage of guidewire and microcatheter during a CTO-PCI and found that polymer-jacketed guidewires and torquable microcatheters were the most commonly used equipment (97). Nikolakopoulus along with other authors also did a 1 year follow up for adverse cardiovascular events comparing CTO-PCI patients with prior CABG and without and had reported that the CTO- PCI patients with prior CABG patients had less procedural success and higher incidence of acute cardiovascular events and follow up of major heart-related events (98). Danek *et al*. created a scoring tool called the PROGRESS CTO complication score to predict complication of peri procedures during CTO-PCI, which could determine health vulnerability and guide clinical decision-making (99). Another complication score, the PROGRESS-CTO Complication score, has also been defined which is independently associated with a significantly higher occurrence of major adverse cardiac event (MACE) over the 1-year follow-up period (100). Successful CTO-PCI was shown to be associated with the improvement of angina and lower incidence of MACE. Christopoulos *et al*. examined the relationship of the J-CTO score with technical and total procedural time in the PROGRESS CTO registry(101). They confirmed that a high J-CTO score is associated with a greater risk of technical failure, MACE, and lengthy process. Tajti *et al*. reported on the outcomes of patients with prior CABG who have undergone CTO-PCI. CTO PCI in CABG patients is associated with decreased procedural success rates and higher perforation rates, possibly because of the difficult anatomy of the lesion (102). Martinez-Parachini *et al*. examined the impact of diabetes mellitus on procedural outcomes of patients who underwent CTO PCI and found that the complication rates and procedural success were similar in both people with and without diabetes (103). Tajti *et al*. also reported the largest study on CTO PCI using the hybrid approach. Overall, the articles based on the PROGRESS-CTO registry show that CTO PCI can currently be carried out with high chance of success and acceptable complication rates among various operators and patient populations in the United States, Europe and Russia (13).

OPEN CTO: This investigator-initiated, multicenter, prospective observational registry included consecutive 1000 CTO patients undergoing PCI at 12 U.S. centers gathered during 2014 to 2015 (104). Salisbury and collaborators compared patient-reported health status after CTO PCI in patients with and without diabetes. They found that the safety of CTO PCI was similar in patients with or without diabetes, and that both groups of patients experienced large, clinically meaningful improvements in health status after CTO PCI. There were no significant differences in coronary disease-specific health status or dyspnea benefits of CTO PCI in patients with and without diabetes (104). Salisbury and other authors conducted a study using the hybrid algorithm to formally analyse the cost of CTO-PCI and to investigate the effect of procedure-related complication on hospital costs for this complex patient population (105). The mean cost for the index hospitalization were 17,048 ± 9,904 USD. If a patient had complications, the mean hospital cost would increase by $8603. Periprocedural complications accounted for $911 of the overall expenses of CTO PCI, which was 5.3 percent of the procedure's total hospitalisation expenditures. (105). Pershad *et al*. investigated if outcomes vary by the sex of the patient and found that women obtain the same benefit from CTO-PCI as males (106). Khariton and collaborators conducted a study to investigate the relation between CTO – PCI and health outcomes in patients with and without cardiomyopathy. They concluded that each group experienced substantial beneficial impact after CTO-PCI, while there was less advancement in health status in patients with severely reduced LVEF relative to those with average LVEF (107). Kalra *et al*. assessed long-term and in-hospital outcomes and compared retrograde with antegrade CTO PCI (108). It was reported that in the OPEN-CTO registry 51.3 % received retrograde CTO-PCI while 48.7% received antegrade-only procedure. In comparison to the antegrade-only group, the retrograde patients were more likely to have a history of myocardial infarction (MI), coronary artery bypass graft (CABG), diabetes mellitus and peripheral arterial disease and severe angina. Among the recanalization strategies resulting in a successful CTO PCI, antegrade wire escalation was used in most cases (40.8%), followed by retrograde dissection re-entry (24.6%), antegrade dis-section re-entry (24.3%), and retrograde wire-escalation (10.3%). The rates of technical and procedural success were lower with retrograde in comparison to antegrade-only techniques. Rates of technical success were lower in patients with prior CABG versus without (80.5vs. 92.3%), regardless of the recanalization approach. The overall in-hospital major adverse cardiac and cerebrovascular events (MACCE) rate was 7.1%. Unadjusted in-hospital MACCE rates were higher following retrograde CTO PCI compared to antegrade-only procedures. After a year, the rates of MACCE were higher in the retrograde group in comparison to the antegrade-only group, while the unadjusted rates of death and target vessel failure (TVF) were similar between groups.

RECHARGE CTO: The Registry of Crossboss and hybrid procedures in FrAnce, NetherRlands, BelGium and UnitEd Kingdom (RECHARGE) registry aimed to provide a real-world image of current results using the hybrid algorithm and assess the contribution of different crossing techniques to successful CTO revascularization from January 2014 to October 2015 based on data from 17 centres (48). A sub-study of the RECHARGE registry was pursued to determine the long-term effectiveness and safety of the hybrid CTO-PCI and its post-discharge methods. For 1067 patients, follow-up information was available, reporting on 1-year results after contemporary hybrid CTO-PCI. The use of the hybrid algorithm by moderate to highly skilled operators for CTO-PCI with contemporary techniques was found to be safe and consistent with a low 1-year event rate. One-year MACE-free survival rate was 91.3% (974/1067). MACE included death (1.9%; n = 20), myocardial infarction (1.4%; n = 15), target-vessel failure (5.9%;

n = 63), and target-vessel revascularization (5.5%; n = 59). Risk of MACE was significantly lower in successful CTO-PCI cases (8.0% vs 13%), even after adjusting for baseline differences (adjusted hazard ratio, 0.59; 95% confidence interval, 0.36-0.98) (109). A study by Maeremans *et al*. reported on a group of CTO-PCIs done by the hybrid algorithm where the operator had the choice to choose the strategy (48) . There were 832 PCIs performed in continental Europe and 421 in UK centres. The first strategy suggested was antegrade wire escalation for CTOs made up of clear proximal cap, a good distal landing zone, and a short lesion length (⩽20 mm). ADR was preferable for longer lesions. CTOs with proximal cap ambiguity or a diseased distal landing zone but good "interventional" collaterals, a retrograde approach was recommended. An overall success of 86% was achieved per procedure and the average success of centers or operators performing >100 cases/year was significantly higher compared with lower-volume operators (91% vs. 82% vs. 83%). The ADR success was higher (66%) than the retrograde technique success 23% (48).

Chapter 3 : Methodology

This chapter describes details of the Canadian CTO PCI (CCTOP) registry which is the primary focus of this thesis and its analysis. The impact of predictors of short-term procedural success following CTO-PCI (defined as technical success without major complication) previously reported in the literature was studied. Outcomes are compared among patients who underwent an antegrade-only vs. a retrograde CTO PCI. Classification and regression tree analysis (CART) is also introduced which will be used to find interaction terms as a secondary approach.

3.1 Data Source

The data source was the Canadian CTO-PCI(CCTOP) registry. It was a multi-centre Canadian cohort of patients who received CTO-PCI from six major tertiary centres from 2014 to 2019. Three centres were located in the province of Quebec (Centre hospitalier de l'Université de Montréal, CHUM; l'Institut universitaire de cardiologie et de pneumologie de Québec, IUCPQ; McGill University Health Centre, MUHC), two were in British Columbia (Vancouver General Hospital, VGH; Victoria Hospital), and one in Ontario (Sunnybrook Health Sciences Centre). All the data was pooled without any center specific analyses.

All patients undergoing CTO PCI and entering the CCTOP registry were considered for the analysis. The only exclusion criterion was the impossibility to determine if an antegrade-only or a retrograde approach was used. At the time of analysis, subjects with incomplete data (procedural data, baseline data or in-hospital outcomes) were also excluded. Although this was a cohort study with a 1 year follow up, for the purpose of the thesis, procedural outcome was measured during the time of the procedure with a 30 day window prior and post to the PCI date.

Each of the centres input data through a user-friendly interface. All CTO PCI patients who would consent for data collection at each centre during the study period were included in the registry. The variables gathered covered the disease history of the patients, which included cardiac history, cardiovascular risk factors and pre-procedure status, results of laboratory tests, procedural information including coronary angiogram details, details of medication, PCI, and procedural complications. Variables measured by healthcare professionals in the patient's clinical chart were entered into an online database by research personnel. The majority of variables had categorical responses entered via drop-down menus in order to minimize the loss of information. The database was hosted on a French server, and built by MediReport, Paris. Data entry was web-based, and all data was encrypted to protect patients' identifiers. For outcomes measured after discharge from the hospital, participants were assessed through telephone follow up or in-person follow up. Telephone follow up was self-reported by the patient.

Patients provided signed informed consent before entering the CCTOP. Institutional review boards were approved at each study centre. The study was compliant with the Declaration of Helsinki and Good Clinical Practice.

3.2 Definition of key variables

The database recorded up to three CTO-PCI attempts on each patient. The *type of strategy* was recorded as either retrograde or antegrade-only in each case. The *type of crossing* was also recorded in each case as dissection and reentry or none. The number of CTO-PCI strategies attempted on each patient was recorded. J-CTO score was constructed by adding a series of dichotomous variables coded as 0 vs. 1: occlusion length ≥20mm, angulation ≥45 degrees, calcification, blunt proximal cap, and a failure during a previous attempt, where yes=1 and no=0. The maximum possible J-CTO score is 5 and the minimum is 0. Major complications were defined as death, stroke, tamponade, and urgent surgery. The following terms have been used throughout the thesis and in the tables.

Box 3.1 Description of terms.

Term	Description
Chronic Angina	Chest pain or discomfort caused due to poor flow of blood through the blood vessels in the heart, that is chronic and respecting a stable pattern
Dyslipidemia	Elevated total or low-density lipoprotein (LDL) cholesterol levels, or low levels of high-density lipoprotein (HDL) cholesterol, or treatment for secondary prevention
Hypertension	Long-term high blood pressure
Normal LVEF	Left ventricular ejection fraction (LVEF) is a measure of how much blood is being pumped out of the heart’s left ventricle. The normal LVEF ranges from 50%-75%
Occluded Graft	A complete occlusion of a saphenous vein or arterial graft

Prior CABG	A previous coronary artery bypass graft treatment
Prior MI	A previous event of myocardial infarction
Prior PCI	A previous percutaneous coronary intervention treatment
Bifurcation	Division into two branches
Bridging Collaterals	A collateral channel that bridges between the proximal and distal parts of a coronary artery occlusion outside the vessel structure
CTO Course Ambiguity	Lack of clarity as to the vessel course
Diagonal Branches	Left anterior descending coronary artery supply blood flow to the anterior and anterolateral walls of the left ventricle. Branches to the lateral wall are called diagonal branches, which are branching from their parent vessel at acute angles.
Left Anterior Descending Artery	Artery that branches off the left coronary artery and supplies blood to the front of the left side of the heart.
Left Circumflex	The artery branches off the left coronary artery and encircles the heart muscle which supplies blood to the lateral side and back of the heart.
Left Main	The coronary artery supplies blood to the left side of the heart muscle
Obtuse Marginal Vessels	Branches of coronary arteries that come off the circumflex artery
Ostial Location	The opening of the right coronary artery is in the right aortic sinus and that of the left coronary artery is in the left aortic sinus, just above the aortic valve ring. Also, branches arising from a mother branch have their ostium.

Dual access	Two arterial access sites
Access sites	The location on the patient's body where a catheter or wire is inserted to gain access to the occluded coronary artery.
Second Attending Operator	The second interventional cardiologist assists the primary operator in performing the procedure. The second attending operator typically stands on the opposite side of the patient and helps with wire manipulation, catheter positioning, and device delivery.
Rotablator	Device used at a high-speed rotational burr that is attached to a flexible drive shaft, which is guided through a small catheter and into the blocked artery.
StingRay	A type of microcatheter that is used to facilitate the crossing of a CTO during a minimally invasive procedure.
Bifurcation PCI	A minimally invasive procedure used to treat a CTO in a branch of the main coronary artery
Unprotected LM PCI	A minimally invasive procedure used to treat a CTO in the left main coronary artery, without the protection of a guiding catheter
Fluro time	Duration of time that X-ray imaging is used during a CTO PCI
Dose-area product	A measure of the amount of radiation delivered to a specific area of the body during the CTO PCI
Air Kerma	A measure of the radiation exposure received by the patient
Activated Clotting Time	A measure that monitors the level of anticoagulation achieved during the procedure
Drug-Eluting Stent	A medical device that is designed to be inserted into the blocked artery to help keep it open and allow blood to flow through
Septal Collateral Channel	Small blood vessel that develops within the septum of the heart muscle

Epicardial Collateral Channel	Natural bypass vessels that develop in the heart muscle over time in patients with CTOs due to lack of blood flow
Graft	It is used to bridge the gap created by the channel, allowing blood to flow past the blockage by creating a small channel or tunnel through the blockage and then inserting a wire and a balloon to expand the channel.
Guide size	The diameter of the guiding catheter used
Doner vessel	Refers to an artery or collateral vessel that provides blood flow to the area of the heart beyond the occlusion being treated.
Werner Class	A grading system that assesses the complexity of CTO lesions based on the level of difficulty to cross them with a guidewire.
Tortuosity	The degree of curvature or bending of the coronary artery that is affected by the CTO
Residual Distal Disease	Presence of residual blockages or narrowing of the coronary artery located beyond the site of the occlusion that has been successfully opened through PCI.
Distal cap	Proximal end of the occluded coronary artery, where the occlusion begins.
Cardiac Tamponade	When fluid accumulates in the space around the heart.
Creatine kinase elevation	When the protein, creatine kinase, level rises in the blood.
CTO perforation	A hole that develops through the wall of the artery in a CTO and are classified into 4 groups: Type 1, Type 2, Type 3, and Type 4.
Troponin	A protein found in the cardiac muscles. This protein is released into the bloodstream when the cardiac muscles are damaged.

3.3 Classification and regression tree methods

One of the challenges in studying the relative importance of risk factors from registry studies is the large number of potentially interesting risk factors compared to the sample size. Standard regression models cannot simultaneously examine all predictors in such situations. A widely used rule of thumb requires at least 10 subjects who have the outcome per each predictor, though more recent work has suggested that the criteria for determining the minimum sample size are more complex (110). We review here an alternative analytical approach that we considered for application in this thesis.

The Classification and Regression Tree (CART) statistical method, which is a technique employed in retrograde procedures that shares the same acronym) is a nonparametric statistical framework that may be used for determining the most essential variables, in terms of explanatory power (111). Breiman and his colleagues were the first to propose the CART methodology (112) in 1984.

CART is used to repeatedly split the observed sample into mutually exclusive and exhaustive subgroups with shared characteristics that impact the dependent variable of interest resulting in a multilevel structure that resembles tree branches as a visual output. Any combination of categorical and continuous variables can be used as independent variables. CART splits observations using a simple decision rule at each step. Splits, on the other hand, are always binary. In the case of an ordinal or continuous variable, CART searches the entire range of values for the optimum combination of categories or cut-point selection of the best splitting criterion, (113). To convey observations with missing split values via its nodes, CART implements "surrogate splits" (114). A terminal node, also known as a leaf node or ending, is a node that does not split any further. It is the endpoint of a particular branch or path. The Gini's diversity index was used as the statistical criteria for the splitting, as suggested by Breiman et al (112).

Main effects regression models enable researchers to evaluate, whether there is an association between a particular correlate and a dependent measure, while adjusting for confounding factors. The average effect of an independent variable on a dependent variable is determined via regression models. As a result, when treatments are designed based on regression model findings, without considering the special needs of population subgroups, they are targeted toward the average member of the population. Statistical interactions, on the other hand, can be hard to interpret, especially when there is an assessment of three or more variables the simultaneously. (113, 115).

Developing a model to predict outcomes for a disease is one of the most intriguing and difficult challenges for which different statistical techniques can be used (116) . One advantage of CART methodology is that it has the ability to detect interactions and non-monotonic relations (117).

Several studies have attempted to compare the performance of different statistical techniques for prediction though there is no clear evidence that one method is more advantageous. For example, a retrospective analysis of 1245 subjects suspected with coronary artery disease (CAD) compared performances of logistic regression (LR), CART and multi-layer perceptron (MLP), radial basis function, and self-organizing feature maps for predicting CAD. The following classification techniques were also compared: receiver operating characteristic curve analysis, hierarchical cluster analysis, and multidimensional scaling. The receiver operating characteristics curve showed that MLP (area under the receiver operating characteristic curve = 0.783) performed better than other techniques, followed by logistic regression (area under the receiver operating characteristic curve = 0.753), CART (area under the receiver operating characteristic curve = 0.745), radial basis function (area under the receiver operating characteristic curve = 0.721) and finally SORM (area under the receiver operating characteristic curve = 0.675) in predicting CAD. Five classification techniques were clustered into two distinct groups, the first group included MLP, CART, LR, and radial basis function and the second group included only self-organizing feature maps. The authors conducted a multidimensional scaling analysis and found that the first dimension explained 98.7% of the variation and the second dimension accounted for 1.3% of the variation. The multidimensional scaling had a pseudo- R^2 of 1 and a stress factor of 0.00037. The results were plotted in a two-dimensional plot, where MLP, CART, LR, and radial basis function were located close to each other but further from self-organizing feature maps. In accordance with hierarchical cluster analysis and multidimensional scaling, the prediction of CAD was performed better by MLP, followed by CART and LR (116). According to Stark and Pfeiffer, classification trees (CART), were shown to be well-suited for exploratory data analysis in complicated data sets in veterinary epidemiology (118). On the contrary, Colombet *et al*. concluded that CART's prediction performance was somewhat lower than that of LR and artificial neural networks (119).

3.4 Statistical methods

Descriptive statistics were used to characterize the cohort. Subjects who received antegrade-only and retrograde procedures were compared. For the purposes of this thesis, if the lesion crossing was attempted from the distal cap, after delivery of a guidewire through a collateral vessel or bypass graft supplying the target vessel distal to the lesion, the procedure is defined as "retrograde. Otherwise, the classification of the procedure is "antegrade only".

The Chi square and Fisher exact tests were used to compare the distribution of categorical variables, while t-test was used to compare the distribution of continuous variables. For each hypothesis test a p-value was reported. A p-value less than or equal to 0.05 was interpreted as evidence of a statistically significant association. On the other hand, a p-value greater than 0.05 should not be interpreted as the true lack of an association but merely as the lack of sufficient evidence in the data to reject the null hypothesis of no association. Differences in proportions between the retrograde and antegrade groups and the corresponding 95% confidence intervals were calculated.

Procedural success, defined as technical success without major complication. The primary analysis estimating the association between various predictors and the chances of procedural success, focused on univariate and multivariate logistic regression models. Multivariate logistic regression requires that there are a sufficient number of subjects in the dataset with and without the outcome, especially for every additional predictor included in the model (120).

Given the relatively small number of individuals with failure, we explored Classification and Regression Tree (CART) models as a secondary approach to analysis. This approach was expected to be potentially useful within strata defined by procedure type (antegrade-only vs retrograde), as the sample size within strata is further reduced. Even when presented with many predictors, the CART model only selects a few best predictors based on pre-defined criteria that are designed to split the dataset so that there is a maximal separation between the sub-groups in terms of the probability of a successful CTO. Another advantage of CART is that there is no need to specify the form of the relationship between outcome and predictor, e.g., whether it is linear or non-linear, or whether there is an interaction between some variables.

The choice of variables in the logistic regression and CART models were based on expert opinion which identified predictor variables reported by previous studies. An effort was made to separate variables measured prior to the procedure (which cannot be controlled at the time of the intervention) from the procedural variables. All the variables in univariate analysis were also used in the multivariate analysis. Therefore, there was no variable selection.

All statistical analyses were carried out using the R statistical software environment. The missing values were replaced by not available (NA).

Chapter 4 : Result

4.1 Description of the cohort

A total of 1194 patients were recruited over a period of 6 years and used in the analysis. Patients were classified into two groups, 549 patients (46%) underwent an antegrade-only CTO-PCI procedure, while 525 (44%) underwent a retrograde strategy or a failed antegrade followed by a retrograde procedure. For the short-term outcomes, during the follow up of 30 days, there were 1077 (90%) patients among 1194 whom had complete information. Outcome information was missing on 118 (9.9%) patients and predictor variables were missing on 224 (19%) patients.

4.1.1 Baseline demographic and clinical characteristics of subjects

Table 4.1 summarizes the distribution of baseline demographic and clinical characteristics of the patients. Several technical terms are used to describe the baseline demographic and clinical characteristics. These are summarized in box 3.1 to facilitate interpretation for the lay reader. The average age was 66.2 years and male patients made up 83% of the study sample. The majority of patients had a prior PCI (64%), 44% of them had a prior MI and 29% of them had a prior CABG. Among these post-CABG patients, most (74%) had three or more grafts. Hypertension and dyslipidemia were the most common cardiovascular risk factors, being present in 82% and 89%, respectively, of patients. Most patients (69%) had a normal LVEF. The most common indication for CTO-PCI was stable angina, being present in 80% of patients. The number of diseased vessels was most likely to be 1 (46%), followed by 2 (32%) and 3 (22%). A very small minority (5.1%) of patients had 2 CTOs treated during the same procedure. Most procedures (78%) were documented in three centres located in Quebec City, Montreal, and Toronto.

Comparison of antegrade-only and retrograde groups: Antegrade-only was classified as patients without any attempt at crossing a collateral. Retrograde was defined if the lesion crossing was attempted from the distal cap, after delivery of a guidewire through a collateral vessel or bypass graft supplying the target vessel distal to the lesion. Distribution of age and sex was similar in both antegrade and retrograde groups. Previous cardiac history was similar in both groups except for prior CABG, which were slightly higher among the retrograde group. In post-CABG patients, antegrade patients were more likely to have fewer grafts (1-2 grafts vs. 3 grafts) than those who underwent a retrograde procedure. For many cardiovascular risk factors, their presence was higher to some degree in the retrograde than the antegrade group. The proportion of patients without angina and silent ischemia were slightly higher in antegrade compared to retrograde patients (14% vs. 10%). The number of diseased vessels were similar in both groups. There was a difference in frequency of use of the retrograde strategy across the hospital centres. It was more common than the antegrade strategy in two centres in Quebec City and Montreal, but the other way around for other centers.

4.1.2 CTO lesion characteristics at baseline

Table 4.2 presents the distribution of baseline CTO lesion characteristics of the patients. Several technical terms are used to describe the CTO lesion. These are summarized in box 3.1 to facilitate interpretation for the lay reader. For most patients, the right coronary artery was the target CTO vessel (50%), followed by the left anterior descending artery (29%). Left circumflex and obtuse marginal (OM) vessels made up 14% of the target vessels and the left main, diagonal branches and others accounted for less than 5 % of target CTO vessels. The mean J-CTO score was 2.2 whereas more than half of the study sample had a JCTO score of 3 or more (55%), 31% had a score of 2 and 14% had a score of 1. Among the clinical and angiographic CTO parameters used to calculate the J-CTO score, calcification was the most common with a prevalence of 78%, followed by occlusion length >20mm of 62%, bending >45° of 46%, blunt proximal cap of 36% and finally previous attempt of 27%. In-stent occlusions accounted for less than 10% of the cohort, among which post drug eluted stent was the highest (4.8%) cause. Many patients had a good distal landing zone (73%). Presence of CTO course ambiguity, bifurcation at distal cap, bridging collaterals and proximal cap ambiguity ranged from 27% to 37%. There were a small number of patients for whom the CTO was in an ostial location (18%). Among the interventional collaterals, the majority were septal (45%). Half of the patients had a branch at proximal entry.

Comparison of antegrade-only and retrograde groups: The distribution of target CTO vessel was similar in both antegrade and retrograde for the left main (LM), diagonal branches and others. The left anterior descending artery, left circumflex and OM vessels were slightly higher in the antegrade group. The right coronary artery in the target CTO vessel was more frequent in the retrograde group. The mean J-CTO score was higher in the retrograde group along with the proportion with J-CTO score of 3 or more. Similarly, the clinical and angiographic CTO parameters used to calculate the J-CTO score were significantly more present in the retrograde group. The distribution of in-stent occlusion was similar in both groups. Ostial location, CTO course ambiguity, bifurcation at distal cap, proximal cap ambiguity was significantly higher in the retrograde group. On the other hand, bridging collateral and good distal landing zone were higher in the antegrade group. Among interventional collaterals, septal and epicardial combined and septal was significantly higher in retrograde while epicardial was higher in antegrade group, and branch at proximal entry were similar in both groups.

4.1.3 CTO procedure description

Table 4.3 contains the distribution of procedural data per patient of the study population. Almost half of the procedures took place between 2016 and 2017 (48%). Most of the patients had dual access (91%), among which the most common combination of access sites was radial and femoral (46%), followed by dual radial (26%). In all patients, 70% had a femoral approach. During the procedure, 42% had a second attending operator involved and more than half of the procedures had a resident or fellow assistant (57%). Use of Rotablator, bifurcation PCI, unprotected left main PCI were below 13%. Patients that had a non-CTO PCI site treated accounted for 40% of the cohort and 71% had complete revascularization. Radiation doses, measures with dose-area product and Air Kerma were within expected range. The number of drug eluting stents implanted was more likely to be 1-3 (70%). The types of drug-eluting stent were Combination, Promus Everolimus ES and Xience Everolimus ES, 34%, 33% and 30% respectively. The average total stent length was 61.7 mm with an average maximal stent diameter of 3.4 mm.

Comparison of antegrade and retrograde groups: The year of the procedure, procedures with a second attending operator involved and resident or fellow assistant were similar between both groups. Dual access and any femoral approach were used more often in retrograde procedures. More Stingray devices were used in procedures that had a retrograde component, likely a marker of complexity. Complete revascularization was more commonly achieved in the antegrade group. The mean contrast volume used, fluoroscopic time, dose-area product and air kerma was significantly higher in the retrograde group. The number of drug-eluting stent implanted was lower in the antegrade group. The type of drug-eluting stent used did not vary much across the groups. The mean total stent length and maximal stent diameter was slightly higher in the retrograde group.

4.1.4 Procedural data, per CTO lesion

Table 4.4 contains a summary of the descriptors of the CTO PCI procedure. Almost half (54%) of the procedures employed only one CTO PCI strategy. CTO-PCI success was 88% overall. Among the successful procedures, less than 3% of the procedures had a final dissection with type A being the highest (1.3%). Distal slow flow was observed in 2.7% of the procedures. Majority successful procedures were achieved with antegrade wiring techniques. Half of the procedures took more than 30 minutes to cross the CTO, while half took less than 30 minutes. The most common types of wire used were stiff penetrating wire (32%), medium stiffness non polymeric wire (25%) and harder polymeric wire (24%). Residual distal disease, defined as distal stenoses not touched with further intervention, was present in 14% of the procedures.

Comparison of antegrade and retrograde groups: Dissection-re-entry techniques were more frequently used in antegrade procedures as the first and second strategy, 59% and 39%, respectively. Antegrade procedures were more likely to rely on a single strategy (81%), whereas 2 or more strategies were more often used in the retrograde group. In the latter group, 35% of the procedures had a retrograde approach as the first strategy. The majority of the retrograde pathway was crossed using the septal collateral channel (CC) (49%) and using the 6F retrograde guide (73%). An left anterior descending artery was the most common type of donor collateral vessel (64%). Among the collateral channel werner class, CC1 were the most prevalent (58%). CC tortuosity was more likely to be moderate (50%) than mild (31%) and severe (corkscrew) was only seen in 19%. The retrograde crossing success was 64%. Among the types of wire used, Sion (Asahi Intecc, Japan) was the most commonly used (37%) to traverse the collateral channel. CTO PCI success was significantly higher in antegrade compared to retrograde procedures (91% vs 81%). Among the antegrade approach, the antegrade wiring with true-to-true lumen approach was the most commonly (79%) successful, while retrograde cases relied more often on retrograde dissection re-entry (32%). The distribution was similar in both groups for distal slow flow and wires used, except for the stiff penetrating wire, more often used in the retrograde group. Residual distal disease was similar in both groups.

4.1.5 In-hospital complications

Table 4.5 summarizes the distribution of in-hospital complications per patient. For the short-term outcomes, during the follow up of 30 days, there were 1077 (90%) patients among 1194 whom had complete information. Outcome information was missing on 118 (9.9%) patients and predictor variables were missing on 224 (19%) patients. For the short-term outcomes, during the follow up of 30 days, there were only 4 deaths. Mortality was low, with 0.3% overall. A few terms are summarized in box 3.1 to facilitate interpretation for the lay reader. There was a 5.4% risk of CTO perforation among which type 1 was the most common (2.9%). Collateral damage was found in 2.5% of the patients. Distal dissection and troponin or creatine kinase elevation were the most common types of complications occurring in 4.5% and 5.5% of patients respectively.

CTO perforation, collateral damage, cardiac tamponade, distal dissection, troponin or creatine kinase elevation, donor artery thrombosis and CABG were all slightly higher among the retrograde patients.

4.2 Logistic regression models

Table 4.6 provides the results of univariate and multivariate logistic regression analyses of the association between the predictors of interest and a technically successful CTO PCI. The predictors considered were based on input from the clinical expert who led the CCTOP project (Dr. Stéphane Rinfret). They included cardiovascular history, severity of CTO, lesion characteristics and procedural factors. Thus, both non-modifiable factors (e.g., cardiovascular history) as well as modifiable factors (e.g., CTO PCI strategy) were included.

Statistically significant univariate predictors of a successful CTO PCI procedure included: no prior CABG procedure, low JCTO score, no ambiguity in the proximal cap, no ambiguity in the CTO course, not good distal landing zone, antegrade vs retrograde, no dissection-re-entry and fewer number of strategies used. Of these, no prior CABG, severely reduced LVEF, no proximal cap ambiguity, no good distal landing zone and the collateral that were not crossed were also significant in the multivariate model after adjusting for other predictor variables.

4.3 Classification and regression tree (CART) analyses

Classification and Regression Tree (CART) analysis was used to try to identify possible interactions between predictor variables studied. The same predictor variables used in the logistic regression analyses were used here to see if CART could provide a different perspective. Further progression was done in a sequential fashion. First, a CART model was fit that only the baseline variables (which could not be modified) followed by CART models that included both baseline variables and procedure variables (which can be modified at the time of the CTO PCI procedure). The goal was to distinguish between the impact of those variables that predispose a subject towards a successful outcome prior to the intervention separately from those that can be modified during the intervention. The second CART analysis was repeated within sub-groups of subjects who underwent an antegrade or retrograde CTO PCI strategy. This was done as it was known that many of the procedural variables are strongly associated with the choice of either of these strategies.

4.3.1 All patients

The CART model involving baseline variables only was as follows:

CTO PCI Success ~ Prior CABG + JCTO score + Proximal cap ambiguity + CTO course ambiguity + Good distal landing zone + Interventional collateral (septal) + Branch at proximal entry + retrograde vs antegrade + Stingray wire + number of strategies

This model resulted in no predictor variables being selected, implying that none of the baseline variables resulted in separating groups with a large disparity in success probability even though some of these variables were statistically significant in the logistic regression model (Figure 4.1).

Therefore, the following CART model including baseline variables and procedural variables was fit with for all patients in the study:

CTO PCI Success ~ Prior CABG + Diabetes + Severely reduced LVEF + Target CTO Vessel + JCTO score + In-stent occlusion + Bridging collaterals + Proximal cap ambiguity + CTO course ambiguity + Bifurcation at distal cap + Good distal landing zone + Interventional collateral + Branch at proximal entry + retrograde vs antegrade + Any femoral approach + Stingray wire + Dissection reentry + number of strategies + Collateral crossed.

Each box of the tree depicts a group of patients prior to being split (unless it is a terminal node). The text in each box gives the percentage of patients in the box (lowest row), the percentage of success among those patients (middle row) and the variable resulting in the greatest separation in the success proportion (first row).

The CART procedure generated a tree containing 4 terminal (or ending) nodes (Figure 4.2). Across the terminal nodes, the proportion of success ranged from 23% to 90%. The largest terminal node was associated with 93% of the subjects along with high success of 90%. A few of the smaller nodes had a lower percentage of success.

The most important splits were caused by collateral crossed, JCTO score and proximal cap ambiguity. From this tree it can be seen that most people benefit from a CTO PCI. Two smaller nodes were identified which had a smaller percentage of success. Inference based on these small sized groups is expected to be less robust, therefore we tried to limit the minimum number of patients per node. When requiring that at least 30 subjects be present in each terminal model we found that there was only 1 possible split (collateral crossed – Yes vs. No or not attempted).

4.3.2 Retrograde patients

The following model was used to run a CART analysis among patients who underwent a retrograde approach in the study:

CTO PCI Success ~ Prior CABG + Diabetes + Severely reduced LVEF + Target CTO Vessel + JCTO score + In-stent occlusion + Bridging collaterals + Proximal cap ambiguity + CTO course ambiguity + Bifurcation at distal cap + Good distal landing zone + Interventional collateral +

Branch at proximal entry + Any femoral approach + Stingray wire + Dissection reentry + number of strategies + Collateral crossed.

The CART procedure generated a tree containing 6 nodes (Figure 4.3). The most important splits were caused by collateral not crossed and JCTO score. Across the terminal nodes, the outcome of success ranges from the lowest value 0% to the highest value of 89% success. The largest terminal nodes contain 86% of the subjects with a high success of 89%. The smaller terminal nodes had lower percentage of success, except two of the smaller terminal nodes with 1% and 4% of the patients with a high success of 71% and 64%. However, as noted for the previous tree, these estimates may not be robust. When trying to fit a CART model resulting in at least 30 subjects in each terminal node, the tree did not result in any splits.

4.3.3 Antegrade patients

The following model was used to run a CART analysis for patients that had an antegrade approach in the study:

CTO PCI Success ~ Prior CABG + Diabetes + Severely reduced LVEF + Target CTO Vessel + JCTO score + In-stent occlusion + Bridging collaterals + Proximal cap ambiguity + CTO course ambiguity + Bifurcation at distal cap + Good distal landing zone + Interventional collateral + Branch at proximal entry + Any femoral approach + Stingray wire + Dissection reentry + number of strategies + Collateral crossed.

The CART procedure generated a tree containing 4 terminal (or ending) nodes (Figure 4.4). The most important split was caused by good distal landing. Across the terminal nodes, the outcome of success ranges from the lowest value 37% to the highest value of 94% success. The largest terminal nodes contain 12% and 83% of the subjects with a high success of 87% and 94% respectively. The smallest terminal nodes had a lower percentage of success, Similar for the previous trees, these estimates may not be robust. When trying to fit a CART model resulting in at least 30 subjects in each terminal node, the tree did not result in any splits.

4.4 Tables and figures

Table 4.1: Summary of demographic and clinical characteristics

	All Patient	Antegrade	Retrograde	p value	Difference (Retrograde - Antegrade)	95% Confidence Interval
	N = 1194	N = 549	N = 525			
Demographic Characteristics						
Age (years)	66.2 ± 10.2	66.3± 10.2	66.3 ± 10.6	0.952	0.039	(-1.30, 1.22)
Male sex	995 (83)	452 (82)	446 (85)	0.281	0.026	(-0.020, 0.072)
Previous Cardiac History						
Prior MI	474 (44)	241 (44)	225 (43)	0.803	-0.009	(-0.052, 0.071)
Prior PCI	690 (64)	355 (65)	321 (62)	0.275	-0.034	(-0.026, 0.094)
Prior CABG	310 (29)	139 (26)	164 (31)	0.036	0.06	(-0.116, -0.004)
Number of grafts				0.147		
1 to 2	77 (26)	41 (30)	35 (22)		-0.008	(-0.024, 0.041)
≥3	223 (74)	96 (70)	125 (78)		0.063	(-0.113, -0.013)
Occluded grafts				<0.001		
1	140 (58)	55 (55)	84 (60)		0.06	(-0.102, -0.018)
2	76 (31)	33 (33)	42 (30)		0.02	(-0.052, 0.013)
3 or more	27 (11)	12 (12)	15 (11)		0.007	(-0.027, 0.014)
Cardiovascular Risk Factors						
Smoker	580 (55)	280 (53)	288 (57)	0.184	0.043	(-0.105, 0.020)
Hypertension	886 (82)	440 (81)	431 (83)	0.337	0.025	(-0.073, 0.024)
Dyslipidemia	972 (89)	484 (88)	470 (90)	0.321	0.021	(-0.059, 0.018)
Diabetes	379 (35)	178 (33)	191 (37)	0.176	0.041	(-0.100, 0.018)
Chronic Renal Failure	124 (11)	64 (12)	59 (11)	0.912	-0.004	(-0.036, 0.044)
Family History of CAD	310 (43)	156 (45)	148 (41)	0.266	-0.002	(-0.054, 0.058)
Left Ventricular Ejection Fraction Evaluation				0.435		
Normal (>50%)	707 (69)	366 (71)	330 (68)		-0.038	(-0.044, 0.040)
Mildly reduced (41-50%)	145 (14)	71 (14)	69 (14)		0.002	(-0.064, 0.011)
Moderately reduced (30-40%)	108 (11)	47 (9.1)	59 (12)		0.027	(-0.022, 0.036)
Severely reduced (<30%)	58 (5.7)	31 (6.0)	26 (4.3)		-0.007	(-0.021, 0.097)
Documented Reversible ischemia	472 (86)	248 (87)	214 (83)	0.128	-0.044	(-0.003, 0.013)
PCI Centres				<0.001		
CHUM, Montreal	199 (23)	92 (23)	39 (11)		-0.093	(0.053, 0.134)
Sunnybrook Health Sciences Centre, Toronto	199 (23)	83 (21)	113 (31)		0.064	(-0.112, -0.016)
MUHC, Montreal	193 (22)	106 (26)	85 (23)		-0.031	(-0.016, 0.079)
VGH, Vancouver	160 (18)	65 (16)	78 (21)		0.03	(-0.073, 0.012)
IUCPQ, Québec	85 (10)	37 (9.2)	30 (8.1)		-0.01	(-0.020, 0.041)

Victoria	46 (5.2)	21 (5.2)	24 (6.5)		0.007	(-0.033, 0.018)
Indication for CTO PCI						
Chronic angina				0.704		
CCS 1-2 angina pectoris	646 (75)	319 (74)	313 (76)		0.015	(-0.076, 0.046)
CCS 3 angina pectoris	205 (24)	109 (25)	95 (23)		-0.018	(-0.031, 0.066)
CCS 4 angina pectoris	9 (1.0)	4 (0.9)	5 (1.2)		0.002	(-0.015, 0.011)
Acute coronary syndrome	82 (7.6)	34 (6.3)	45 (8.7)		0.024	(-0.057, 0.009)
STEMI	5 (0.5)	3 (0.6)	2 (0.4)		-0.002	(-0.008, 0.011)
No angina + silent ischemia	132 (12)	74 (14)	54 (10)		-0.032	(-0.009, 0.072)
Number of Diseased Vessels				0.936		
1-vessel disease	490 (46)	249 (46)	234 (45)		-0.008	(-0.054, 0.069)
2-vessel disease	344 (32)	176 (32)	163 (32)		-0.01	(-0.047, 0.068)
3-vessel disease	238 (22)	120 (22)	118 (23)		0.006	(-0.058, 0.045)
Unprotected Left Main Disease	59 (5.5)	27 (4.9)	32 (6.2)	0.452	0.012	(-0.042, 0.017)
2 CTOs during same procedure	41 (5.1)	16 (3.8)	25 (6.4)	0.13	0.026	(-0.059, 0.007)

Abbreviations:
CABG, coronary artery bypass graft
CAD, coronary artery disease
CCS, Canadian Cardiovascular Society
CHUM, Centre hospitalier de l'Université de Montréal
CTO, chronic total occlusion
IUCPQ, Institut Universitaire de Cardiologie et de Pneumologie de Québec
STEMI, ST-segment elevation myocardial infarction
MI, myocardial infarction
MUHC, McGill University Health Centre
PCI, percutaneous coronary intervention

Table 4.2: Summary of CTO lesion characteristics at baseline

	All Patients	Antegrade	Retrograde	p value	Difference (Retrograde - Antegrade)	95% Confidence Interval
	N = 1253	N = 565	N = 550			
Target CTO Vessel				<0.001		
Diagonal branches	16 (1.5)	7 (1.3)	9 (1.8)		0.004	(-0.020, 0.012)
Left anterior descending	304 (29)	169 (32)	135 (27)		-0.054	(-0.00028, 0.11)
Left circumflex and obtuse marginal	141 (14)	93 (17)	48 (10)		-0.077	(0.037, 0.12)
Left Main	57 (5.5)	29 (5.4)	27 (5.4)		-0.0022	(-0.025, 0.030)
Other	6 (0.6)	4 (0.7)	2 (0.4)		-0.0034	(-0.006, 0.014)
Right coronary artery	516 (50)	232 (43)	281 (56)		0.1	(-0.16, -0.040)
JCTO score	2.2 ± 1.3	2.2 ± 1.1	2.7 ± 1.1	<0.001	0.44	(-0.57, -0.31)
0	146 (14)	99 (19)	46 (8.8)	<0.001	-0.092	(0.051, 0.13)
1	330 (31)	182 (35)	147 (28)		-0.055	(-0.000, 0.11)
2	572 (55)	240 (46)	330 (63)		0.18	(-0.23, -0.12)
3 or more	673 (62)	288 (52)	383 (71)	<0.001	0.19	(-0.25, -0.13)
Occlusion length > 20mm	495 (46)	239 (43)	254 (48)	0.185	0.042	(-0.10, 0.019)
Bending > 45°						
Blunt proximal cap	400 (36)	162 (29)	236 (43)	<0.001	0.14	(-0.20, 0.082)
Calcified (any calcification)	860 (78)	407 (74)	450 (83)	0.001	0.087	(-0.14, 0.037)
mild	348 (40)	171 (42)	175 (39)	0.036	0.016	(-0.072, 0.041)
moderate	205 (24)	108 (27)	97 (22)		-0.015	(-0.032, 0.062)
severe	307 (36)	128 (31)	178 (40)		0.097	(-0.15, 0.043)
Previous failure	301 (27)	159 (28)	140 (26)	0.354	-0.027	(-0.028, 0.081)
In-stent occlusion						
Post BMS	34 (3.1)	20 (3.6)	14 (2.6)		-0.0099	(-0.012, 0.032)
Post drug-eluting stent	53 (4.8)	29 (5.2)	24 (4.4)		-0.0077	(-0.019, 0.034)
Post - PCI (other)	17 (1.5)	7 (1.3)	10 (1.8)		0.0058	(-0.022, 0.010)
Post-stent	9 (0.8)	7 (1.3)	2 (0.4)		-0.0088	(-0.003, 0.021)
Ostial location	203 (18)	95 (17)	108 (20)	0.309	0.026	(-0.073, 0.022)
Bridging collaterals	376 (35)	199 (37)	176 (33)	0.195	-0.039	(-0.019, 0.098)
Proximal cap ambiguity	412 (37)	154 (28)	257 (47)	<0.001	0.19	(-0.25, -0.13)
CTO course ambiguity	297 (27)	100 (18)	196 (36)	<0.001	0.18	(-0.23, -0.12)
Bifurcation at distal cap	336 (31)	146 (27)	190 (35)	0.004	0.083	(-0.14, 0.026)
Good distal landing zone	740 (73)	384 (77)	355 (69)	0.008	-0.076	(0.020, 0.13)
Interventional collaterals				<0.001		
Septal	497 (45)	199 (36)	297 (54)		0.19	(-0.25, -0.13)
Epicardial	207 (19)	124 (22)	81 (15)		-0.072	(0.025, 0.12)
Both septal and epicardial	145 (13)	40 (7.2)	105 (19)		0.12	(-0.16, 0.079)
Diseased graft	26 (2.4)	8 (1.4)	18 (3.3)		0.019	(-0.038, .0010)

Branch at proximal entry	547 (50)	255 (46)	289 (53)	0.03	0.067	(-0.13, 0.010)
Abbreviations: BMS, bare metal stents						

Table 4.3: Procedural data per patient

	All Patient	Antegrade	Retrograde	p value	Difference (Retrograde - Antegrade)	95% Confidence Interval
	N = 1194	N = 549	N = 525			
Year of procedure				0.739		
2014-2015	382 (32)	188 (34)	172 (33)		-0.015	(-0.043, 0.073)
2016-2017	569 (48)	262 (48)	263 (50)		0.024	(-0.085, 0.038)
2018-2019	243 (20)	99 (18)	90 (17)		-0.0089	(-0.039, 0.056)
Dual access	957 (91)	455 (86)	492 (97)	<0.001	0.11	(-0.15,-0.075)
Access sites				<0.001		
Single radial	202 (19)	74 (14)	128 (25)		0.11	(-0.16,-0.061)
Single femoral	271 (26)	150 (28)	117 (23)		-0.05	(-0.003, 0.10)
Dual radial	484 (46)	231 (44)	247 (49)		0.05	(-0.110, 0.012)
Dual femoral	43 (4.1)	36 (6.8)	6 (1.2)		-0.054	(0.030, 0.079)
Radial and femoral	47 (4.5)	38 (7.2)	9 (1.8)		-0.052	(0.026, 0.078)
Any femoral approach	729 (70)	341 (64)	381 (75)	<0.001	0.11	(-0.16, -0.049)
Second attending operator involved	408 (42)	205 (42)	198 (42)	1	0.0011	(-0.065, 0.062)
Resident or fellow assistant	552 (57)	259 (53)	291 (62)	0.009	0.086	(-0.15,-0.022)
Rotablator	31 (2.9)	14 (2.6)	17 (3.2)	0.623	0.0069	(-0.029, 0.015)
StingRay	136 (13)	55 (10)	81 (15)	0.011	0.054	(-0.096, -0.012)
Non-CTO PCI site treated	376 (40)	212 (39)	163 (32)	0.021	-0.07	(0.011, 0.13)
Bifurcation PCI	109 (13)	50 (9.3)	35 (6.9)	0.197	-0.034	(-0.0050, 0.073)
Unprotected LM PCI	24 (2.8)	11 (2.5)	13 (3.3)	0.627	0.0052	(-0.025, 0.015)
Complete revascularisation	624 (71)	346 (77)	273 (65)	<0.001	-0.12	(0.063, 0.19)
Contrast (cc)	318.8 ± 145.4	291.6 ± 140.7	348.2 ± 145.5	<0.001	57	(-74, -39)
Fluoro time (min)	59.0 ± 34.7	45.3 ± 27.2	73.6 ± 35.9	<0.001	28	(-32, -24)
Dose-area product	44468.6 ± 70138.2	36859.1 ± 61762.4	53257.7 ± 78230.0	0.001	16399	(-26104, -6693)
Air Kerma	2593.7 ± 3094.6	2059.7 ± 1920.7	3130.9 ± 3898.4	<0.001	1071	(-1483, -659)
Lowest ACT	264.4 ± 63.7	265.7 ± 65.8	262.8 ± 61.8	0.591	-3	(-8, 14)
Highest ACT	334.0 ± 64.8	326.6 ± 66.3	341.0 ± 62.1	0.032	14	(-28, -1)
Procedure duration (min)	80.7 ± 11.6	81.3 ± 11.4	79.2 ± 12.3	0.255	-2	(-2, 6)
Number of drug-eluting stent implanted				<0.001		
1-3	753 (70)	428 (79)	324 (62)		-0.16	(0.11, 0.22)
4-5	156 (15)	64 (12)	91 (17)		0.057	(-0.10,-0.013)
6 and more	16 (1.5)	5 (0.9)	11 (2.1)		0.012	(-0.028,0.0046)
Type of drug-eluting stent				0.084		
Xience Everolimus EES	319 (34)	163 (33)	155 (36)		-0.0017	(-0.055, 0.058)
Promus Everolimus ES	306 (33)	152 (31)	153 (36)		0.015	(-0.070, 0.041)
Zotarolimus ES	280 (30)	168 (34)	112 (26)		-0.093	(0.039, 0.15)

Combination	10 (1.1)	4 (0.8)	6 (1.4)		0.0041	(-0.018,0.0093)
Other	11 (1.2)	7 (1.4)	4 (0.9)		-0.0051	(-0.0087, 0.019)
Total stent strength	61.7 ± 40.2	59.2 ± 36.1	64.4 ± 43.9	0.037	5	(-10, -0.3)
Maximal stent diameter (mm)	3.4 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	<0.001	0.14	(-0.2, -0.072)
Maximum balloon diameter (mm)	3.6 ± 3.9	3.4 ± 2.7	3.7 ± 4.9	0.221	0.3	(-0.79, 0.19)
Abbreviations: ACT, activated clotting time. ES, eluting stent LM, left main						

Table 4.4: Procedural data per CTO lesion

	All Patients N= 1194	Antegrade N= 549	Retrograde N= 525	p value	Difference (Retrograde - Antegrade)	95% Confidence Interval
Dissection re-entry				<0.001		
First strategy	227 (41)	108 (59)	119 (32)		0.03	(-0.081, 0.021)
Second strategy	179 (32)	71 (39)	108 (29)		0.076	(-0.12, -0.030)
Third strategy	145 (26)	5 (2.7)	140 (38)		0.26	(-0.30, -0.22)
Number of total strategies used				<0.001		
1	523 (54)	392 (81)	131 (27)		-0.46	(0.41, 0.52)
2	234 (24)	80 (17)	154 (31)		0.15	(-0.20, -0.097)
3 or more	213 (22)	9 (1.9)	204 (42)		0.37	(-0.42, -0.33)
Retrograde as first strategy		-	186 (35)			
Retrograde pathway						
Epicardial CC		-	62 (12)			
Graft		-	42 (8.1)			
Septal CC		-	254 (49)			
Retrograde guide size						
6F		-	252 (73)			
7F		-	65 (19)			
8F		-	30 (8.6)			
Doner vessel of collateral channel (CC)						
Diag		-	1 (0.4)			
IMA		-	5 (1.8)			
LAD		-	181 (64)			
LCX		-	18 (6.4)			
PDA		-	33 (12)			
SVG		-	30 (11)			
Other		-	14 (5.0)			
CC Werner class						
CC0		-	32 (9.2)			
CC1		-	202 (58)			
CC2		-	113 (33)			
CC tortuosity						
Mild		-	109 (31)			
Moderate		-	175 (50)			
Corkscrew		-	65 (19)			
Retrograde crossing success		-	257 (50)			
Type of wire used						

Fielder FC		-	29 (5.7)			
Fielder XT		-	16 (3.1)			
Pilot 50		-	9 (1.8)			
Sion		-	189 (37)			
Whisper		-	3 (0.6)			
Other		-	40 (7.8)			
MC at distal cap		-	217 (42)			
CTO PCI success	928 (88)	499 (91)	427 (81)	<0.001	-0.099	(0.056, 0.14)
Final dissection				0.112		
Type A	12 (1.3)	3 (0.6)	9 (2.1)		0.015	(-0.032, 0.0023)
Type B	8 (0.9)	2 (0.4)	6 (1.4)		0.01	(-0.025, 0.0046)
Type C	4 (0.4)	2 (0.4)	2 (0.5)		0.00068	(-0.009, 0.0085)
Type D	1 (0.1)	0 (0.0)	1 (0.2)		0.0023	(-0.0091, 0.0044)
Type F	1 (0.1)	1 (0.2)	0 (0.0)		-0.002	(-0.0039, 0.0079)
Distal slow flow	25 (2.7)	14 (2.9)	11 (2.6)	0.968	-0.0026	(-0.021, 0.026)
Successful strategy				<0.001		
Antegrade (true lumen)	518 (56)	393 (79)	125 (30)		-0.49	(0.44, 0.55)
Anterograde (dissection re-entry)	165 (18)	103 (21)	62 (15)		-0.061	(0.010, 0.11)
Retrograde (true lumen)	100 (11)	0 (0.0)	100 (24)		0.23	(-0.28, -0.19)
Retrograde (dissection re-entry)	135 (15)	0 (0.0)	135 (32)		0.32	(-0.36, -0.27)
Time to cross CTO >30 min	299 (47)	156 (46)	143 (49)	0.61	0.023	(-0.10, 0.058)
Stiffest wire used				<0.001		
Soft non-polymeric wire	249 (24)	137 (26)	112 (22)		-0.036	(-0.016, 0.088)
Soft polymeric wire	264 (25)	138 (26)	125 (24)		-0.013	(-0.040, 0.067)
Medium stiffness non polymeric wire	45 (4.3)	23 (4.3)	22 (4.3)		1.04E-05	(-0.024, 0.024)
Harder polymeric wire	149 (14)	100 (19)	49 (10)		-0.089	(0.046, 0.130)
Stiff penetrating wire	338 (32)	131 (25)	207 (40)		0.16	(-0.21, -0.099)
Residual distal disease	152 (14)	63 (12)	89 (17)	0.015	0.054	(-0.097, -0.010)
Abbreviations: CC, collateral channel IMA, Internal Mammary Artery LAD, Left Anterior Descending Artery LCX, Left Circumflex Artery MC, microcatheter PDA, posterior descending artery SVG, saphenous vein graft	Fielder FC, guidewire with tip diameter of 0.014 inches Fielder XT, guidewire with tip diameter of 0.009 inches					

Table 4.5: In-hospital complications per patient

Name of Variable	All Patients N = 1194	Antegrade N = 549	Retrograde N = 525	p Value	Difference (Retrograde - Antegrade)	95% Confidence Interval
Death	4 (0.3)	0 (0.0)	4 (0.8)	0.121	0.0076	(-0.017, 0.0017)
Stroke	3 (0.3)	1 (0.2)	2 (0.4)	0.96	0.002	(-0.010, 0.0063)
CABG				0.198		
Planned	2 (0.2)	0 (0.0)	2 (0.4)		0.0038	(-0.011, 0.0033)
Urgent	4 (0.4)	1 (0.2)	3 (0.6)		0.0039	(-0.013, 0.0053)
Urgent PCI	12 (1.1)	7 (1.3)	5 (1.0)	0.85	-0.0031	(-0.011, 0.018)
Troponin or creatine kinase elevation	59 (5.5)	19 (3.5)	39 (7.5)	0.005	0.041	(-0.070, -0.011)
Acute congestive heart failure	7 (0.6)	3 (0.5)	4 (0.8)	0.938	0.0023	(-0.014, 0.0094)
CTO Perforation				0.031		
Type1	31 (2.9)	11 (2.0)	19 (3.7)		0.016	(-0.038, 0.0055)
Type2	13 (1.2)	5 (0.9)	8 (1.5)		0.0061	(-0.021, 0.0089)
Type3	14 (1.3)	3 (0.5)	11 (2.1)		0.015	(-3.1e-, .1e-05)
Collateral Damage				0.284		
Contrast around	2 (0.2)	0 (0.0)	2 (0.4)		0.0038	(-0.011, 0.0033)
Hematoma	4 (0.4)	1 (0.2)	3 (0.6)		0.0039	(-0.013, 0.0053)
Lakes	11 (1.0)	3 (0.5)	8 (1.5)		0.0098	(-0.024, 0.0042)
Perforation in heart chamber	2 (0.2)	1 (0.2)	1 (0.2)		8.30E-05	(-0.005, 0.0052)
Perforation in pericardium	4 (0.4)	1 (0.2)	3 (0.6)		0.0039	(-0.013, 0.0053)
Other	3 (0.3)	1 (0.2)	2 (0.4)		0.002	(-0.010, 0.0062)
Cardiac tamponade	10 (0.9)	3 (0.5)	7(1.3)	0.296	0.0081	(-0.022, 0.0055)
Distal dissection	49 (4.5)	20 (3.7)	28 (5.4)	0.22	0.017	(-0.044, 0.0094)
Donor Artery Thrombosis	6 (0.6)	2 (0.4)	4 (0.8)	0.634	0.0041	(-0.015, 0.0069)

Abbreviations:
CABG, Coronary Artery Bypass Graft
CTO, Chronic total occlusion
PCI, **Percutaneous** coronary intervention

Table 4.6 : Predictors of CTO PCI success

	Univariate analysis		Multivariate Analysis	
Variable	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**
Age	0.98(0.97, 1.00)	0.081	1(0.97,1.03)	0.9
Sex (male vs female)	0.87(0.52, 1.38)	0.568	0.9(0.38,1.98)	0.797
Chronic renal failure	0.76(0.47, 1.30)	0.296	1.34(0.57,3.36)	0.514
Prior CABG vs not	0.64(0.45, 0.93)	<0.05	0.46(0.22,0.94)	<0.05
Diabetes vs not	0.77(0.54, 1.10)	0.145	0.99(0.52,1.94)	0.975
LVEF severely reduced vs not	0.52(0.28, 1.04)	<0.05	0.29(0.1,0.88)	<0.05
Right coronary artery vs Others	1.02(0.70, 1.49)	0.922	1.86(0.95,3.75)	0.075
J-CTO score	0.78(0.66, 0.91)	<0.05	0.88(0.65,1.19)	0.414
In-stent vs no previous PCI	0.96(0.56, 1.73)	0.879	0.7(0.29,1.87)	0.455
Bridging collateral vs not	1.25(0.86, 1.85)	0.249	0.76(0.39,1.48)	0.41
Proximal cap ambiguity vs not	0.52(0.36, 0.75)	<0.05	0.5(0.25,0.99)	<0.05
CTO course ambiguity vs not	0.47(0.33, 0.68)	<0.05	0.71(0.35,1.43)	0.331
Bifurcation at distal cap vs not	1.23(0.84, 1.84)	0.294	1.46(0.75,2.94)	0.279
Good distal landing zone vs not	2.70(1.78, 4.05)	<0.05	2.9(1.47,5.77)	<0.05
Interventional collateral				
No	1			
Septal	1.42(0.90, 2.20)	0.122	0.81(0.33,1.95)	0.646
Other	1.24(0.78, 1.96)	0.36	1.12(0.45,2.76)	0.804
Branch at proximal entry vs not	0.77(0.52, 1.13)	0.184	0.78(0.4,1.5)	0.464
Retrograde vs antegrade	0.41(0.28, 0.60)	<0.05	0.96(0.37,2.53)	0.928
Any femoral approach vs other	0.69(0.45, 1.03)	0.08	0.8(0.35,1.71)	0.569
Use of stingray vs not	0.66(0.42, 1.08)	0.086	0.46(0.2,1.08)	0.069
Dissection-re-entry vs not	0.45(0.30, 0.67)	<0.05	0.51(0.22,1.16)	0.116
Number of total strategies used				
1	1			
2 or more	0.35(0.23,0.51)	<0.05	1.08(0.48,2.42)	0.848
Collateral crossed				
Not attempted	1			
Not crossed	0.06(0.03, 0.10)	0.568	0.1(0.04,0.29)	<0.05
Crossed	1.03(0.64, 1.71)	0.296	1.73(0.65,4.71)	0.274

Abbreviations:
J-CTO, Japanese-CTO
LVEF, Left Ventricular Ejection Fraction Evaluation

Figure 4.1: Classification tree of all patients based on baseline variables.

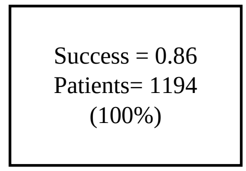


Figure 4.2: Classification tree of all patients based on baseline and procedural variables.

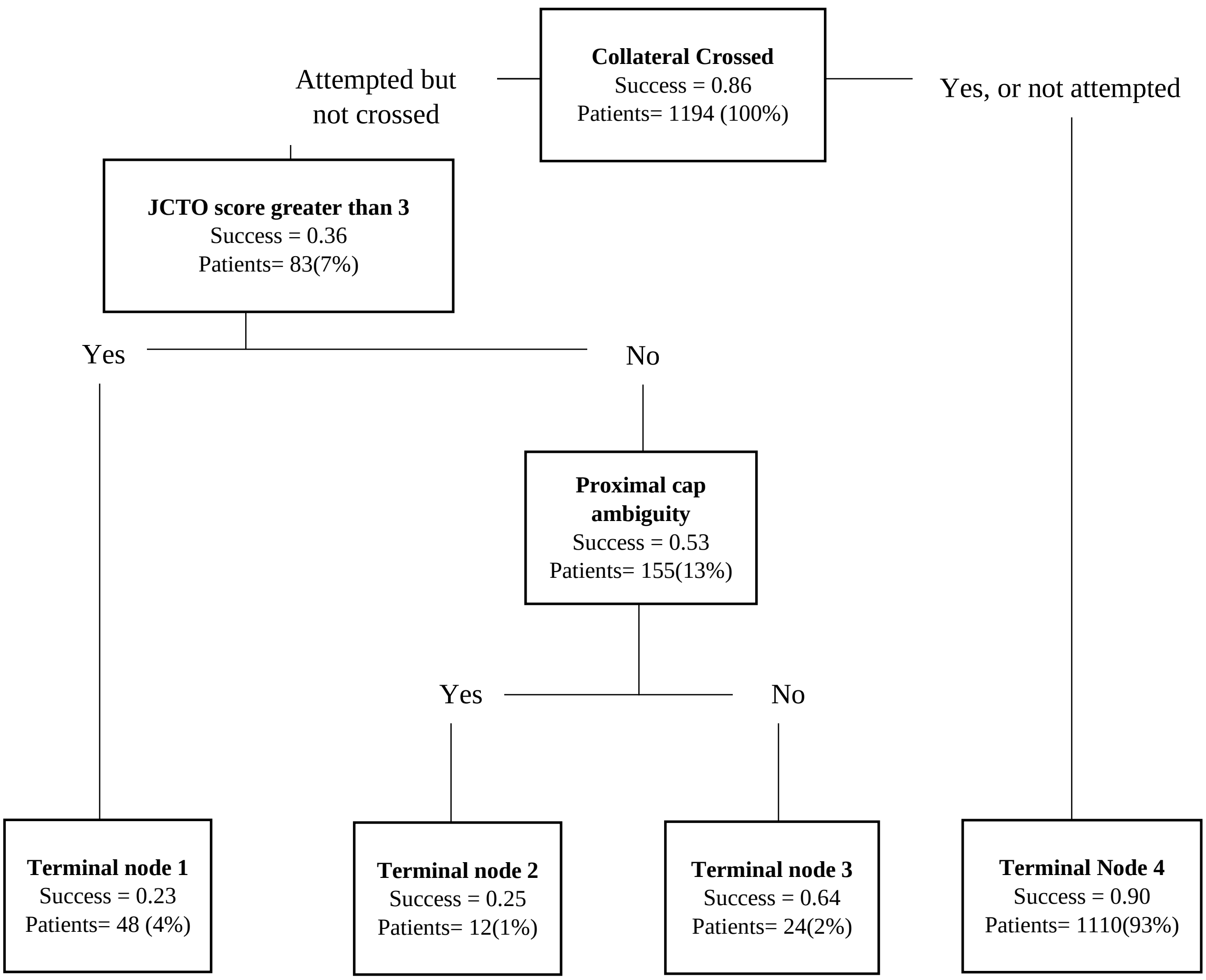


Figure 4.3: Classification tree of retrograde patients based on baseline and procedural variables.

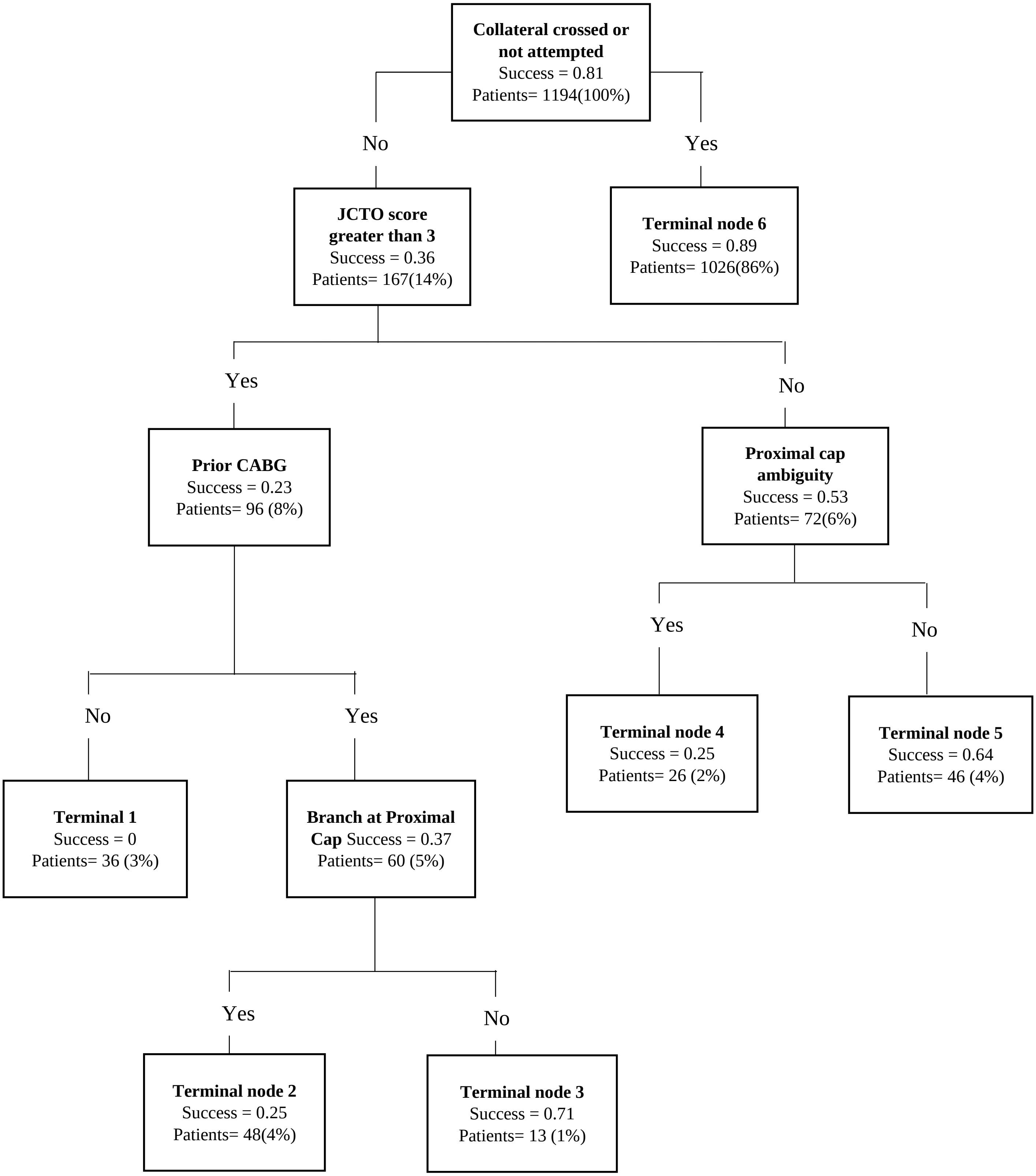
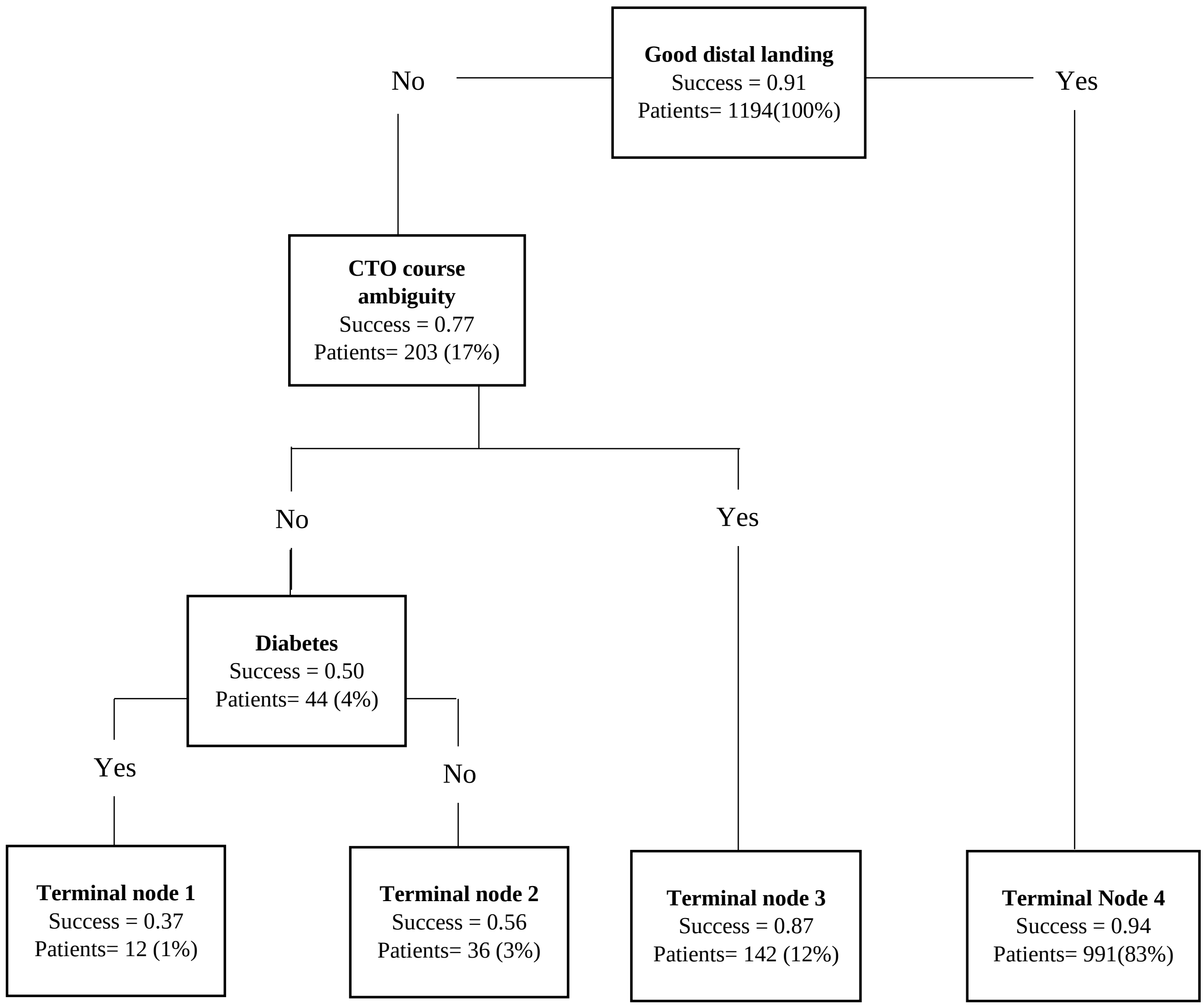


Figure 4.4: Classification tree of antegrade patients based on baseline and procedural variables.



Chapter 5 : Discussion

This thesis gives results from the largest multicentre Canadian CTO PCI registry done so far. The CCTOP registry involved 6 hospitals in 3 provinces from 2014 to 2019. The analyses were carried out within strata defined by two common technical approaches for CTO PCI – antegrade and retrograde. Usage of the retrograde approach has been associated with improving procedural outcomes of CTO PCI over the last few decades, but also with increasing complications, raising questions about its value to patient care. The focus of the thesis was not to find any new predictors nor to compare prediction models. Rather it was simply to repeat models reported previously in this literature, in a Canadian cohort to see if we could replicate the earlier results. It examined the frequency of use of the retrograde approach at major Canadian centres, as well as the patient characteristics associated with an increased chance of using the retrograde approach and outcomes following the retrograde approach. Table 1 presents the frequency of antegrade, and retrograde techniques used in each centre. Comparison of procedural outcomes at the centres was not the focus of the analyses in this thesis, though it could be addressed in future work. Logistic regression and CART were used because of the interest in studying the associations between potential risk factors previously reported in the literature and procedural success in a Canadian cohort. CART was employed specifically to discover interaction terms. Differences were present in the regression models and CART approach because they use different criteria. CART finds the greatest separation possible when creating the splits.

More patients underwent antegrade-only than retrograde procedure. Only around 20% of the cohort was female, as reported by others (50, 83, 84, 88, 91, 93). It was observed that only a very small percentage of patients (3.7%) had a second CTO PCI. The most common comorbidities among patients in the CCTOP database included hypertension, dyslipidemia, diabetes, chronic renal failure, all of which were slightly higher among the retrograde patients. This observation is also similar to most registry studies (84, 93). On the contrary, in a study by Michael *et al*, and in the European registry, antegrade patients had higher diabetes, and hypertension (85, 87, 94).

More than half of the patients (51%) had a J-CTO score of 3 and above, indicating that Canadian operators in these specialized centers were treating complex cases, and retrograde was more often used in more complex procedures. Dautov's study and the Asia-Pacific multicentre registry had a percentage of 70 to 80% of the retrograde patients having a JCTO score of 3 and above (83, 93). Similarly, Bijuklic *et al* had a higher percentage, 92.8%, of retrograde patients being complicated cases (88). But the Hybrid Sirolimus-eluting Versus Everolimus-eluting Stents for Total Coronary Occlusions, PRISON IV trial, had only 55% of retrograde patients who were described as very difficult cases (89).

The percentage of CTO PCI procedural success was 87%. It was found that patients who underwent an antegrade-only approach had 17% higher chances of success than those undergoing a retrograde approach (92% vs. 75%). However, patients who were treated with the retrograde approach has clearly more complex lesions, as assessed with a J-CTO score. Patients were more patients with J-CTO score of 3 or above in the retrograde group (67%) than the antegrade group (43%). Nevertheless, in-hospital complications such as death (0.4%), stroke (0.3%), CABG (0.6%), urgent PCI (1.2 %), troponin or creatine kinase elevation (5.4 %), acute congestive heart failure (0.7%), CTO perforation (5.4%), collateral damage (2.1%), cardiac tamponade (1.0%), distal dissection (4.6%), donor artery thrombosis (0.6%) were quite low, all below 6% overall and similar in both antegrade and retrograde groups. This was comparable to US, Taiwan, and Japanese registry studies all of which reported complication risks below 4% (50, 84, 91).

The patients with favorable anatomical characteristics including good distal landing zone, presence of a septal interventional collateral and a collateral successfully crossed for retrograde were more likely to end up with technical success. Similarly, Karmpaliotis *et al*. also observed that the presence of interventional collaterals was associated with higher technical success, as well as when the left anterior descending artery was the target vessel (84)

Clinical characteristics or markers associated with success included the presence of a good distal landing zone, relying on an antegrade-only rather than a retrograde, or when a retrograde procedure was attempted, successful crossing of the collateral with a wire to the distal cap. In Wu *et al* study's, a multivariate analysis reported that prior PCI and prior MI were correlated with success of retrograde approach (93). Another multivariate analysis showed that age, diabetes, and moderate to severe tortuosity were significantly correlated with failure of retrograde approach after conducting a univariate analysis with a p value <0.10.

5.1 Limitations

Although we attempted to study the risk of Major Adverse Cardiac Events (MACE) in a secondary analysis, our results were inconclusive as the number of subjects who experienced these outcomes was very small in number making it impossible to identify a robust multivariate model. On the other hand, such a finding was very reassuring from a clinical standpoint. We employed the classification tree analysis (CART) approach as an exploratory analytical approach to provide a different perspective from the more widely used logistic regression analysis. The CART model provided an ordering of the most important predictors; however the sample size is small. As this study was an observational study, there was some loss to follow up limiting our ability to look at longer-term data. Patients with incomplete data were dropped from the analysis as we did not adjust for the missing values. Future work should consider techniques such as multiple imputation for addressing this issue. Although the ultimate way to compare 2 treatment strategies is through randomization, it is clinically impossible for retrograde or antegrade procedures, as several factors influence the choice of either technique; causal inferences therefore cannot be drawn from the non-randomized comparisons presented here. While this was a multicenter registry, the overall sample size was small making it difficult to study risk factors for complications and other rare outcomes. Outcome adjudication was not done. While we focused on 30-day procedural success as the primary outcome of interest, further work is needed to analyze the long term (1-year) outcomes that were recorded in the CCTOP study.

5.2 Implications

The results from this can contribute to the advancement of knowledge on patient characteristics and factors associated with successful outcome from a Canadian context. The analysis can also foster international collaboration between researchers, clinicians, and institutions that are involved in CTO PCI research and practice. This can lead to the exchange of knowledge, best practices, and expertise. Insight could be provided for decisions on resource allocation in healthcare for CTO PCI for example training operators and increasing centres to carry out the procedures. Comparing the variation in procedural success and the frequency of antegrade and retrograde techniques used in each centres could be done as another analysis. Follow-up on patients of this cohort on quality of life and long-term complications is another topic that could be looked into and compared to patients who have gone through CABG. Clinical prediction model could be made using this type of data. Further analysis needs to be done of long-term outcomes.

Chapter 6 : Conclusion

There was a low level of CTO PCI procedural failure in the CCTOP registry despite the large number of complex cases treated. The high overall success was observed among both antegrade and retrograde groups, albeit higher when no retrograde procedure was needed. The results from the CCTOP study are comparable to those reported from other registries from around the world over the last 10 years. Complex cases are now being treated successfully and safely in Canada using the antegrade and the retrograde approach. Clinical prediction model could be made using this type of data. Further analysis needs to be done of long-term outcomes.

Chapter 7 : Bibliography

1. Government of Canada. Heart Disease in Canada 2017 [updated February 10, 2017. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/heart-disease-canada.html.
2. Preventing heart attacks and more Heart & Stroke [Available from: https://www.heartandstroke.ca/what-we-do/mca-councils/coronary-artery-disease-council.
3. Corrigan minehan heart center. Chronic Total Occlusion Percutaneous Coronary Intervention Massachusetts General Hospital [Available from: https://www.massgeneral.org/heart-center/treatments-and-services/chronic-total-occlusion-percutaneous-coronary-intervention-cto-pci#:~:text=CTOs%20are%20blockages%20that%20have,coronary%20artery%20disease%20(CAD).
4. Ybarra LF, Rinfret S, Brilakis ES, Karmpaliotis D, Azzalini L, Grantham JA, et al. Definitions and clinical trial design principles for coronary artery chronic total occlusion therapies: CTO-ARC consensus recommendations. Circulation. 2021;143(5):479-500.
5. Koelbl CO, Nedeljkovic ZS, Jacobs AK. Coronary chronic total occlusion (CTO): a review. Reviews in cardiovascular medicine. 2018;19(1):33-9.
6. Aziz S, Ramsdale DR. Chronic Total Occlusions–The Challenge Continues. 2006.
7. Shah PB. Management of coronary chronic total occlusion. Circulation. 2011;123(16):1780-4.
8. Coronary Artery Bypass Grafting National Heart, Lung, and Blood Institute [Available from: https://www.nhlbi.nih.gov/health-topics/coronary-artery-bypass-grafting#:~:text=Also%20known%20as%20Heart%20Bypass.
9. Heart and Stroke Foundation of Canada. Percutaneous coronary intervention (PCI or angioplasty with stent) Heart and Stroke foundation of Canada2020 [https://www.heartandstroke.ca/heart-disease/treatments/surgery-and-other-procedures/percutaneous-coronary-intervention]
10. Tajti P, Burke MN, Karmpaliotis D, Alaswad K, Werner GS, Azzalini L, et al. Update in the Percutaneous Management of Coronary Chronic Total Occlusions. JACC: Cardiovascular Interventions. 2018;11(7):615-25.
11. Maeremans J, Knaapen P, Stuijfzand WJ, Kayaert P, Pereira B, Barbato E, et al. Antegrade wire escalation for chronic total occlusions in coronary arteries: simple algorithms as a key to success. Journal of Cardiovascular Medicine. 2016;17(9):680-6.
12. Maran A, Bidwell KA. Antegrade Wire Escalation Case Selection and Strategies: Four Wires for Success. Interventional Cardiology Clinics. 2021;10(1):33-9.
13. Tajti P, Karmpaliotis D, Alaswad K, Jaffer FA, Yeh RW, Patel M, et al. The hybrid approach to chronic total occlusion percutaneous coronary intervention: update from the PROGRESS CTO registry. JACC: Cardiovascular Interventions. 2018;11(14):1325-35.
14. Danek BA, Karatasakis A, Karmpaliotis D, Alaswad K, Yeh RW, Jaffer FA, et al. Use of antegrade dissection re-entry in coronary chronic total occlusion percutaneous coronary intervention in a contemporary multicenter registry. International journal of cardiology. 2016;214:428-37.
15. Brilakis ES, Grantham JA, Rinfret S, Wyman RM, Burke MN, Karmpaliotis D, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC: Cardiovascular Interventions. 2012;5(4):367-79.
16. V Rangan B, Kotsia A, Christopoulos G, Spratt J, Rinfret S, Banerjee S, et al. The hybrid approach to intervention of chronic total occlusions. Current cardiology reviews. 2015;11(4):299-304.
17. Michael TT, Papayannis AC, Banerjee S, Brilakis ES. Subintimal dissection/reentry strategies in coronary chronic total occlusion interventions. Circulation: Cardiovascular Interventions. 2012;5(5):729-38.
18. Brilakis ES, Grantham JA, Thompson CA, DeMartini TJ, Prasad A, Sandhu GS, et al. The retrograde approach to coronary artery chronic total occlusions: a practical approach. Catheterization and Cardiovascular Interventions. 2012;79(1):3-19.

19. Hsu JT, Tamai H, Kyo E, Tsuji T, Watanabe S. Traditional antegrade approach versus combined antegrade and retrograde approach in the percutaneous treatment of coronary chronic total occlusions. Catheterization and Cardiovascular Interventions. 2009;74(4):555-63.
20. Grantham JA, Marso SP, Spertus J, House J, Holmes DR, Rutherford BD. Chronic total occlusion angioplasty in the United States. JACC: Cardiovascular Interventions. 2009;2(6):479-86.
21. Ng R, Hui PY, Beyer A, Ren X, Ochiai M. Successful retrograde recanalization of a left anterior descending artery chronic total occlusion through a previously placed left anterior descending-to-diagonal artery stent. The Journal of invasive cardiology. 2010;22(1):E16-8.
22. Tsujita K, Maehara A, Mintz GS, Kubo T, Doi H, Lansky AJ, et al. Intravascular ultrasound comparison of the retrograde versus antegrade approach to percutaneous intervention for chronic total coronary occlusions. JACC: Cardiovascular Interventions. 2009;2(9):846-54.
23. Rinfret S, Joyal D, Spratt JC, Buller CE. Chronic total occlusion percutaneous coronary intervention case selection and techniques for the antegrade-only operator. Catheterization and Cardiovascular Interventions. 2015;85(3):408-15.
24. Colombo A, Mikhail GW, Michev I, Iakovou I, Airoldi F, Chieffo A, et al. Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. Catheterization and Cardiovascular interventions. 2005;64(4):407-11.
25. Werner GS. The BridgePoint devices to facilitate recanalization of chronic total coronary occlusions through controlled subintimal reentry. Expert Review of Medical Devices. 2011;8(1):23-9.
26. Whitlow PL, Burke MN, Lombardi WL, Wyman RM, Moses JW, Brilakis ES, et al. Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FAST-CTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. JACC: Cardiovascular Interventions. 2012;5(4):393-401.
27. Aljabbary T, Katyukha A, Elbaz-Greener G, Gressmann K, Bagai A, Graham JJ, et al. Overview of Contemporary Chronic Total Occlusion Percutaneous Coronary Intervention Techniques: A Narrative Systematic Review. CJC Open. 2021;3(10):1273-81.
28. Abuzeid W, Zivkovic N, Elbaz-Greener G, Yaranton B, Patel V, Strauss B, et al. Association between revascularization and quality of life in patients with coronary chronic total occlusions: a systematic review. Cardiovascular Revascularization Medicine. 2021;25:47-54.
29. Lee SK, Rowe BH, Mahl SK. Increased private healthcare for canada: is that the right solution? Healthcare Policy. 2021;16(3):30.
30. Mitomo S, Demir OM, Colombo A, Nakamura S, Chieffo A. What the surgeon needs to know about percutaneous coronary intervention treatment of chronic total occlusions. Annals of Cardiothoracic Surgery. 2018;7(4):533.
31. Ybarra LF, Buller CE, Rinfret S. The Canadian Contribution to Science, Techniques, Technology, and Education in Chronic Total Occlusion Percutaneous Coronary Intervention. CJC open. 2021;3(1):22-7.
32. Xenogiannis I, Gkargkoulas F, Karmpaliotis D, Alaswad K, Jaffer FA, Yeh RW, et al. Temporal Trends in Chronic Total Occlusion Percutaneous Coronary Interventions: Insights From the PROGRESS-CTO Registry. The Journal of invasive cardiology. 2020;32(4):153-60.
33. Megaly M, Buda K, Mashayekhi K, Werner GS, Grantham JA, Rinfret S, et al. Comparative analysis of patient characteristics in chronic total occlusion revascularization studies: Trials vs real-world registries. Cardiovascular Interventions. 2022;15(14):1441-9.
34. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. American heart journal. 1993;126(3):561-4.
35. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. Journal of the American College of Cardiology. 2012;59(11):991-7.
36. Azzalini L, Jolicoeur EM, Pighi M, Millán X, Picard F, Tadros V-X, et al. Epidemiology, management strategies, and outcomes of patients with chronic total coronary occlusion. The American journal of cardiology. 2016;118(8):1128-35.

37. Pereg D, Fefer P, Samuel M, Wolff R, Czarnecki A, Deb S, et al. Native coronary artery patency after coronary artery bypass surgery. JACC: Cardiovascular Interventions. 2014;7(7):761-7.
38. Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. The American journal of cardiology. 2005;95(9):1088-91.
39. Patel SM, Pokala NR, Menon RV, Kotsia AP, Raja V, Christopoulos G, et al. Prevalence and Treatment of ‚ÄúBalloon-Uncrossable ‚Äù Coronary Chronic Total Occlusions. J Invasive Cardiol. 2015;27(2):78-84.
40. Doshi R, Patel N, Kalra R, Arora H, Bajaj NS, Arora G, et al. Incidence and in-hospital outcomes of single-vessel coronary chronic total occlusion treated with percutaneous coronary intervention. International journal of cardiology. 2018;269:61-6.
41. Mannem S, Rattanawong P, Riangwiwat T, Vutthikraivit W, Putthapiban P, Sukhumthammarat W, et al. Sex Difference and Outcome after Percutaneous Intervention in Patients with Chronic Total Occlusion: A Systematic Review and Meta-Analysis. Cardiovascular Revascularization Medicine. 2020;21(1):25-31.
42. Hafeez Yamama Y. Chronic Total Occlusion Of The Coronary Artery. 2021.
43. Prasad A, Rihal CS, Lennon RJ, Wiste HJ, Singh M, Holmes DR. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: a 25-year experience from the Mayo Clinic. Journal of the American College of Cardiology. 2007;49(15):1611-8.
44. Abbott JD, Kip KE, Vlachos HA, Sawhney N, Srinivas VS, Jacobs AK, et al. Recent trends in the percutaneous treatment of chronic total coronary occlusions. The American journal of cardiology. 2006;97(12):1691-6.
45. Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. Journal of the American College of Cardiology. 2001;38(2):409-14.
46. Jaber WA. Chronic total occlusion intervention: the case for more evidence. JACC: Cardiovascular Interventions; 2018.
47. Stone GW. Percutaneous Coronary Intervention of Chronic Total Occlusions: Conquering the Final Frontier. JACC: Cardiovascular Interventions. 2018;11(14).
48. Maeremans J, Walsh S, Knaapen P, Spratt JC, Avran A, Hanratty CG, et al. The hybrid algorithm for treating chronic total occlusions in Europe: the RECHARGE registry. Journal of the American College of Cardiology. 2016;68(18):1958-70.
49. Luo C, Huang M, Li J, Liang C, Zhang Q, Liu H, et al. Predictors of interventional success of antegrade PCI for CTO. JACC: Cardiovascular Imaging. 2015;8(7):804-13.
50. Suzuki Y, Tsuchikane E, Katoh O, Muramatsu T, Muto M, Kishi K, et al. Outcomes of percutaneous coronary interventions for chronic total occlusion performed by highly experienced Japanese specialists: the first report from the Japanese CTO-PCI Expert Registry. JACC: Cardiovascular Interventions. 2017;10(21):2144-54.
51. Salinas P, Gonzalo N, Moreno VH, Fuentes M, Santos-Martinez S, Fernandez-Diaz JA, et al. Choice of CTO scores to predict procedural success in clinical practice. A comparison of 4 different CTO PCI scores in a comprehensive national registry including expert and learning CTO operators. Plos one. 2021;16(4):e0245898.
52. Christopoulos G, Wyman RM, Alaswad K, Karmpaliotis D, Lombardi W, Grantham JA, et al. Clinical utility of the Japan–Chronic Total Occlusion Score in coronary chronic total occlusion interventions: results from a multicenter registry. Circulation: Cardiovascular Interventions. 2015;8(7):e002171.
53. Morino Y, Abe M, Morimoto T, Kimura T, Hayashi Y, Muramatsu T, et al. Predicting Successful Guidewire Crossing Through Chronic Total Occlusion of Native Coronary Lesions Within 30 Minutes. JACC: Cardiovascular Interventions. 2011;4(2):213-21.

54. Nombela-Franco L, Urena M, Jerez-Valero M, Nguyen CM, Ribeiro HB, Bataille Y, et al. Validation of the J-chronic total occlusion score for chronic total occlusion percutaneous coronary intervention in an independent contemporary cohort. Circulation: Cardiovascular Interventions. 2013;6(6):635-43.
55. Karatasakis A, Iwnetu R, Danek BA, Karmpaliotis D, Alaswad K, Jaffer FA, et al. The impact of age and sex on in-hospital outcomes of chronic total occlusion percutaneous coronary intervention. J Invasive Cardiol. 2017;29(4):116-22.
56. Lee W-C, Wu P-J, Fang C-Y, Chen H-C, Wu C-J, Fang H-Y. Impact of chronic kidney disease on chronic total occlusion revascularization outcomes: a meta-analysis. Journal of Clinical Medicine. 2021;10(3):440.
57. Roffi M, Angiolillo DJ, Kappetein AP. Current concepts on coronary revascularization in diabetic patients. European Heart Journal. 2011;32(22):2748-57.
58. Liu M-J, Chen C-F, Gao X-F, Liu X-H, Xu Y-Z. In-hospital outcomes of chronic total occlusion percutaneous coronary intervention in patients with and without prior coronary artery bypass graft: A systematic review and meta analysis. Medicine. 2020;99(23).
59. Hoebers LP, Claessen BE, Elias J, Dangas GD, Mehran R, Henriques JP. Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. International journal of cardiology. 2015;187:90-6.
60. Patel VG, Brayton KM, Tamayo A, Mogabgab O, Michael TT, Lo N, et al. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. JACC: Cardiovascular Interventions. 2013;6(2):128-36.
61. Grantham JA, Jones PG, Cannon L, Spertus JA. Quantifying the early health status benefits of successful chronic total occlusion recanalization: results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) Trial. Circulation: Cardiovascular Quality and Outcomes. 2010;3(3):284-90.
62. Finci L, Meier B, Favre J, Righetti A, Rutishauser W. Long-term results of successful and failed angioplasty for chronic total coronary arterial occlusion. The American journal of cardiology. 1990;66(7):660-2.
63. Baks T, van Geuns R-J, Duncker DJ, Cademartiri F, Mollet NR, Krestin GP, et al. Prediction of left ventricular function after drug-eluting stent implantation for chronic total coronary occlusions. Journal of the American College of Cardiology. 2006;47(4):721-5.
64. Claessen BE, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjauw KD, et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. JACC: Cardiovascular Interventions. 2009;2(11):1128-34.
65. Noguchi T, Miyazaki MD S, Morii I, Daikoku S, Goto Y, Nonogi H. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Determinants of primary success and long-term clinical outcome. Catheterization and cardiovascular interventions. 2000;49(3):258-64.
66. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. American heart journal. 2010;160(1):179-87.
67. Safley DM, House JA, Marso SP, Grantham JA, Rutherford BD. Improvement in survival following successful percutaneous coronary intervention of coronary chronic total occlusions: variability by target vessel. JACC: Cardiovascular Interventions. 2008;1(3):295-302.
68. Hirai T, Grantham JA, Sapontis J, Cohen DJ, Marso SP, Lombardi W, et al. Quality of life changes after chronic total occlusion angioplasty in patients with baseline refractory angina. Circulation: Cardiovascular Interventions. 2019;12(3):e007558.
69. Research overview Sunnybrook Research Institute [Available from: https://sunnybrook.ca/research/content/?page=sri-groups-cto-info.

70. Strauss BH, Knudtson ML, Cheema AN, Galbraith PD, Elbaz-Greener G, Abuzeid W, et al. Canadian Multicenter Chronic Total Occlusion Registry: Ten-Year Follow-Up Results of Chronic Total Occlusion Revascularization. Circulation: Cardiovascular Interventions. 2021;14(12).
71. Widimsky P, Straka Z, Stros P, Jirasek K, Dvorak J, Votava J, et al. One-Year Coronary Bypass Graft Patency. Circulation. 2004;110(22):3418-23.
72. Sapontis J, Salisbury AC, Yeh RW, Cohen DJ, Hirai T, Lombardi W, et al. Early Procedural and Health Status Outcomes After Chronic Total Occlusion Angioplasty. A Report From the OPEN-CTO Registry (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures). 2017;10(15):1523-34.
73. Morino Y, Kimura T, Hayashi Y, Muramatsu T, Ochiai M, Noguchi Y, et al. In-hospital outcomes of contemporary percutaneous coronary intervention in patients with chronic total occlusion: insights from the J-CTO Registry (Multicenter CTO Registry in Japan). JACC: Cardiovascular Interventions. 2010;3(2):143-51.
74. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. Journal of clinical nursing. 2003;12(1):77-84.
75. Henriques JP, Hoebers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, et al. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE trial. Journal of the American College of Cardiology. 2016;68(15):1622-32.
76. Claessen BE, Hoebers LP, Elias JE, van Dongen IM, Henriques JP. Meta-analyses and randomized trials investigating percutaneous coronary intervention of chronic total occlusions: what is left to explore? Journal of thoracic disease. 2016;8(9):E1100.
77. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. European heart journal. 2018;39(26):2484-93.
78. Lee S-W, Lee PH, Ahn J-M, Park D-W, Yun S-C, Han S, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion: the DECISION-CTO trial. Circulation. 2019;139(14):1674-83.
79. Buller CE, Dzavik V, Carere RG, Mancini GJ, Barbeau G, Lazzam C, et al. Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of Canada (TOSCA). Circulation. 1999;100(3):236-42.
80. Dzavik V, Carere RG, Teo KK, Knudtson ML, Marquis JF, Buller CE. An open design, multicentre, randomized trial of percutaneous transluminal coronary angioplasty versus stenting, with a heparin-coated stent, of totally occluded coronary arteries: rationale, trial design and baseline patient characteristics. Total Occlusion Study of Canada (TOSCA) Investigators. Can J Cardiol. 1998;14(6):825-32.
81. Ybarra LF, Buller CE, Rinfret S. The Canadian contribution to science, techniques, technology and education in chronic total occlusion percutaneous coronary intervention. CJC open. 2020.
82. Megaly M, Ali A, Saad M, Omer M, Xenogiannis I, Werner GS, et al. Outcomes with retrograde versus antegrade chronic total occlusion revascularization. Catheterization and Cardiovascular Interventions. 2020;96(5):1037-43.
83. Dautov R, Manh Nguyen C, Altisent O, Gibrat C, Rinfret S. Recanalization of chronic total occlusions in patients with previous coronary bypass surgery and consideration of retrograde access via saphenous vein grafts. Circulation: Cardiovascular Interventions. 2016;9(7):e003515.
84. Karmpaliotis D, Karatasakis A, Alaswad K, Jaffer FA, Yeh RW, Wyman RM, et al. Outcomes with the use of the retrograde approach for coronary chronic total occlusion interventions in a contemporary multicenter US registry. Circulation: Cardiovascular Interventions. 2016;9(6):e003434.
85. Michael TT, Mogabgab O, Alomar M, Kotsia A, Christopoulos G, Rangan BV, et al. Long-term outcomes of successful chronic total occlusion percutaneous coronary interventions using the antegrade and retrograde approach. Journal of interventional cardiology. 2014;27(5):465-71.
86. Galassi AR, Tomasello SD, Reifart N, Werner GS, Sianos G, Bonnier H, et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the

ERCTO (European Registry of Chronic Total Occlusion) registry. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2011;7(4):472-9.
87. Werner GS, Coenen A, Tischer K-H. Periprocedural ischaemia during recanalisation of chronic total coronary occlusions: the influence of the transcollateral retrograde approach. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2014;10(7):799-805.
88. Bijuklic K, Schwencke C, Schofer J. Long-term MACCE rate after retrograde compared to Antegrade recanalization of chronic total coronary occlusions. J Health Med Inform. 2016;7(224):2.
89. Zivelonghi C, van Andel M, Venturi G, Amoroso G, Teeuwen K, Tijssen JG, et al. Angiographic and clinical outcomes of antegrade versus retrograde techniques for chronic total occlusion revascularizations: insights from the PRISON IV trial. Catheterization and Cardiovascular Interventions. 2019;93(2):E81-E9.
90. Kwon O, Lee PH, Lee S-W, Lee J-Y, Kang D-Y, Ahn J-M, et al. Retrograde approach for the percutaneous recanalisation of coronary chronic total occlusions: contribution to clinical practice and long-term outcomes. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2019;15(4):e354-e61.
91. Lee C-K, Chen Y-H, Lin M-S, Yeh C-F, Hung C-S, Kao H-L, et al. Retrograde approach is as effective and safe as antegrade approach in contemporary percutaneous coronary intervention for chronic total occlusion: a Taiwan single-center registry study. Acta Cardiologica Sinica. 2017;33(1):20.
92. Tanaka H, Ohya M, Kubo S, Miura K, Otsuru S, Habara S, et al. Impact of retrograde approach on long-term clinical outcomes of patients undergoing coronary chronic total occlusion interventions. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2018;14(11):e1183-e91.
93. Wu EB, Tsuchikane E, Ge L, Harding SA, Lo S, Lim ST, et al. Retrograde versus antegrade approach for coronary chronic total occlusion in an algorithm-driven contemporary Asia-Pacific Multicentre Registry: comparison of outcomes. Heart, Lung and Circulation. 2020;29(6):894-903.
94. Galassi AR, Sianos G, Werner GS, Escaned J, Tomasello SD, Boukhris M, et al. Retrograde recanalization of chronic total occlusions in Europe: procedural, in-hospital, and long-term outcomes from the multicenter ERCTO registry. Journal of the American College of Cardiology. 2015;65(22):2388-400.
95. Konstantinidis NV, Werner GS, Deftereos S, Di Mario C, Galassi AR, Buettner JH, et al. Temporal trends in chronic Total occlusion interventions in Europe: 17 626 procedures from the European registry of chronic Total occlusion. Circulation: Cardiovascular Interventions. 2018;11(10):e006229.
96. Xenogiannis I, Gkargkoulas F, Karmpaliotis D, Alaswad K, Krestyaninov O, Khelimskii D, et al. The Impact of Peripheral Artery Disease in Chronic Total Occlusion Percutaneous Coronary Intervention (Insights From PROGRESS-CTO Registry). Angiology. 2020;71(3):274-80.
97. Nikolakopoulos I, Choi JW, Alaswad K, Khatri JJ, Krestyaninov O, Khelimskii D, et al. Equipment utilization in chronic total occlusion percutaneous coronary interventions: Insights from the PROGRESS-CTO registry. Catheterization and Cardiovascular Interventions. 2020.
98. Nikolakopoulos I, Choi JW, Khatri JJ, Alaswad K, Doing AH, Dattilo P, et al. Follow-up Outcomes After Chronic Total Occlusion Percutaneous Coronary Intervention in Patients With and Without Prior Coronary Artery Bypass Graft Surgery: Insights From the PROGRESS-CTO Registry. The Journal of invasive cardiology. 2020;32(8):315-20.
99. Danek BA, Karatasakis A, Karmpaliotis D, Alaswad K, Yeh RW, Jaffer FA, et al. Development and validation of a scoring system for predicting periprocedural complications during percutaneous coronary interventions of chronic total occlusions: the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS CTO) complications score. Journal of the American Heart Association. 2016;5(10):e004272.

100. Xenogiannis I, Nikolakopoulos I, Krestyaninov O, Khelimskii D, Khatri JJ, Doing AH, et al. Impact of Successful Chronic Total Occlusion Percutaneous Coronary Interventions on Subsequent Clinical Outcomes. J INVASIVE CARDIOL. 2020.
101. Christopoulos G, Wyman RM, Alaswad K, Karmpaliotis D, Lombardi W, Grantham JA, et al. Clinical Utility of the Japan–Chronic Total Occlusion Score in Coronary Chronic Total Occlusion Interventions. Circulation: Cardiovascular Interventions. 2015;8(7):e002171.
102. Tajti P, Karmpaliotis D, Alaswad K, Jaffer FA, Yeh RW, Patel M, et al. In-Hospital Outcomes of Chronic Total Occlusion Percutaneous Coronary Interventions in Patients With Prior Coronary Artery Bypass Graft Surgery: Insights From an International Multicenter Chronic Total Occlusion Registry. Circulation: Cardiovascular Interventions. 2019;12(3):e007338.
103. Martinez-Parachini J, Karatasakis A, Karmpaliotis D, Alaswad K, Jaffer F, Yeh R, et al. Impact of diabetes mellitus on acute outcomes of percutaneous coronary intervention in chronic total occlusions: insights from a US multicentre registry. Diabetic Medicine. 2017;34(4):558-62.
104. Salisbury AC, Sapontis J, Grantham JA, Qintar M, Gosch KL, Lombardi W, et al. Outcomes of chronic total occlusion percutaneous coronary intervention in patients with diabetes: insights from the OPEN CTO registry. JACC: Cardiovascular Interventions. 2017;10(21):2174-81.
105. Salisbury AC, Karmpaliotis D, Grantham JA, Sapontis J, Meng Q, Magnuson EA, et al. In-hospital costs and costs of complications of chronic total occlusion angioplasty: insights from the OPEN-CTO registry. JACC: Cardiovascular Interventions. 2019;12(4):323-31.
106. Pershad A, Gulati M, Karmpaliotis D, Moses J, Nicholson WJ, Nugent K, et al. A sex stratified outcome analysis from the OPEN-CTO registry. Catheterization and Cardiovascular Interventions. 2019;93(6):1041-7.
107. Khariton Y, Airhart S, Salisbury AC, Spertus JA, Gosch KL, Grantham JA, et al. Health Status Benefits of Successful Chronic Total Occlusion Revascularization Across the Spectrum of Left Ventricular Function. Insights From the OPEN-CTO Registry. 2018;11(22):2276-83.
108. Kalra S, Doshi D, Sapontis J, Kosmidou I, Kirtane AJ, Moses JW, et al. Outcomes of retrograde chronic total occlusion percutaneous coronary intervention: A report from the OPEN-CTO registry. Catheterization and Cardiovascular Interventions. 2021;97(6):1162-73.
109. Maeremans J, Avran A, Walsh S, Knaapen P, Hanratty CG, Faurie B, et al. One-year clinical outcomes of the hybrid CTO revascularization strategy after hospital discharge: a subanalysis of the multicenter RECHARGE registry. Journal of Invasive Cardiology. 2018;30(2):62-70.
110. Riley RD, Ensor J, Snell KI, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. Bmj. 2020;368.
111. Morgan J. Classification and regression tree analysis. Boston: Boston University. 2014;298.
112. Brieman L, Friedman JH, Olshen RA, Stone CJ. Classification and regression trees. Wadsworth Inc. 1984;67.
113. Lemon SC, Roy J, Clark MA, Friedmann PD, Rakowski W. Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. Annals of behavioral medicine. 2003;26(3):172-81.
114. Loh W-y. Classification and Regression Tree Methods (In Encyclopedia of Statistics in Quality and Reliability. 2008.
115. Forthofer MS, Bryant CA. Using audience-segmentation techniques to tailor health behavior change strategies. American Journal of Health Behavior. 2000;24(1):36-43.
116. Kurt I, Ture M, Kurum AT. Comparing performances of logistic regression, classification and regression tree, and neural networks for predicting coronary artery disease. Expert systems with applications. 2008;34(1):366-74.
117. Lu F, Petkova E. A comparative study of variable selection methods in the context of developing psychiatric screening instruments. Statistics in medicine. 2014;33(3):401-21.
118. Stärk KD, Pfeiffer DU. The application of non-parametric techniques to solve classification problems in complex data sets in veterinary epidemiology–An example. Intelligent Data Analysis. 1999;3(1):23-35.

119. Colombet I, Ruelland A, Chatellier G, Gueyffier F, Degoulet P, Jaulent M-C, editors. Models to predict cardiovascular risk: comparison of CART, multilayer perceptron and logistic regression. Proceedings of the AMIA Symposium; 2000: American Medical Informatics Association.
120. van Smeden M, Moons KG, de Groot JA, Collins GS, Altman DG, Eijkemans MJ, et al. Sample size for binary logistic prediction models: beyond events per variable criteria. Statistical methods in medical research. 2019;28(8):2455-74.