SINGLE CENTRE ANALYSIS OF REVASCULARIZATION STRATEGY IN NEWFOUNDLAND AND LABRADOR MULTIVESSEL DISEASE PATIENTS

by ©Kieran Vasanthan

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Abstract

Background: Coronary artery disease (CAD) can be managed with Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG). Management of subtypes of CAD, including Multivessel Disease (MVD) and isolated Left Main Coronary Artery (LMCA) disease, continue to evolve in the literature. An observational registry may provide implications for management of CAD.

Methods: All isolated LMCA and triple-vessel disease patients who received either PCI or CABG in Newfoundland & Labrador (NL) were analyzed in two separate studies. The first study evaluated isolated LMCA patients for freedom from Major Adverse Cardiac Events (MACE). The second study evaluated triple vessel disease patients for in-hospital mortality post revascularization.

Results: Firstly, 115 patients with isolated LMCA disease (n=7 PCI, n=99 CABG, n=9 medical management) were identified from May 2006 to October 2015. The rate of MACE at 1 year was 5.1% in the CABG cohort. Secondly, a total of 1604 triple vessel disease patients (n=45 PCI, n=1559 CABG) were analyzed with a median follow up of 5.4 years. The in-hospital mortality rate was 2.2% and 1.2% in the PCI and CABG cohorts, respectively (p=0.533).

Conclusion: CABG represented the most common revascularization strategy for both study populations. Freedom from MACE at one year in the CABG isolated LMCA patients was comparable to the literature. Early survival rates were comparable in low-risk triple vessel disease patients revascularized with either therapy and further evaluation is warranted to account for an increasing number of this population being revascularized via PCI.

General Summary

Cardiac research has been a personal interest of mine for several years now. This project was created to further understand the treatment of heart disease, specifically Coronary Artery Disease (CAD), in Newfoundland and Labrador (NL). There are many large studies that have looked at the treatment of CAD over the years; however, there is limited research on our local population. NL offers a unique opportunity to study treatment of CAD because the entire population is treated at the Health Science Center in St. John's. Prior to receiving treatment for CAD, every patient must have a Cardiac Catheterization (also known as an angiogram or "dye test"). Therefore, this allows us to study every patient with CAD and see what treatment they received, which is either a stent placement or open-heart surgery typically. The data at our hospital allowed us to better understand how we are treating our population and what we can change going forward.

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Secondly, I would like to thank my primary supervisor Dr. Corey Adams (Department of Cardiothoracic Surgery). His expertise, research experience, and accessibility significantly aided the design and execution of this particular study. Furthermore, his knowledge of the intricacies of the database used was a critical component in the completion of this project. Additionally, I would like to thank my committee member Dr. Sean Connors (Department of Cardiology) who also provided his expertise along with first introducing me to the field of cardiac research. Furthermore, I would like to thank the contributions of Jennifer Matthews, data custodian of the APPROACH database. Additionally, partial financial contributions for this thesis were made by NL Support through the TPMI funding program for graduate students.

Finally, I would like to thank my loving family members and my partner, Emily Pittman, for their kindness and support throughout not only this project, but also my everyday life.

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List of Abbreviations and Symbols

ACC = American College of Cardiology
ACE = Angiotensin Converting Enzyme
AMI = Acute Myocardial Infarction
APPROACH = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
BIMA = Bilateral Internal Mammary Artery
BMI = Body Mass Index
BMS = Bare Metal Stents
CABG = Coronary Artery Bypass Grafting
CAD = Coronary Artery Disease
CCS = Canadian Cardiovascular Society
COPD = Chronic Obstructive Pulmonary Disease
DES = Drug Eluting Stent
FFR = Fractional Flow Reserve
GI = Gastrointestinal
HREB = Human Research Ethics Board
IABP = Intra-Aortic Balloon Pump
IVUS = Intravascular Ultrasound
LAD = Left Anterior Descending Artery
LCx = Left Circumflex Artery
LMCA = Left Main Coronary Artery
LVEF = Left Ventricular Ejection Fraction
MACCE = Major Adverse Cardiovascular and Cerebrovascular Events
MI = Myocardial Infarction
MVD = Multivessel Disease
NL = Newfoundland & Labrador
NYHA = New York Heart Association
OR = Operating Room
PCI = Percutaneous Coronary Intervention
RCA = Right Coronary Artery
RCT = Randomized Controlled Trial
RPAC = Research Projects Approval Committee
SCD = Sudden Cardiac Death
SD = Standard Deviation
SIMA = Single Internal Mammary Artery
STS = Society of Thoracic Surgeons
SYNTAX = Synergy between PCI with TAXUS drug-eluting stent and Cardiac Surgery
WHO = World Health Organization

Co-Authorship Statement

I (Kieran Vasanthan) made all primary author contributions to the entire body of work presented in this thesis, including the research question design, methodology, analysis, and discussion. Contributions from Dr. Kathleen Hodgkinson, Dr. Corey Adams, & Dr. Sean Connors were as supervisors, mentors and teachers.

This thesis is designed in a manuscript format that includes two studies that are prepared for submission to peer-reviewed journals. The goal of this thesis was to investigate management strategies and outcomes of CAD at single, provincial tertiary cardiac care centre in St. John's, NL. Two separate studies are included that investigate two different sub-populations that ultimately offer contributions to CAD management. This thesis will include an introductory chapter on the topic of CAD, general management principles, and current literature. Following this, Chapter 2 and Chapter 3 are composed of the two individual studies, respectively. These studies are prepared as individual manuscripts and thus will contain their own references listed within. The overarching bibliography at the end of this thesis includes all literature referenced throughout Chapters 1 to Chapter 4. Finally, Chapter 4 will explore discussion topics from our research as a whole and my personal experience with the APPROACH database.

Chapter 1: Introduction and Overview

Chapter 1: Introduction and Overview

1.1 Background

1.11 Coronary Artery Disease

Coronary artery disease (CAD), also known as ischemic heart disease or coronary heart disease, is a condition that results in a reduction of blood flow through the arteries that supply the heart. The sequelae of CAD include a lack of essential nutrients and oxygen supply to the muscle of the heart that are responsible for generating cardiac output and systemic blood flow. A reduction in blood flow to these muscles can result in damage and subsequent death of those cells. The reduction in blood flow itself is a result of atherosclerosis, which is the deposition of cholesterol plaques on the interior wall of the coronary vessels. This cholesterol-based mass propagates on the arterial wall through a series of biochemical processes that are multifactorial in their etiology (Libby & Theroux, 2005). The resulting plaque can proceed to grow as a thrombus and occlude the vessel from which it originated, or it can embolize and migrate to a smaller vessel, often resulting in an acute occlusion and myocardial infarction (Libby & Theroux, 2005). The resulting symptoms of coronary artery disease often include angina pectoris (either with exertion or at rest), shortness of breath, general fatigue and radiation of pain into areas such as the arms, jaw, or back (Ashley EA & Niebauer J., 2004). CAD is a major cause of morbidity and mortality in the modern era and is a major issue in cardiac medicine as it continues to affect a large proportion of the population around the globe.

1.12 Epidemiology of Coronary Artery Disease

The World Health Organization (WHO) recognizes ischemic heart disease CAD as the leading cause of death worldwide, and thus this disease poses a significant burden on the general population (WHO, 2015). In 2013, there were approximately thirty-four thousand deaths due to CAD in Canada (Statistics Canada, 2013). Epidemiologically, CAD has been a topic of discussion since the early 20th century and several risk factors have been identified, varying by population (Wong 2014). The first major study to identify risk factors for CAD was the Seven Countries Study (Keys 1980), and a forty-year follow up analysis of the original participants revealed that age, smoking habits, total cholesterol, and BMI were significant predictors of mortality in the population that was studied (Pitsavos et al., 2003). The multitude of epidemiological studies assessing the various risk factors for CAD led to various population level approaches of primordial, primary, and secondary prevention of CAD around the world (Wong 2014). This project will focus on the secondary prevention of complications that arise from patients who have been diagnosed with CAD, such as MI, stroke, and cardiac mortality.

1.13 Classifications of CAD

The anatomy of the heart is structured through a four-chamber system that assists in the flow of blood for oxygenation in the lungs and then systemic circulation for the rest of the body. The muscles of the heart are constantly working and thus demand a constant blood flow throughout the organ in order to maintain function. The cardiac blood flow is achieved through the main coronary vessels (Figure 1), which include the left main coronary artery (LMCA), the left anterior descending artery (LAD), the circumflex artery (LCx), and the right coronary artery (RCA). The intricate branching system of these vessels supply the muscles of the heart and are a delicate system that poses a high risk for complication if they are occluded. Pathologically, atherosclerosis can affect any number of these vessels in various ways including partial or diffuse occlusion and complete occlusion. Therefore, there are multiple types of CAD that have different

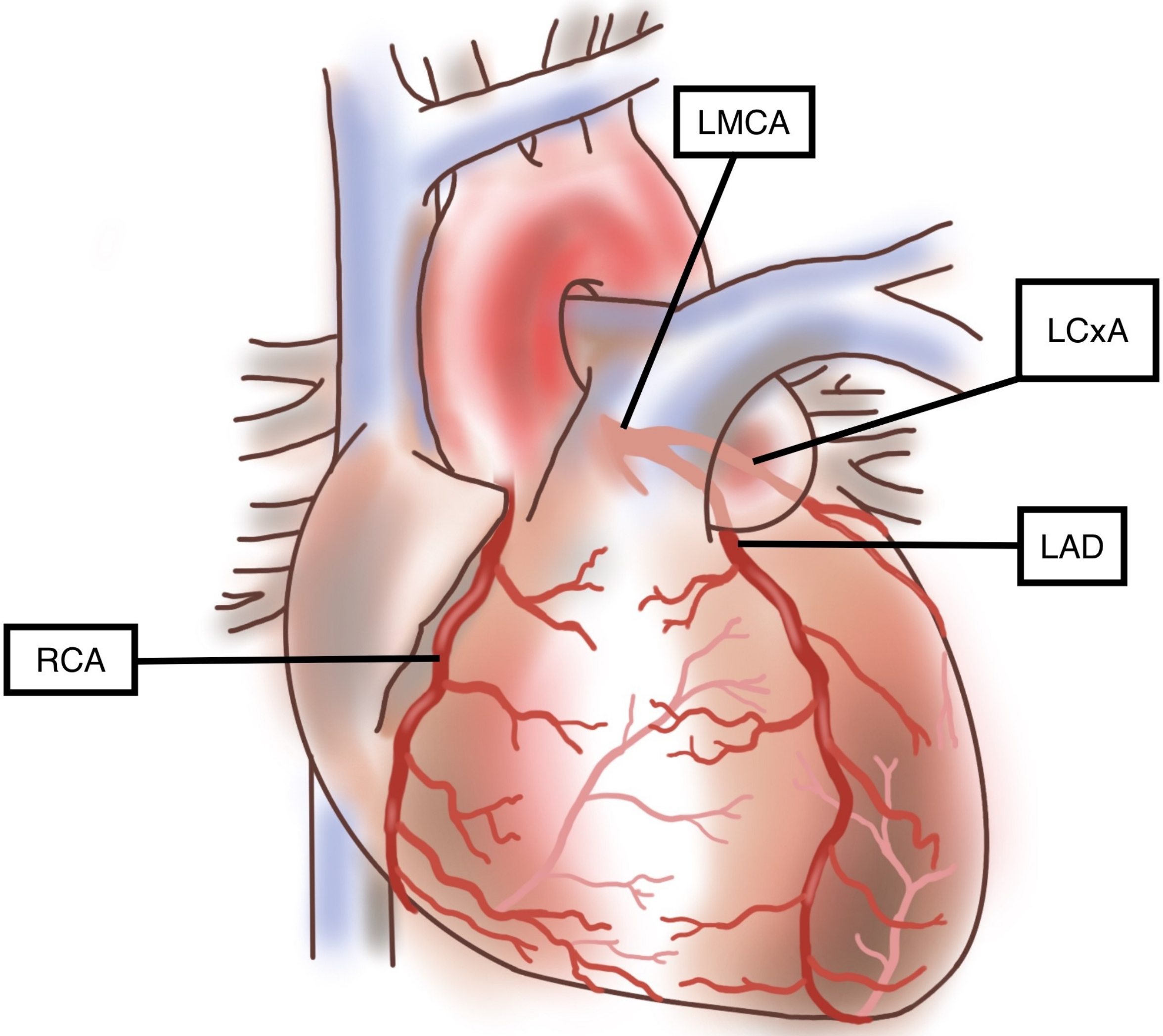

Figure 1: Major coronary vasculature of the heart. Depicted above are the main branches of coronary arteries and the areas of the heart that they supply. LMCA = Left Main Coronary Artery, LCxA = Left Circumflex Artery, LAD = Left Anterior Descending Artery, RCA = Right Coronary Artery. Used with permission from Emily Pittman ©.

indications for treatment and different prognoses. Understanding the underlying pathology of a given patient's CAD is a vital component of the immediate and long-term management. Typically, to determine the extent of a patient's pathology, a coronary angiogram is required. The coronary angiogram procedure requires an interventional cardiologist to guide a catheter through the radial or femoral artery retrogradely to the coronary vasculature, subsequently injecting a dye to image the site(s) of the lesion(s). This procedure allows the disease pathology to be accurately evaluated allowing for accurate classification of CAD. Coronary angiograms have been shown to provide significant prognostic information, including left ventricular function, number of diseased vessels and number of diseased proximal artery segments, that enable an effective patient risk profile to be established (Ringqvist et al., 1983).

The major category of interest for this project is triple-vessel CAD, which is defined as at least one occlusion in all three major coronary systems (LAD, LCx, and RCA). Another classification of CAD that will be discussed is isolated LMCA disease, defined as an occlusion in the LMCA with no other vessels significantly affected. Each of the aforementioned presentations have a unique set of risk factors to consider when deciding on management. A major objective of this project is to provide insights on various management strategies for triple vessel disease and LMCA disease in the Newfoundland and Labrador population.

1.14 Management of CAD

CAD has a variety of presentations and risk factors that must be considered when establishing a treatment plan for any given patient. Recent guidelines indicate that following patient education, a medical management plan may include statins (cholesterol-lowering drugs) and anti-hypertensives including ACE-inhibitors, beta-blockers, and calcium channel blockers (Finn et al., 2012). Chronic and acute patient presentations are managed differently, with presentations of acute coronary syndromes often resulting in intervention via revascularization.

Coronary revascularization, via coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is recommended as a class one indication in patients with significant stenosis in one or more major cardiac arteries despite treatment with the guideline-recommended medical therapy (Finn et al., 2012). CABG is a surgical technique that involves using a peripheral vessel, such as the saphenous vein or internal mammary artery, as a graft to create a route that bypasses the site of the occlusion, thereby allowing the vessel to regain normal blood flow to the affected heart muscle. CABG was initially introduced as a coronary revascularization technique in 1967 (Favaloro, 1967). Patients with complex comorbidities, poorly controlled risk factors for cardiac disease, and multivessel involvement are said to have severe disease. CABG grew in popularity for CAD management, especially in those considered to have severe disease. Initial clinical trials demonstrated long-term survival advantages associated with surgery among high severity patients when compared to medical management alone (Varnauskas et al., 1982; Detre et al., 1984). However, the development of PCI in 1978 (Gruntzig, 1978) prompted the need for more conclusive evidence regarding each respective coronary revascularization. PCI is a less-invasive technique that involves accessing the arterial vasculature via a peripheral vessel, such as the femoral or radial artery, and introducing a catheter with a balloon tip inside the vessel to the site of the occlusion. Once the occlusion site is reached via fluoroscopy, the balloon is expanded to revascularize the site of occlusion from within. Furthermore, modern methodology involves using stents instead of a balloon as an alternative option. PCI can now be used in a variety of presentations as an alternative to CABG therapy (Finn et al., 2012). Although CABG has been the gold standard for most forms of CAD, PCI is a less-invasive technique with fewer short-term risks to the patient and is therefore an important consideration for management of CAD. Furthermore, PCI presents a presumptive cost-effective strategy to revascularize patients with CAD. The discussion on indications for either PCI or CABG has been ongoing for several decades resulting in a dense base of literature from which to draw guidelines for CAD management.

1.15 Progression of trials evaluating CAD management

The vast literature on CAD management indicates there is a constant evolution of therapeutic options available and accordingly, several studies have been published in the field (Appendix A). When discussing the management of multivessel CAD, there are three “eras” of coronary revascularization trials that are established in the literature. The progression from one era to another is a result of newer techniques in surgical and stent-based management over the years which warranted updated literature. The vast majority of publications in coronary revascularization are Randomized Controlled Trials (RCTs) that directly compare the two major therapeutic options: PCI and CABG.

Approximately 4% of all patients undergoing coronary angiography are diagnosed with left main coronary artery disease (LMCA) and of these <20% have isolated LMCA (Fihn et al., 2014)..

Historically, isolated LMCA has been treated exclusively with coronary artery bypass graft (CABG) surgery (Buszman et al., 2008). The EXCEL (Stone et al., 2016) trial revealed comparable long-term rates of major adverse cardiac or cerebrovascular events (MACCE) following revascularization with either CABG or PCI for LMCA, while the NOBLE Makikallio et al., 2016) trial reported a significantly higher long-term rate of MACCE associated with PCI.

Clinical questions regarding optimal conduit selection for CABG, the need for quantitative assessment via intravascular ultrasound (IVUS) or Fractional Flow Reserve (FFR), and long term follow up remain understudied in the LMCA population. Moreover, the bilateral internal mammary arterial (BIMA) grafts conduit strategy remains underutilized in CABG patients (Windecker et al., 2014; Iribarne et al., 2017). In addition to isolated LMCA disease patients, multivessel disease patients have been studied extensively in the literature as well.

Initial RCT evaluations of PCI and CABG compared balloon angioplasty to conventional CABG surgery; however, no definitive conclusions were drawn (Rodriguez et al., 1993; Hampton et al., 1993; King et al., 1994; Ham et al., 1994; Chaitman et al., 1997; Carrie et al., 1997). Limitations of these initial trials included loss to follow-up, underpowered design due to sample size, and outdated procedural methodology. Although there was a general trend towards a significantly fewer number of patients with angina and fewer patients requiring a subsequent revascularization associated with CABG, the primary outcomes from these trials were nonsignificant and thus these secondary findings were limited to hypothesis-generating speculation (Rodriguez et al., 1993; Hampton et al., 1993; King et al., 1994; Ham et al., 1994; Chaitman et al., 1997; Carrie et al., 1997). One of the more notable findings from this early era of revascularization trials was the significance of diabetes as a poor prognostic factor for PCI. Chaitman and colleagues demonstrated that there is a significantly increased risk of cardiac mortality in diabetic patients in the long-term (median follow up = 5.4 years; Chaitman et al., 1997). This finding continues to play a significant role in current management of patients with CAD and comorbid diabetes mellitus.

The development of bare-metal stents (BMS) in the late 1990s resulted in a new series of

RCTs comparing the updated PCI methodology to CABG (Serruys et al., 2001; Rodriguez et al., 2001; SoS investigators, 2002; Heub et al., 2010). The trials in this era were well designed and led to many of the mainstays of coronary revascularization that are fundamental in modern practice. The general consensus remained that CABG is associated with superior long-term outcomes, despite a higher immediate post-operative risk, with a consistent finding that PCI is associated with significantly higher occurrences of subsequent revascularizations (Serruys et al., 2001; Rodriguez et al., 2001; SoS Investigators, 2002; Heub et al., 2010).

In accordance with the constant evolution of coronary revascularization, newer techniques such as drug-eluting stent (DES) placement and hybrid coronary revascularization were developed and necessitated more clinical trials (Htay & Liu, 2005; Riess et al., 1998). In fact, a recent meta-analysis demonstrated that patients with a DES PCI had significantly better outcomes than those with a BMS PCI (Pandya et al., 2010). Several well-designed RCTs evaluated various outcomes following either drug-eluting PCI or CABG surgery; however, the results remained dependent on the specific population being studied in addition to the significance of the primary outcome being driven by subsequent repeat revascularization procedures (Serruys et al., 2009; Farkouh et al., 2012; Kamelesh et al., 2013; Park et al., 2015).

One of the most notable trials in the drug-eluting stent era is the SYNTAX trial, conducted by Dr. Patrick Serruys and colleagues (Serruys et al., 2009). The results from this large multi-centre trial revealed a significant reduction in the occurrence of major adverse cardiac or cerebrovascular events (MACCE) at 12 months in patients treated with CABG compared to those treated with PCI ($p=0.002$) (Serruys et al., 2009). Furthermore, a subgroup analysis revealed the utilization of a SYNTAX score based on pre-procedural anatomical severity had significant predictive value with respect to the occurrence of future MACCEs (Serruys et al., 2009). This significant finding resulted in the ability to predict negative outcomes based on severity of disease prior to reaching a treatment decision. Thus, high score patients could be confidently sent to surgery while low score patients could receive a stent or surgery depending on patient preference and physician recommendation. The SYNTAX trial remains one of the most influential studies in this field and underpins CAD management today.

The decision to treat multivessel disease patients with either CABG or PCI however remains the subject of ongoing research. The Canadian Cardiovascular Society (CCS) indicates a strong quality of evidence in favor of CABG for high severity MVD presentations and a strong quality of evidence indicating no significant advantage for either treatment in low severity MVD presentations based on the SYNTAX scoring system (Teo et al., 2014). American guidelines also recommend a heart-team approach (vs single consultant approach) for determining the optimal revascularization strategy for various clinical presentations of different patients (Finn et al., 2012). The American and Canadian guidelines both outline the importance of the SYNTAX score in evaluating the risk for a patient undergoing an interventional revascularization procedure. Despite this, there remains limited comparative literature of triple vessel disease patients that are both determined low risk via SYNTAX score and are completely revascularized (via either PCI or CABG).

1.16 Gaps in Literature

The literature on coronary revascularization is evidently vast and covers a wide range of topics. RCTs are widely accepted as the most effective way to evaluate treatment efficacy questions and thus the guidelines for CAD management are generally based on the outcomes and conclusions of RCTs (Teo et al., 2014). Despite the strength of the literature and RCT study designs, there is an indication for critical validation of the present guidelines through evaluation of a real-life population in a non-interventional manner. The population in NL offers a unique opportunity to retrospectively evaluate outcomes in coronary revascularization due to the full ascertainment of the population through a tertiary referral catheterization laboratory. A study of this type is warranted to retrospectively evaluate revascularization outcomes in a population that is completely captured. Furthermore, an emphasis on outcome assessment in low-risk patients with complete revascularization achieved has been limited in the literature.

The Newfoundland & Labrador population therefore offers a unique opportunity to study a subset of the Canadian population and evaluate the effectiveness of a small-moderate volume centre in the management of CAD patients. There are no previous studies comparing outcomes following PCI or CABG in triplevessel disease patients in the NL population. Given that NL is a founder population, with high rates of some genetic cardiac diseases causing Sudden Cardiac Death (SCD; Merner et al., 2008) and an apparently higher rate of SCD compared to Ontario unrelated to environmental issues such as BMI and smoking (Hamilton, 2016), it is reasonable to consider the possibility this population will differ from the overall general population represented in the larger clinical trials. Furthermore, there is a continued need for studies in this area of research, evident through the continuous publication of studies over the past three decades (Appendix A). This study aims to provide a benchmark for mortality and morbidity statistics for NL specifically, but data derived may also be useful for other medium-volume centres, similar to the Health Science Centre, when managing multivessel CAD. There has been little written on low-risk triple vessel disease populations, defined by those with low SYNTAX scores, who undergo complete coronary revascularization and the data from APPROACH offers the opportunity to assess this specific population. Moreover, data on secondary outcomes such as the effectiveness of which vessels to use as a graft within CABG procedures and LMCA disease management can also be assessed with the data from APPROACH. Physicians and health care teams are faced with a wide range of MVD patients with various co-morbidities and environmental influences (lifestyle, socioeconomic status, etc.) on a regular basis. Therefore, the continued evaluation of MVD treatment remains an important topic and ongoing research is needed to support and update policy and guidelines in NL.

1.2 Area of Investigation

The setting of this project is at the Health Science Centre in St. John's, NL (Figure 2). This Canadian province operates a tertiary referral centre in the capital city of St. John's and treats cardiac patients from the entire province. Therefore, there is a unique opportunity to obtain clinical outcomes and complete follow up information on a fully ascertained population. All cardiac patients therefore requiring revascularization are assessed at the cardiac catheterization laboratory in St. John's and their clinical data is collected and stored by trained professionals. The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database has been active in NL since 2006 and contains clinical data on all cardiac patients from the point of catheterization onwards. Once a patient presents at the catheterization laboratory, they are assigned an APPROACH ID number that links with their provincial health records. Therefore, the APPROACH database can be screened for patients of various presentations, such as valvular heart disease, CAD, LMCA disease, etc. This annually populated prospective database offers a unique opportunity to conduct retrospective studies on patient outcomes and clinical care in NL over the past ten years allowing for complete assessment.

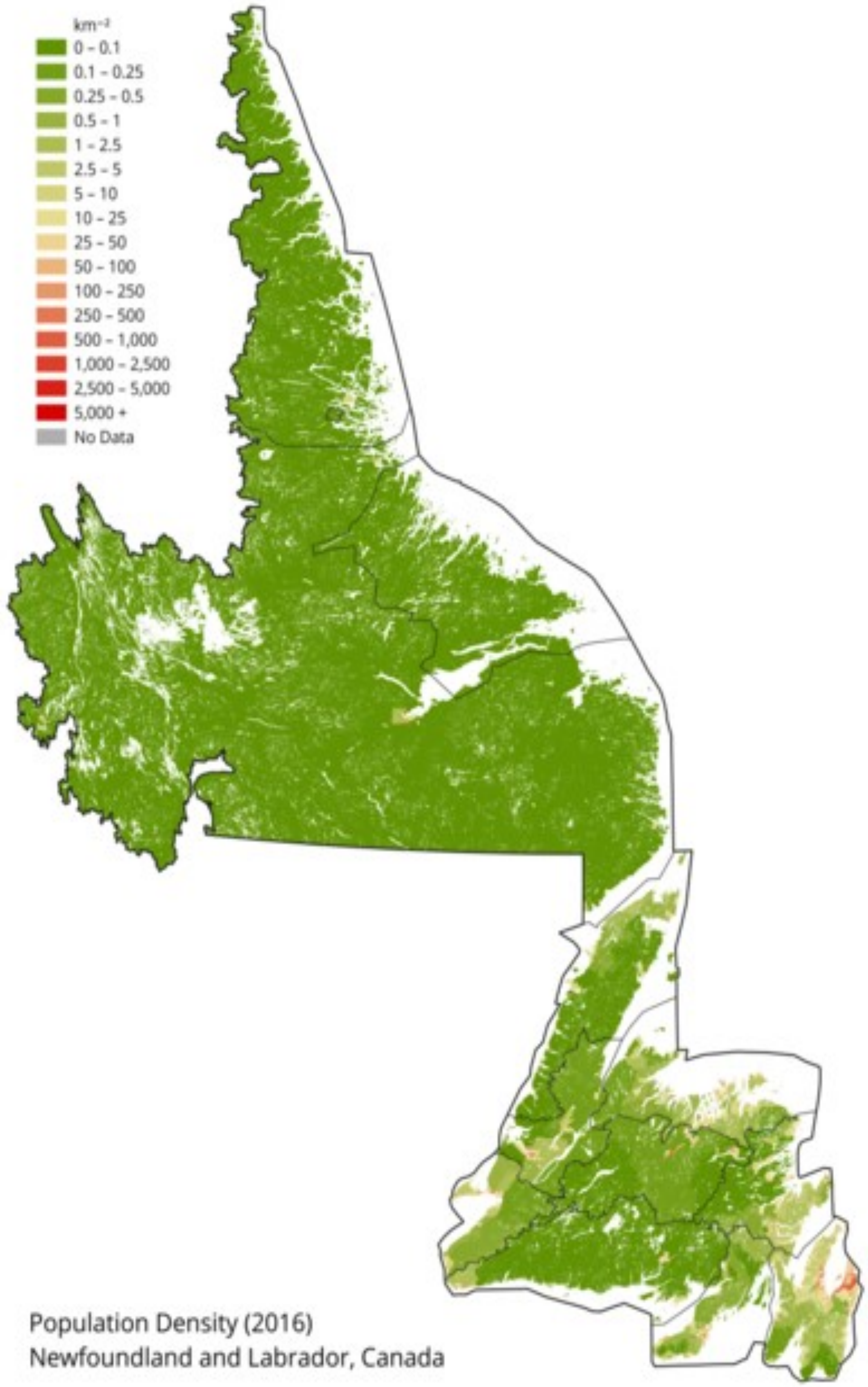

Figure 2: Map of Newfoundland & Labrador, Canada. Image obtained from the public domain at https://upload.wikimedia.org/wikipedia/commons/2/2b/Canada_Newfoundland_and_Labrador_Density_2016.png

1.3 Research Objectives

The purpose of this study is to evaluate clinical outcomes following coronary revascularization of multi-vessel disease patients at a medium volume cardiac catheterization centre through a retrolective cohort study design. Furthermore, this project seeks to assess clinical outcomes in low-risk triple vessel disease patients who have undergone complete revascularization to address an under-studied population in the literature. Therefore, the following research question is addressed upon the completion of this project:

How does the management of LMCA disease in NL compare to the literature and are there significantly different mortality rates in low-risk triple vessel disease patients treated by complete revascularization via CABG or PCI from May 2006 to November 2015 in NL?

Thus, the primary objective of this project is to provide one-year MACE statistics in isolated LMCA disease patients as well as mortality statistics, at varying levels of follow up, on low-risk triple vessel disease patients undergoing complete revascularization. Secondary objectives of this project are (a) assessing and comparing demographic and operative data from the NL patient cohort to larger clinical trials, (b) assessing long-term trends in post-operative mortality in low risk triple-vessel disease patients, and (c) assessing early and long term mortality in isolated LMCA disease patients undergoing treatment at the Health Science Centre, and (d) assessing the effect of conduit strategy on early and long term outcomes in CABG patients.

Chapter 2: LMCA Study

Single centre experience of isolated left main disease management

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Chapter 2: Single centre experience of isolated left main disease management

2.1 Abstract

2.11 Background

Coronary artery bypass graft (CABG) surgery has traditionally been the recommended revascularization strategy for isolated left main coronary artery (LMCA) disease. However, studies are emerging comparing PCI to CABG as a potential alternative in managing this population. The primary objectives of this study are to (a) evaluate single centre management of isolated LMCA disease through assessing freedom from Major Adverse Cerebrovascular and Cardiac Events (MACCE) at one year and (b) report on strategies and outcomes over a ten year period in comparison to the literature.

2.12 Methods

We performed a retrospective analysis using an institutional database of consecutive patients with isolated LMCA disease defined as an angiographically significant lesion ≥70%. Patients were excluded if they had an angiographically significant lesion in any additional coronary artery of >50%, or required cardiac surgery for another class I indication.

2.13 Results

115 patients with isolated LMCA disease were identified from May 2006 to October 2015. Ninety-nine patients were revascularized with CABG, seven with PCI, and nine treated medically, with an overall median follow up of 4.45 years. Five-year mortality rates were: 8.1% with CABG, 42.9% with PCI (high risk patients), and 0% with medical therapy patients. The rate of major adverse cardiac or cerebrovascular events at 1 year was 5.1% in the CABG cohort. 33% of CABG patients were revascularized with bilateral internal mammary artery and this strategy was associated with a non-significant trend towards improved five-year survival.

2.14 Conclusions

The majority of isolated LMCA disease patients in our centre continued to be treated with CABG with excellent short and mid-term results. Bilateral internal mammary arteries represented a common safe revascularization strategy.

2.2 Introduction

Approximately 4% of all patients undergoing coronary angiography are diagnosed with left main coronary artery disease (LMCA) and of these <20% have isolated LMCA[1]. Historically, isolated LMCA has been treated exclusively with coronary artery bypass graft (CABG) surgery[2]. However, recent trials suggest a role for percutaneous coronary intervention (PCI) in patients with LMCA. The EXCEL[3] trial indicated comparable long-term rates of major adverse cardiac or cerebrovascular events (MACCE) following revascularization with either CABG or PCI for LMCA, while the NOBLE[4] trial reported a significantly higher long-term rate of MACCE associated with PCI.

Given the restricted inclusion criteria for randomized controlled trials and the relative infrequency of isolated LMCA, it remains important to assess outcomes from prospectively collected databases to evaluate clinical practice in real-world populations. Additionally, clinical questions regarding optimal conduit selection for CABG, the need for quantitative assessment via intravascular ultrasound (IVUS) or Fractional Flow Reserve (FFR), and long term follow up remain understudied in the LMCA population. Despite observational trials showing improved survival with bilateral internal mammary arterial (BIMA) grafts, this conduit strategy remains underutilized in CABG patients[5,6].

The cardiac catheterization centre in St. John's, NL offers a unique opportunity to evaluate and compare management of isolated LMCA in a small volume centre. Therefore, the primary objective of this study is to retrospectively evaluate management of isolated LMCA disease by describing treatment patterns and outcomes in comparison to current global practice. A secondary objective is to compare surgically treated patients with bilateral internal mammary arterial (BIMA) grafts to single internal mammary arterial (SIMA) grafts.

2.3 Methods

2.31 Study Population

All consecutive patients treated for isolated LMCA disease in the province of Newfoundland & Labrador (NL) between May 1st, 2006 and October 31st, 2015 were screened for inclusion into this study. Patient data procurement and screening was accomplished utilizing the electronic Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database. The APPROACH database captured all patients who presented with clinical symptoms of coronary artery disease at the cardiac catheterization laboratory, located at the sole cardiac tertiary referral centre (The Health Science Centre, St. John's) in the province. Therefore, all cardiac patients in the province of NL were captured by this prospectively collected database. The anonymous patient data was extracted with the following inclusion criterion: interventional cardiologist confirmed angiographically significant isolated LMCA disease, defined as left main stenosis greater than or equal to 70% with no other coronary artery stenosis of greater than 50% on coronary angiogram. Patients with indications for cardiac surgery other than coronary disease, such as concomitant valvular heart disease were excluded. All co-morbid variables included in analysis were based on information collected and stored in the APPROACH database. Co-morbid conditions were diagnosed and stored in APPROACH using standard diagnostic criteria. Variables were then extracted as "yes" or "no" data points during collection. Approval from the local human research ethics board and institutional review board (RPAC) was obtained prior to patient data extraction and analysis (HREB#2016.275).

2.32 Statistical Analysis

Categorical variables are presented as frequency and percentage. Continuous variables are presented as mean and standard deviation (SD). As there is no deliberate comparison of treatment modalities in this analysis, descriptive statistics compose the majority of the results. Cumulative survival of the CABG cohort was displayed on a Kaplan Meier curve. Hypothesis tests were evaluated using the alpha=0.05 level of significance (two-tailed). A regression analysis was completed with an entry level of $p<0.05$ and a stay level of $p<0.20$ for inclusion into the model. All statistical analyses were conducted using ©IBM SPSS 23 statistical software package.

2.33 Outcomes

The objectives of this retrospective study were to evaluate the management of isolated LMCA disease at a single centre and report on outcomes and practice patterns over a ten-year period. Statistical comparison between the three treatment modalities, CABG, PCI, and medical management, was unable to be attained due to limitations in sample size of the population studied. Thus, the primary outcome was freedom from MACCE (defined as a composite of all-cause mortality, non-fatal stroke, or repeat revascularization) at one year. The secondary outcome of this study was all-cause mortality post BIMA compared to all-cause mortality post SIMA in the CABG cohort.

2.4 Results

2.41 Patient Selection

A total of 26,697 patients were screened in the APPROACH database with the specified inclusion criteria in NL. Subsequently, 115 patients were identified as having isolated LMCA of >70% stenosis without any angiographically significant lesion in any other coronary artery of >50% from May 1st, 2006 to October 31st, 2015. Treatment modalities included CABG (n=99), PCI (n=7), and medical management (n=9). The patient selection process is shown in *Figure 1*. Approximately one quarter of the patients selected for this study were diabetic (n=27) and 14 patients had a left ventricular ejection fraction (LVEF) of less than 50%. Furthermore, the majority of patients (n=88) in this study were classified as class 1 under the New York Heart Association (NYHA) classification system for heart failure. The remaining demographic data for each treatment modality are displayed in *Table 1*.

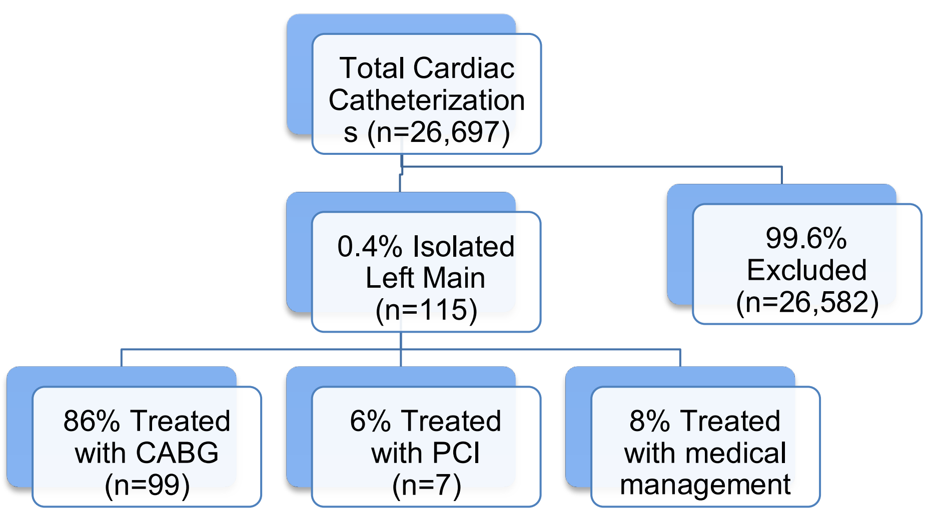

Figure 1: Patient Selection. During the timeframe of this study, n=26,697 patients were identified to have received a cardiac catheterization at our centre. Of those patients, n=115 (0.4%) meet the criteria for isolated LMCA disease. Of the isolated LMCA disease patients, 86% received CABG, 6% received PCI, 8% received medical management.

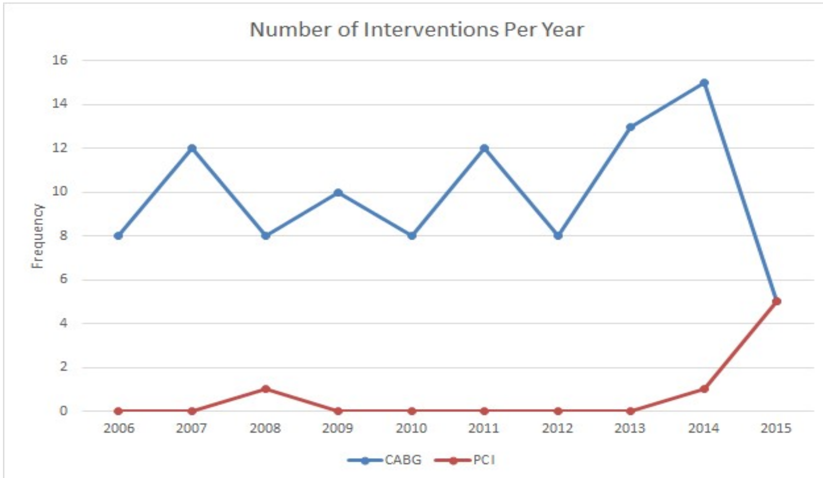

Figure 2: Distribution of CABG vs PCI patients with isolated LMCA disease. CABG continues to represent the dominant Treatment modality for this sub-population. In recent years the number of isolated LMCA PCI cases have been rising, reflecting global trends and changes in the operator experience.

Table 1

	CABG Cohort (N=99)	**PCI Cohort (N=7)**	**Medical Cohort (N=8)**
Age (years)	62.4 *(9.98)*	57.0 *(10.91)*	67.3 *(13.07)**
Male	67 *(67.7%)*	3 *(42.9%)*	7 *(77.8%)*
Body-Mass Index (kg/m^2)	29.8 *(4.99)*	26.8 *(3.14)*	27.4 *(3.06)*
Diabetes (T1 or T2)	22 *(22.2%)*	2 *(28.6%)*	3 *(33.3%)*
Family History	58 *(58.6%)*	4 *(57.1%)*	6 *(66.7%)*
Hyperlipidemia	87 *(87.9%)*	4 *(57.1%)*	8 *(88.9%)*
Hypertension	70 *(70.7%)*	2 *(28.6%)*	5 (55.6%)
Active Smokers	23 *(23.2%)*	3 *(42.9%)*	2 *(22.2%)*
Previous Revascularization			
PCI	8 *(8.1%)*	0	1 (11.1%)
CABG	0	0	0
NYHA Class			
I	87 *(87.9%)*	1 (11.1%)	
II	4 *(4.0%)*	1 (11.1%)	
III	2 *(2.0%)*	0	
IV	2 *(2.0%)*	0	
Indication			
Stable Angina	6 *(6.1%)*	1 (14.3%)	5 *(55.6%)*
Unstable Angina	19 *(19.2%)*	/	/
Acute Coronary Syndrome	*0*	6 *(85.7%)*	1 (11.1%)
Renal Insufficiency	3 *(3.0%)*	0	1 (11.1%)
Peripheral Vascular Disease	4 *(4.0%)*	1 (14.3%)	1 (11.1%)
Pulmonary Disease	18 *(18.2%)*	1 (14.3%)	0
Obesity (BMI>30.0kg/m^2)	41 *(41.4%)*	0	2 *(22.2%)*
Liver Disease	1 *(1.0%)*	0	0
Cerebrovascular event	12 *(12.1%)*	1 (14.3%)	0
LVEF <50%	10 *(10.1%)*	3 *(42.9%)*	1 (11.1%)

*Table 1. Demographic characteristics of each treatment group. Continuous variables are presented as mean (standard deviation) and categorical variables are presented as frequency (percentage). LVEF = Left Ventricular Ejection Fraction; NYHA = New York Heart Association. *Average age at time of catheterization .*

2.42 Procedural Details

The distribution of isolated LMCA patients treated with either CABG or PCI per year is shown in *Figure 2.* As expected, the majority of patients in this population are treated with CABG (n=99), with a small proportion treated with PCI (n=7) and medically (n=9). Of the patients treated surgically, there were an average 2.26 grafts per patient with 94.9% of patients having an internal mammary artery graft. Furthermore, 79.8% of the surgically managed patients were treated via cardiopulmonary bypass machine. Approximately one third of surgical patients received bilateral internal mammary artery grafts (n=33). Further operative details for the CABG cohort are presented in *Table 2.* The median length of time from catheter angiogram to operation was 6 days with no mortality prior to surgery.

2.43 Composite MACCE

The rates of composite MACCE at 30 days and 1 year for the CABG cohort were 2.0% and 5.1%, respectively. The rates of composite MACCE at 30 days and 1 year for the PCI cohort were 28.6% and 57.1 %, respectively. Composite MACCE rates for surgical and PCI patients are shown in *Table 3*. The survival curve for 1-year MACCE in the CABG cohort is presented in *Figure 3.*

Table 2

CABG Cohort	N=99
On Pump	*79 (79.8%)*
Total Number of Grafts	*224*
Average Grafts per Person	*2.26 (0.06)*
Patients with > 2 Grafts	*30 (30.3%)*
No. of Patients with Arterial Grafts	*94 (94.9%)*
Patients with an Internal Mammary Graft	*94 (94.9%)*
No. of Patients with BIMA Grafts	*33 (33.3%)*
No. of Patients with SIMA Plus Vein Grafts	*54 (54.5%)*
No. of Patients <65 Years Old with Arterial Grafts	*33/37 (89.4%)*
No. of Patients >65 Years Old with Arterial Grafts	*61/62 (98.4%)*
No. of Patients with an IABP	*7 (7.1%)*

Table 2: Operative details for CABG cohort. BIMA = Bilateral Internal Mammary Artery; IABP = Intra Aortic Balloon Pump; SIMA = Single Internal Mammary Artery.

Table 3

	CABG (N=99)	PCI (N=7)
Composite MACCE		
30 Days	2 *(2.0%)*	2 *(28.6%)*
1 Year	5 *(5.1%)*	4 *(57.1%)*
Mortality		
30 Days	1 *(1.0%)*	2 *(28.6%)*
1 Year	4 *(4.0%)*	3 *(42.9%)*
3 Years	5 *(5.1%)*	3 *(42.9%)*
5 Years	8 *(8.1%)*	3 *(42.9%)*
Stroke	1 *(1.0%)*	0
Repeat Revascularization		
1 Year	0	1 *(14.3%)*
5 Years	1 *(1.0%)*	1 *(14.3%)*

Table 3. Outcome data. MACCE = Major Adverse Cardiac or Cerebrovascular Events (composite of all-cause mortality, stroke or repeat revascularization).

2.44 All-cause Mortality and Repeat Revascularization

A total of 11 deaths occurred with a median follow up of 4.45 years (range 0.03 to 9.59 years), with n=8 (8.1%) in the CABG cohort and n=3 (42.9%) in the PCI cohort (*Table 3*). Survival at 30 days, 1 year, and 5 years in the CABG cohort was 99.0%, 96.0%, and 91.9%, respectively. Five of the seven PCI patients (71.4%) survived to 30 days and 4 (57.1%) survived for the duration of the study period. There were two repeat revascularizations throughout the study period, with n=1 (1.0%) in the CABG cohort and n=1 (14.3%) in the PCI cohort (*Table 3)*. Overall Kaplan-Meier survival at 5 years in the CABG cohort is shown in *Figure 4*.

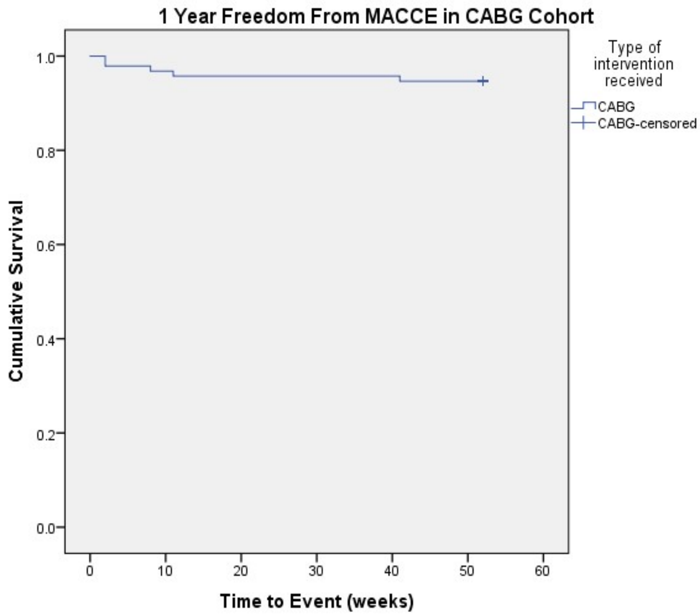

Figure 3: 1-year freedom from MACCE in the CABG cohort. MACCE = Major Adverse Cardiac or Cerebrovascular Events

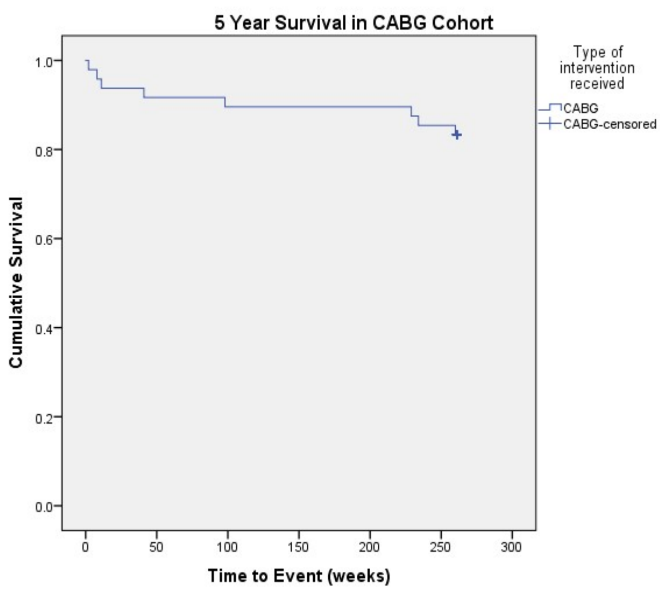

Figure 4: 5-year Kaplan-Meier survival curve for the CABG cohort. Due to small number of patients in the PCI arm (n=7) adequate 5 year follow up data was not available. The CABG cohort only survival is presented here.

2.45 Comparison of Bilateral Mammary Artery Usage to Single Mammary with Saphenous Vein

In the CABG cohort, 33 patients (33%) received BIMA, 54 patients (55%) received a SIMA and a vein and 12 patients (12%) received other graft strategies. In patients younger than 65, 46.8% (n=29) received BIMA grafts as a conduit strategy, while 40.3% (n=25) of patients received SIMA grafts as a conduit strategy. The 5-year survival rates in the BIMA and SIMA groups are 93.9% and 88.9%, respectively. *Figure 5* shows the Kaplan-Meier survival of BIMA grafted patients versus SIMA grafted patients. At 1, 3, and 5-year follow up there is no significant difference in survival between each subgroup (p=0.838, p=0.987, p=0.459, respectively).

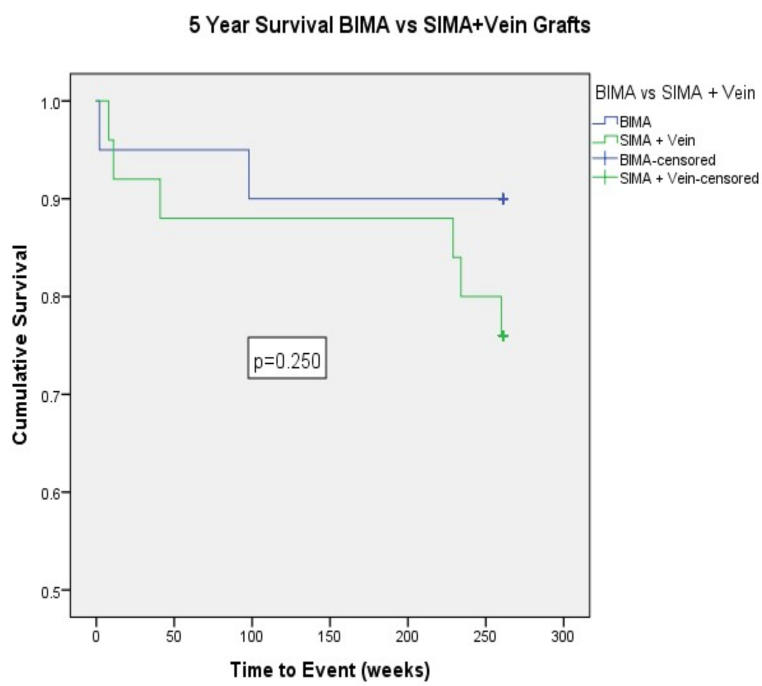

Figure 5: 5-year Kaplan-Meier survival curve for LMCA patients revascularized with CABG and either BIMA or SIMA + vein grafts. BIMA = Bilateral Internal Mammary Artery; SIMA = Single Internal Mammary Artery

2.46 Regression Analysis

To predict mortality for the CABG cohort, variables including LVEF<50%, hypertension, hyperlipidemia, prior PCI, age at procedure, urgency of procedure (emergent vs urgent vs elective), angina status, BIMA versus SIMA grafts, Type 1 Diabetes, and Type 2 Diabetes, were included into the regression model. Of the included variables, LVEF<50% and Type 2 Diabetes were the only significant predictors of mortality at 5 years (p=0.003, p=0.008, respectively).

2.5 Discussion

Results of this single centre experience of revascularization for isolated LMCA show that a high proportion of patients continue to be treated with CABG. This result was to be expected, given the historical context of CABG in isolated LMCA management. The results indicate that CABG surgery is associated with excellent short and medium-term survival and freedom from MACCE. The results from this study also indicate an 8.1% 5-year mortality rate associated with isolated LMCA patients who are treated with a surgical modality.

It is notable that the 5-year mortality rate in the CABG cohort (8.1%) is comparable to 5year mortality rates in other studies (14.6% in SYNTAX[7], 7.9% in PRECOMBAT[8], and 9% in NOBLE[4]). Moreover, in the CABG cohort, only Type 2 diabetes and a reduced ejection fraction were significant predictors of mortality. In the PCI cohort, the 5-year mortality rate (42.9%) was much higher than reported in larger trials (12.8% in SYNTAX[7], 5.7% in PRECOMBAT[8], and 12% in NOBLE[4]). However, only seven patients were treated with PCI in this study, giving a sample size that is too small to draw any significant conclusions. Of the seven patients who were treated with PCI, five were deemed unstable and the remaining two had ostial lesions that were stented in accordance with the 2014 ACC guidelines[9]. The unstable patients were declined for surgery and went for salvage PCI because of ongoing hemodynamic instability. This suggests that PCI in our centre was used more often in patients who were in an emergency state and likely accounts for the increased primary outcome.

In total nine patients were treated with medical management despite having an angiographic lesion between 50 and 60%. All of these patients remained alive at five-year follow up. On further evaluation, none of these patients had presented with acute coronary syndrome and five patients were asymptomatic with normal exercise stress tests. The additional four patients who remained on medical therapy underwent FFR or IVUS and did not have significant flow limiting lesions. This result suggests the importance of both patient symptoms and quantitative measurements of lesion severity over purely angiographic appearance.

The rate of MACCE one-year post CABG, as per our definition, is 5.1% and this is comparable to the one-year data from PRECOMBAT[8] (5.7%). The CABG cohort has a 5-year repeat revascularization rate lower than that seen in randomized trials (1% vs 15.5% in SYNTAX[7], 21% in PRECOMBAT[8], and 10% in NOBLE[4]). Our cohort is younger than the cohort in SYNTAX[7] and NOBLE[4] and less likely to be diabetic than the patients in PRECOMBAT[8]. As well, the patients in previous studies were more likely to have concomitant multivessel disease[4,7,8]. Finally, our lower rates of repeat revascularization may be partly due to our more frequent use of arterial grafts.

Within the CABG cohort, the surgical strategy consisted of at least a single mammary in 94.9% of patients and bilateral mammary grafts in 33% of patients. This is even more pronounced in patients under 65 years of age where 46.8% received BIMA grafting. The ability to perform BIMA grafting in one-third of patients in this study demonstrates how this strategy can be used in urgent situations. The rate of BIMA usage in this study is significantly higher than that reported in the STS database (33% vs. 4.1%)[10]. The BIMA group demonstrates a nonsignificant trend towards a lower 5-year mortality rate (93.9% compared to 88.9%), which is comparable with results seen in other observational trials[5]. Despite the potential survival benefit demonstrated with BIMA, there has been no increase in the use of BIMA grafting with CABG[6]. Longer follow up is likely needed before a statically significant survival benefit is seen with BIMA revascularization in isolated LMCA; however, the results from this study suggest a potentially beneficial result and this strategy remains the preferred technique at our centre.

Prior to 2014 there was only a single case of PCI for isolated LMCA performed in NL, however with resulting changes in guidelines[9], six PCI procedures were done between 2014 and 2016. The use of PCI may be underutilized at our centre and the reasons for this are likely multifactorial. Our study only extends to October 2015 and the guidelines only support PCI as an alternative to CABG as of 2014. Further follow up data is likely needed before adequate conclusions can be drawn regarding PCI use at our centre.

This study has several limitations. The retrospective, non-randomized study design may result in selection bias. Five of the seven patients in the PCI cohort were too unstable and declined for surgical revascularization and thus underwent PCI. Therefore, a direct comparison of different treatment modalities for isolated LMCA was not possible due to the differences in prognostic variables and indications for long term complications. Furthermore, the recent guideline change in the literature may ultimately result in a change in practice that will not be evident through this study population. Despite the limitations of this study, single centre evaluation of isolated LMCA disease treatment remains an effective method of assessing local practice with respect to global trends. The results from this study provide confidence that CABG is safe for isolated left main disease and that revascularization can be achieved with high rates of bilateral internal mammary usage.

2.6 Conclusion

The results from this study provide confidence that CABG is safe for isolated left main disease and that revascularization can be achieved with high rates of bilateral internal mammary usage. CABG represented the most common form of revascularization for isolated left main coronary disease in this single centre with excellent short and mid-term morbidity and mortality. These results provide a benchmark for real world outcomes and medium volume cardiac centres.

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Chapter 3: MVD Study

Low Risk Percutaneous Coronary Intervention versus Coronary Artery Bypass Grafting in Completely Revascularized Triple Vessel Disease Patients

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3.1 Abstract

3.11 Background

Multivessel coronary artery disease (MVD) predisposes patients to increased risk of cardiovascular morbidity and mortality. Current guidelines from the Canadian Cardiovascular Society (CCS) outline evidence for Coronary Artery Bypass Grafting (CABG) in high anatomically complex coronary lesions. However, in low and intermediate anatomically complex coronary disease, percutaneous coronary intervention (PCI) has demonstrated non-inferior outcomes.

3.12 Methods/Results

This study captures all patients who were treated for triple-vessel disease via PCI or CABG in the province of Newfoundland & Labrador between 2006 and 2015. Patients were screened for >70% stenosis in three major cardiac territories (Right Coronary, Left Anterior Descending, & Left Circumflex), not including the left main coronary artery. Included patients were required to have been completely revascularized in each territory for both CABG and PCI. Complex anatomical lesions, including left main disease, proximal lesions, lesions at bifurcations, diffuse disease, and completely occluded vessels were excluded. A total of 1604 patients were extracted from the Alberta Provincial Project for Outcome Assessment in Coronary Heart disease (APPROACH) database, with 45 patients in the PCI cohort and 1559 patients in the CABG cohort (median follow up = 5.4 years). The primary outcome of in-hospital mortality rates was 2.2% and 1.2% in the PCI and CABG cohorts, respectively (p=0.533). A matched comparison was completed using a propensity score model. After matching 36 patients in the PCI cohort to 36 patients in the CABG cohort, the in-hospital mortality rates were 0% and 2.8%, respectively (p=0.317). Finally, a secondary outcome of 5 year mortality rates within the CABG cohort based on graft strategy was assessed. 5-year mortality rates were 5.4% for the 296 patients treated with bilateral internal mammary artery grafts and 15.2% for the 564 patients treated with single internal mammary artery grafts.

3.13 Conclusion

Early survival rates are comparable in low-risk triple-vessel disease patients revascularized with either therapy. A secondary outcome of this study shows that the graft strategy of using bilateral internal mammary artery compared to a single internal thoracic artery appears to have a medium-term survival benefit; however, further investigation is warranted to evaluate this group as a primary outcome.

3.2 Introduction

Multi-vessel coronary artery disease (MVD) predisposes patients to an increased risk of cardiovascular morbidity and mortality. Therapeutic interventions for MVD include optimal medical management, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). CABG was introduced as a coronary revascularization technique in 1967[1] and initial clinical trials demonstrated a long-term survival advantage associated with surgery among patients with reduced ejection fraction, more complex disease, and diabetes, when compared to conventional medical management[2,3]. However, the development of PCI in 1978[4] prompted the need for more conclusive evidence regarding the long-term outcomes following each respective coronary revascularization. Initial randomized controlled trials (RCTs) compared balloon angioplasty to conventional CABG surgery; however, no definitive conclusions were drawn[5-10]. Modern advancements in PCI, namely bare-metal and drug-eluting stents, motivated several RCTs directly comparing PCI to CABG[11-15]. However, the results from these trials are conflicting and loss to follow-up is a limitation[11-15]. Although CABG may have a long-term survival advantage, PCI presents a potential safe cost-saving alternative thus warranting further comparative evaluation[16].

There have been extensive studies published on comparative outcomes between PCI and CABG patients, but there has been little comparative outcome evidence in completely revascularized patients with low anatomical complexity. The SYNTAX trial reports a non-significant difference in all-cause mortality between completely revascularized and incompletely vascularized triple-vessel disease patients[17]; however, a direct comparison between completely revascularized CABG and PCI patients was not included. Furthermore, although the results from large RCTs have a significant impact on guideline establishment for MVD, the use of a real-world registries is critical in validating the conclusions of controlled trials in clinical settings.

Therefore, the primary objective of this study is to retrospectively compare triple-vessel disease patients with low to intermediate coronary complexity who underwent complete revascularization with either PCI or CABG over a nine-year period at the sole, tertiary cardiac care centre responsible for providing advanced cardiac care for the entire population of Newfoundland and Labrador (NL), the furthest east Canadian province. Within the context of CABG revascularization, bilateral mammary artery grafting represents a common conduit strategy used at our centre. Thus, secondary objectives include determining significant predictors of early and late mortality and determining the effect of conduit strategy (including BIMA) on mortality in surgical patients.

3.3 Patients and Methods

3.31 Patient Population

All patients treated for triple-vessel coronary artery disease in NL between May 1st, 2006 and October 31st, 2015 were screened for inclusion into this retrospective study. De-identified patient data were extracted with the following inclusion criteria: confirmed ≥70% stenosis in all three major coronary artery systems and complete functional revascularization in each affected territory with either CABG or PCI. Complete functional revascularization was defined as an intervention (via stent or graft) in all affected territories. All patients included in this study were reviewed at a multidisciplinary team rounds post initial coronary angiogram. In discussion with Cardiac Surgeons and Interventional Cardiologists, it was deemed that the patients' coronary anatomy was considered of sufficiently "low anatomical complexity" with focal lesions in a coronary artery of each major territory that could be treated via either CABG or PCI. The final decision for revascularization therapy was determined based on several factors including patient preference, patient comorbidities, symptom characteristics, and timing of presentation. Patients with valvular heart disease, critical left main coronary artery disease, proximal lesions, lesions at bifurcations, diffuse disease, and completely occluded vessels and/or incomplete functional re-vascularization were excluded from this cohort. While Syntax score information was not available for patients in this database, the patients were assumed to be equivalent to low-syntax scores due to the exclusion criteria. Patients with complex disease patterns and/or prognostic factors that would make them poor surgical candidates were not included in this study. Local multidisciplinary rounds occur weekly and include discussion about a given patient's indication for either PCI or CABG. Patient's included in this study were presumed to be eligible for both interventions based on definite indications, clinician discussion, and patient preference. Patients excluded from this study are presumed to be of higher Syntax scores, based on the exclusion criteria, and thus in a high-risk category.

3.32 Study Design

In this single-centre retrospective cohort analysis, all patients who met the criteria for this study were analyzed and compared. Data from the prospectively collected Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database, which has been active in NL since 2006, allowed for the opportunity to assess long-term complications and outcomes of each respective intervention, including a complete follow up. APPROACH contains clinical information that is collected by trained professionals through the cardiac catheterization laboratory. Thus, the database captured all patients who presented with clinical symptoms at the cardiac catheterization laboratory, located at the sole tertiary referral centre in the province, due to local practice requiring a catheterization procedure prior to any revascularization operation. Approval from the local human research ethics board (HREB) and institutional review board (RPAC) was obtained prior to patient data extraction and analysis (HREB #2016.347). The primary outcome of this study was in-hospital mortality in the CABG and PCI cohorts, respectively. Secondary outcomes included unmatched and matched short to long term mortality in CABG and PCI cohorts, mortality based on graft utilization, significant predictors of mortality, and descriptive statistics on the study population. All outcome data were available in the APPROACH database and were extracted using keyword searches. APPROACH captures post-operative details in hospital up to thirty days with long-term mortality rates beyond 30 days obtained via a provincial health database. The provincial database is robust and contains health records of all patients in the province, including long-term mortality. Significant predictors of mortality were assessed at 30 days, 1 year, 3 years, and 5 years in the overall patient cohort as well as the unmatched CABG cohort and PCI cohort separately.

3.33 Statistical Analysis

Categorical variables were presented as frequency and percentage. Continuous variables were presented as a mean and standard deviation (SD). Categorical variables and continuous variables were compared using a chi-squared test and a student's t test, respectively. Patients in the CABG population were matched to patients in the PCI population in a 1:1 ratio via propensity score weighting based on the following variables: sex, age, type 2 diabetes, ejection fraction < 50% and renal insufficiency. These variables were determined via clinical judgement.

A match tolerance level of 0.05 was used to match variables in the propensity score model. Cumulative survival was assessed in the matched and unmatched population using the Kaplan-Meier method with factors compared via the log-rank test. Cox regression analysis was used to identify any significant predictors of outcome variables in the overall cohort as well as several of the subgroups. An entry level of $p<0.05$ and a stay level of $p<0.10$ was used for all independent covariates entered into the model. Hypothesis tests were evaluated using the alpha=0.05 level of significance (two-tailed), with $p<0.05$ considered to be significant. All statistical analyses were done using the ©IBM SPSS 23 statistical software package.

3.4 Results

3.41 Subjects

Of the 26,697 patients screened, 6.0% (n=1,604) of patients met the inclusion criteria for this study, with 1559 in the CABG cohort and 45 in the PCI cohort (*Figure 1)*. The CABG cohort had a significantly higher number of moderate urgency cases ($p<0.001$). The PCI cohort had a significantly higher number of extreme cases (i.e. either elective or emergent; $p<0.001$ and $p=0.007$ respectively). Furthermore, the PCI cohort had a significantly higher number of cases with previous coronary revascularization history through stent placement. The baseline demographic characteristics of the unmatched study population at baseline are shown in *Table 1*. Following the propensity score match model, 36 matched cases remained in each cohort. The majority of baseline characteristics did not differ between the two cohorts following the match. However, there were a higher number of cases with previous coronary revascularization history through stent placement in the PCI cohort. Baseline demographic characteristics of the matched population are shown in *Table 2.* Operative details and statistics are shown in *Table 3*.

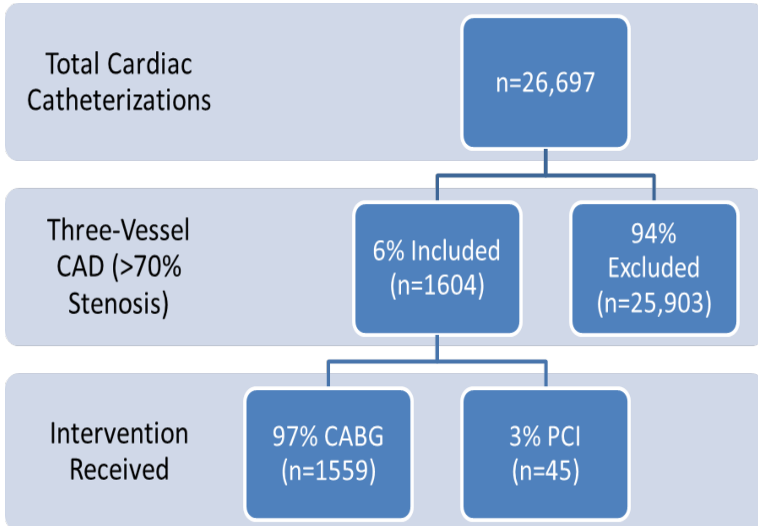

Figure 1: Patient selection. Total cardiac catheterizations reflect the total number of patients assessed at the cardiac cath lab from May 2006 to October 2015. From these patients, 6% of patients met the inclusion criteria for this particular study. Morover, 97% of patients in this study were revascularized with CABG, while 3% were revascularized with multivessel PCI.

Table 1

	CABG (n=1559)	PCI (n=45)	Significance
Age	64.01 *(9.0)*	63.26 *(11.5)*	NS
Male	1007 *(81%)*	36 (80%)	NS
BMI	29.68	30.17	NS
Obesity	658 (42%)	23 (51%)	NS
Current Smokers	403 (26%)	9 (20%)	NS
Priority			
Emergency	24 (1.5%)	4 (8.9%)	p=0.007
Urgent	1437 (92.2%)	31 (68.9%)	p<0.001
Emergency Salvage	1 (0.1%)	1 (2.2%)	p=0.0550
Elective (Low Risk)	97 (6.2%)	9 (20%)	p<0.001
Previous Revascularization			
PCI	140 (9%)	10 (22%)	p=0.003
CABG	0	0	/
Type 2 Diabetes	516 (33%)	16 (36%)	NS
Family History	1002 (64%)	27 (60%)	NS
Hypertension	1176 (76%)	31 (69%)	NS
Heart Failure	83 (5%)	2 (4%)	NS
Renal Insufficiency	103 (7%)	2 (4%)	NS
Peripheral Vascular Disease	123 (8%)	2 (4%)	NS
Cerebrovascular Disease	128 (8%)	4 (9%)	NS
Pulmonary Disease	270 (17%)	7 (15.6%)	NS
Liver Disease	6 (0.4%)	0	NS
LVEF < 50%	443 (28%)	16 (36%)	NS

Table 1. Demographic characteristics of each treatment group in the unmatched population. Continuous variables are presented as mean (standard deviation) and categorical variables are presented as frequency (percentage). BMI = Body Mass Index, LVEF = Left Ventricular Ejection Fraction.

<u>**Table 2**</u>

	CABG (n=36)	PCI (n=36)	Significance
Age	64.53	62.69	NS
Male	32	29	NS
BMI	29.63	29.7	NS
Obesity	15	19	NS
Current Smokers	10	7	NS
Priority			
Emergency	1	2	NS
Urgent	31	26	NS
Emergency Salvage	0	0	NS
Elective (Low Risk)	4	8	NS
Previous Revascularization			
PCI	18	9	p=0.029
CABG	0	0	NS
Family History	24	21	NS
Type 2 Diabetes	14	14	NS
Hypertension	29	27	NS
Heart Failure	3	2	NS
Renal Insufficiency	3	2	NS
Peripheral Vascular Disease	12	2	NS
Cerebrovascular Disease	5	4	NS
Pulmonary Disease	5	5	NS
Liver Disease	0	0	NS
LVEF < 50%	15	14	NS

Table 2. Demographic characteristics of each treatment group in the unmatched population. Continuous variables are presented as mean (standard deviation) and categorical variables are presented as frequency (percentage). BMI = Body Mass Index, LVEF = Left Ventricular Ejection Fraction.

3.42 Mortality

There was a total mortality rate of 9.5% (n=153) during the study timeline in the total patient population. The primary outcome of in-hospital morality rates was 1.2% (n=19) and 2.2% (n=2) in the unmatched CABG cohort and PCI cohort, respectively (p=0.533). The in-hospital mortality rates for the CABG cohort and PCI cohorts in the matched analysis were 0% and 2.8%, respectively (p=0.317). The 1-year mortality rates for the CABG and PCI cohort in the matched analysis were 2.7% (n=1 of 34) and 9.7% (n=3 of 31), respectively (p=0.266). The 3-year mortality rates for the CABG and PCI cohort in the matched analysis were 6.9% (n=2 of 29) and 16.7% (n=3 of 18), respectively (p=0.283). Finally, the 5-year mortality rates for the CABG and PCI cohort in the matched analysis were 12.0% (n=3 of 25) and 37.5% (n=3 of 8), respectively (0.075). The mortality rates of both cohorts in the unmatched and matched comparison are shown in *Table 4.* Of the 1,604 patients enrolled in this study, 90.5% (n=1,451) survived until censorship with a median follow up of 5.4 years. Kaplan-Meier survival curves comparing CABG and PCI survival for the unmatched population are shown in *Figure 2*, while the survival curves for the matched population are shown in *Figure 3*.

3.43 Cox Regression Analysis

In the overall population, poor ejection fraction (<50%) was a significant predictor of mortality at all stages of follow up (p=0.046, p=0.008, p<0.001, and p<0.001 respectively). Renal insufficiency, defined as presence of CKD or an event that requirement medical management and/or dialysis, was a significant predictor at 1 year, 3 years, and 5 years post intervention (p=0.001, p<0.001, and p<0.001, respectively). Finally, age and year of procedure were significant predictors of mortality at 3 years (p=0.030 and p=0.011, respectively) and 5 years (p=0.004 and p<0.001, respectively). Within the CABG and PCI cohort stratifications, there were no significant predictors of mortality at any length of follow up in the PCI cohort. In the CABG cohort, there were no predictors at 30 days; however, age, poor ejection fraction, and renal insufficiency were significant predictors of mortality at 1 year (p=0.003, p=0.001, and p<0.001 respectively) and at 3 years (p=0.006, p<0.001, and p<0.001 respectively) whilst at 5 years the significant predictors of mortality were age, year of procedure, poor ejection fraction, and renal insufficiency (p=0.001, p<0.001, p<0.001, and p<0.001 respectively).

Table 3

PCI (n=45)		CABG (n=1559)	
Stent Type		Off-pump	135 (9%)
BMS	9 (20%)	Average Pump Time*	119.8
DES	42 (93%)	Thoracic Artery Usage	1512 (97%)
Balloon	43 (96%)	Bilateral Artery Usage	440 (28%)
Access Site		IABP	45 (3%)
Left Femoral	6 (13%)	Complications	782 (50%)
Left Radial	1 (2%)	Returned to OR	69 (4%)
Right Femoral	21 (47%)	Cardiac Complications	5 (0.3%)
Right Radial	17 (38%)	Infection	138 (9%)
Second Access Site (PCI)	5 (11%)	Neuro Complication	198 (13%)
Average Size	2.7 (0.36)	Renal Complication	149 (10%)
Average Length	14.4 (2.9)	Vascular Complication	14 (0.9%)
Average Pressure	15.9 (3.6)	Cardiac Arrest	28 (2%)
Average Duration	19.6 (8.9)	Perioperative MI	5 (0.3%)
Total Stents	441	Cardiac Tamponade	3 (0.2%)
No. BMS	38 (9%)	Atrial Fibrillation	437 (28%)
No. DES	202 (46%)	New Q wave	2 (0.1%)
No. Aspiration Catheters	3 (0.6%)	GI Complications	54 (4%)
No. Balloon	198 (45%)	Renal Insufficiency	121 (8%)
Average Stents	9.8 (5.5)		

Table 3: Operative details and complications. BMS = Bare metal stent; DES = Drug eluting stent; IABP = Intra-aortic balloon pumpl; MI = Myocardial infarction; GI = gastrointestinal complications. *Average pump time in minutes.

Table 4

	UNMATCHED POPULATION		MATCHED POPULATION	
	CABG	PCI	CABG	PCI
30 Days	19/1559 (1.2%)	2/45 (2.2%)	0	1 (2.8%)
1 Year	38/1409 (2.7%)	3/35 (8.6%)	1/34 (2.9%)	3/31 (9.7%)
3 Years	73/1138 (6.4%)	3/21 (14.3%)	2/29 (6.9%)	3/18 (16.7%)
5 Years	112/890 (12.6%)	3/10 (30%)	3/25 (12.0%)	3/8 (37.5%)

Table 4: Mortality data for the unmatched and matched populations. Follow up is measures from the time of procedure. The fraction of people represent the patients with each respective level of follow up.

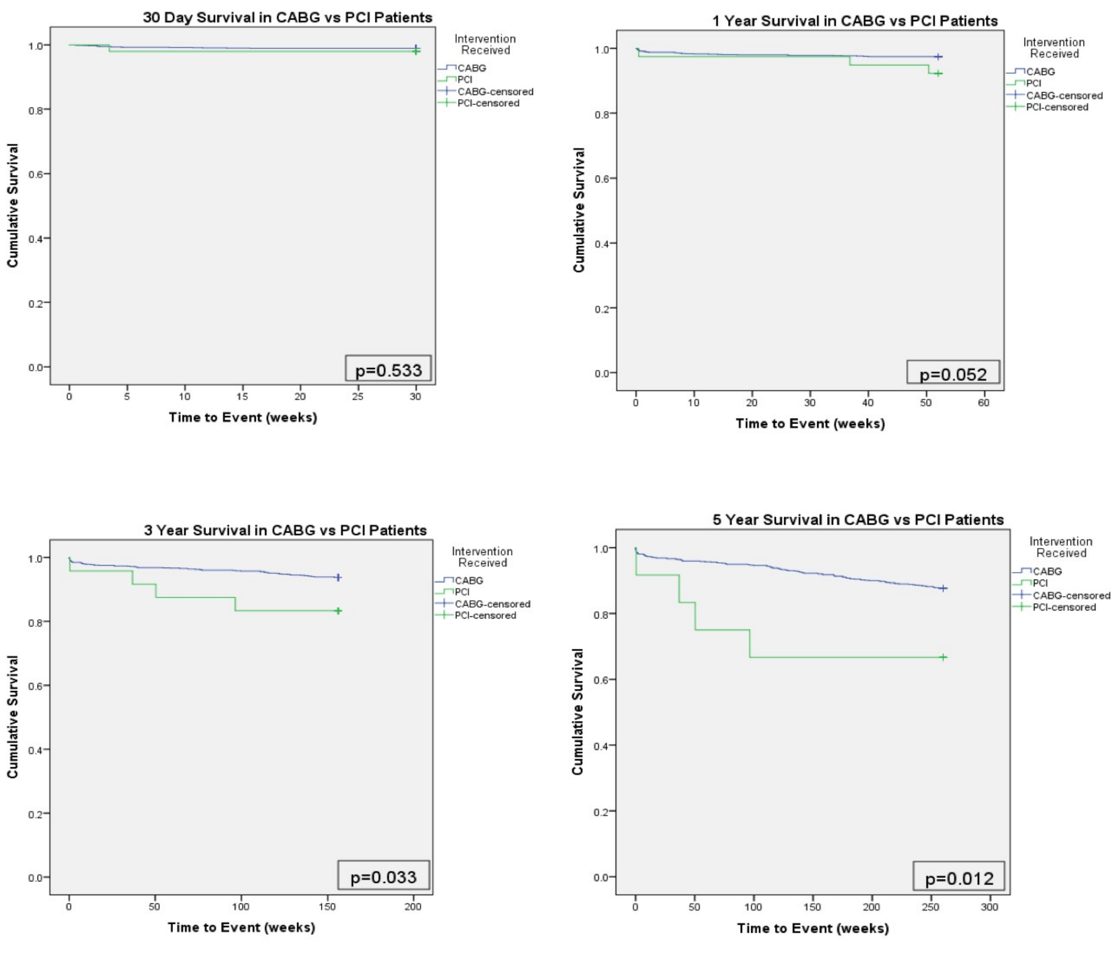

Figure 2: Survival in unmatched patient cohort. Kaplan-Meier Survival curves for follow up at 30 days, 1 year, 3 years, and 5 years. Median level of follow up was 5.4 years in the study population.

3.44 Conduit Strategy Stratification

A total of 1,512 patients (97%) received an internal mammary artery graft, 440 (29%) of which were bilateral internal mammary grafts. Furthermore, 47 patients had either missing graft utilization data or were treated with no internal mammary artery graft. Operative details for the CABG cohort are presented in Table 3. Comparison of the patients with Bilateral Internal Mammary Grafts (BIMA) versus patients with a Single Internal Mammary Graft (SIMA) revealed a significantly younger population in the BIMA group (average age = 59.6 vs 65.8, respectively; $p<0.001$). Moreover, the SIMA group had a significantly higher proportion of patients with Type 2 Diabetes ($p<0.001$), renal insufficiency ($p=0.001$), and poor LVEF ($p<0.001$). Mortality rates in the BIMA group at 30 days, 1 year, 3 years, and 5 years were 0.5%, 0.7%, 2.2%, and 5.4% respectively. Mortality rates in the SIMA group at 30 days, 1 year, 3 years, and 5 years were 1.4%, 3.1%, 7.8%, 15.2% respectively.

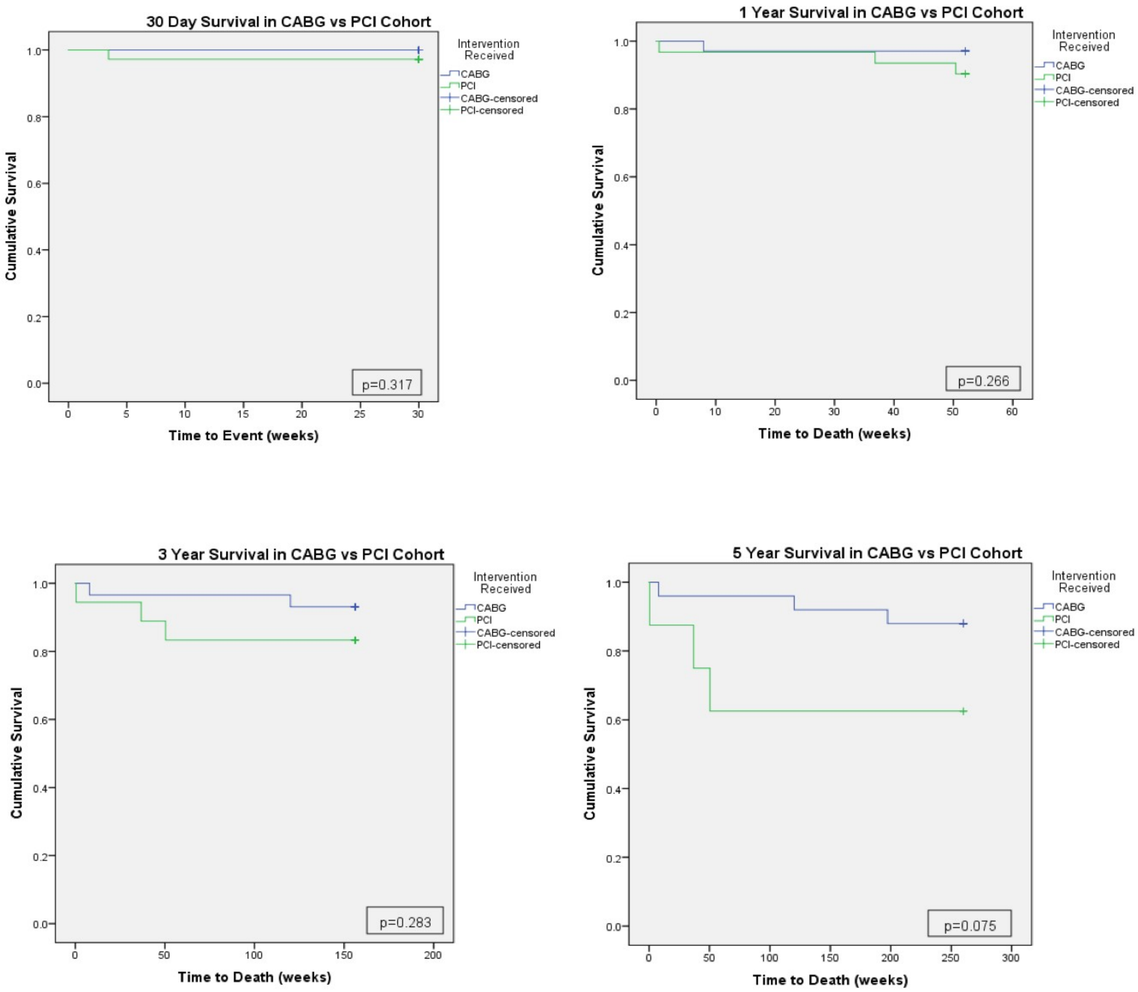

Figure3: Survival in matched cohort. Patients in the PCI cohort were matched to patients in the CABG cohort based on 5 prognostic factors, yielding n=36 patients in each matched cohort. Kaplan-Meier Survival curves for follow up at 30 days, 1 year, 3 years, and 5 years are shown here.

3.5 Discussion

Although many studies have evaluated outcomes in coronary revascularization[5-15], this study presents short and long-term outcomes following complete coronary revascularization in triple-vessel disease patients with low anatomical complexity. In this population, prior to revascularization it was felt by cardiac surgeons and interventional cardiologists that PCI and CABG would both provide full revascularization with equivalent mortality outcomes. The data collected over a retrospective nine-year period indicated that surgical revascularization is the dominant intervention chosen for triple-vessel presentation in NL. However, recent years have showcased an increasing number of triple-vessel PCI cases. Firstly, the results of this study show that there were no significant differences in short- or long-term mortality between the CABG and PCI cohorts, after accounting for important prognostic variables with a propensity score. Secondly, there are increasing numbers of PCI cases at our medium volume centre for patients with triple-vessel disease. Thirdly, poor ejection fraction, renal insufficiency, and age at time of procedure were significant predictors of long-term mortality. Finally, there is a suggestive trend towards a long-term survival advantage in CABG patients that were treated with bilateral mammary artery grafts as opposed to a single internal mammary graft that warrants further investigation.

Our results are consistent with several large randomized controlled trials, including the clinical SYNTAX, MASS II, and ERACI II Trials. The SYNTAX trial included patients with three vessel disease and/or Left Main Coronary Artery Disease demonstrated significantly higher rates of Major Adverse Cardiac or Cerebrovascular Events (MACCE) in the PCI cohort when compared to the CABG cohort. In comparison to our results, the SYNTAX trial had comparable rates of mortality in the CABG cohort (3.5% vs 2.7%), but lower rates of mortality in the PCI cohort (4.4% vs 8.6%) at one year[19]. At long-term follow up, comparable rates in the CABG cohort remained consistent (11.4% vs 12.6%) and mortality rates in the PCI cohort were significantly lower (13.9% vs 30%)[20]. The ERACI II trial concluded there was no significant difference in survival in multivessel disease patients treated with either PCI or CABG revascularization strategies. Initial outcome data from the ERACI II trial revealed a higher mortality rate in the CABG cohort compared to our results (5.7% vs 1.2%) and lower mortality rate in the PCI cohort compared to our results (0.9% vs 2.2%)[21]. A long-term follow up of the ERACI study cohort at 5 years showed a similar mortality rate in CABG patients compared to our results (11.5% vs 12.6%) and a significantly lower mortality rate in the PCI cohort compared to our results (7.1% vs 30%)[22]. Finally, the MASS II randomized multi-vessel disease patients to either CABG, PCI, or medical management and determined that there was no significant difference in all-cause mortality between any treatment modality. At 5 years of follow up, the MASS II trial had a similar mortality rate in the CABG cohort compared to our results (12.8% vs 12.6%) and a significantly lower mortality rate in the PCI cohort compared to our results (15.5% vs 30%)[13].

The population assessed in this study were discussed at multidisciplinary rounds and are assumed to be of low SYNTAX score. Exclusion criteria for this study were designed to avoid patients with the higher disease complexities that are seen in typical high SYNTAX score patients. Studies have examined comparative outcomes in low-syntax score patients and the SYNTAX trial demonstrated that CABG shows improved outcomes over PCI in patients with intermediate/high SYNTAX scores, while there is no significant survival advantage to either revascularization modality in patients with low syntax scores. Head et al. completed a report on the three-vessel disease population of the SYNTAX Trial[18] and evaluated outcomes in low syntax score patients. The 5-year mortality rate in their population was 9.3% in the CABG cohort and 10.2% in the PCI cohort, with no significant difference in all-cause mortality[20]. Our results had a higher mortality rate in both cohorts (12.6% and 30%, respectively).

Several studies emphasize the importance of complete revascularization in patients undergoing therapeutic revascularization via PCI and CABG[17,18]. Garcia et al. meta-analyzed data from 35 RCTs including approximately ninety thousand patients who were separated into those who were completely revascularized versus incompletely revascularized and a 30% reduction in overall mortality was shown with complete revascularization versus incomplete revascularization[17]. Complete revascularization in their study was achieved more commonly in the CABG group versus the PCI group; however, a significantly higher mortality rate was shown in the incompletely revascularized patients in both the CABG and PCI groups (RR: 0.70, $p<0.001$ and RR: 0.72, $p<0.001$, respectively). Head et al. examined subgroup data from the SYNTAX trial and also observed a higher rate of incomplete revascularization in the PCI cohort compared to the CABG cohort (43.3% versus 36.8%)[18]. However, in this study there was evidence of a higher rate of MACCE associated with the incompletely revascularized PCI patients (76.2% versus 66.5%, $p<0.001$), but no such evidence was found in the CABG cohort[18]. Furthermore, when mortality was assessed independently as a secondary outcome, no evidence was found in favor of complete revascularization.

This study has several limitations. Firstly, the propensity score model cannot account for all selection bias in the treatment modality. At this local centre, ambiguous patients are presented at multi-disciplinary rounds for consultation on a treatment modality. Thus, there are a multitude of factors that are discussed at rounds and not all of those can be accounted for through the propensity score match model, including patient preference. This is certainly a limitation because there is no data collected on an objective measure, such as the SYNTAX score, that would determine these patients to be low risk. Secondly, although the APPROACH database is an excellent resource for collecting local outcome data, many of the variables from the earlier stages of the active database contained missing values and therefore could not be assessed properly. Thirdly, the regression analysis is significantly limited with regards to the overall population because it is driven by the CABG cohort. Finally, this study timeline encompasses many technological and procedural advancements in both CABG and PCI operations that may bias the outcomes assessed in this study. Further evaluation is warranted to account for the increasing PCI triple-vessel disease cases in recent years to fully understand the comparative efficacy relative to CABG therapy.

3.6 Conclusion

Early survival rates are comparable in low-risk triple-vessel disease patients revascularized with either therapy. A secondary outcome of this study shows that the graft strategy of using bilateral internal mammary artery compared to a single internal thoracic artery may have a medium-term benefit.

3.7 References

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Chapter 4: Summary & Synthesis

Chapter 4: Summary & Synthesis

4.1 Summary

Coronary artery disease continues to have significant demand on the modern healthcare system as our population ages. According to data from the Canadian Institute for Health Information, Acute Myocardial Infarction (AMI), a common and potentially lethal progression of CAD, is the third most common cause for inpatient hospitalization behind Chronic Obstructive Pulmonary Disease (COPD) exacerbation and childbirth (Canadian Institute for Health Information, 2019). One of the main goals of this project was to evaluate outcomes related to secondary prevention following confirmed CAD. The study design was created accordingly to offer primary literature on the efficacy of our current management and to potentially contribute to limiting the number of inpatient hospitalizations due to complications from CAD. Reducing the risk of an AMI would presumably improve quality of life of people affected by CAD. Although the published literature is vast on this CAD secondary prevention strategies, this study offers outcomes of our local management practices and how they compare with larger centres across the world.

There are many strategies to approaching management of patients with CAD, including that of coronary revascularization, which has been discussed at length. The decision of how to optimally manage a patient with CAD is multifactorial and depends on anatomical complexity of the lesion, patient comorbidities, clinical severity of the disease, and patient preference. This project evaluates two different manifestations of CAD and outlines how each are specifically managed at a medium-volume cardiac centre in Newfoundland & Labrador, Canada.

In the first study, isolated LMCA patients are evaluated and compared to larger centres. Historically, CABG tends to be the dominant treatment modality in this population, which is reflected in our local practice as well. However, recent years have shown a slight increase in the number of isolated LMCA cases that are being managed percutaneously. The second study offers a detailed comparison of complete revascularization, through either PCI or CABG, in patients that are of a low-risk category of three-vessel disease. Similar to the first study, CABG tends to be the most common approach to these patients; however, multivessel PCI is becoming a more common option in our local practice with good outcomes. This also reflects global practice where the operator experience with percutaneous stenting continues to evolve. Although isolated LMCA disease and MVD are two separate entities of CAD with differing guidelines on surgical vs percutaneous management, there are similarities in how we can evaluate the efficacy of our management of these sub-categorizations of CAD. The APPROACH database offers an excellent opportunity to complete this goal and is the foundation of this project.

The original design of this project was to evaluate mortality outcomes in patients with low-risk triple vessel disease only. However, the course of this project offered the opportunity to additionally evaluate outcomes in the isolated LMCA population. Thus, the retrospective cohort design was the same in both studies; however, the MVD study revealed a much larger cohort of patients to work with. As such, a more detailed comparison was possible between revascularization strategies in the MVD population. As more patients are undergoing PCI now than the early stages of this database, more data becomes available for robust comparison. Nonetheless, the CABG cohort comprised the dominant strategy in both studies and we were able to assess some outcomes within this cohort based on differences in surgical strategy.

Notably, we were able to assess the BIMA vs SIMA graft strategy with regards to early and long-term mortality. The results from this project show that our centre is comfortably using the BIMA strategy in both isolated LMCA and MVD populations, while producing excellent outcomes with respect to post-operative mortality in the short and long term. In fact, the results from this study suggest that further analysis of the BIMA grafting strategy is warranted. There are excellent numbers in the APPROACH database to create a follow-up retrospective cohort study, with a similar design to this one, that will produce meaningful results for our patient population.

The two research studies completed through this project also reflect the operator experience for both our cardiovascular surgeons and interventional cardiologists. This project allowed us to review our intra-operative and post-operative outcomes and complications from a quality assurance point of view. We were able to evaluate intra-procedural variables, such as infection, stroke, graft failure rates, etc., although not as the primary focus of this project. The quality assurance aspect of this project is valuable in evaluating our management strategies and clinical decisions at this centre, especially given that fact that the entire population of NL is managed at this centre.

4.2 Limitations

This retrospective cohort study is designed to evaluate revascularization strategies in two separate sub-categories of patients with CAD. The APPROACH database has the benefit of prospectively collecting and coding clinical data relevant to our research question. However, this project design has limitations.

Firstly, APPROACH does not contain SYNTAX scores for patients, which take into account the precise anatomical complexity of a given patient's lesion on a standardizing scoring system. Although these patients are reviewed on a case-by-case basis at interdisciplinary cardiovascular team rounds, there is no formal scoring system utilized for the patient population. Despite not obtaining a standardized and objective risk assessment for this population, they are required to be of a low complexity of disease by design in order to be included in the cohort. Secondly, the retrospective study design of this project introduces an inherent selection bias and information bias when collecting and analyzing data. Patients are selected for this study based on an outcome they have already experienced. Propensity score matching and logistical regression methods are used to address these biases; however, a prospective randomized controlled trial would be the best option to minimize these biases. Thirdly, the data analyzed in this study over a nine-year span is subject to changes in the operator experience over that same time frame. The literature has evolved significantly over the years and that has been reflected in updated clinical practice (Appendix A). Perhaps the most obvious example of this evolution is demonstrated in the changes in numbers of patients receiving PCI, especially in the MVD population. Despite these limitations, there remains value to publishing this research.

4.3 Advantages

The project has offered the opportunity to conduct a detailed analysis of patient outcomes in both cardiovascular surgery and interventional cardiology. Moreover, it has offered insight into the level of detail and effort required to maintain a clinical database. The APPROACH database has been collected prospectively since 2006 and has provided an excellent opportunity to evaluate outcomes in specific patient populations, as discussed at length in this project. Additionally, it has created an outlook on the challenges of obtaining clinical data for research purposes. Robust inclusion and exclusion criteria were important factors in answering our research question. The primary benefit of the APPROACH database was allowing us to select a specific patient population to analyze outcomes in, which ultimately lead to being able to provide a benchmark for medium volume centres similar to ours. Clinical databases similar to APPROACH are excellent for providing real-world information on patients that are being treated in our medical system. Evaluating outcomes as a whole population provided the opportunity to assess where our local management practices align next to larger-scale guidelines and global practice. Despite the inherent selection bias with operating a retrospective cohort study, the upside was that it allows evaluation of what has been done and where local practice is trending towards. The results of this project have demonstrated several conclusions about CAD management.

Firstly, the results showed that CABG represented the most common form of revascularization for isolated LMCA disease in this single centre with excellent short and midterm morbidity and mortality. We believe that the results of this first study can be expanded and used as a benchmark for other small-moderate volume centres. Furthermore, the BIMA grafting strategy can be effectively used with excellent outcomes, especially in patients younger than 65. Secondly, this project evaluated if there were significantly different mortality rates in low-risk triple vessel disease patients treated by complete revascularization via either CABG or PCI. The results of the second study showed that there were no significant differences in mortality rates for this subset of patients receiving either CABG or PCI as a revascularization option. However, there have been fewer patients receiving PCI (n=45) as an intervention for complete revascularization of MVD than there are patients receiving CABG for the same indication (n=1559). The APPROACH database also revealed that the number of PCI patients are growing for this sub-population, reflecting a global trend in practice. Thus, future evaluation is warranted as the changes in clinical practice guidelines continue. Ultimately, we conclude that there was certainly a trend towards better long-term survival in the CABG cohort of patients; however, the number of patients receiving PCI continued to grow and it has become a viable option for the revascularization of low-risk triple vessel disease. Our morbidity and mortality statistics were on par with other larger centres published in the literature.

4.4 Lessons Learned

This project has yielded insight into the complexities of developing sound research methodology. The realities of a prospectively collected database include difficulties in obtaining clean data representing the precise research question we have sought out to answer. Firstly, the APPROACH database started as a pilot project in 2006 (in NL) and has evolved in collection standards since that time. Several aspects of the database tend to be clinician-dependent and as a result, there were often key data-points missing. In this scenario, a more detailed chart review is necessary to obtain further information. In the context of this project, a significant amount of time was spent cleaning up the data provided to us from our initial capture. Key-word searches were able to identify the patients who were eligible for this study; however, at times a more detailed chart review within the APPROACH database was necessary to obtain missing data points. This was a process that consumed much of the data-collection phase of this study. The PCI cohort in particular was difficult to identify because of the nature of how the data was stored. Thus, for these patients they had to be identified by complete revascularization in all three territories and then retrospectively identified by their cardiac catheterization date and accompanying information. This was opposed to the CABG cohort that could be identified by having triple vessel disease on cardiac catheterization and then followed forward until they were chosen for CABG. Nonetheless, this project has identified an important need to maintain clean clinical databases that can be used for the purposes of identifying gaps in current literature. The journey of cleaning up the data for this project presented great insights into managing and researching with a clinical registry. The advice I can offer to future students undertaking a similar project is a clinical registry may not always have the exact information you are searching for in order to answer a given research question; however, working with and cleaning up what you have is a vital component to successfully completing a research project.

4.5 Conclusion

This project was completed in partial requirement for the M.Sc. program in Clinical Epidemiology, within the Faculty of Medicine at Memorial University of NL. Throughout the course of this research, I have gained the opportunity to survey and summarize literature, design a retrospective cohort study, and complete data collection and analysis of clinical information. Furthermore, I have been able to develop the competencies to write this thesis throughout the course of the Clinical Epidemiology M.Sc. program. This project has offered its challenges; however, the conclusions drawn may provide input during interdisciplinary rounds and hopefully offer a benchmark to small-moderate volume centres for their own clinical practice.

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Appendices

Appendix A: Literature Summary Table

The following is a summary of the major RCT studies published regarding MVD treatment. All cells in green indicate a significant difference in favor of CABG (unless marked by *, which means a significant advantage for PCI), all cells in red indicate a non-significant difference, and all cells in yellow indicate that particular outcome wasn't measured.

Trial Type	Year	MVD?	Primary Outcome	Primary sig?	angina	MI	stoke	repeat	all-cause	cardiac
RCT (Balloon PCI vs CABG)	1993	yes	death, MI, repeat,or angina	NS	p<0.02	NS	N/A	p<0.001	NS	N/A
RCT (Balloon PCI vs CABG)	1993	yes	5year death or MI	NS	p<0.001	N/A	NS	N/A	NS	NS
RCT (Balloon PCI vs CABG)	1994	yes	death, MI, large ischemic defect	NS	N/A	NS	N/A	p<0.001	NS	N/A
RCT (Balloon PCI vs CABG)	1994	yes	freedom from angina at 12 months	NS	NS	NS	N/A	p<0.001	N/A	N/A
RCT (Balloon PCI vs CABG)	1997	yes	All-cause death	NS	N/A	p<0.001	N/A	N/A	NS	p=0.022

Trial Type	Year	MVD?	Primary Outcome	Primary sig?	angina	MI	stoke	repeat	all-cause	cardiac
RCT (BMS PCI vs CABG)	2001	yes	MACE (death, stroke, transient ischmic attack, reversible ischemic defects, Non-fatal MI, repeat revascularization)	RR=2.14	RR=1	RR=1.29	N/A	RR=5.52	RR=0.89	N/A
RCT (BMS PCI vs CABG)	2002	yes	Repeat Revascularization	p<0.0001	p<0.0001*	N/A	N/A	N/A	p=0.01	N/A
RCT (BMS PCI vs CABG)	2010	yes	death, MI, repeat revascularization	p=0.0026	NS	p=0.016	NS	p=0.021	NS	p=0.019
RCT (BMS PCI vs CABG)	2001	yes	Death, MI, or stroke	p=0.002	p=0.01	N/A	N/A	p<0.001	p<0.017*	N/A

Trial Type	Year	MVD?	Primary Outcome	Primary sig?	angina	MI	stoke	repeat	all-cause	cardiac
RCT (DES PCI vs CABG)	2009	yes	MACCE (death, stroke, MI, repeat revascularization)	p=0.002	N/A	NS	p=0.003*	p<0.001	NS	p=0.05
RCT (DES PCI vs CABG)	2012	yes	MACE (death, MI, or stroke)	p=0.005	N/A	p<0.001	p=0.03	p<0.001	p=0.049	NS
RCT (DES PCI vs CABG)	2012	yes	death or MI	NS	N/A	0.0275	N/A	N/A	p=0.0106	N/A
RCT (DES PCI vs CABG)	2015	yes	death, MI, or repeat revascularization	p=0.04	N/A	NS	NS	p=0.003	NS	NS

Primary Sig? = Was the primary outcome significant at alpha = 0.05	MAC(C)E = Major adverse Cardiac (or Cerebrovascular) Events
MI = Myocardial Infarction	NS = Not Significant
Repeat = Repeat Revascularization	N/A = Outcome Not Assessed
All-cause = Mortality from all causes	Cardiac = mortality from cardiac causes

Appendix B: Ethics Approval

NEWFOUNDLAND AND LABRADOR HREB HEALTH RESEARCH ETHICS BOARD

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

January 27, 2017

11 Nautilus Street
St. John's, NL
A1B 0G5

Dear Mr. Vasanthan:

Researcher Portal File # 20171389
Reference # 2016.347

RE: "Single-Center Long Term Comparison of Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting"

Your application received a delegated review by a sub-committee of the Health Research Ethics Board (HREB). ***Full approval*** of this research study is granted for one year effective **January 27, 2017**.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- List of Variables, approved
- Letter of request, approved

MARK THE DATE

This approval will lapse on January 27, 2018 . It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event form.

If you do not return the completed Ethics Renewal form prior to date of renewal:

- ***You will no longer have ethics approval***
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

③ *Lapse in ethics approval **may result in interruption or termination of funding***

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; **to Research Grant and Contract Services** should your research depend on funding administered through that office.

Modifications of the protocol/consent are not permitted without prior approval from the HREB. **Implementing changes without HREB approval may result in your ethics approval being revoked, meaning your research must stop**. Request for modification to the protocol/consent must be outlined on an amendment form (available on the Researcher Portal website as an Event form) and submitted to the HREB for review.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval of the HREB.

We wish you every success with your study.

Sincerely,

[redacted]

Ms. Patricia Grainger (Chair, Non-Clinical Trials Health Research Ethics Board)
Dr. Joy Maddigan (Vice-Chair, Non-Clinical Trials Health Research Ethics Board)

CC: Supervisor