Surgical, Pharmacological, and Patient Factors Affecting Early and or Late Outcomes Following Coronary Artery Bypass Grafting Surgery

Saswata Deb, MD, BSc Hon

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Health Policy Management and Evaluation
University of Toronto

© Copyright by Saswata Deb, 2018
Abstract

Coronary heart disease continues to be one of the leading causes of death globally. In patients with advanced complex coronary disease, coronary artery bypass grafting surgery (CABG) is considered to be the standard of care. In this thesis, we conducted three studies examining surgical, pharmacological and/or patient factors that can potentially improve patient outcomes after CABG.

The first study was an international multi-centre randomize control trial (mRCT) with a 2x2-factorial design (Surgical arm: No-Touch (NT) saphenous vein graft (SVG) harvesting versus conventional (CON) and Pharmacological arm: Fish-oil supplementation versus placebo). We found that NT was not statistically superior to CON for 1-year angiographic and clinical outcomes; however, all major outcomes trended towards favoring the use of the NT technique encouraging longer follow-up and larger studies. Furthermore, 1-year angiographic and clinical outcomes were similar between fish-oils and placebo.

The second study was a secondary analysis of another mRCT investigating the use of radial arteries versus SVG in diabetics; we determined that radial artery patency was superior to
SVG beyond 5-years after CABG in diabetics and that radials should be used to bypass high grade lesions.

Ethnicity is an important patient factor affecting cardiovascular outcomes. The third study was a large propensity matched administrative database study investigating whether South Asians (SA) had poorer outcomes compared to the General Population (GP) after CABG in Ontario; we determined that SA have superior outcomes including event-free late survival compared to GP. These findings, contrary to the previous notion that SA do worse after CABG, will hopefully empower physicians when making recommendations for cardiac procedures.

In conclusion, through the above studies, we determined that early patency and clinical outcomes were not statistically different between NT and CON, however, longer and larger studies are warranted. Fish-oils supplementation was not beneficial in improving CABG outcomes. In diabetics, we recommend the use of radial arteries over SVG, especially for high grade stenotic targets. Finally, being a SA seems to be a protective patient factor after CABG and therefore physicians should not be reluctant to recommend CABG to this ethnic group if the decision otherwise is deemed appropriate.
Acknowledgements

Isaac Newton said, ‘If I have seen a little further, it is by standing on the shoulder of giants.’ I am humbled and fortunate to have stood on the shoulders of Dr. Stephen Fremes, who has not only been a phenomenal supervisor, but also an amazing mentor for the past 14 years. His support, guidance, and mentorship both professionally and personally along with his unwavering commitment to excellence are reasons I am eternally grateful. He is someone I aspire to become.

I am thankful to Drs. Jack Tu, Dennis Ko, and David Mazer, for their guidance in the formulation of this thesis, helping me to navigate through the Institute of Clinical Evaluative Sciences, and their invaluable input in ensuring that each study is performed with scientific rigor.

I am thankful to Drs. Alex Kiss, Peter Austin, and George Tomlinson for their guidance in statistics and data analysis.

I am thankful to Drs. Rob Fowler, Sharon Dell, Rhonda Cockerill, and all the faculty and staff at the Institute of Health Policy Management and Evaluation for providing the insightful courses in addition to the support required to complete this program.

I am thankful to the Institute of Clinical and Evaluative Sciences and the Population Health Research Institute for providing the resources necessary to complete the studies. I also thank the Vanier Committee at the Canadian Institute of Health Research for giving me the prestigious Vanier Scholarship and also for the funding provided by the Surgeon Scientist Program.
Thank you to all the cardiac surgeons, cardiologists and research staff at Sunnybrook Health Sciences Centre along with all the centres that were involved in our multi-centre trials.

Thank you to all the office administrative staff at Sunnybrook that made completion of the administrative requirements very smooth.

Lastly, I am eternally grateful and forever thankful to my family. During my PhD, I lost my best friend, my Father (Mr. Bipulananda Deb), whose dream was one day to see this. I am forever indebted to my mother (Mrs. Sikha Deb) who stood strongly and encouraged the best of us during the most difficult times. My parents inspired humility, perseverance and dedication to excellence through hard work. I am very thankful to my sister (Ms. Saswati Deb) for her sharp thought process and in many times, being the voice of reason. Finally, I am grateful to my wife (Mrs. Amrita Mukherjee Deb) for her patience, support and unconditional love. I dedicate this thesis to my late father and my family.
Table of Contents

Acknowledgements ................................................................................................................. iv
List of Tables .............................................................................................................................. viii
List of Figures ............................................................................................................................ ix
Glossary of Commonly Used Abbreviations .............................................................................. xi

Chapter 1 .................................................................................................................................. 1

1.1 - History of Coronary Artery Disease and Myocardial Revascularization ................................................. 2
1.2 – Surgical Factors ........................................................................................................ 8
1.3 – Pharmacological Factors ..................................................................................... 33
1.4 – Patient Factors ........................................................................................................ 41
1.5 – Thesis Objective, Overall Study Objectives and Hypotheses ............................................. 47
1.6 – Chapter Preview ..................................................................................................... 49

Chapter 2 .................................................................................................................................. 51
SUrgical and Pharmacological novel intERventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting surgery: An International Multi-centre Randomized Controlled Clinical Trial ............................................................................................................................... 51

2.1 Abstract ............................................................................................................................ 52
2.2-Background ................................................................................................................... 54
2.3-Methods ........................................................................................................................... 55
2.4-Results ............................................................................................................................ 63
2.5-Discussion ...................................................................................................................... 69
2.6-Conclusion ...................................................................................................................... 73
2.7-Tables and Figures ..................................................................................................... 75

Chapter 3 .................................................................................................................................. 92
Long-Term Impact of Diabetes on Graft Patency after Coronary Artery Bypass Grafting Surgery: A Sub-study of the Multi-Centre Radial Artery Patency Study ............................................................................................................................... 92

3.1-Abstract ........................................................................................................................... 93
3.2-Background .................................................................................................................... 94
3.3-Methods .......................................................................................................................... 95
# Table of Contents

## Chapter 3

3.4-Results ........................................................................................................................... 100  
3.5-Discussion .................................................................................................................... 104  
3.6-Conclusions .................................................................................................................. 107  
3.7-Tables and Figures ....................................................................................................... 107  

## Chapter 4

Impact of South Asian Ethnicity on Long-Term Outcomes after Coronary Artery Bypass Grafting Surgery: A Large Population-Based Propensity Matched Study .................................................................................. 116  
4.1-Abstract ......................................................................................................................... 117  
4.2-Introduction .................................................................................................................. 119  
4.3-Methods ......................................................................................................................... 121  
4.4-Results ........................................................................................................................... 125  
4.5-Discussion .................................................................................................................... 127  
4.6-Conclusion .................................................................................................................... 133  
4.7-Tables and Figures ....................................................................................................... 134  

## Chapter 5

General Discussion, Appraisal of Hypotheses and Conclusions .................................................. 144  
5.1-General Discussion ...................................................................................................... 145  
5.2-Appraisal of Hypothesis 1 ......................................................................................... 146  
5.3-Appraisal of Hypothesis 2 ......................................................................................... 151  
5.4-Appraisal of Hypothesis 3 ......................................................................................... 155  
5.5-Appraisal of Hypothesis 4 ......................................................................................... 160  
5.6-Conclusions .................................................................................................................. 163  
6.0-References ...................................................................................................................... 164
List of Tables
Table 2.1: Inclusion/Exclusion Criteria
Table 2.2: Baseline Demographics
Table 2.3: Operative Characteristics
Table 2.4: Outcomes for the Surgical Arm
Table 2.5a-e: Descriptive results of the major surgical outcomes accounting for the 2x2 factorial design
Table 2.6: Outcomes for the Pharmacological Arm
Table 2.7a-e: Descriptive results of the major pharmacological outcomes accounting for the 2x2 factorial design
Table 2.8: 1-year Graft Status assessed by CT Angiography
Table 2.9: Leg Status (Infection)
Table 3.1: Baseline Characteristics of Patients With and Without Diabetes
Table 3.2a: Comparison of Complete Graft Occlusion Between the Radial Artery versus SVG by Diabetic Status
Table 3.2b: Comparison of Complete Graft Occlusion of the Same Conduit between Diabetics vs. Non-Diabetics
Table 3.3: Multivariable Predictors of Complete Graft Occlusion
Table 3.4: Clinical endpoints between Diabetics vs. Non-Diabetics
Table 4.1: Baseline Demographics
Table 4.2: Time to Event Analysis for Freedom from Major Adverse Cardiac and Cerebrovascular Events after adjustment using Propensity Match Analysis (MACCE)
Table 4.3: Time to Event Analysis for Freedom from All-cause Mortality after adjustment using Propensity Match Analysis
Table 4.4: Predictors of Freedom from Major Adverse Cardiac and Cerebrovascular Events (MACCE) After CABG in South Asians and the General Population
Table 4.5: Overall Outcomes for Duration of Follow-up
List of Figures

Figure 2.1: Central picture - A 2x2 factorial design of No-touch vs conventional vein technique and fish-oils vs placebo

Figure 2.2a: Consort diagram of the surgical arm (No touch versus Conventional technique)

Figure 2.2b: Consort diagram of the pharmacological arm (Fish oils versus Placebo)

Figure 2.3a: Kaplan Meier plot of the secondary outcome, MACCE (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the WHO definition, stroke, repeat revascularization), between the No Touch and Conventional groups. Comparison between the treatments was based on Cox proportion hazard model.

Figure 2.3b: Kaplan Meier plot of the tertiary outcome, MACCE-O (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the old definition, stroke, repeat revascularization), between the No Touch and Conventional groups. Comparison between the treatments was based on Cox proportion hazard model.

Figure 2.3c: Kaplan Meier plot of the secondary outcome, MACCE (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the WHO definition, stroke, repeat revascularization), between the Fish Oils and Placebo groups. Comparisons between the treatments was based on Cox proportion hazard model.

Figure 2.3d: Kaplan Meier plot of the tertiary outcome, MACCE-O (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the old definition, stroke, repeat revascularization), between the Fish Oils and Placebo groups. Comparison between treatments was based on Cox proportion hazard model.

Figure 3.1a: Freedom from complete occlusion of the radial artery graft stratified by diabetic status. The log-rank p-value is testing for statistical significance between the radial artery graft patency curve of diabetics (DM) versus non-diabetics (Non-DM).

Figure 3.1b: Freedom from complete occlusion of the saphenous vein graft stratified by diabetic status. The log-rank p-value is testing for statistical significance between the saphenous vein graft patency curve of diabetics (DM) versus non-diabetics (Non-DM).

Figure 3.2: Major adverse cardiac event free survival (MACE) stratified by diabetic status. The log-rank p-value is testing for statistical significance between the MACE curves of diabetics (DM) versus non-diabetics (Non-DM). MACE is defined as cardiac death, or late myocardial infarction or repeat re-intervention of percutaneous coronary intervention or coronary artery bypass surgery.

Figure 4.1a: Freedom from MACCE. MACCE defined by all-cause mortality, myocardial infarction, stroke or re-intervention.

Figure 4.1b: Freedom from MACCE, scale adjusted to highlight the first year. MACCE defined by all-cause mortality, myocardial infarction, stroke or re-intervention.
Figure 4.2a: Freedom from all-cause mortality.

Figure 4.2b: Freedom from all-cause mortality, scale adjusted to highlight the first year. MACCE defined by all-cause mortality, myocardial infarction, stroke or re-intervention.

Supplemental Figure S1: Meta-analysis of in-hospital or 30-day mortality of South Asians and the General Population after coronary artery bypass grafting surgery excluding study by Brister.

Figure 5.1 - Meta-analysis of vein graft occlusion at 1-year. NT=no touch, CON=conventional.
## Glossary of Commonly Used Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
<th>Source/Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitor – Angiotensin converting enzyme inhibitor</td>
<td>CCHS – Canadian community health survey</td>
<td>DART Study - The Diet and Re-infarction Trial</td>
</tr>
<tr>
<td>AHA – American heart association</td>
<td>CCN – Cardiac Care Network</td>
<td>DES – Drug eluting stent</td>
</tr>
<tr>
<td>AMI – Acute myocardial infarction</td>
<td>CCS – Canadian Cardiovascular Society Classification</td>
<td>DHA – Docosahexaenoic acid</td>
</tr>
<tr>
<td>Ang II – Angiotensinogen II</td>
<td>CHF – Congestive heart failure</td>
<td>DM – Diabetes Mellitus</td>
</tr>
<tr>
<td>ARB – Angiotensin II receptor blocker</td>
<td>CI – Confidence Interval</td>
<td>DSWI – Deep sternal wound infection</td>
</tr>
<tr>
<td>ASA - Aspirin</td>
<td>CIHI-DAD – Canadian Institutes for Health Information discharge abstract database</td>
<td>ECG – Electrocardiogram</td>
</tr>
<tr>
<td>BB – Beta-blocker</td>
<td>CK-MB – Creatinine kinase myocardial B fraction</td>
<td>EF – Ejection fraction</td>
</tr>
<tr>
<td>BCE – Before common era</td>
<td>CON – Conventional saphenous vein graft harvesting technique</td>
<td>eNOS – Endothelial nitric oxide synthase</td>
</tr>
<tr>
<td>BIMA – Bilateral internal mammary artery</td>
<td>COPD – Chronic obstructive sleep apnea</td>
<td>EPA – Eicosapentaenoic acid</td>
</tr>
<tr>
<td>BMS – Bare metal stent</td>
<td>CPB – Cardiopulmonary bypass</td>
<td>FO – Fish-oil supplementation</td>
</tr>
<tr>
<td>BP – Blood pressure</td>
<td>CTA – Computed tomography angiography</td>
<td>FREEDOM - In the Future Revascularization Evaluation in Patients with DM: Optimal Management of Multivessel Disease</td>
</tr>
<tr>
<td>CABG – Coronary artery bypass grafting surgery</td>
<td>CURE - Clopidogrel in Unstable Angina to Prevent Recurrent Events</td>
<td>GISSI – Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico</td>
</tr>
<tr>
<td>CAD – Coronary artery disease</td>
<td>CV – Cardiovascular</td>
<td>GP – General population</td>
</tr>
<tr>
<td>CASCADE - Clopidogrel After Surgery for Coronary Artery Disease</td>
<td>Cx – Circumflex artery</td>
<td>HR – Hazard ratio</td>
</tr>
<tr>
<td>CCB – Calcium channel blocker</td>
<td>DAPT – Dual antiplatelet therapy</td>
<td>HTN – Hypertension</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICES</td>
<td>Institute of Clinical Evaluative Sciences</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Off-pump coronary artery bypass surgery</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical application software</td>
</tr>
<tr>
<td>IMA</td>
<td>Internal mammary artery</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>IVUS</td>
<td>Intravascular ultrasound</td>
</tr>
<tr>
<td>ORGD</td>
<td>Office of the Registrar General death database</td>
</tr>
<tr>
<td>SHARE Study</td>
<td>Study of Health Assessment and Risk in Ethnic Groups</td>
</tr>
<tr>
<td>KM</td>
<td>Kaplan-Meier</td>
</tr>
<tr>
<td>P</td>
<td>Placebo</td>
</tr>
<tr>
<td>STD</td>
<td>Standardized differences</td>
</tr>
<tr>
<td>LAD</td>
<td>Left anterior descending artery</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>STS</td>
<td>Society of Thoracic Surgeons</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>PREVENT IV</td>
<td>Project of Ex-vivo Vein Graft Engineering via Transfection study</td>
</tr>
<tr>
<td>SUPERIOR SVG Study</td>
<td>Surgical and Pharmacological novel interventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting surgery</td>
</tr>
<tr>
<td>LIMA</td>
<td>Left internal mammary artery</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acids</td>
</tr>
<tr>
<td>SVG</td>
<td>Saphenous vein graft</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery study</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>RA</td>
<td>Radial artery</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in myocardial infarction</td>
</tr>
<tr>
<td>MACCE</td>
<td>Major adverse cardiac and cerebrovascular events (as defined within the specific study)</td>
</tr>
<tr>
<td>RAPCO Study</td>
<td>The Radial Artery Patency and Clinical Outcomes</td>
</tr>
<tr>
<td>URS</td>
<td>Urgency rating score</td>
</tr>
<tr>
<td>MACCE-O</td>
<td>Major adverse cardiac and cerebrovascular events using an older definition (as defined within the specific study)</td>
</tr>
<tr>
<td>RAPS Study</td>
<td>The Radial Artery Patency Study</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affair</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiac events (as defined within the specific study)</td>
</tr>
<tr>
<td>RCA</td>
<td>Right coronary artery</td>
</tr>
<tr>
<td>VSMC</td>
<td>Vascular smooth muscle cell</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized control trial</td>
</tr>
<tr>
<td>RIMA</td>
<td>Right internal mammary artery</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>MVD</td>
<td>Multi-vessel disease</td>
</tr>
<tr>
<td>RIVAL Study</td>
<td>The Radial Vs femoRAL access for coronary intervention</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>RPDB</td>
<td>Ontario registered persons database</td>
</tr>
<tr>
<td>No. (%)</td>
<td>Number and percent</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>Non-DM</td>
<td>Patients who do not have diabetes</td>
</tr>
<tr>
<td>RRR</td>
<td>Relative risk reduction</td>
</tr>
<tr>
<td>NT</td>
<td>No-Touch saphenous vein graft harvesting technique</td>
</tr>
<tr>
<td>RSVP Study</td>
<td>The Radial Artery Versus Saphenous Vein Patency</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>RA</td>
<td>Radial artery</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in myocardial infarction</td>
</tr>
<tr>
<td>MACCE-O</td>
<td>Major adverse cardiac and cerebrovascular events using an older definition (as defined within the specific study)</td>
</tr>
<tr>
<td>RAPS Study</td>
<td>The Radial Artery Patency Study</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affair</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiac events (as defined within the specific study)</td>
</tr>
<tr>
<td>RCA</td>
<td>Right coronary artery</td>
</tr>
<tr>
<td>VSMC</td>
<td>Vascular smooth muscle cell</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized control trial</td>
</tr>
<tr>
<td>RIMA</td>
<td>Right internal mammary artery</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>MVD</td>
<td>Multi-vessel disease</td>
</tr>
<tr>
<td>RIVAL Study</td>
<td>The Radial Vs femoRAL access for coronary intervention</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>RPDB</td>
<td>Ontario registered persons database</td>
</tr>
<tr>
<td>No. (%)</td>
<td>Number and percent</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>Non-DM</td>
<td>Patients who do not have diabetes</td>
</tr>
<tr>
<td>RRR</td>
<td>Relative risk reduction</td>
</tr>
<tr>
<td>NT</td>
<td>No-Touch saphenous vein graft harvesting technique</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction
This chapter provides the background and foundation on which the studies of this thesis were undertaken. Given that the thesis is predicated on ischemic heart disease and coronary artery bypass grafting surgery (CABG), we began broadly with a brief history of coronary artery disease and myocardial revascularization including CABG. We then honed in on surgical, pharmacological and patient factors that can impact CABG outcomes. We concluded this chapter with specific study objectives, hypotheses and subsequent chapter previews. For this introductory chapter, we provided a brief synopsis of the content of each section at the beginning of that section.

### 1.1 - History of Coronary Artery Disease and Myocardial Revascularization

**Synopsis:** *Given this is a thesis dissertation, this section provides a historical background of coronary artery disease (CAD). It highlights some of the important time points in cardiovascular medicine that helped us in understanding cardiac pathophysiology and coronary anatomy. We then transition from pathophysiology to management of CAD describing broadly the options in medical management, percutaneous coronary interventions (PCI) and coronary artery bypass grafting surgery (CABG).*

Cardiovascular disease is one of the leading causes of mortality globally accounting for more than 17 million deaths each year; atherosclerosis leading to coronary artery disease (CAD) is its largest contributor. Although coronary disease has captured much of the medical spotlight in the past five decades, its existence has long been present throughout history. A recent study has shown that definite atherosclerosis was present in ancient
Egyptian mummies including a princess who lived between 1550 and 1580 BCE; she represents the earliest documentation of coronary atherosclerosis in a human.²

William Harvey’s publication DeMotuCordis in 1628,³,⁴ described the circulation and function of the heart; this was the seminal paper that paved the path for cardiovascular physiology that was to follow a few centuries later.⁴ In the medical literature, heart disease made its mark almost 300 years ago when Dr. William Heberden presented his paper titled ‘Some Account of a Disorder of the Breast’ to members of the Royal College of Physicians of London;⁵ this was subsequently published in the Transactions of the Royal College in 1772.⁴,⁶ About 40 years after this publication, the New England Journal of Medicine and Surgery (currently the New England Journal of Medicine), released its first issue with the first article by Dr. John Warren, titled ‘Remarks of Angina Pectoris’.⁴,⁷

During the last 2 centuries, giant leaps have been made in all aspects of coronary disease from understanding its risk factors and pathophysiology to advanced evidence based treatment. One of the first pivotal landmarks in understanding heart disease was the creation of the Framingham Heart Study in 1948 which unveiled the major risk factors of ischemic heart disease including diabetes, hypertension, hyperlipidemia and smoking.⁴,⁸,⁹ ¹⁰,¹¹

In 1929, Dr. Werner Forssman, performed the first human cardiac catheterization, which was performed on himself.¹² In the early 1940s, diagnostic catheterization was introduced by Drs. Andre Cournand and Dickinson Richards¹² and in October of 1958, Dr. F. Mason Sones Jr, while attempting to image the aortic root, inadvertently performed the first selective coronary angiogram in a 26 year old patient with rheumatic heart disease in the Cleveland Clinic;¹³ a few decades later, Dr. Andreas Gruentzig pioneered catheter-based
The early work of Forssman, Cournand and Richards led to a greater understanding of cardiac hemodynamics for which they were awarded the Nobel Prize in Physiology or Medicine in 1956.4

As understanding of pathophysiology and its effect on clinical sequelae began to unfold, many avenues of pharmacotherapy as well as methods of myocardial revascularization began to emerge. With respect to medical management, thrombolytics and anticoagulation were some of the initial pharmacological agents for treating acute coronary syndromes. One of the first, very large studies in cardiology (n=11806) was the GISSI trial14 (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico), which showed that intravenous streptokinase reduced early mortality in patients with acute myocardial infarction (AMI). In addition to thrombolytics, in 1916, William Henry Howell, at Johns Hopkins University, extracted a phosphatide from canine liver which he termed heparin. This was later purified at the Connaught Laboratories in Toronto and reported as a safe and effective anticoagulant by Murray and Best.15 Other categories of drugs were also introduced in the past 6 decades for ischemic heart disease including antiplatelet agents, nitrates, beta-blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers.16

In addition to medical management, significant advances were also being made in direct myocardial revascularization. Percutaneous coronary intervention (PCI) has greatly evolved since its debut in 1977 by Gruentzig, from balloon angioplasty to bare-metal stents (BMS) to the present day drug-eluting stents (DES).17 Significant advances have been made in DES technology resulting in its progress from first generation to the current third
generation stents with modification in stent platform, the polymer coating, and anti-proliferative agents that are eluted.\(^{17-19}\)

Coronary artery bypass grafting surgery actually happened well before the first PCI. The early concepts of CABG were initially conceived by Dr. Alex Carrel during his Nobel Prize winning research in vascular anastomosis.\(^{20}\) The first successful CABG was performed on a taxi driver from New York, by Dr. Robert Goetz and colleagues, at the Albert Einstein College of Medicine, New York on May 2, 1960.\(^{21}\) Over the past 5 decades, there have been many developments and advances in this operation. Much of current day success of CABG would not have been possible without the invention of the cardiopulmonary bypass (CPB). In 1937, Dr. John Gibbon reported his first experience with bypassing blood around a partially obstructed pulmonary artery in cats using a perfusion apparatus;\(^{15,22}\) an idea he conceived after watching a patient die from pulmonary embolectomy.\(^{23}\) Major advances over the next few decades pursued including that of Dr. Wilfred Bigelow demonstrating the efficacy of hypothermia in reduction of oxygen consumption.\(^{15}\) Such advances along with a partnership with the International Business Machine (IBM) company, Dr. Gibbon and his team at the University of Pennsylvania developed the first effective CPB machine and performed the first procedure using CPB in 1952 on a 15-month old child thought to have an atrial septal defect.\(^{15}\) Over the last few decades, several medical institutions and companies joined the task in advancing CPB to its current state with state of the art oxygenators, pumps, filters and evidence based training for perfusionists.

Around the same time as the mechanics of the CPB machine were being developed, Dr. Arthur Vineburg, at McGill University, began experimenting with the internal mammary
artery (IMA). In 1945, Vineburg implanted the IMA in the ventricular myocardium of dogs and in 1950, eventually became the first to perform this procedure in humans, known as the Vineburg Operation, to treat cardiac ischemia and angina. He essentially pulled the left IMA (LIMA) into a myocardial tunnel parallel with the left anterior descending artery (LAD). Although the first patient only survived 62 hours, postmortem examination revealed that the LIMA was patent with no evidence of an MI. This procedure was mainly performed in Vineburg’s institution as it was not widely accepted by the global community for multiple reasons including lack of reproducibility in animal studies conducted by others. In 1958, the revolutionary invention of selective angiography by Sones and Shirley in the Cleveland Clinic demonstrated that Vineburg’s concepts were indeed correct in that implantation of the LIMA would improve the myocardial perfusion deficit of the anterior wall due to an obstructed LAD. The Vineburg technique was further modified by Dr. Rene Favalaro in 1966 when he dissected the IMA following a sternotomy with a special self-retaining retractor allowing for harvesting of bilateral IMAs, named the double Vineburg approach. This technique eventually led way to the current practice of utilizing the IMA as an arterial conduit for direct myocardial revascularization. Further work by Dr. Floyd Loop confirmed the excellent long-term patency of the IMA, which became a key part of CABG surgery.

In addition to advancements in CPB, there has been significant progress in the area of myocardial protection. Since the initial practice of arresting the heart by simply cross-clamping the aorta and reperfusing by declamping, which resulted in irreversible severe myocardial damage called ‘stone heart’, improvement in myocardial protection techniques have resulted due to significant research in the areas of myocardial perfusion solutions,
including its molecular composition, whether to use blood versus crystalloid, and temperature.

In addition to developments in CPB and better myocardial protection, advances in other areas of CABG have also taken place over the past few decades in areas of off-pump coronary artery bypass techniques (OPCAB), minimally invasive surgery including robotics and hybrid surgery.

Since the initial publication by Harvey 400 years ago introducing the phenomena of the cardiovascular system to the medical literature, there have been rapid historical advances in cardiovascular medicine, especially in the last 6 decades, including CABG and PCI. As these therapeutic options have evolved, the choice of which intervention is most appropriate has become an area of controversy. Recent publications of mid-term results of large studies including the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) study have shown that CABG is the standard of care for advanced coronary disease while PCI is appropriate for less complex coronary lesions as assessed by grading mechanisms like the SYNTAX score. Furthermore, the decision of which intervention is superior is not only based on the coronary anatomy but also other components including patient factors such as co-morbidities, patient preference, procedural factors including conduit availability, and expertise of the institution. Thus, it is now recommended that a multi-disciplinary heart team approach be taken to determine the optimal intervention for the patient. The remainder of this thesis will hone in on CABG and investigate patient and surgical factors that can influence early and late outcomes after CABG.
1.2 – Surgical Factors

This section highlights the surgical factors that can affect CABG outcomes. More specifically, this section focuses on 1) conduit choices and 2) harvesting techniques.

1.2.1 – Conduits

**Synopsis:** *Given two of the three studies are related to conduits used in CABG, this section broadly highlights the different conduits.*

Conduit selection is a crucial process in CABG as graft performance, defined by graft patency, is a strong prognostic factor of early and long-term clinical outcomes after CABG.\(^{39}\) Factors that are pertinent to conduit selection include conduit availability, target vessel characteristics, and patient comorbidities.\(^{40}\)

Available conduits can be stratified into autologous, non-autologous and synthetic;\(^{39}\) they are further sub-stratified into arterial and venous grafts. Autologous venous conduits include the great saphenous vein, the short saphenous vein, and arm veins including cephalic and basilica veins. Autologous arterial conduits include LIMA, RIMA (right internal mammary artery), radial, right gastroepiploic, inferior epigastric, splenic, gastroduodenal, left gastric and intercostal arteries. Non-autologous synthetic vein conduits include umbilical and great saphenous vein homografts; bovine IMA is an example non-autologous arterial conduit. Synthetic conduits include dacron grafts and polytetrafluoroethylene (PTFE).\(^{39}\) Of these, given that the most utilized conduits are the greater saphenous vein, the IMA, and radials, the next section will delve further into these conduits.
1.2.1.1 - Saphenous Vein Graft (SVG)

**Synopsis:** This section focuses on the saphenous vein graft highlighting its advantages and disadvantages. Given two of the three studies of this thesis is related to the saphenous vein graft (SVG), we delve into more detail regarding the pathophysiology of SVG failure.

Ever since the beginning of CABG in the early 60s, the greater saphenous vein is the most frequently used conduit in CABG.\(^39,40\) This conduit is harvested from the leg and is reversed due to the presence of valves. In the majority of cases, it is proximally anastomosed to the ascending aorta and distally to the circumflex or right territory.\(^39\) The advantages of using a saphenous vein graft (SVG) are that it is long, easy to handle, and are usually readily available.\(^41\) Use of this conduit in the presence of severe varicosities are contraindicated.\(^39\)

The main disadvantage of the SVG is increased graft failure, particularly late after CABG.\(^42,43\) Several studies, including the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT IV) study, has shown that rates of SVG occlusion at one year postoperatively ranges from 10-25%\(^44-47\) The PREVENT IV study also showed that a composite of death, MI or repeat revascularization was 13 times more likely in patients with a SVG failure compared to patients with no SVG failure,\(^44\) highlighting the importance of graft failure. Following the first year, the attrition rate of SVGs are 1-2% per year up to 5 years and 4% per year between 6-10 years. At 10 years, 60% are patent and about 50% are free from significant stenosis.\(^43\)

The pathophysiology of SVG failure can be segregated into 3 main stages.\(^42,43\) Early (within 1 month) failure is usually attributed to graft thrombosis,\(^42\) present in between 3-12% of
SVGs. This occurs mainly due to technical factors. An important technical concept (discussed in more detail below) is postulated to be the conventional harvesting technique associated with endothelial injury. Endothelial damage can result in a focal prothrombotic state within the vein. In addition, vein grafts in general have less production of nitric oxide and prostacyclin (potent inhibitors of platelets), thereby further exacerbating the prothrombotic state. Additional technical factors include small size of target vessel resulting in poor distal runoff; size mismatch between graft and target resulting in turbulent flow and graft ischemia.

In the subacute period (1 month to 12 months), the cause of SVG failure is intimal hyperplasia. Intimal hyperplasia is the accumulation of smooth muscle cells and extracellular matrix in the intima of the vein. While most saphenous veins have mild intimal hyperplasia prior to being harvested, once grafted into the aorto-coronary arterial circulation, these grafts undergo further intimal hyperplasia around 4-6 weeks, which may decrease the lumen by 25%. This process of intimal hyperplasia is a sentinel process for atherosclerosis to develop; regions where this occurs has therefore been defined by the American Heart Association (AHA) as either focal or diffuse ‘atherosclerosis-prone regions’. Endothelial cells play an important role in modulating (inhibiting) intimal hyperplasia. If there is endothelial damage, these modulating mechanisms are lost. Layers of platelets and fibrin form in the regions with exposed basement membranes as a result of endothelial loss; neointimal endothelial cells form on the platelet-fibrin layer organizing into a nonocclusive thrombus. This process along with platelets releasing growth factors, promotes intimal hyperplasia. Thus, unlike arterial remodeling, the majority of intimal hyperplasia, occur only after endothelial regeneration; thus endothelial loss is an
important trigger. Furthermore, veins are exposed to transient ischemia during explanation with consequent reperfusion following grafting. This process is exacerbated when the vasovasorum blood supply is lost. This ischemia-reperfusion cycle decreases endothelial production of nitric oxide, prostacyclin, and adenosine along with inducing superoxide radical formation further enhancing smooth muscle proliferation. Furthermore, arterializing a SVG decreases internal shear stress through constrictive remodeling, which further upregulates factors causing intimal hyperplasia. Thus, endothelial injury, in addition to ischemia-reperfusion from explanation and loss of vasovasorum, along with arterialization of a venous graft lead to intimal hyperplasia.

The main etiology of SVG failure beyond 1 year is atherosclerosis; significant hemodynamic lesions resulting in symptoms usually occur after 3 years. Angiographic studies have shown that among patients who present with unstable angina or acute coronary syndrome after CABG, 70-85% of these are due to vein graft stenosis secondary to atherosclerosis. The rapidly progressive nature of atherosclerosis in SVGs has been associated with endothelial injury and dysfunction. SVG atherosclerosis differs from native vessel disease in that there is more foam and multinucleate giant cells leading to an appearance of immune-mediated atherosclerosis; in SVGs, the disease is usually diffuse, concentric, and friable with a poorly developed fibrous cap whereas in native coronary disease, the lesions are focal, eccentric and robust with a well-developed fibrous cap. Furthermore, a spatial association has been suggested between the presence of large number of foam cells, smooth muscle cell loss, and cell death in segments of occluded vein grafts. These factors along with impaired rate of lipolysis present in SVGs, have been postulated as major mechanisms responsible for SVG failure beyond 1 year.
1.2.1.2 - Internal Mammary Artery

Synopsis: This section focuses on the internal mammary artery and highlights its histological properties as well as its utilization including single versus bilateral mammary artery revascularization.

The IMA is a paired artery with the left (LIMA) and right (RIMA) coursing under the left and right anterior chest wall lateral to the sternum respectively supplying the anterior chest. In a majority of cases, both right and left arteries arise proximally from the subclavian artery above and behind the sternal end of the clavicle and bifurcate distally into superior epigastric and musculophrenic arteries with a minority (7%) trifurcating into a third branch, the diaphragmatic branch. While the time required to harvest the IMA is a disadvantage, thereby precluding its use in salvage emergency cases, the major advantage of IMA is its superior and durable patency compared to other conduits.

The landmark study by Loop et al., that highlighted the excellent performance of this artery, showed that patients receiving only SVGs had a 1.61 times greater risk of death throughout the first decade after surgery compared to patients who received an IMA. Furthermore, Cameron et al showed that the presence of an IMA was an independent predictor of improved survival over 15 years (Relative Risk (RR) 0.73). Compared to the poor long term SVG patency, long-term graft patency of IMAs have been reported to be up to 90-95% at 10-15 years. The large difference in patency rates and therefore clinical significance of the IMA compared to the SVG has been attributed to structural difference of these conduits. More specifically, IMAs have fewer fenestrations in the endothelium compared to the SVGs which may prevent lipoproteins from entering the subendothelial
space (less lipid uptake) as well as prevent disruption of the endothelial layer; the rate of lipolysis is faster in IMAs compared to SVGs. The endothelial layers of IMAs are also rich in heparin sulfate and endothelial nitric oxide synthase which are associated with antithrombotic properties and prevent atherosclerosis. Furthermore, arterial remodeling in IMA is associated with differential gene expression in response to flow, rendering it more adaptive to the changing coronary physiology over time; more specifically, chronic flow increase results in enlargement of the IMA lumen whereas decreased flow results in intimal thickening and reduction of luminal diameter. Finally, the size of the IMA is similar to the size of the coronary artery, thereby reducing turbulent or stagnant flow and the process towards atherosclerosis.

Given the above properties of the IMA and the superior patency of the gold-standard LIMA to LAD grafting, surgeons have pondered the potential benefit of using bilateral IMAs (BIMA) rather than single IMAs (SIMA). Many studies, mostly observational, have been undertaken to assess the benefits of BIMA. While there seems to be a long-term survival advantage of using BIMA over SIMA, the utilization of BIMA grafting in CABG is less than 5% in the United States. The underutilization of BIMA grafting has been largely associated with higher rates of sternal wound complications, especially in patients with diabetes. However a large single centre study by Raza et al (n=11,922), investigating the risk variables for decreasing in-hospital and long-term mortality showed a 21% lower late mortality in BIMA versus SIMA grafting in the context of a small increase in deep sternal wound infections and the consequent minimal effect on overall survival in diabetics; this study recommended the use of BIMA in diabetics with low risk of deep sternal wound infections. It did suggest that the use of BIMA should be avoided in higher
risk patients such as obese diabetic women. A recent meta-analysis (not including the above study)\textsuperscript{62} of 7264 patients, further supported the use of BIMA in diabetics. Finally, Taggart et al.,\textsuperscript{72} has undertaken a large RCT comparing BIMA versus SIMA showing that at 1 and 5-years,\textsuperscript{72,73} BIMA and SIMA are comparable with regards to mortality and cardiovascular events. However since the benefit of BIMA has not largely been found until the second decade following surgery,\textsuperscript{70} the surgical community eagerly awaits the 10-year results of this study.

1.2.1.3 - Radial Artery

**Synopsis:** Given one of the studies in the thesis involves the radial artery, this section focuses on this conduit. Moreover, this section begins with a brief historical background of the radial artery and its revival, histological properties, advantages and disadvantages, preoperative assessment methods, and comparative patency data especially between the radial artery and SVG.

Given the success of the IMA compared to the SVG, surgeons have looked to other potential arterial conduits that may parallel this success. The radial artery was first used as a bypass conduit in 1971 by Dr. Alain Carpentier,\textsuperscript{74,75} at Broussais Hospital in Paris, France. He presented his experience of 30 patients (26 men, 4 women) receiving 40 radial grafts using the aorta-to-coronary technique, at the 9\textsuperscript{th} Annual Society of Thoracic Surgeons meeting in January 1973. He reported no in-hospital deaths, and angiography between 1 and 10 months showed all grafts to be patent. While extremely encouraging, he noted that these results were early and only longer follow-up would dictate the fate of this new potential bypass conduit.\textsuperscript{75} His forethought was important as the fate of the radial artery
soon looked dismal; within a few years, angiography of a subset of patients that initially underwent radial grafting, showed 22 of 34 radial grafts (64.7%) to be unsatisfactory.76 Recovered grafts from 3 patients that required a second operation showed generalized intimal hyperplasia which was postulated to be multifactorial including harvesting techniques (particularly skeletonization and mechanical dilatation) resulting in vessel trauma and spasm.77 Such mechanisms and the resulting high failure rate led to the abandonment of this conduit. However, 2 decades later, with better understanding of graft physiology and protection of the endothelium through ‘no-touch’ harvesting technique and pharmacological dilating agents rather than mechanical dilation, Dr. Christopher Acar, reported 100% radial graft patency post-operatively.78 This fundamental study, reported in 1992, led to the resurgence of the radial artery and paved way for further investigations comparing the patency of the radial artery compared to the SVG.78-84

With regards to histology, the radial artery is a muscular artery with a thin intima and thick tunica media composed of numerous smooth muscle cells.85 The internal elastic lamina is well defined however, it has been associated with fenestrations which can make it susceptible to atherosclerosis. The radial artery is usually harvested from the non-dominant hand. The radial artery is a muscular artery lying under the antebrachial fascia between the brachioradialis muscle and the flexor carpi radialis.86 Advantages of using the radial artery include: 1) its length (>20 cm) – allowing it to reach any target, 2) its inner diameter being between 2 to 3 mm – similar to that of the coronary arteries, 3) thicker wall – making the anastomosis easier to perform, 4) relatively easy to harvest.87 Its disadvantages include: 1) having a thick smooth muscle layer that increases its propensity to spasm, 2) the need of ensuring good ulnar artery supply to compensate for the radial artery 3) the slightly higher
degree of atherosclerosis in radials compared with the LIMA and 4) risk of hand sensory or motor dysfunction.\textsuperscript{87}

The modified Allen’s test is commonly used to determine whether sufficient ulnar collateral circulation is present in the hand; the diagnostic accuracy of this test has been shown to be greatest at a cutoff time of 5-6 seconds.\textsuperscript{88} While considered the gold-standard clinical test for excluding patients for radial artery harvesting, the Allen’s test however has a high false positive rate; therefore other supplementary techniques have been used including digital plethysmography and Doppler ultrasonography.\textsuperscript{89} Abu-Omar et al,\textsuperscript{90} showed that 88% of patients with a positive Allen’s went on to have normal arterial duplex ultrasound. Therefore, for patients with an abnormal Allen’s test, Doppler ultrasonography can predict safe radial harvesting;\textsuperscript{90} furthermore, Doppler ultrasound can also assess the quality of the radial arteries including vessel diameter, arteriosclerosis or calcification\textsuperscript{89}. In addition to abnormal Allen’s or Doppler ultrasound, other contraindications for using a radial artery as a bypass conduit include history of damage or trauma to the radial artery, presence of an arteriovenous fistula for hemodialysis, vasculitis, or Raynaud’s disease.\textsuperscript{87}

Another factor in deciding to whether using radial arteries include previous radial catheterization for angiography or PCI. A study by Kotowycz et al.,\textsuperscript{91} showed that 1-10\% of patients undergoing radial catheterization had radial occlusions associated primarily with arterial thrombosis and vascular injury from sheath insertion. Furthermore, Kamiya et al.,\textsuperscript{92} performed a retrospective study that showed radial artery patency was significantly lower in radials that had catheterization compared to a non-catheterized radial artery (77\% vs 98\%, p=0.02). The findings of this study led the authors to recommend using radial artery
as a conduit for bypass surgery with caution if it was previously catheterized. These findings, along with the results of the multi-centre RIVAL study (The RadIal Vs femorAL access for coronary intervention) that showed comparable safety and efficacy of both radial and femoral catheterization, may encourage cardiologists to pursue femoral catheterization especially in patients who are potential CABG candidates.

Given the superior patency of the IMA compared to the SVG, numerous studies have been undertaken to assess whether the radial artery also demonstrates such favorable angiographic and clinical results. To date, there have been numerous observational studies comparing the radial artery to the SVG. Amano et al., performed a study on 920 consecutive patients undergoing isolated CABG in Japan, and performed selective angiography (first 50 patients underwent angiography within 3 months after CABG and thereafter, early angiography was performed either due to poor quality of native coronary arteries or request of referring cardiologists). Angiography beyond 3-months postoperatively was proposed to all patients and encouraged for all symptomatic patients. Of the 98 patients that underwent early angiography within 3 months of surgery, 137/139 (98.6%) radials were patent compared to 34/38 (89.5%) SVGs. Of the 167 patients that underwent angiography beyond 3 months, (mean 1.5 years after CABG), 213/229 (95.3%) radials were patent compared to 71/79 (89.8%). Zacharias et al., performed a large propensity matched study (n=925 in each group) comparing radials to veins. Angiography in restudied symptomatic patients at a median of 545 days postoperatively, showed greater vein graft failure (Radials: 46/157 (29.3%) vs SVG: 66/161 (41.0%), p=0.04); 6-year survival was better in the radial group (92.1% vs 86.8%). Possati et al., described long-term angiographic results (105 months) in 90 consecutive patients undergoing CABG using
radials and vein grafts and reported 7/84 (8.3%) radial artery and 24/73 (32.9%) SVG occlusion respectively. Cohen et al\textsuperscript{94} performed a 1:2 case-matched study of 478 patients receiving a radial artery and 956 patients receiving a SVG and reported actuarial freedom from events at 36 months to be better in the radial artery group (Radial 95\% vs SVG 86\%, p=0.01). With regards to late outcomes, Gaudino et al.,\textsuperscript{103} reported 20-year follow-up on the first 100 patients that received a radial artery in their institution; they reported probability of radial failure at 20 years was 25\% (compared to 19\% LIMA failure and 55\% SVG failure). Another study by Acar et al.,\textsuperscript{104} assessed 629 radial grafts over 20 years and found that the overall patency was 83\%; graft patency was affected most in the first postoperative year, however beyond 1 year, the attrition rate was 0.37\%/year up to 20 years.

To date, there have been 5 randomized trials comparing radials to SVGs. The Radial Artery Patency Study (RAPS), is the largest multi-centre radial artery trial that has reported both early and late angiographic results.\textsuperscript{79,80} In this study, patients under 80 years of age with 3-vessel disease, undergoing CABG across 13 centres were enrolled. Different from other RCTs in this area, the study design of this study included a within patient randomization of the radial artery to the territory; more specifically, if the radial artery was randomized to the right territory, the study SVG was grafted to the circumflex and if the radial artery was randomized to the circumflex, the study SVG was grafted to the right. The LIMA was grafted to the LAD territory. Thus, all patients received the LIMA, the radial and SVG grafts. Year 1 angiography was performed in 440 patients that showed Radials were superior compared to SVG (Radial occlusion 36/440 (9.2\%) vs SVG 60/440 (13.6\%), p=0.009).\textsuperscript{80} Sub-studies of early angiographic analysis showed that radials performed better in targets with severe proximal stenosis (>90\%)\textsuperscript{105} and was associated with a protective
effect in diabetics compared to SVGs. Target vessel stenosis less than 90% was also a predictor of radial artery string sign. With regards to late angiography at a mean of 7.7 years after CABG, n=269, radials continued to out-perform SVGs (Radial occlusion 24/269 (8.9%) vs SVG 50/269 (18.6%), p=0.002); severe proximal target vessel disease was again associated with decreased radial artery occlusion.

Another large multi-centre RCT involving 11 Veterans Affair (VA) medical centres, including 757 patients (99% men) undergoing CABG randomized either the radial or SVG to the next best target after the LAD, which was revascularized using a LIMA. They reported no difference in graft patency at year 1 angiography (Radials 238/266 (89.0%) vs SVG 239/269 (89.0%), p=0.98). There was also no difference in early mortality, MI, stroke or repeat revascularization between the two groups.

The Radial Artery Versus Saphenous Vein Patency (RSVP) trial study was a single centre RCT that enrolled 142 patients randomizing patients to either the radial artery or SVG to a stenosed branch of the native circumflex artery. They reported decreased graft occlusion in the radials at 5-years (Radial occlusion 1/59 (1.7%) vs SVG 6/44 (13.6%), p=0.04).

The Radial Artery Patency and Clinical Outcomes (RAPCO) is a single centred double-armed RCT that compared the radial artery to SVG in patients >70 years of age (Group Rad-SVG, n=225) and the radial artery to the free RIMA in patients < 70 years of age (or < 60 years of age if diabetic) (Group Rad-RIMA, n=394) undergoing multi-vessel CABG. The randomization of either the radial/SVG or radial/RIMA was for the largest non-LAD target with the LIMA going to the LAD. Patients were scheduled to have 10-years of clinical follow-up and randomly assigned staggered angiograms at 1,2,5,7 and 10-years
with the bulk of angiogram timings favoring the second half. The primary outcome was 10-year event free survival and patent study grafts. Their group has published mid-term results. At mean follow-up of 5.5 years, there were no differences in graft patency in the RA-SVG group (n=113 patients that underwent protocol angiography, p=0.54) and the RA-RIMA group (n=237 patients that underwent protocol angiography, p=0.06). There were also no differences in survival or event-free survival in these groups. The final results were presented at the Annual Meeting of the AATS in Baltimore, USA; the manuscript is under review at LANCET.

Gaudino et al. performed a RCT with 60 patients with in-stent restenosis and 60 controls randomizing patients to either arterial (Radial or RIMA) or SVG to the first obtuse marginal artery. At a mean of 52 months, they reported 2/40 (5%) RIMA occlusion, 1/40 (2.5%) Radial occlusion and 17/40 (17.5%) SVG occlusion including patients with in-stent restenosis.

Finally, Munoretto et al. randomized 100 patients to total arterial revascularization (TAR) and 100 patients with conventional revascularization with LIMA and SVG. They performed angiography at mean of 18 months and reported in the TAR group (99% LIMA, 100% RIMA, 96.7% radial artery patency) and the conventional group (100% LIMA, 84% SVG patency).

A large meta-analysis including 35 studies (observational and RCTs) suggested that earlier (< 1 year) SVG patency was similar to that of radial grafts (OR 1.04, p=0.84); however mid-term (1-5 years: OR 2.06, p=0.002) and late (>5-years: OR 2.28, p=0.003) favored radials. A network meta-analysis of RCTs involving 2780 patients showed that
SVGs were associated with a 4-fold (compared to RIMA) and 3-fold (compared to radials) increase in late (beyond 4 years) functional graft occlusion. Another current meta-analysis involving 63 studies\textsuperscript{112} (observational and RCTs) concluded that radials should be preferred to the SVG and should be deemed at least equivalent to the RIMA as a second conduit.

1.2.2 – Harvesting Techniques

**Synopsis:** The above section introduced the commonly used conduits and highlighted some of its important properties and patency characteristics. This section focuses on harvesting techniques of these conduits. Given that one of the studies in the thesis is largely related to harvesting techniques, a broad review and background on this topic is warranted.

The choice of harvesting techniques of conduits can influence early and late outcomes of CABG.\textsuperscript{113-116} This section will delve into the different types of harvesting options associated with each of the conduits discussed above - IMA, radial, and the saphenous vein conduits.

1.2.2.1 - Internal Mammary Harvesting Techniques

**Synopsis:** This section focuses on harvesting techniques of the internal mammary artery. Moreover, we focus on skeletonized versus pedicled harvesting, its evidence, and its association with sternal infection.

Given that LIMA to LAD anastomosis is considered one of the most important components of CABG, the harvesting of the LIMA is an important step in the operation. While the LIMA is usually harvested in an in-situ fashion, the main concern with IMA harvesting is deep sternal wound infections (DSWI), which may be related to a reduction in sternal perfusion.\textsuperscript{56,115} The factors that are often associated with DSWI and harvesting technique
are whether the IMA should be harvested skeletonized or pedicled (defined below), and whether one IMA should be used or both.\textsuperscript{115}

The incidence of deep sternal wound infection after cardiac surgery has been reported to be between 0.4-5\%;\textsuperscript{117} mortality in patients with DSWI ranges from 10-14\%.\textsuperscript{118} DSWI is associated with reduction of sternal perfusion with IMA harvesting.\textsuperscript{115} Sternal perfusion is based on 6 types of vessels:\textsuperscript{56,115} 3 are non-collateral branches (sternal, intercostal, and perforating branches of the IMA) and 3 are collateral branches (sternal/intercostal (S/I), sternal/perforating (S/P), and persistent posterior intercostal artery). Of the collaterals, the S/I and S/P arise from the IMA and also anastomose with the muscular and cutaneous branches of the acromiothoracic artery (S/P branch) and the posterior intercostal artery (S/I branch).\textsuperscript{56} These trunk branches from the IMA should therefore be protected, by ligating these branches as close to the IMA as possible, during the IMA harvest to improve collateral sternal blood supply.\textsuperscript{115}

Pedicled IMA harvesting (the commonly performed technique) usually includes freeing the IMA with its surrounding neurovascular structures and fascia,\textsuperscript{115,119} it has been suggested that preserving the surrounding tissue provides a homeostatic milieu helping the IMA retain its function.\textsuperscript{115} In contrast, the skeletonization technique first described by Keeley in 1987,\textsuperscript{120} involves dissecting the IMA from the accompanying neurovascular structures and fascia for the length of the IMA (usually from the first rib to the bifurcation), with the intention of improving length and preserving sternal blood flow.\textsuperscript{115}

While superiority of skeletonized or pedicle harvesting technique is still controversial,\textsuperscript{119} Boodwani et al.,\textsuperscript{121} performed a within patient randomization of skeletonized or pedicled in
patients undergoing bilateral IMA CABG; each patient received a skeletonized IMA on one side and pedicled on the other; the side of pedicled vs skeletonized IMA harvesting was determined by randomization. They reported that while skeletonization required a longer harvest time (27 vs 24 min), sternal perfusion was significantly higher on the side of skeletonized harvesting. A meta-analysis by Sa et al.,\textsuperscript{122} of 22 studies (observational and RCTs) involving 4817 patients with 2424 skeletonized and 2393 pedicled IMA concluded that skeletonized IMAs reduced the incidence of postoperative sternal wound infections (OR 0.44, p<0.0001). Another meta-analysis by the same group,\textsuperscript{123} involving 5 studies with 1764 conduits (1145 skeletonized, 619 pedicled) concluded that skeletonized IMA was non-inferior in comparison to pedicled IMA with regards to graft patency within 1 year.

With respect to bilateral versus single IMA and sternal perfusion, Korbmacher et al.,\textsuperscript{124} performed bone scintigraphy and reported no significant difference in sternal perfusion or healing disturbances between bilateral and single use of IMA. While Kajimoto et al.,\textsuperscript{62} performed a meta-analysis of 13 studies comparing bilateral versus single IMA in diabetics and concluded that bilateral IMA is an excellent strategy even for diabetics, a meta-analysis by Sa et al.,\textsuperscript{125} involving 2633 patients undergoing bilateral IMA (1698 skeletonized vs 935 pedicled) concluded that when both IMAs are used, skeletonized technique appears to reduce incidence of sternal wound infection (OR 0.33, p<0.001).

1.2.2.2 - Radial Artery Harvesting Techniques

**Synopsis:** This section focuses on radial artery harvesting techniques. Moreover, while we focused on the open technique (as two of the studies in the thesis utilizes this technique), we did briefly discuss endoscopic harvesting; furthermore we also discussed skeletonized
versus pedicled harvesting. We also concluded this section with the perioperative practices that are often employed after harvesting the radial artery as well as early and long-term outcomes of the hand from which the radial artery is harvested.

An important component of the resurgence of the radial artery was the harvesting technique of this conduit. Moreover, it has been suggested that the initial early occlusion rates of the radials were associated with vessel trauma related to harvesting techniques including mechanical dilation using metal dilators and hydrostatic dilation. Furthermore, the presence of a thicker media in the radial arteries leading to more vasoconstriction was likely underestimated. At present, the radial artery is usually harvested from the non-dominant hand using a curvilinear incision extending from 2cm below the antebrachial fossa to the wrist crease, following the medial contour of the brachioradialis muscle. After careful mobilization of the brachioradialis, the entire course of the radial artery becomes visible. Meticulous dissection along with clipping of smaller branches are performed to harvest the radial artery and its pedicle. Following harvesting, this conduit is usually cannulated in the proximal end and gently flushed with a vasodilator solution such as papaverine. The entire conduit is then wrapped in a papaverine-soaked gauze.

Some important concepts in radial artery harvesting include avoiding electrocautery to divide branches and avoiding excessive manipulation. Moreover, while the standard adopted technique of radial artery harvesting is with a pedicle encompassing venae comitantes, perivascular fat and areolar tissue, some surgeons also have suggested harvesting the radial artery in a skeletonized fashion. Amano et al compared skeletonized versus pedicled radials and showed that the patency of skeletonized radials
(96.5%) was higher than pedicled grafts (84.9%) at 3 months. While the data are limited and mostly restricted to less than 5 years after CABG, Ali et al. performed a systematic review of 4 studies comparing skeletonization to pedicled harvesting and concluded that the patency of pedicled radials is excellent, however skeletonization may offer the radial conduit some additional patency benefit.

Another factor in radial artery harvesting is endoscopic versus open. While there are no current published RCTs, Cao et al. performed a large meta-analysis of 12 observational studies comparing endoscopic versus open radial harvesting involving 3314 patients and reported no significant differences in overall mortality or recurrent MI; however the endoscopic group had significant lower incidence of wound infection, hematoma, and paresthesia. Furthermore, Wu et al. performed a meta-analysis of 10 studies involving 2782 patients and reported no differences in graft occlusion early or mid-term after CABG between endoscopic and open techniques.

Finally, to prevent radial artery spasm, in addition to using vaso-dilator therapy intraoperatively using solutions like papaverine, and avoiding excessive vasoconstrictor use in the CVICU, surgeons also tend to send patients home on oral calcium channel blockers (CCB). To this end, Gaudino et al. performed a RCT with 53 patients allocated to CCB and 47 allocated to no-CCB after undergoing radial artery harvesting and reported no difference in clinical outcomes and patency rate in the first year after CABG; these similarities also persisted after 5 years. Patel et al. performed a systematic review including 14 studies and concluded that routine use of CCBs in order to reduce vasospasm,
showed no clinical benefit. Perioperative use of these agents has been suggested by the STS practice guidelines.134

A concern often associated with radial artery harvesting is peripheral neurological complications.135 The three most common nerves that tend to be involved during radial artery harvesting are the lateral antebrachial cutaneous nerve associated with sensation to the radial aspect and adjacent dorsal surface of the forearm, the superficial radial nerve associated with sensation to the dorsal skin of the thumb and proximal interphalangeal joints, and the median nerve associated with sensation to the palm and motor function of the thumb.135-137 To this end, Meharwal et al.,138 investigated 3977 patients that underwent CABG using a radial and reported low morbidity and good functional outcome of the hand. Saeed et al.,139 conducted a cross-sectional telephone survey of 127 patients that underwent radial artery harvest and found that a large portion of patients (67.7%) reported altered sensation around the thenar eminence, however this was self-limiting and clinically insignificant in the majority. They found greater patient satisfaction for radials compared to SV. Another study by Budillon et al.,140 prospectively studied 271 patients that underwent radial artery harvesting and found no symptoms of ischemia or motor dysfunction; however 3.7% reported cutaneous paresthesia. Zhu et al.,141 studied 408 patients using questionnaires with a follow-up of 9.3 years after CABG and concluded that radial artery harvesting was associated with high patient satisfaction and less scar discomfort compared to SV harvesting. Furthermore, a small proportion of patients seemed to experience forearm pain and numbness, however this was not different than those who did not undergo radial artery harvesting suggesting these sensations maybe due to non-surgical causes. Finally, Holman et al.,142 as part of a secondary analysis of the previously mentioned VA radial artery trial,82
reported that the radial artery group had significant more pain than the saphenous vein group at 3 months, however this was similar at 12 months; grip strength and manual dexterity were not significantly affected by radial artery harvesting.

1.2.2.3 - Saphenous Vein Harvesting

**Synopsis:** This section focuses on SVG harvesting techniques. Given one of the studies of the thesis is directly related to the harvesting techniques of the SVG, we therefore have elaborated on how potential steps in the pathology of SVG failure have been postulated to involve SVG harvesting techniques. Furthermore, we have described the two types of harvesting techniques that are of question – 1) Conventional and 2) The novel no-touch technique – and provided a detailed knowledge to date of the biological and clinical evidence comparing these two methods. To be complete, we concluded this section with description and evidence of endoscopic vein harvesting.

While SVGs are a commonly utilized conduit, this type of conduit is associated with an increased proportion of graft failure.\textsuperscript{143} It is estimated that within 1 year, 15% of SVGs are occluded and about 50% occluded beyond 10 years with an annual attrition rate of 1-2% between 1-6 years and 4-6% beyond 6 years.\textsuperscript{143} The pathogenesis of vein graft failure has been associated with endothelial injury.\textsuperscript{144} Damage to endothelial injury can lead to thrombosis and early graft failure; furthermore, endothelial injury along with vessel wall damage and ischemia can lead to inflammation and vessel wall remodeling resulting in intimal hyperplasia. The thickened intimal layer is highly vulnerable to infiltration of monocytes that differentiate into macrophages and develop into foam cells ultimately responsible in accelerated atherosclerosis;\textsuperscript{144} majority of late SVG failure are associated
with progression of atherosclerosis. To date, despite numerous clinical trials, other than anti-thrombotic and lipid-lowering agents, no other pharmacological agents have been effective in preventing early vein graft remodeling or subsequent atherosclerosis. As such, one of the preventative foci has been on minimizing endothelial injury during the harvesting technique.

Conventional SVG harvesting (CON) usually consists of a continuous longitudinal incision of the leg, stripping the perivascular tissue, ligating the side branches and removing the saphenous vein in a skeletonized fashion. The vein is then manually distended with saline and then stored in saline soaked solution at room temperature until it is ready to use.

A novel technique of harvesting the SVG involves an atraumatic no-touch (NT) method. This technique consists of the same longitudinal continuous incision of the leg along with ligating side branches. However, the vein is harvested with its surrounding tissue (pedicled) and left in-situ until required and allowed to dilate when exposed to arterial pressure (as oppose to manual dilation).

Given one of the studies in the thesis compares CON vs NT, this section will elaborate on the existing studies that have provided the foundation for the study that was undertaken.

Multiple biohistochemical and a few clinical studies from Orebro Sweden, led by de Souza, have been performed comparing NT to CON. A single RCT was performed and longitudinal patency was reported after short (18 months after CABG, 118 NT grafts vs 112 CON grafts), mid (8.5 years after CABG, 91 NT grafts vs 77 CON grafts) and long-term (16 years after CABG, 27 NT grafts vs 27 CON grafts) follow-up. Using cineangiograms, they reported superior NT graft patency in both the early (95.4% NT vs
86.2% CON),\textsuperscript{146} mid (90% NT vs 76% CON)\textsuperscript{148} and long-term period (83% NT vs 64% CON).\textsuperscript{149} They used intravascular ultrasound (IVUS) to assess mechanistic reasons for this over time and reported less mean intimal thickness and hyperplasia in the NT grafts compared to CON in the early period; in the late period, fewer NT grafts were associated with multiple plaques, less advanced plaques with lipids and less maximal plaque thickness compared to CON. They concluded that NT veins maybe associated with a significantly slower progression of atherosclerosis.\textsuperscript{147}

While multiple factors may be contributing to a slower atherosclerosis progression in NT veins, Dashwood et al.,\textsuperscript{150} performed a histological study to investigate some of these pertinent factors. The investigators obtained samples of veins using the NT and CON technique and examined tissue distribution and protein expression of endothelial nitric oxide synthase (eNOS). eNOS is involved in production of nitric oxide (NO) that is a potent vasodilator and has multiple anti-graft failure properties including inhibition of platelet aggregation, thrombus formation, leukocyte adhesions and vascular smooth muscle cell proliferation.\textsuperscript{150} This group determined that NT veins with minimal surgical trauma and endothelial injury retained a normal architecture including intimal folds and intact endothelial luminal cells. In contrast, the intimal folds were absent from the CON veins along with areas of endothelial denudation likely from high pressure distention. Furthermore, the adventitial endothelial cells of the NT veins were largely undamaged likely due to the adventitial layer being cushioned in the pedicle layer that is harvested along with the vein. On the other hand, CON veins had areas of damage in the media and adventitia and the vasa vasorum. Immunohistochemical staining showed reduced eNOS staining in the CON veins, in areas of endothelial damage whereas in the NT veins, eNOS
staining was continuous. These findings shed light on the fact that CON veins, as a result of endothelial injury and mechanical distention have a distorted vein architecture and reduction of eNOS and NO which are important components of keeping grafts patent.

Another study by Dashwood et al.,\textsuperscript{151} focused on the function of perivascular tissue and effect of high pressure (300 mmHg) distention. Using immunohistochemical techniques, they examined 26 veins with each vein having 4 prepared segments (CON with distention, CON without distention, NT with distention, NT without distention). They reported that distention induced substantial damage to the luminal endothelium and vessel wall. As shown in a previous study,\textsuperscript{150} this study showed that eNOS expression was also reduced in those veins with high pressure distention likely due to endothelial damage. Furthermore, eNOS was also reduced where there was removal or damage to the perivascular tissue. The damaging effects of distention was more pronounced in veins without perivascular tissue than with perivascular tissue suggesting that the adventitial layer has a protective effect against mechanical injury. Moreover, a significant proportion of eNOS is associated with the adventitial layer; thus damage to this layer further reduces eNOS production.\textsuperscript{151}

An important component of the adventitial layer is the vasa vasorum (VV). The VV is a network of microvessles that provides nutrients and oxygen to the SVG vessel wall.\textsuperscript{152} Furthermore, increased luminal pressure (as that seen with mechanical distention of CON veins) is associated with a shape change in the VV from circular to an elliptical, which reduces blood flow to the media of the vessel wall, thereby reducing elasticity.\textsuperscript{152} In addition to this, the VV layer is surrounded by densely innervated sympathetic nerves and smooth muscle cells suggesting that the microvessles in the VV can autoregulate their tone;
as such, distention and surgical induced trauma can induce constriction of these microvessels in the VV and cause reduced flow to the vein wall.\textsuperscript{152} Dreifaldt et al.,\textsuperscript{152} showed that the total area of VV in CON veins were significantly reduced in the medial and adventitial layer compared to the NT veins. Furthermore, in the NT veins, the VV was intact whereas the CON veins, it was not. Finally, they were able to show by video footage that luminal blood flow occurs through the VV to the vessel wall via retrograde flow after vein implantation using the NT technique. Thus, the preservation of the VV can prevent vein ischemia and malnutrition.

While there has been growing histological and biochemical evidence showing the importance of endothelial preservation, avoidance of mechanical distention and preservation of the pedicle containing adventitia and the VV, there have been a few clinical studies. One small study, the PATENT SVG\textsuperscript{153} enrolled 17 patients that underwent CABG using SVGs from both legs. These patients were randomly allocated to have SVGs harvested by NT from one leg and CON technique from the other; endpoints were composed of histological and clinical outcomes. Histological endpoints demonstrated that NT veins had early molecular and morphological patterns consistent with decreased vascular smooth muscle cell activation (VSMC) compared with CON; as mentioned earlier, smooth muscle cell activation is associated with neointimal hyperplasia which can lead to atherosclerosis and graft failure.\textsuperscript{153} Furthermore, functional leg recovery was similar in both groups at 12 months.
While the above results are encouraging, the data (both basic and clinical studies) largely stems from a single centre in Sweden and needs to be replicated in a large scale elsewhere for generalizability.

Another option of harvesting the SVG is through endoscopic techniques. Using a few small incisions, a camera, and videoscopic instruments including cautery and long scissors, the vein is harvested. There are usually two techniques of doing this – the sealed and non-sealed system. The sealed device (such as the Vasoview System, MAQUET Getinge Group) uses carbon dioxide insufflation to create an endoscopic tunnel. In contrast, the non-sealed system (such as Genzyme), uses a retractor with an endoscopic camera for video-assisted conduit exposure. The theoretical advantages of endoscopic vein harvesting over an open technique include less wound complications, reduced postoperative pain, along with improved cosmesis. However, Lopes et al., performed a sub-analysis of the PREVENT IV trial studying 1753 patients that underwent endoscopic vein harvesting versus 1247 that underwent an open technique and reported a significantly higher vein graft failure at 12 to 18 months in the endoscopic group (46.7% vs 38.0%, p<0.001). At 3-years, endoscopic harvesting was also associated with higher rate of clinical events (death, MI or repeat revascularization (20.2% vs 17.4%, p=0.04). Following the publication of this study, Sastry et al., performed a meta-analysis of 267,525 patients comparing clinical outcomes between endoscopic and open vein harvesting techniques and found no difference in mortality, MI, repeat revascularization, angina, vein graft stenosis or occlusion at 2.6 years. Furthermore, to date, the NT technique cannot be employed using endoscopic techniques. As mentioned previously, single centred biochemical and clinical studies have shown
favorable SVG remodeling properties and superior late graft patency compared to the conventional open vein harvesting.\textsuperscript{149,156} To this end, Mannion et al.,\textsuperscript{157} retrospectively compared 87 patients receiving NT SVG versus 123 patients receiving endoscopically harvested SVGs, that underwent early symptom directed catheterization and reported superior significant vein graft patency in the NT cohort (94\% vs 27\%, \(p<0.02\)) at 2 years; however, harvest site complications were significant higher in the NT cohort (18\% requiring vacuum-assisted wound closure or intravenous antibiotics vs \(2\%, \ p<0.0001\)). Thus, while NT confers better graft patency, studies thus far seem to show that this technique is associated with more wound complications.

1.3 – Pharmacological Factors

\textbf{Synopsis:} In addition to surgical factors, pharmacotherapy is also a mechanism in optimizing CABG outcomes. We briefly describe the usual conventional classes of drugs that are given following CABG include anti-platelets, beta-blockers, ACE-inhibitors, and anti-lipids.\textsuperscript{158} We then delve into another potential medical therapy (fish oil supplementation following CABG) and highlight its potential mechanisms in cardiovascular protection and CABG and present the current knowledge to date in this topic.

1.3.1 – Aspirin, Dual Anti-platelets and Anti-thrombotics

\textbf{Synopsis:} This section focuses on common anti-platelets and anti-thrombotics used after CABG. We also discuss the role of dual anti-platelets therapy.
The importance of aspirin (ASA) after CABG was demonstrated by a landmark study by Goldman et al.,\textsuperscript{159} that randomized various regimens of ASA alone, ASA with dipyridamole, sulfinpyrazone and placebo. They reported that early vein graft patency was improved with ASA containing regimens. Another study by Goldman et al.,\textsuperscript{160} determined that 325mg of ASA started the night before compared to 6 hours following surgery offered no additional benefit with regards to early graft patency; however preoperative ASA was associated with increased bleeding. The administration of ASA within 6 hours of CABG and continued indefinitely to reduce graft occlusion and adverse cardiac events is a Class I, Level A recommendation.\textsuperscript{161}

The appropriate use of ASA along with another antiplatelet therapy (DAPT) following CABG is less clear.\textsuperscript{162} The CASCADE trial\textsuperscript{163} (Clopidogrel After Surgery for Coronary Artery Disease) randomized 113 patients to receive ASA alone or ASA with Clopidogrel after CABG. They reported that at 1-year, there were no difference in SVG intimal area, overall graft patency and SVG patency; there were also no difference in clinical events. A meta-analysis of 5 RCTs comparing single vs DAPT,\textsuperscript{164} showed no difference in patency between single and DAPT for arterial grafts; however, DAPT had a protective effect for SVG (OR 1.7, p=0.003). They concluded that DAPT increases patency of venous grafts but noted that definitive clinical trials adequately controlling for bleeding risk and graft type are required. Deo et al.\textsuperscript{165} performed another meta-analysis of 11 studies (5 RCTs and 6 observational studies) comparing single versus DAPT and concluded that DAPT improved early SVG patency and was most beneficial in OPCAB patients; DAPT was also associated with a higher incidence of bleeding. Most of the supportive evidence of DAPT comes from patients who have had a recent acute coronary syndrome (ACS).\textsuperscript{162,166} Another area where
DAPT may be beneficial are patients with recent ACS. The CURE trial randomized 12,562 patients with unstable angina or NSTEMI to ASA or ASA and Plavix and reported similar positive benefits for the DAPT group in early and long-term clopidogrel therapy in those undergoing revascularization (either CABG or PCI); the benefits of clopidogrel therapy outweighed the risk in this study. Bomb et al. performed a review and concluded that while there is no clear consensus regarding the use of DAPT in patients after CABG, it is reasonable to use in patients with ACS; this is largely predicated on and extrapolated on from the success of DAPT in ACS patients being managed medically and invasively through PCI. Current AHA guidelines based on the existing evidence recommends that DAPT should be administered for 1-year after OPCAB (Class I, Level A) and reasonable to administer in patients who had an ACS (Class IIa, Level B).

With regards to anti-coagulants, the AHA guidelines do not recommend the use of warfarin after CABG unless there are other indications including atrial fibrillation, deep vein thrombosis or the patient has a mechanical valve prosthesis.

1.3.2 – Beta-blocker

**Synopsis:** *This section focuses on the effects of beta-blockers on patients after CABG including some of the important trials in this topic.*

The use of a beta-blocker perioperatively, while common practice, is controversial with respect to benefit after CABG. Most patients are usually on a beta-blocker preoperatively. Ferguson et al. conducted an observational STS database study including 629,877 patients undergoing isolated CABG from 1996-1999 investigating the influence of b-blockers (BB). They reported reduced 30-day mortality in the BB group (OR
0.8, 95% CI (0.72-0.82)); however, those with LVEF < 30%, the use of BB was associated with a non-significant higher mortality (OR 1.13, 95% CI (0.96-1.33)). They concluded that preoperative BB use was associated with small but consistent survival benefit except in patients with decreased LVEF <30%. In contrast, Brinkman et al.,[168] conducted another study using the STS database of 12,855 patients undergoing isolated CABG from 2000-2008; using propensity matching, they concluded that preoperative use of BB was not a predictor of mortality. Furthermore, the use of BB as an antihypertensive agent is also controversial; Bangalore et al.,[169] critically reviewed the existing literature of the efficacy of BB on patients with uncomplicated hypertension and showed that the risk benefit ratio for BB was not acceptable as a long-term antihypertensive agent compared to other agents.[169] However, Freemantle et al.,[170] performed a meta-analysis of 54,000 patients, and reported a 23% reduction in mortality with BB for long-term secondary prevention after MI. Patients with heart failure have also been shown to benefit from BB with regards to a decrease in mortality.[161] Finally, BB is one of the main agents to treat atrial fibrillation following CABG.[161] As such, the use of BB is recommended in CABG patients with a history of MI, or LV dysfunction and perioperatively to prevent AF.[161]

1.3.3 – ACE-Inhibitors or Angiotensin Receptor Blockers (ACE-inhibitor/ARB)

Synopsis: This section focuses on the effects of ACE-inhibitor/ARB on patients after CABG including some of the important trials in this topic.

The Renin-Angiotensin system is an important pathway involved in fluid regulation and consequently a target for antihypertensive agents.[171] ACE-inhibitors work by inhibiting the angiotensin converting enzyme released from the lungs involved in converting
The function of Ang II (potent vasoconstrictor, stimulator of LVH, release of aldosterone) is therefore suppressed. Furthermore ACE-inhibitors also inhibit the breakdown of bradykinin, a molecule that has antihypertensive and antiremodeling properties. Angiotensin receptor blocker (ARB) directly inhibits Ang II by inhibiting Ang II receptors. In patients with previous MI or reduced EF, ACE-inhibitors have been reported to reduce heart failure symptoms and mortality; however, in patients with CABG, the use of ACE-inhibitor is not recommended for patients with EF>40%. In patients with intolerance to ACE-inhibitor, an ARB can be used in the same type of patients. Thus according to current guidelines, ACE-inhibitors should be given to patients following CABG with recent MI, LV dysfunction, DM or chronic kidney disease (Class 1, Level B) aiming for a target BP of less than 140/85 (Class IIa, Level B).

1.3.4 – Statins

Synopsis: This section focuses on the effects of statins on patients after CABG including some of the important trials in this topic.

Elevated cholesterol levels, especially LDL, is associated with SVG disease and progression of native vessel disease after CABG. Statins, a commonly used antihyperlipidemic agent, competitively inhibit 3-hydroxy 3-methylglutaryl CoA reductase that catalyzes the rate limiting step in the cholesterol synthesis pathway. The Post Coronary Artery Bypass Graft Trial (Post-CABG trial) was the first RCT to show the effectiveness of statins after CABG. In this 2x2 factorial study, 1351 patients who had undergone CABG was randomized to moderate or aggressive statin therapy using lovastatin
and warfarin versus placebo therapy. They reported that at 4 years, aggressive lipid lowering therapy to below 100 mg/dl reduced progression of atherosclerosis in bypass grafts. Low dose warfarin did not reduce progression of atherosclerosis. An extended follow-up of this study (7.5 years) showed a 30% reduction in revascularization and 24% reduction in composite clinical endpoints were seen in the aggressive lipid lowering group. A systematic review of published studies of statins following CABG showed that statins reduces the recurrence of cardiovascular events and improve all-cause mortality. According to the current AHA guidelines, unless contraindicated, all CABG patients should receive statin therapy. It is worth noting that proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors has become another pharmacological anti-lipid agent of interest. The GLAGOV study (GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound), recently published in JAMA showed that in patients with angiographically documented coronary disease who are on a statin, evolocumab (PCSK9 inhibitor) compared to placebo, resulted in a greater decrease in percent atheroma volume (measured by serial intravascular ultrasound) after 76 weeks of treatment. Further studies are required to confirm these findings.

1.3.5 – Fish Oils

**Synopsis:** Given that the efficacy of fish-oils after CABG is one of the studies in this thesis, the section focuses on the effects of fish-oils on cardiovascular disease and specifically ischemic heart disease. The section begins with a description of the biologically important fatty acids in fish-oils followed by potential mechanisms of cardiovascular protection. The
section concludes with important studies investigating the efficacy of fish-oils in cardiovascular outcomes, especially in patients that have undergone CABG.

In addition to conventional medications, fish oils, a source of omega-3 (also known as n-3 polyunsaturated fatty acids), that includes eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to be cardioprotective.\textsuperscript{177-179} The concept of fish oils as a potential therapy in cardioprotection was conceived in the late 1960s as a result of reports showing that Greenland Eskimos had a low prevalence of coronary disease.\textsuperscript{177} Compared to Danish controls, the Inuit had a low incidence of myocardial infarction and reduced platelet activity; these findings were largely attributed to the Inuit diet composed mainly of seal and whale rich in n-3 fatty acids.\textsuperscript{177} Such studies undertaken by Dyerberg and Bang\textsuperscript{180-182} in 60s and 70s, led to their seminal paper in 1978 that proposed n-3 fatty acids offer protection against atherosclerosis and thrombosis.\textsuperscript{182}

Briefly, because mammals lack enzymes to insert the double bond in the n-6 or n-3 position, these fatty acids (linoleic acid, 18:2 n-6; Alpha-linoleic acid (ALA), 18:3 n-3) are therefore essential nutrients. These fatty acids are eventually converted to longer chain or highly unsaturated polyunsaturated fatty acids including EPA and DHA.\textsuperscript{177} While both EPA and DHA are associated with important physiological functions including fetal development, Alzheimer’s disease and cardiovascular function,\textsuperscript{179} both EPA and DHA predominantly require direct dietary consumption.\textsuperscript{183} In Western diets, the main source of EPA and DHA is fish, especially oily fish including salmon, herring and trout.\textsuperscript{177}

Since the seminal papers by Dynerberg and colleagues\textsuperscript{180-182}, there have been a number of studies that have investigated the effects of fish oils on cardiovascular outcomes. The Diet
and Re-infarction trial (DART)\textsuperscript{184} was an RCT of 2033 men who were recovering from a MI and were allocated to either receive or not receive advice on three dietary factors (1: advise to reduce fatty food intake (n=1018) versus no fat advice (n=1015), 2: increase fatty fish intake (n=1015) versus no advise on fish intake (n=1018) or 3: fiber advise(n=1017) or no fiber advice (n=1016)). The authors found a 29\% reduction in 2-year all-cause mortality in patients who received advice on increasing fish intake versus no advice; the advice on fat reduction was not associated with a difference in mortality leading the group to conclude that a modest intake of fish may reduce mortality in men who have recovered from a MI.

The GISSI-Prevenzione trial\textsuperscript{185} was another study of 11,324 patients who survived a recent MI (≤ 3 months) randomly assigned to 1 gram daily n-3 supplement (n=2836), 300 mg daily vitamin E (n=2830), both (n=2830) or placebo (n=2828) for 3.5 years. They showed that treatment with n-3 PUFA but not vitamin E significantly lowered the risk of death, non-fatal MI or stroke; there was a 45\% reduction in sudden death in MI survivors taking n-3 polyunsaturated fatty acids compared to controls.

While not clearly understood, potential mechanisms by which these fatty acids are cardioprotective include reduction in ventricular arrhythmias, reduction in hypertriglyceridemia, its anti-inflammatory properties and inhibitory effects of atherosclerotic growth.\textsuperscript{177,186} As such, the American Heart Association recommends at least 1 gram of EPA and DHA in the form of fish oil per day in patients with documented coronary heart disease.\textsuperscript{187} However, the effects of fish oils, in patients following CABG is unclear. An experimental study has shown that n-3 fatty acids reduces intimal hyperplasia in autologous vein grafts.\textsuperscript{188} Eritsland et al,\textsuperscript{189} randomized 610 patients undergoing CABG to 4g/day of fish oil versus control; all patients received either aspirin or warfarin. They
found that at 1-year, patients assigned to fish oil supplementation, had lower vein graft occlusion compared to controls (27% versus 33%, p=0.03). Furthermore, 43% of patients in the fish oil group compared to 51% in the control group (OR 0.72, p=0.05) had ≥ 1 occluded vein graft. Another observational study of 2,100 patients\textsuperscript{190} undergoing isolated CABG of which 930 (44%) were put on n-3 PUFA therapy at discharge showed that patients on n-3 PUFA supplements had a lower unadjusted and adjusted risk of late mortality (unadjusted HR 0.51, p=0.0002) and (Cox-regression adjusted HR 0.55, p=0.02). Adjusted risk of composite endpoints of death, Q-wave MI or stroke was lower in patients on n-3 PUFA compared to patients who did not receive this (HR 0.56, p=0.001). Furthermore, these patients on n-3 PUFA also had a lower risk of repeat revascularization, suggesting possible lesser graft disease.\textsuperscript{190} Given the limited number of studies showing the potential benefits of fish oils in patients following CABG, and the importance of addressing vein graft failure in these patients, further studies in this topic are warranted.

1.4 – Patient Factors

Synopsis: The above sections have highlighted surgical and pharmacological factors that may influence CABG outcomes. This section highlights patient-specific factors that may impact early or long-term CABG outcomes. Two such factors (and studies in this thesis) are Diabetes Mellitus and Ethnicity – both of these will be discussed in the subsequent sections.

1.4.1 – Diabetes Mellitus
Synopsis: This section will focus on patients with diabetes undergoing CABG. More specifically, it begins by highlighting the benchmark studies that are guiding current myocardial revascularization strategies in diabetics. This section then transitions into the use of multi-arterial grafting in diabetics and hones in on the use of radial arteries compared to SVG in diabetics.

Diabetes Mellitus (DM) currently affects more than 285 million people globally and is projected to nearly double to 489 million by 2030. Diabetics are associated with a diffuse and accelerated rate of atherosclerosis leading to a 2 to 4 fold increased risk of coronary artery disease. While patients with DM account for an increasing need for coronary revascularization, clinical outcomes following either PCI or CABG are worse in diabetics compared to non-diabetics (Non-DM). To this end, the superiority of PCI or CABG, was a focus of investigation in diabetics and their late results have been recently reported from 2 large trials.

In the Future Revascularization Evaluation in Patients with DM: Optimal Management of Multivessel Disease (FREEDOM) trial, 1,900 diabetic patients with multivessel coronary disease from 140 international centres were randomized to either PCI (predominantly sirolimus or paclitaxel-eluting stents) or CABG (arterial revascularization encouraged) from 2005 to 2010. At 5-years, the primary outcome of death, non-fatal MI or non-fatal stroke was significantly higher after PCI (PCI:26.6%, CABG:18.7%, p=0.005). While this was driven largely by MI and all-cause mortality, stroke was more frequent in the CABG group.
In the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial,\(^{195}\) 1,800 patients with left main and/or 3-vessel disease were randomized to either receive TAXUS eluting stents or CABG; 5-year subgroup results were reported in 452 diabetics and 1,348 non-diabetics. There were significantly higher MACCE in diabetics undergoing PCI compared to CABG (PCI: 46.5%, CABG: 29.0%, \(p<0.001\)); the rates of revascularization were also higher with PCI.

A large meta-analysis composed of 8 RCTs comparing PCI to CABG in diabetic patients by Verma et al,\(^{196}\) (n=7,468 patients, 3,612 diabetic), reported that diabetic patients with multivessel disease who undergo CABG have a decreased long-term mortality by about a third compared with PCI (bare-metal stents or DES). Deb et al., performed a cumulative meta-analysis\(^{197}\) of the included studies in the above meta-analysis by Verma\(^{196}\) and showed that following the publication of the FREEDOM trial in 2012, CABG was statistically favorable over PCI with respect to all-cause mortality (Cumulative OR 0.69, 95% CI (0.53-0.89), \(p=0.005\)). After inclusion of all 8 RCTs, the revised cumulative OR was 0.62, 95% CI (0.46-0.82), \(p=0.001\), favoring CABG.

Furthermore, a large systematic review suggested that in view of all the current evidence, the recommendations of the current guidelines (both American and European) for CABG in patients with diabetes and multivessel disease should be upgraded to Class I, Level A.\(^{18}\) To this end, in 2014, the American revascularization guidelines have been updated to make CABG a Class I, Level B (from Class IIa, Level B) recommendation for diabetic patients with multivessel disease.\(^{38}\)
Given the increasing support of CABG in diabetics, studies have been undertaken to determine how best to optimize long-term graft patency in this cohort.\textsuperscript{71} It has been shown that internal mammary arteries are more resistant to atherosclerosis.\textsuperscript{59} Given the higher propensity of atherosclerosis in diabetics,\textsuperscript{192} surgeons have questioned whether arterial grafting would be more beneficial in this cohort compared to SVG.

In this regard, Raza et al.,\textsuperscript{71} performed a retrospective study of 11,922 diabetic patients that underwent isolated CABG using BIMA versus SIMA; at a median follow-up of 7.8 years, they reported BIMA grafting with complete revascularization maximizes long-term survival and recommended its use in diabetics whose risk of deep sternal wound infection is low.

The Radial Artery Patency Study (RAPS), is a multi-centre randomized trial comparing radial versus SVGs in patients with multivessel disease undergoing CABG.\textsuperscript{80} In a sub-analysis, Singh et al\textsuperscript{106} reported that at 1-year (n=440 patients), a higher proportion of SVG were occluded in diabetics compared to radial arteries (SVG: 19\%, RA: 12\%, p=0.04); furthermore, radial artery grafting compared to SVG, was protective in the diabetic cohort (RR=0.42, p=0.05). With regards to late results, there are observational studies that document the benefit of radials over SVG with regards to survival,\textsuperscript{198,199} however, to our knowledge, there are no RCTs examining long-term patency between radials and SVG in diabetics.

1.4.2 – Ethnicity

Synopsis: This section focuses on ethnicity as a potential predictor of CABG outcomes. More specifically, it hone\textsubscript{s} in on South Asians and describes its high risk cardiovascular profile. The section concludes with the current evidence to date comparing South Asians to
Non-South Asians (predominantly Caucasians) with respect to clinical outcomes after CABG.

Another patient factor that has been recognized to influence CABG outcomes is ethnicity. One of the seminal studies that highlighted the importance of ethnicity was a study performed by Hartz et al. that utilized the STS database to analyze 441,542 patients that underwent isolated CABG between 1994-1996 and concluded that race (defined in this study as Caucasian versus non-Caucasian) is an independent predictor of adverse outcomes following CABG.

South Asians (SA), defined as people originating from India, Pakistan, Sri Lanka, Nepal and Bangladesh, is one of the largest ethnic groups in the world, representing about one-fifth of the world’s population. Migration has resulted in a large portion of SA in the western world including Canada, the United States and the United Kingdom. In Canada, SA represents one of the largest visible minority groups projected to increase from 1.3 million in 2006 to approximately 4.1 million by 2031.

In addition to being one of the largest visible minorities, the landmark SHARE study (Study of Health Assessment and Risk in Ethnic Groups) showed that SA had the highest prevalence of cardiovascular disease compared to Europeans and Chinese. There are many possible reasons for this including a higher incidence of diabetes, hypertension, and lower high density lipoprotein levels in South Asians compared to other ethnic groups. SA also tend to have higher abdominal visceral fat along with a higher risk of metabolic syndrome. Furthermore, besides dietary risk factors including a higher consumption of ghee (clarified butter) which may be associated with more atherogenic cholesterol, SA
have also been shown to have a higher level of lipoprotein A (Lpa). This protein may impair fibrinolysis which has been shown to be decreased in SA compared to Africans and Europeans. Additionally, SA have been associated with small LDL particles, as well as increased levels of inflammatory markers including high-sensitivity C-reactive proteins which are all associated with atherosclerosis.

Furthermore, SA have been shown to have more extensive coronary disease and systolic dysfunction at time of coronary angiography. In addition to a high burden of coronary disease, there is a notion that coronary artery size is smaller in SA compared to other ethnic groups. Small coronaries along with diffuse coronary disease can make CABG difficult in this large ethnic group.

A study by Quan suggested that physicians may consider ethnicity when deciding which procedure to recommend. With respect to PCI, Jones et al. performed a retrospective analysis of 279,256 patients (SA: 19,938, Caucasians: 259,318) that underwent PCI in the UK between 2004-2011. They reported that in-hospital and medium-term mortality was no worse in SA compared to Caucasians and concluded that ethnicity itself is not an independent predictor of clinical outcomes after PCI. With regards to CABG however, the evidence is more controversial. This is largely because there are a small number of studies and these studies are limited by small sample size, short follow-up or lack of adjusting methods. Given that physicians may consider ethnicity as a factor in determining the type of revascularization procedure, determining long-term clinical outcomes after CABG is important.
1.5 – Thesis Objective, Overall Study Objectives and Hypotheses

In the US, coronary revascularization procedures are amongst the most costly interventions compared to other medical or surgical procedures;\textsuperscript{216} CABG is one of the most common myocardial revascularization procedures performed in North America\textsuperscript{216} As such, it is imperative to continuously strive for excellence in early and late outcomes after CABG; in this regard, both surgical, pharmacological and patient factors are important considerations as knowledge in this regard can enhance patient selection and surgical decision making.

The underlying objective of this thesis is to investigate surgical, pharmacological and patient factors affecting early and late outcomes after CABG.

1.5.1 – Study 1 Objectives and Hypotheses – Surgical and Pharmacological Factors

The objectives of this study were 2 fold:

1) Surgical - To determine whether the NT was superior to the CON harvesting technique of the SVG with respect to angiographic patency and clinical outcomes at 1 year.

**Hypothesis 1:** We hypothesized that the NT technique would result in superior angiographic patency and clinical outcomes at 1-year after CABG compared to patients receiving the CON technique.
2) Pharmacological – To determine whether fish oil supplementation for 1-year following CABG compared to placebo resulted in superior angiographic patency and clinical outcomes at 1 year.

**Hypothesis 2:** We hypothesized that patients that received fish-oil would result in superior angiographic patency and clinical outcomes at 1-year compared to patients receiving a placebo.

1.5.2 – Study 2 Objectives and Hypotheses – Surgical Factor, Conduit Selection

The objective of this study was to determine whether the radial artery is superior to the SVG with respect to angiographic patency and clinical outcomes beyond 5-years after CABG in patients with and without diabetes.

**Hypothesis 3:** We hypothesized that radial artery patency would be significantly greater than SVG in both diabetics and non-diabetics. We also hypothesized that non-diabetic patients would have better late clinical outcomes compared to diabetics following CABG.

1.4.3 – Study 3 Objectives and Hypotheses – Patient Factor, Ethnicity

The objective of this study was to determine whether ethnicity, specifically the high risk South Asian cohort compared to the general population in Ontario, Canada, resulted in worse late clinical outcomes after CABG.

**Hypothesis 4:** We hypothesized that being a South Asian would result in worse clinical outcomes following CABG than the general population.
1.6 – Chapter Preview

Preview to Chapter 2 – Surgical and Pharmacological Factors

Chapter Title: Surgical and Pharmacological Factors: Surgical and Pharmacological novel intERventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting surgery: An International Multi-center Randomized Controlled Clinical Trial (SUPEROR SVG Study, NCT 01047449)

A major limitation of CABG is SVG failure. This chapter addressed whether harvesting techniques (NT vs CON) and pharmacological measures (Fish oil supplementation versus placebo), can improve angiographic patency in SVGs and clinical outcomes after 1-year. This was investigated in an international multi-centre RCT using a 2x2 factorial design.

Preview to Chapter 3 – Surgical Factors

Chapter Title: The long-term impact of diabetes on graft patency after coronary artery bypass grafting surgery: A substudy of the multicenter Radial Artery Patency Study (RAPS)

While there is more evidence of arterial grafting, it is not yet clear whether arterial grafting is beneficial and appropriate in diabetics. This chapter therefore addressed whether radial artery grafting compared to SVG, was beneficial in diabetics compared to non-diabetics beyond 5-years following CABG. This was a sub-study of the RAPS trial, which was an international multi-centre RCT comparing radial artery with SVG.
Preview to Chapter 4 – Patient Factor

Chapter Title: Impact of Ethnicity on Long-Term Outcomes after Coronary Artery Bypass Grafting Surgery: A Large Population-Based Propensity Matched Study

Ethnicity has become an important variable in risk-stratification for CABG; reports have suggested that physicians may consider ethnicity in recommending certain types of procedures. There is a notion that South Asians, one of the largest visible minorities with a high burden of cardiovascular disease, may do worse after CABG compared to other ethnic groups. This chapter addressed whether there was a difference in long-term clinical outcomes between South Asians (SA) and the general population (GP) after CABG. This study was an administrative database study using ICES (Institute of Clinical Evaluative Sciences) databases and utilized propensity score matching techniques to adjust for baseline differences.

Preview to Chapter 5 – Discussion / Synthesis

This chapter aggregated the relevant findings from the 3 major studies. It discusses the relevance of the findings along with discussing supporting and contradicting evidence. Furthermore, the novelty of our findings and its integration to clinical practice is discussed and future gaps for further research are identified in order to further enhance early and long-term success of CABG.
Chapter 2
Surgical and Pharmacological novel interventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting surgery: An International Multi-centre Randomized Controlled Clinical Trial

(SUPERIOR SVG Study, NCT 01047449)
2.1 Abstract

Objectives: To determine whether the no touch (NT) versus conventional (CON) saphenous vein graft (SVG) harvesting technique and fish oil supplementation (FO) versus placebo (P) are associated with superior SVG patency and clinical outcomes 1 year after CABG.

Methods: Adults undergoing isolated CABG with at least one SVG were enrolled in an international multi-centre randomized clinical trial using a 2x2 factorial design; surgical intervention compared NT (atraumatic, pedicled without mechanical dilation) versus CON (skeletonized, mechanical dilation) technique; pharmacologic intervention compared 2 grams/day of FO or P for 1 year post-CABG. CT angiography (CTA) and clinical follow-up at 1-year post CABG were performed.

Results: A total of 250 patients were randomized across 13-centres (NT 127 versus CON 123 patients, FO 70 versus P 70 patients). Surgical Intervention: The proportion of study SVGs occluded or cardiovascular death at 1-year was not significantly different in NT versus CON (NT: 7/127 (5.5%), CON 13/123 (10.6%), p=0.14). Furthermore, the proportion of study SVGs with significant stenosis or total occlusion (SSTO) (NT: 8/102 (7.8%), CON: 16/107 (15.0%), p=0.11) was also not significantly different between groups. Pharmacologic Intervention: The proportion of patients with \( \geq 1 \) graft occlusion or cardiovascular death were not significantly different between groups (FO 21/70 (30.0%), P: 14/70 (20.0%), p=0.17). Major adverse cardiac and cerebrovascular events (death, myocardial infarction, stroke, repeat revascularization) were similar between NT and CON (p=0.59), and in FO and P groups respectively ((17/70 (24.3%) vs 11/70 (15.7%), p=0.22).
**Conclusion:** Neither the NT technique nor fish oil supplementation were associated with improved patency of SVGs at 1-year following CABG. The limited sample size cannot exclude a clinically meaningful benefit of the NT technique and longer term follow-up or studies of larger sample size are warranted.

Figure 2.1 – Central picture - A 2x2 factorial design of No-touch vs conventional vein technique and fish-oils vs placebo
2.2-Background
Graft patency is an important determinant of long-term clinical success after coronary artery bypass graft surgery (CABG). The most common utilized graft in CABG continues to be the saphenous vein (SVG); contemporary studies continue to show 1 year occlusion rates ranging from 10-30% which is associated with cardiac events.

It has been postulated that vessel wall damage from endothelial injury, as can occur with conventional skeletonized SVG harvesting (CON) and routine manual SVG dilation, can lead to inflammation, vessel wall remodeling, and intimal hyperplasia, providing a milieu for neointimal hyperplasia, accelerated atherosclerosis and graft closure. The atraumatic no-touch technique (NT) of harvesting the SVG with its pedicle intact has been shown to result in favorable biochemical and histological properties of the NT-SVG compared to CON-SVG. Furthermore, a single-centred randomized control trial (RCT) of 156 patients has shown that early (18 months, NT: 95.4%, CON: 88.9%, p=0.03), mid (8.5 years, NT: 90%, CON: 76%, p=0.01) and late (16 years, NT: 83%, CON: 64%, p=0.03) graft patency was superior in NT compared to CON SVGs. While there is growing evidence in support of the NT technique, most of this evidence stems from small-scale studies from a few centres, necessitating a need for a larger multi-centre RCT before potential widespread application of this technique.

Fish oils, a large source of n-3 polyunsaturated fatty acids that includes eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to be cardioprotective. While not clearly understood, potential mechanisms by which these fatty acids are cardioprotective include reduction in ventricular arrhythmias, reduction in hypertriglyceridemia, anti-inflammatory properties and inhibitory effects of atherosclerotic
growth. As such, the American Heart Association (AHA) recommends at least 1 gram of eicosapentaenoic and docosahexaenoic acid in the form of fish oil per day in patients with documented coronary heart disease. There has been some potential protective effect associated with patients taking fish-oils undergoing CABG with regards to cardiac outcomes and vein graft patency, however, the evidence is limited.

The objectives of this study were to determine whether the NT compared to the CON technique and fish oil (FO) supplementation compared to placebo (P) are associated with superior graft patency and clinical outcomes 1 year after CABG, using a factorial design to test both interventions simultaneously.

2.3-Methods

Design

This was an international, prospective, multi-centre, randomized control trial utilizing a 2x2 factorial design involving 13 centres (10 Canada, 2 Sweden, 1 Israel). The surgical arm compared NT versus CON technique and the pharmacological arm compared FO to P. For the surgical arm, surgeons were unblinded while participants, care providers, data collectors and outcome adjudicators were blinded; for the pharmacological arm, all were blinded. This study was approved by the ethics committee at each of the participating centres and all participants provided written informed consent.

Randomization: Eligible and consenting patients were randomized using a computer generated randomization schedule. The randomization was stratified by site using a factorial design (NT vs CON and FO vs P) in variable block sizes to preserve concealment.
Randomization was centralized using a web based service. Surgery was to occur within 30 days of randomization.

**Population:** Adults > 18 years of age, undergoing isolated elective CABG with left ventricular ejection fraction (LVEF) above 20%, requiring at least one SVG were included. Details of inclusion and exclusion criteria can be found in Table 2.1.

**Interventions:** In the NT approach, patients had their SVG harvested using an open atraumatic technique with its surrounding tissue (pedicle). Instead of manual dilation, the harvested vein was left in-situ until required and allowed to dilate and check for bleeding branches only when exposed to arterial pressure (typically when attached to the arterial cannula, or following proximal anastomosis during off-pump surgery). In contrast, patients randomized to the CON technique had their SVG harvested in a skeletonized fashion stripping the vein of its adventitial layer. It was then excised and distended using heparinized saline. To reflect contemporary trends in practice, the CON technique could be performed open or endoscopic. The NT or CON study SVG was directed to the most important target for vein grafting as deemed by the surgeon prior to surgery. Patients underwent duplex scan vein mapping prior to surgery to assess vein quality and prevent flaps during harvesting. In cases of poor vein quality, the thigh was used to harvest the SVG using the respective techniques. All patients had the left anterior descending artery grafted with an internal mammary artery. Additional arterial grafts were used at the discretion of the operating surgeon. By protocol, the allocated SVG harvesting technique was to be used as well for additional SVGs. For standardization, all participating Canadian and International centres received NT harvesting training by SEF and DDS respectively.
In the pharmacological arm, patients were randomized to either 2-grams fish oil supplement (composed of 340mg EPA and 170mg of DHA per 1 gram capsule) or 2-grams of a colour, shape and taste matched placebo of 50/50 corn/soybean 1 gram capsule; both the fish oil and placebo capsules were supplied by Ocean Nutrition, Dartmouth, NS. The drug arm was started immediately after the patient was randomized. The drug was held on the day of surgery and restarted on postoperative day 1 until 1 year. Daily doses of fish oil supplement were based on existing studies.\textsuperscript{187,189,222}

Outcomes: Surgical Arm

Primary outcome

The proportion of study SVGs which are totally (100%) occluded on 64-slice cardiac CT angiography (CTA) at 1-year post-CABG or death (due to cardiovascular or unknown causes).

Secondary outcome

i. The number of study SVGs with a significant (50-99\%) stenosis on 1-year CTA.

ii. The number of study SVGs with a significant stenosis or total occlusion at 1-year CTA.

iii. The incidence of and severity of adverse SV harvesting events by 1-year (infection, hematoma, swelling, neuropathy,).

iv. The incidence of the major adverse cardiac and cerebrovascular events (MACCE, defined as the composite endpoint of all-cause mortality, perioperative and 1-year non-fatal MI (using the WHO definition, see below), stroke, and repeat revascularization (redo CABG or PCI).
Tertiary outcome

The incidence of major adverse cardiac and cerebrovascular events (MACCE-O, defined as the composite endpoint of all-cause mortality, perioperative and 1-year non-fatal MI (using an older definition, see below), stroke, and repeat revascularization (redo CABG or PCI).

Outcomes: Pharmacological Arm.

In contrast to surgical arm where we assessed study SVGs only for angiographic outcomes, in this arm, we assessed overall graft status (of all the grafts, not just study SVGs) for angiographic outcomes as we anticipate a more systemic effect to all the grafts as oppose to only the selective study SVG.

Primary outcome

The proportion of patients with ≥1 graft totally (100%) occluded on 64-slice cardiac CT angiography at 1-year post-CABG or death due to cardiovascular or unknown causes.

Secondary outcome

i. The proportion of patients with ≥1 graft with a significant (50-99%) stenosis on 1-year CTA.

ii. The proportion of patients with ≥1 graft with a significant stenosis or total occlusion at 1-year CTA.

iii. The proportion of venous and arterial grafts considered separately with total occlusion and/or stenosis, defined above.

iv. The incidence of the major adverse cardiac and cerebrovascular events (MACCE, defined as the composite endpoint of all-cause mortality, perioperative and 1-year non-fatal MI (using the WHO definition, see below), stroke, and repeat revascularization (redo CABG or PCI).
Tertiary outcome

The incidence of major adverse cardiac and cerebrovascular events (MACCE-O, defined as the composite endpoint of all-cause mortality, perioperative and 1-year non-fatal MI (using an older definition, see below), stroke, and repeat revascularization (redo CABG or PCI).

Outcome Definitions

Cardiovascular (CV) death: All deaths in the first 30 days are considered to be CV deaths. All deaths after the first 30 days are considered CV deaths unless a specific non-cardiovascular cause is evident and considered to be the cause of death (e.g. malignancy). Furthermore, patients who die during the index hospitalization but after the initial 30 days period (for example long ICU stay with sepsis) will be considered as CV deaths.

Myocardial infarction: The pathophysiology of myocardial injury sustained perioperatively (Type V) is likely different from that when injury is sustained later. Early injury can be a manifestation of either graft occlusion, or of a more general insult secondary to ischemia reperfusion, inflammation, and coronary embolization or spasm. Late injury is likely much more similar to the traditional acute coronary syndrome/atherosclerotic process with native vessel or graft occlusion. The definitions for these events differ as below:

(a) Early perioperative myocardial infarction (within 72 hours of surgery):

WHO Definition223:

1) A creatinine kinase myocardial B fraction (CK-MB) measurement ≥ 5 times the upper limit of normal with either:
   a. New pathological Q waves or new left bundle branch block (Q wave MI) or
b. Angiographic evidence of graft occlusion or native coronary artery occlusion or
c. Imaging evidence of new loss of viable myocardium.

**Old Definition**\(^{224}\): Early MI is defined as CK-MB ≥ 70 ng/mL and ECG changes consistent with myocardial injury or CK-MB ≥ 100 ng/mL in all patients.

(b) Late perioperative myocardial infarction (later than 72 hours after surgery): ECG changes consistent with myocardial infarction (new significant Q waves in two contiguous leads) or evolving ST-segment or T-wave changes in two contiguous leads signifying ischemia or new left bundle branch block or ST segment elevation and elevated cardiac markers (troponins or CK-MB) in the necrosis range. Myocardial injury occurring after a PCI are included in the late perioperative Myocardial Injury group but are defined as elevation of cardiac markers ≥ 3 times upper limit of normal within 24 hours of PCI or characteristic evolution of new ECG changes.

**Stroke:** Diagnosis of stroke is defined as focal neurological symptoms with rapid onset, lasting at least 24 hours. It is strongly recommended (but not required) that an imaging procedure such as a CT scan or magnetic resonance imaging be performed. All strokes will be classified as definite ischemic, definite hemorrhagic or type uncertain. A vascular imaging procedure such as a carotid ultrasound is recommended whenever possible (but not required) for sub-classification of ischemic strokes into cardioembolic, lacunar or large artery.
**Repeat coronary revascularization:** New CABG procedure or PCI associated with documented ischemia by ECG and graft failure or new culprit lesion (≥ 70% luminal stenosis).

**Infection score assessment:** Infection was assigned a score of 0 for no infection, or 1-3 for low, moderate or severe infection.\(^{153}\) There was an additional infection treatment score of 0-7 according to the treatment received (no treatment, topical antibiotics, oral antibiotics, dressings, readmission for leg wound infection, intravenous antibiotics, debridement, and vacuum assisted closure). Patients with more than one type of treatment for the infection were coded as the highest code of their combination of treatments. The range of the possible infection scores was therefore 0-10. The incidence of infection (proportion of infection) and severity (mean infection score) was compared between NT and CON harvesting techniques.

**Post-operative management and Follow-up:** General post-operative medical management were prescribed according to institutional practices. Patients underwent assessment of their grafts at 1-year using a non-invasive 64-slice CTA. All images were recorded on compact discs and transferred to a central system read by a blinded chest radiologist or interventional cardiologist with CTA reading expertise. All patients were also monitored clinically with visits at 30-days, 3, 6, 9 and 12 months post-operatively. Clinical outcomes were all reviewed centrally by an adjudication committee that was blinded to the patients’ treatment allocation.

**Statistical Analysis**
Baseline demographics of the treatment groups were compared in the surgical arm and separately in the pharmacological arm. Normality for continuous variables was tested using the Kolmogorov-Smirnov test – continuous variables were reported as the mean +/- standard deviation or Median (25th-75th percentiles). Categorical variables are reported as the absolute frequency and as a percentage.

Given the 2x2 factorial design, the stratified analysis was performed if the interaction term between the surgical and pharmacological arm was significant for the major primary, secondary and tertiary outcomes. The treatment effect for the primary outcome in both arms was estimated using odds ratio and the corresponding 95% confidence interval. Categorical variables were compared using the chi-square test or Fisher’s Exact test where appropriate. All continuous variables were compared using the t-test for independent samples if parametric and Wilcoxon rank-sum test if non-parametric. The time to first event for the composite outcomes, MACCE and MACCE-O were tested using the log-rank test. The treatment effect was estimated using the hazard ratio with 95% confidence interval using the Cox proportional hazard model; the proportional hazards assumption was assessed by including a time-treatment interaction term. A 2-tailed p-value of <0.05 was considered statistically significant. All analyses were performed using SAS, version 9.4 for UNIX (Cary NC, USA).

**Sample Size**

For the surgical arm, a sample size of 615 patients in each group would provide 80% power for a 2-tailed alpha of 0.05, to identify a relative risk reduction of 30% (NT: 14%, CON: 20%) for study graft occlusion. For the pharmacological arm, a sample size of 540 in each
group would provide 80% power to detect a RRR of 25% (FO: 22.5%, P: 30%) for the primary outcome. After adjusting for potential protocol violations and loss to follow-up, the corrected sample size was 769 patients in each group (total sample size 1538) to reach adequate statistical power for each arm of the study.

Funding was acquired for a vanguard phase of 250 patients. Unfortunately, further funding was not secured and study enrollment was stopped after those 250 patients.

2.4-Results

Patients

From August 2011 to September 2013, 250 of the 1069 eligible patients across 13 centres (10 Canada, 2 Sweden and 1 Israel), were enrolled into this study (Figure 2.2a and 2.2b). In the surgical arm, randomization resulted in 127 and 123 in the NT and CON group respectively; in the pharmacological arm, 140 patients were randomized into the drug arm (70 FO, 70 P), due to the manufacturer discontinuing the study placebo, (and without the investigators’ knowledge of the study outcomes).

Overall, patients in this study were generally young (64.8 +/- 8.6 years), predominantly males 219/250 (87.6%) with mean left ventricular ejection fraction (LVEF) of 52.7 +/- 10.7%. The incidence of diabetes was 86/250 (34.4%) and the mean Standard Additive Euroscore was 2.9 +/- 1.9. In the surgical arm, there were no significant differences with respect to the baseline covariates between the NT and CON, with the exception of a smaller proportion of males in the NT group (NT: 106 (83.5%), CON: 113 (91.9%), p=0.04); similarly in the pharmacological arm, the majority of the baseline covariates were well
balanced between the FO and P cohort, however, patients were older in the FO group (FO: 66.8 +/- 8.6 years, P: 62.4 +/- 9.0 years, p=0.002) (Table 2.2).

Intra-operative data

Overall, CABG surgery was typically performed on-pump (97.2%) (Table 2.3). The duration of surgery was longer in the NT group (NT: 5.2 +/- 1.6 hours, CON: 4.8 +/- 1.3 hours, p=0.02), however cardiopulmonary bypass (p=0.33) and cross-clamp time were similar (p=0.40). The SVGs were harvested predominantly by assistant physicians (NT: 27.6%, CON: 32.5%) and/or the staff surgeons (NT: 27.6%, CON: 22.8%) in both the NT and CON groups. Fifteen patients (NT: 12, CON: 3) did not undergo the technique assigned (unable to use/no SVG used in 6 patients, emergency scenarios preventing the use of NT in 3 patients, protocol violation in 2 patients, surgeon error in 1 patient, withdrawal of consent in 2 patients, and missing reason in 1 patient) (Figure 2.2a). The two protocol violations were due to surgeon not trained in the NT in one case and absence of vein Doppler/mapping in the other.

The majority of patients randomized to the CON group underwent an open compared to endoscopic technique (Open: 106 (86.2%), Endoscopic: 14 (11.4%)). The mean number of grafts was also similar between NT and CON (NT: 3.2 +/- 0.9, CON: 3.3 +/- 0.9, p=0.22). The size and quality of all of the conduits used were similar between the NT and CON groups as were the quality and size of all of the target vessels. For the pharmacological arm, operative variables were similar between FO and P including overall mean total grafts per patient 3.3 +/- 0.9. Further details of intra-operative data can be found in Table 2.3.

Post-operative management
In this study, the overall proportion of patients at discharge and 1-year on aspirin (ASA) was (Discharge: 240 (96.0%), 1-year: 222 (89.2%)), dual antiplatelet therapy (Discharge: 26 (10.4%), 1-year: 20 (8.0%)), statin (Discharge: 227 (90.8%), 1-year: 224 (90.0%)) and β-blockers (Discharge: 224 (89.6%), 1-year (194 (77.9%)). For the surgical arm, medications at discharge and at 1-year were similar between NT and CON; beta-blocker use trended to be lower at discharge in the NT group (NT 109 (85.8%), CON 115 (93.5%), p=0.047) but similar at 1-year (p=0.77). For the pharmacological arm, the proportion of patients taking ASA at discharge and 1-year was lower in the FO cohort compared to P (ASA – Discharge: FO 64 (91.4%), P 70 (100%), p=0.03; 1-year: FO 57 (82.6%), P 65 (92.9%), p=0.07). This was also true for statins at 1 year (FO: 60 (87.0%), P 67 (95.7%), p=0.07).

Compliance of drug arm

At 1-year, 139/140 (99.3%) reported their compliance history; 31 patients (FO: 18/69, P: 13/70, p=0.31) had permanently discontinued the study drug at a point during the study; reasons for discontinuation included death in 1 patient, swallowing problems in 7 patients, disinterest in taking a study drug in 7 patients, gastrointestinal concerns in 7 patients, end of drug supply in 2 patients, withdrawal of consent in 2 patients, non-study medical reasons in 4 patients and unknown reason in 1 patient. Compliance, defined by study drug interruption at any time < 5 days, was 37 (52.9%) in FO vs 44 (62.9%) in P, p=0.231.

Angiographic follow-up

Of the 250 patients enrolled, 212/250 in the surgical arm (84.8%) (NT: 105, CON: 107) underwent a CTA at 1-year (Figure 1a). Mean time to angiography following CABG was
12.7 +/- 2.2 months and was similar between NT and CON (p=0.68), and also between FO and P (p=0.71). Reasons for not undergoing an angiogram are detailed in Figure 2.2a. In the pharmacological arm, 119/140 (85.0%) (FO: 60, P: 59) underwent a CTA; reasons for not undergoing CTA are detailed in Figure 2.2b. Of the 212 patients who underwent angiography, 2 patients had no SVG used, and 1 patient had no study SVG (withdrew from surgery arm) but had SVGs. According to the intention to treat principle, these 3 patients were analyzed for all clinical endpoints in the surgical arm and both angiographic and clinical endpoints in the pharmacological arm.

Clinical follow-up

All patients (with the exception of one due to withdrawal from study at 6 months) had clinical follow-up up to 1 year (mean 13.3 +/- 2.2 months) for major clinical endpoints (i.e. death, MI, stroke, repeat revascularization); Follow-up times were similar between groups (NT vs CON, p=0.39 and FO vs. P, p=0.82).

Surgical Arm Outcomes

The interactions between the surgical and pharmacological arms for the predefined primary, secondary and tertiary outcomes were non-significant (Table 2.4).

Primary Outcome: The proportion of study SVG which were totally occluded at 1-year or death due to cardiovascular or unknown cause (primary outcome) was not significantly different in the NT cohort compared to CON (NT: 7/127 (5.5%), CON: 13/123 (10.6%), Odds Ratio (OR) 0.49, 95% CI (0.19-1.28), p=0.14) (Table 2.4). There were 2/123 (1.6%) cardiovascular deaths in the conventional group. According to the treatment received, the
incidence of the primary outcome was 6/116 (5.2%) in the NT patients and 14/127 (11.0%) in the CON group, p=0.10.

Secondary Outcomes: The proportion of study SVGs with significant stenosis (NT: 1/102 (1.0%), CON 5/107 (4.7%), p=0.12) and the composite of significant stenosis or complete occlusion (NT: 8/102 (7.8%), CON: 16/107 (15.0%), p=0.11 was not significantly different in the NT compared to CON (Table 2.4); the numerical difference was more pronounced according to treatment received (NT: 7/98 (7.1%), CON: 17/111 (15.3%), p=0.06). The proportion of MACCE was similar between NT and CON (p=0.59); most of the events were driven by non-fatal perioperative MI (NT 19/23 (82.6%), CON 14/19 (73.7%)) (Figure 2.3a).

Tertiary Outcomes: The proportion of MACCE-O was also similar between NT and CON (NT: 12/127(9.4%), CON 11/123 (8.9%), p=0.89). The incidence of MACCE-O was less than the secondary outcome MACCE, as the incidence of non-fatal perioperative MI was less using the old definition (Table 2.4, Figure 2.3b).

Descriptive results of all angiographic and clinical outcomes with respect to patients that participated both in the surgical arm and pharmacological arm (ie. 2x2 factorial design, n=140, and those patients that only participated in the surgical arm (n=110) are reported in tables 2.5a-e.

Pharmacological Arm Outcomes

The interactions between the surgical and pharmacological arms for the predefined primary, secondary and tertiary outcomes were non-significant (Table 2.6).
**Primary Outcome:** The proportion of patients with ≥1 graft totally occluded at 1-year or death due to cardiovascular or unknown causes was not significantly different in the FO cohort compared to P (FO: 21/70 (30.0%), P: 14/70 (20.0%), OR 1.71, 95% CI (0.79-3.73), p=0.17) (Table 2.6). There were 2/70 (2.9%) cardiovascular deaths in the fish-oils group.

**Secondary outcomes:** The proportion of patients with ≥1 graft with significant stenosis was similar (p=0.53) between FO and P. The proportion of patients with ≥1 graft with significant stenosis or complete occlusion was not significantly different (FO: 23/60 (38.3%), P: 17/59 (28.8%), p=0.27). The proportion of MACCE was not significantly different with FO (FO: 17/70 (24.3%), P: 11/70 (15.7%), HR 1.62 95% CI (0.75-3.50), p=0.22); this was predominantly driven by non-fatal perioperative MI – FO (11/17, 64.7%), P (11/11, 100%) (Figure 2.3c).

**Tertiary outcomes:** The proportion of MACCE-O was significantly higher in FO (FO: 12/70 (17.1%), P: 3/70 (4.3%), HR 4.36, 95% CI (1.23-15.5), p=0.02); this was predominantly driven by non-fatal perioperative MI (old definition). The incidence of MACCE-O was less than the secondary outcome of MACCE due to reduced number of perioperative myocardial infarctions using the old definition (Table 2.6, Figure 2.3d).

Descriptive results of all angiographic and clinical outcomes with respect to patients that participated both in the surgical arm and pharmacological arm (i.e. 2x2 factorial design, n=140) are reported in table 2.7a-e.

**Overall Graft Status at 1 year**

Of the 204 LIMA grafts assessed at 1-year, 4/204 (2.0%) were occluded (Table 2.8). With respect to RIMA, the proportion of occlusion was 0/4 (0%) and radial 2/29 (10.5%).
Overall, of the 691 grafts assessed in the whole study, 48/691 (6.9%) were occluded at 1-year.

*Leg Assessment*

The proportion of leg infection was higher in the NT group at 30 days (NT 27 (23.3%), CON 11 (9.5%), p<0.01); by 1-year, this was similar (0.9% in both groups, p=0.98). The severity of infection was also higher in the NT group (mean infection score, NT 1 +/- 2.1, CON 0.3 +/- 1.2, p<0.01) but was similar at 1-year (mean score NT 0.02, CON 0.07, p=0.46). (Table 2.9)

**2.5-Discussion**

This is the first multi-centre randomized clinical trial to assess the no touch SVG harvesting technique compared to conventional SVG harvesting; using a factorial design, the efficacy of fish-oil supplementation was also tested. After 250 patients randomized, we failed to demonstrate a statistically significant reduction in the proportion of significant and complete study graft occlusion using the NT technique compared to CON SVGs. In the pharmacological arm, the addition of FO resulted in no significant difference in the proportion of patients with at least one graft with significant stenosis or complete occlusion but was associated with an increased MACCE-O.

The NT technique has been shown to preserve the integrity of endothelium and intimal architecture due to its atraumatic, pedicled method of harvesting and the absence of mechanical dilation of the vein compared to the conventional, skeletonized mechanically dilated SVGs – whether open or endoscopic.\textsuperscript{151,153,156} These findings translated to superior early\textsuperscript{146} and late\textsuperscript{149} angiographic patency in a single centred randomized study comparing
NT versus CON performed in Orebro, Sweden; another study by Kim et al\textsuperscript{220} from Seoul Korea also showed superior early patency in NT vein graft. Given most of the evidence came from a few localized centres, we undertook a multi-centre study.

Although the NT impact on patency and graft stenosis did not reach statistical significance, there was a numerical trend towards benefit that cannot be excluded due to the small sample size of the study. In addition, the control event rate (CON SVG occlusion (10.3%)) was less than postulated, and 235/250 of the enrolled patients received the allocated treatment. The treatment effect we observed by the intent to treat analysis for NT vein harvesting (NT Occlusion 6.9%) was better than the postulated effect but consistent with that seen in the original publication by Souza\textsuperscript{146} (1-year - NT SVG occlusion 4.6%). The effect was stronger when the treatment received results were compared (Significant stenosis or occlusion: NT 7.1%, CON: 15.3%, p=0.06). These findings however did not translate into a difference in MACCE or MACCE-O irrespective of intention to treat (p=0.59, p=0.89) or treatment received analysis (p=0.74, p=0.97 respectively).

There were fewer NT patients who received the treatment allocated, and the length of surgery was longer. Leg infections were significantly higher in the NT legs compared to CON at 30-days. This may be due to the vein being harvested in a pedicle fashion, however, the severity of infection was typically low (mean score 1) at 30-days (Table 2.9). The avoidance of NT vein harvesting may be appropriate particularly for patients with multiple risk factors for surgical site infections. No-touch veins were harvested with an open technique – the use of skin bridges and/or drains as described by Kim and colleagues.
may lead to a reduction in the incidence of leg wound infections. Potentially, endoscopic methods could be adopted for NT vein harvesting.

Supplementation of omega-3 fatty acids has been associated with decreased major cardiac events in patients with hyperlipidemia\textsuperscript{222} or patients that have survived a MI.\textsuperscript{185} The GISSI-Prevenzione trial\textsuperscript{185} showed that there was a 45\% reduction in sudden death in MI survivors taking n-3 polyunsaturated fatty acids compared to controls. The AHA recommends at least 1g of omega-3 fatty acids per day in patients with documented coronary disease.\textsuperscript{187} Benedetto et al.,\textsuperscript{190} has showed that omega-3 fatty acids were associated with lower risk of repeat revascularization and death in patients with poor ventricular function after CABG. Eritsland et al.\textsuperscript{189} showed that patients on FO had a lower vein graft occlusion than those who were not at 1 year (FO 27\% vs Control 33\%, p=0.034). In our study, we found the contrary; graft occlusion was not significantly different although the proportion was higher in FO compared to P. MACCE-0 was significantly higher in patients taking FO compared to P. It is postulated that omega 3-fatty acids reduces formation of atherosclerotic plaque\textsuperscript{186}, which in vein grafts is seen beyond 1 year,\textsuperscript{43} perhaps, any benefits of FO may be seen late rather than early. The proportion of patients in the FO cohort on aspirin both at time of discharge and at 1 year was lower than placebo by almost 10\% which may have potentially contributed to the higher clinical events. The patients in this study were fish oil naïve – while long term benefits may exist, introduction of fish oils early prior to coronary surgery seems ill advised.

The 1 year mortality in the 250 patients was 2.0\%. The incidence of MACCE in the 250 patients at 1 year was 16.8\% (42/250), with an incidence of MI of 13.2\% (33/250). Using
an earlier more conservative definition of perioperative MI, MACCE-O was 9.2% (23/250), due to fewer MIs (12/250, 4.8%). Excluding the 2 MIs which occurred between 31 days and 1 year, the difference in perioperative MI in the overall study was 31 vs 10 (12.4% vs 4.0%). We expect that the frequency of perioperative MI diagnosis would be further increased with high sensitivity troponins (3rd Universal Definition). The prognostic significance related to the enhanced detection of perioperative MI following CABG (Type V) is unclear. This is a problem for clinical management and clinical trials.

One of the main strengths of our study is that it is a multi-centre and international RCT. All outcomes were analyzed in a blinded and standardized manner by a central adjudication committee and all angiograms were read centrally by imaging experts blinded to all interventions. The study was designed to test for graft patency – while patency is a surrogate endpoint, both early graft occlusion and perhaps more importantly, late SVG failure is associated with increasing late cardiac events. One of the criticisms of graft patency studies is that a sizable proportion of patients do not have angiography – i.e. do not have primary outcome assessment. In this study, 84.8% of patients did undergo CTA at 1 year. We also included death from cardiovascular causes – this meant that all patients were included in the primary outcome assessment. For the comparison of NT vs CON, the numbers of NT patients undergoing graft assessment was less, which may have biased the primary outcome results – however, this concern is not relevant for the secondary angiographic endpoints. Moreover, while the angiographic component of the primary outcome in the surgical arm focused on a single study SVG, the pharmacologic arm examined all grafts, as we assumed that FO could affect patency of all grafts. We were also able to achieve near 100% clinical follow-up.
There were important limitations. The most significant limitation is that recruitment was substantially less than the planned enrollment. We also had to discontinue the drug due to the manufacturer halting its production of the matching placebo mid-way through the study. Second, although having a multi-centre study significantly enhances external validity, our patients were predominantly younger and healthy males. Early postoperative CTA was not performed – technical factors may have resulted in graft failure which was not detected and unrelated to the interventions. Lastly, the comparison of the primary study outcomes was not significant; the statistical testing of all secondary and tertiary endpoints should be considered as hypothesis generating and exploratory.

2.6-Conclusion
Fish-oils and no-touch saphenous vein harvesting technique were not associated with superior graft patency or clinical outcomes after CABG. The trial cannot exclude a meaningful improvement of graft patency with the no-touch technique; more extended follow-up of the current study participants is warranted. A longer and perhaps larger clinical outcomes study should be undertaken to further corroborate our findings.
Acknowledgements

SUPERIOR SVG Committee Members and Investigators

INVESTIGATORS: Investigators who recruited at least 1 patient (number of patients enrolled in each country and site are in parentheses)


POPULATION HEALTH RESEARCH INSTITUTE COORDINATING CENTRE:

EVENT ADJUDICATION COMMITTEE:

CENTRAL ANGIOGRAPHY ASSESSORS:
L. Jimenez-Juan, A. Zavodni, A. Al-Saleh.
### 2.7-Tables and Figures

Table 2.1: Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Total patients not eligible</th>
<th>N=1652</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent CABG</td>
<td>51</td>
</tr>
<tr>
<td>Re-do CABG without all previous grafts occluded</td>
<td>17</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 20%</td>
<td>14</td>
</tr>
<tr>
<td>SVG not part of revascularization strategy</td>
<td>214</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate &lt; 30 mL/min</td>
<td>35</td>
</tr>
<tr>
<td>Previous vein stripping or poor vein quality</td>
<td>61</td>
</tr>
<tr>
<td>Contraindication to follow-up CT angiography</td>
<td>33</td>
</tr>
<tr>
<td>Pregnant or women of child-bearing age</td>
<td>3</td>
</tr>
<tr>
<td>Allergy to fish oil/fish products or non-medicinal Ingredients</td>
<td>4</td>
</tr>
<tr>
<td>Already taking fish oil supplements regularly</td>
<td>41</td>
</tr>
<tr>
<td>Congenital or acquired coagulation disorder</td>
<td>8</td>
</tr>
<tr>
<td>Patient considered to be of excessive risk of wound Infection</td>
<td>65</td>
</tr>
<tr>
<td>Patient not able to provide consent (including language barrier)</td>
<td>74</td>
</tr>
<tr>
<td>Non-isolated CABG</td>
<td>761</td>
</tr>
<tr>
<td>Patient unavailable to provide consent/unable to consent prior to surgery</td>
<td>241</td>
</tr>
<tr>
<td>More than one reason not eligible</td>
<td>27</td>
</tr>
<tr>
<td>Reason not eligible not specified</td>
<td>3</td>
</tr>
<tr>
<td>Table 2.2: Baseline Demographics</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical Arm</strong></td>
<td><strong>Pharmacological Arm</strong></td>
</tr>
<tr>
<td>(n=127)</td>
<td>(n=123)</td>
</tr>
<tr>
<td>Age (mean +/- SD years)</td>
<td>65.5 +/- 9.0</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>21 (16.5)</td>
</tr>
<tr>
<td>Body Mass Index (mean +/- SD m/kg(^2))</td>
<td>28.2 +/- 4.6</td>
</tr>
<tr>
<td>Creatinine (mean +/- SD umol/L)</td>
<td>86.5 +/- 19.1</td>
</tr>
<tr>
<td>Additive Euroscore (mean +/- SD)</td>
<td>3.0 +/- 2.0</td>
</tr>
<tr>
<td>Caucasian n (%)</td>
<td>95 (74.8)</td>
</tr>
<tr>
<td>CCS class</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26 (20.4)</td>
</tr>
<tr>
<td>2</td>
<td>42 (33.1)</td>
</tr>
<tr>
<td>3</td>
<td>45 (35.4)</td>
</tr>
<tr>
<td>4</td>
<td>13 (10.2)</td>
</tr>
<tr>
<td>NYHA class n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56 (44.1)</td>
</tr>
<tr>
<td>2</td>
<td>34 (26.8)</td>
</tr>
<tr>
<td>3</td>
<td>27 (21.3)</td>
</tr>
<tr>
<td>4</td>
<td>10 (7.9)</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (mean +/- SD %)</td>
<td>53.2 +/- 11.5</td>
</tr>
<tr>
<td>LV grade n (%)</td>
<td></td>
</tr>
<tr>
<td>1 (&lt;20%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2 (21-34%)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>3 (35-49%)</td>
<td>17 (13.4)</td>
</tr>
<tr>
<td>4 (&gt;50%)</td>
<td>52 (40.9)</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>44 (34.6)</td>
</tr>
<tr>
<td>Insulin controlled n (%)</td>
<td>20 (45.5)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>96 (75.6)</td>
</tr>
<tr>
<td>PVD n (%)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>History of smoking** n (%)</td>
<td>79 (62.2)</td>
</tr>
<tr>
<td>Cerebrovascular Disease n (%)</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>Prior Myocardial Infarction n (%)</td>
<td>50 (39.4)</td>
</tr>
<tr>
<td>Previous Cardiac Surgery n (%)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Previous PCI n (%)</td>
<td>18 (14.2)</td>
</tr>
<tr>
<td>Degree of Stenosis</td>
<td>n (%)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>Left main ≥ 50%</strong></td>
<td>47 (37.0)</td>
</tr>
<tr>
<td><strong>LAD ≥ 50%</strong></td>
<td>117 (92.1)</td>
</tr>
<tr>
<td><strong>Cx ≥ 50%</strong></td>
<td>104 (81.9)</td>
</tr>
<tr>
<td><strong>RCA ≥ 50%</strong></td>
<td>106 (83.5)</td>
</tr>
</tbody>
</table>

≠ P-value – statistically significant between No touch versus Conventional technique - Male (p-value = 0.04). ¥ P-value – statistically significant between Fish Oil versus Placebo – Age (p-value = 0.002). *% of diabetics that are being treated by insulin. **History of former or recent smoking.

Abbreviations: CCS - Canadian Cardiovascular Society, NYHA – New York Heart Association, LV grade – left ventricular grade, PVD – peripheral vascular disease, PCI – percutaneous coronary intervention, LAD – left anterior descending artery, Cx – circumflex artery, RCA – right coronary artery, SD – standard deviation
Table 2.3: Operative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Surgical Arm</th>
<th>Pharmacological Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-Touch (n=127)</td>
<td>Conventional (n=123)</td>
</tr>
<tr>
<td>Time from randomization to Surgery (days)-Median (Q1-Q3)</td>
<td>0.7 (0.2-2.8)</td>
<td>0.7 (0.1-2.0)</td>
</tr>
<tr>
<td>Duration of surgery (hours)</td>
<td>5.2 +/- 1.6</td>
<td>4.8 +/- 1.3</td>
</tr>
<tr>
<td>On-pump n(%)</td>
<td>123 (96.9)</td>
<td>120 (97.6)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>105.3 +/- 36.6</td>
<td>100.6 +/- 37.3</td>
</tr>
<tr>
<td>Mean cross-clamp time (min)</td>
<td>79.4 +/- 34.7</td>
<td>75.6 +/- 34.7</td>
</tr>
<tr>
<td>SVG harvested by n(%)</td>
<td>ASSISTANT PHYSICIAN</td>
<td>35 (27.6)</td>
</tr>
<tr>
<td></td>
<td>PHYSICIAN ASSISTANT</td>
<td>30 (23.6)</td>
</tr>
<tr>
<td></td>
<td>SENIOR RESIDENT</td>
<td>24 (18.9)</td>
</tr>
<tr>
<td></td>
<td>NURSE</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>JUNIOR RESIDENT</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>STAFF SURGEON</td>
<td>35 (27.6)</td>
</tr>
<tr>
<td>Total grafts per patient – Median (Q1-Q3)</td>
<td>3.0 (3.0-4.0)</td>
<td>3.0 (3.0-4.0)</td>
</tr>
<tr>
<td>Type of conduit based on #grafts*</td>
<td>403</td>
<td>407</td>
</tr>
<tr>
<td>SVG n(%)</td>
<td>267 (66.3)</td>
<td>269 (66.1)</td>
</tr>
<tr>
<td>LIMA n(%)</td>
<td>125 (31.0)</td>
<td>122 (30.0)</td>
</tr>
<tr>
<td>RIMA n(%)</td>
<td>4 (1.0)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Radial n(%)</td>
<td>7 (1.7)</td>
<td>12 (2.9)</td>
</tr>
</tbody>
</table>

*-\% is out of total grafts for that group.

Abbreviations: SVG – saphenous vein graft, LIMA – left internal mammary artery, RIMA – right internal mammary artery,
Table 2.4: Outcomes for the Surgical Arm

<table>
<thead>
<tr>
<th>Surgical Arm</th>
<th>No Touch (n=127) n (%)</th>
<th>Convention al (n=123) n (%)</th>
<th>Odds Ratio, (95% Confidence Interval)</th>
<th>p-value*</th>
<th>Interaction ** p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome:</strong> Proportion of study SVG with complete occlusion or death from cardiovascular or unknown cause at 1 year</td>
<td>7 (5.5)</td>
<td>13 (10.6)</td>
<td>0.49 (0.19-1.28)</td>
<td>0.14</td>
<td>0.35</td>
</tr>
<tr>
<td>Proportion of study SVG with complete occlusion</td>
<td>7 (6.9)</td>
<td>11 (10.3)</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular or unknown cause</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of study SVG with significant* stenosis at 1 year</td>
<td>1 (1.0)</td>
<td>5 (4.7)</td>
<td>0.12</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Proportion of study SVG with significant* stenosis or complete occlusion</td>
<td>8 (7.8)</td>
<td>16 (15.0)</td>
<td>0.11</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td><strong>MACCE</strong></td>
<td>23 (18.1)</td>
<td>19 (15.4)</td>
<td>1.19 (0.64-2.19)</td>
<td>0.59</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Tertiary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MACCE-O</strong></td>
<td>12 (9.4)</td>
<td>11 (8.9)</td>
<td>1.06 (0.47-2.41)</td>
<td>0.89</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Components of MACCE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1 (0.8)</td>
<td>4 (3.3)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI (MACCE)*</td>
<td>19 (15.0)</td>
<td>14 (11.4)</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI (MACCE-O)**</td>
<td>8 (6.3)</td>
<td>4 (3.3)</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>2 (1.6)</td>
<td>4 (3.3)</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Test of significance between No-touch and Conventional. **Interaction was tested between surgical and pharmacological arm for each of the primary, secondary and tertiary outcomes. *Hazard ratio. *Significant stenosis defined by 50-99% stenosis. Note, 102 patients with study SVGs in the no touch group and 107 patients in the conventional group underwent 1-year angiogram and therefore contributed to secondary angiographic outcomes. **31/33 non-fatal MI (MACCE) events occurred between 0-31 days after surgery. **10/12 non-fatal MI (MACCE-O) events occurred between 0-31 days after surgery.
Abbreviations: MACCE – major adverse cardiac and cerebrovascular events defined by all-cause mortality, non-fatal myocardial infarction (defined using the WHO definition), repeat revascularization, or stroke at 1 year. MACCE-O – same definition as above using the old definition of non-fatal myocardial infarction. MI – myocardial infarction.

Table 2.5: Descriptive results of the major surgical outcomes accounting for the 2x2 factorial design

The following are descriptive tables of all angiographic and clinical outcomes with respect to patients that participated both in the surgical arm and pharmacological arm (ie. 2x2 factorial design, n=140, shaded area in table) and those patients that only participated in the surgical arm (n=110, non-shaded column in the table). The following are the major outcomes for the surgical arm.

Table 2.5a – Primary Outcome: Study saphenous vein graft occlusion or cardiovascular death

<table>
<thead>
<tr>
<th>Study SVG occlusion or CV death</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
<th>Surgical Arm Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>3/37</td>
<td>3/35</td>
<td>6/72</td>
<td>1/55</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>5/33</td>
<td>2/35</td>
<td>7/68</td>
<td>6/55</td>
</tr>
<tr>
<td>Total</td>
<td>8/70</td>
<td>5/70</td>
<td>13/140</td>
<td>7/110</td>
</tr>
</tbody>
</table>

Shaded area represents results of patients participating in both surgical and pharmacological arm (2x2 factorial design). Surgical arm only column represents outcomes of the patients that only participated in the surgical study arm. Abbreviations: SVG = saphenous vein graft. CV = cardiovascular deaths.

Table 2.5b - Secondary Outcomes: Study saphenous vein graft with significant stenosis defined by 50-99%.

<table>
<thead>
<tr>
<th>Study SVG with significant stenosis (50-99%)</th>
<th>Missing</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
<th>Surgical Arm Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>3*</td>
<td>1/31*</td>
<td>0/28*</td>
<td>1/59</td>
<td>0/43*</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>0</td>
<td>1/28</td>
<td>3/30</td>
<td>4/58</td>
<td>1/49</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>2/59</td>
<td>3/58</td>
<td>5/117</td>
<td>1/92</td>
</tr>
</tbody>
</table>

Shaded area represents results of patients participating in both surgical and pharmacological arm (2x2 factorial design). Surgical arm only column represents outcomes of the patients that only participated in the surgical study arm. Abbreviations: SVG = saphenous vein graft.
* Total missing = 3 (1 from the No Touch SVG and FO group since it was not a study SVG, 1 from the No Touch SVG and Placebo group since it was not a SVG and 1 from the Surgical Arm only (No Touch) who did not have a SVG).

Table 2.5c - Secondary Outcomes: Study saphenous vein graft with significant stenosis (50-99%) or complete occlusion

<table>
<thead>
<tr>
<th>Study SVG with significant stenosis or complete occlusion</th>
<th>Missing</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
<th>Surgical Arm Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>3</td>
<td>4/31*</td>
<td>3/28*</td>
<td>7/59</td>
<td>1/43*</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>0</td>
<td>4/28</td>
<td>5/30</td>
<td>9/58</td>
<td>7/49</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>8/59</td>
<td>8/58</td>
<td>16/117</td>
<td>8/92</td>
</tr>
</tbody>
</table>

* Total missing = 3 (1 from the No Touch SVG and FO group since it was not a study SVG, 1 from the No Touch SVG and Placebo group since it was not a SVG and 1 from the Surgical Arm only (No Touch) who did not have a SVG).

Table 2.5d – Secondary Outcomes: Major adverse cardiac and cerebrovascular events using the WHO definition of perioperative myocardial infarction (MACCE)

<table>
<thead>
<tr>
<th>MACCE-N</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
<th>Surgical Arm Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>10/37</td>
<td>6/35</td>
<td>16/72</td>
<td>7/55</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>7/33</td>
<td>5/35</td>
<td>12/68</td>
<td>7/55</td>
</tr>
<tr>
<td>Total</td>
<td>17/70</td>
<td>11/70</td>
<td>28/140</td>
<td>14/110</td>
</tr>
</tbody>
</table>

Shaded area represents results of patients participating in both surgical and pharmacological arm (2x2 factorial design, n=140). Surgical arm only column represents outcomes of the patients that only participated in the surgical arm (n=110). Abbreviations: SVG = saphenous vein graft. MACCE = major adverse cardiac and cerebrovascular events defined by all-cause mortality, non-fatal myocardial infarction defined by the WHO definition, stroke and repeat revascularization.

Table 2.5e – Tertiary Outcome: Major adverse cardiac and cerebrovascular events using the old definition of perioperative myocardial infarction (MACCE-O)

<table>
<thead>
<tr>
<th>MACCE-O</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
<th>Surgical Arm Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>7/37</td>
<td>1/35</td>
<td>8/72</td>
<td>4/55</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>5/33</td>
<td>2/35</td>
<td>7/68</td>
<td>4/55</td>
</tr>
<tr>
<td>Total</td>
<td>12/70</td>
<td>3/70</td>
<td>15/140</td>
<td>8/110</td>
</tr>
</tbody>
</table>
Shaded area represents results of patients participating in both surgical and pharmacological arm (2x2 factorial design, n=140). Surgical arm only column represents outcomes of the patients that only participated in the surgical arm (n=110). Abbreviations: SVG = saphenous vein graft. MACCE-O = major adverse cardiac and cerebrovascular events defined by all-cause mortality, non-fatal myocardial infarction defined by the old definition, stroke and repeat revascularization.

Table 2.6: Outcomes for the Pharmacological Arm

<table>
<thead>
<tr>
<th></th>
<th>Pharmacological Arm</th>
<th></th>
<th>p-value*</th>
<th>Interaction ** p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fish Oils (n=70) n (%)</td>
<td>Placebo (n=70) n (%)</td>
<td>Odds Ratio, (95% Confidence Interval)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome:</strong></td>
<td>21 (30.0)</td>
<td>14 (20.0)</td>
<td>1.71 (0.79-3.73)</td>
<td>0.17</td>
</tr>
<tr>
<td>Proportion of patients with ≥1 graft with complete occlusion or death from cardiovascular or unknown cause at 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with ≥1 graft with complete occlusion</td>
<td>19 (27.1)</td>
<td>14 (20.0)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Death from Cardiovascular or Unknown Cause</td>
<td>2 (2.9)</td>
<td>0 (0)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with ≥1 graft that has a significant≠ stenosis at 1 year</td>
<td>7 (11.7)</td>
<td>4 (6.8)</td>
<td>0.53</td>
<td>0.94</td>
</tr>
<tr>
<td>Proportion of patients with ≥1 graft that has a significant≠ stenosis or completely occluded at 1 year</td>
<td>23 (38.3)</td>
<td>17 (28.8)</td>
<td>0.27</td>
<td>0.57</td>
</tr>
<tr>
<td>MACCE*</td>
<td>17 (24.3)</td>
<td>11 (15.7)</td>
<td>1.62 (0.75-3.50)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Tertiary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACCE-O**</td>
<td>12 (17.1)</td>
<td>3 (4.3)</td>
<td>4.36 (1.23-15.5)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Components of MACCE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>4 (5.7)</td>
<td>1 (1.4)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI (MACCE)*</td>
<td>11 (15.7)</td>
<td>11 (15.7)</td>
<td>0.94</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.7: Descriptive results of the major pharmacological outcomes accounting for the 2x2 factorial design

The following are descriptive tables of all angiographic and clinical outcomes with respect to patients that participated both in the surgical arm and pharmacological arm (ie. 2x2 factorial design, n=140, shaded area in table). The following are the major outcomes for the pharmacological arm.

Table 2.7a – Primary Outcome: Patients with ≥1 occluded graft or cardiovascular death

<table>
<thead>
<tr>
<th>Patients with ≥1 occluded graft or CV death.</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>9/37</td>
<td>7/35</td>
<td>16/72</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>12/33</td>
<td>7/35</td>
<td>19/68</td>
</tr>
<tr>
<td>Total</td>
<td>21/70</td>
<td>14/70</td>
<td>35/140</td>
</tr>
</tbody>
</table>

Shaded area represents results of the patients participating in both surgical and pharmacological arm (n=140). Abbreviations: SVG = saphenous vein graft. CV = cardiovascular deaths.

Table 2.7b – Secondary Outcomes: Patients with ≥1 graft with significant stenosis defined by 50-99% stenosis.

<table>
<thead>
<tr>
<th>Patients with ≥1 graft with significant stenosis</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
</table>

*Test of significance between No-touch and Conventional. **Interaction was tested between surgical and pharmacological arm for each of the stated primary, secondary and tertiary outcomes. ^Hazard ratio. #Significant stenosis defined by 50-99% stenosis. Note, 60 patients in the fish oil group and 59 patients in the placebo group underwent 1-year angiogram and therefore contributed to secondary angiographic outcomes. *20/22 non-fatal MI (MACCE) events occurred between 0-31 days after surgery. **6/8 non-fatal MI (MACCE-O) events occurred between 0-31 days after surgery.

Abbreviations: MACCE – major adverse cardiac and cerebrovascular events defined by all-cause mortality, non-fatal myocardial infarction (defined using the WHO definition), repeat revascularization, or stroke at 1 year. MACCE-O – same definition as above using the old definition of non-fatal myocardial infarction. MI – myocardial infarction.
<table>
<thead>
<tr>
<th>defined by 50-99% stenosis</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>4/32</td>
<td>0/29</td>
<td>4/61</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>3/28</td>
<td>4/30</td>
<td>7/58</td>
</tr>
<tr>
<td>Total</td>
<td>7/60</td>
<td>4/59</td>
<td>11/119</td>
</tr>
</tbody>
</table>

Shaded area represents results of the patients participating in both surgical and pharmacological arm (n=140). Abbreviations: SVG = saphenous vein graft.

Table 2.7c – Secondary Outcomes: Patients with ≥ 1 graft with significant stenosis defined by 50-99% stenosis or complete occlusion.

<table>
<thead>
<tr>
<th>Patients with ≥ 1 graft with significant stenosis or complete occlusion</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>12/32</td>
<td>7/29</td>
<td>19/61</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>11/28</td>
<td>10/30</td>
<td>21/58</td>
</tr>
<tr>
<td>Total</td>
<td>23/60</td>
<td>17/59</td>
<td>40/119</td>
</tr>
</tbody>
</table>

Shaded area represents results of the patients participating in both surgical and pharmacological arm (n=140). Abbreviations: SVG = saphenous vein graft.

Table 2.7d – Secondary Outcomes: Major adverse cardiac and cerebrovascular events using the WHO definition of perioperative myocardial infarction (MACCE)

<table>
<thead>
<tr>
<th>MACCE</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>10/37</td>
<td>6/35</td>
<td>16/72</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>7/33</td>
<td>5/35</td>
<td>12/68</td>
</tr>
<tr>
<td>Total</td>
<td>17/70</td>
<td>11/70</td>
<td>28/140</td>
</tr>
</tbody>
</table>

Shaded area represents results of patients participating in both surgical and pharmacological arm (2x2 factorial design, n=140). Abbreviations: SVG = saphenous vein graft. MACCE= major adverse cardiac and cerebrovascular events defined by all-cause mortality, non-fatal myocardial infarction defined by the WHO definition, stroke and repeat revascularization.

Table 2.7e – Secondary Outcomes: Major adverse cardiac and cerebrovascular events using the old definition of perioperative myocardial infarction (MACCE-O)

<table>
<thead>
<tr>
<th>MACCE-O</th>
<th>Fish Oils</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch SVG</td>
<td>7/37</td>
<td>1/35</td>
<td>8/72</td>
</tr>
<tr>
<td>Conventional SVG</td>
<td>5/33</td>
<td>2/35</td>
<td>7/68</td>
</tr>
<tr>
<td>Total</td>
<td>12/70</td>
<td>3/70</td>
<td>15/140</td>
</tr>
</tbody>
</table>

Shaded area represents results of patients participating in both surgical and pharmacological arm (2x2 factorial design, n=140). Abbreviations: SVG = saphenous vein graft. MACCE-O = major adverse cardiac and cerebrovascular events defined by all-cause mortality, non-fatal myocardial infarction defined by the old definition, stroke and repeat revascularization.
Table 2.8: 1-year Graft Status assessed by CT Angiography

<table>
<thead>
<tr>
<th>Type of graft</th>
<th>Total # of grafts</th>
<th># of grafts assessed by 1-year CT Angiography</th>
<th># of grafts with 100% Occlusion</th>
<th># of study SVG occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td>214</td>
<td>191</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Open Conventional SVG</td>
<td>282</td>
<td>243</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Endoscopic SVG</td>
<td>40</td>
<td>30</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Radial</td>
<td>19</td>
<td>19</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LIMA</td>
<td>247</td>
<td>204</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>RIMA</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SVG = saphenous vein graft, LIMA = left internal mammary artery, RIMA = right internal mammary artery

Table 2.9: Leg Status (Infection)

<table>
<thead>
<tr>
<th>Incidence of Infection, n(%)</th>
<th>NT</th>
<th>CON</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-days</td>
<td>27 (23.3)</td>
<td>11 (9.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3-months</td>
<td>10 (9.4)</td>
<td>3 (3.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>1-year</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity of Infection (mean +/- SD)</th>
<th>NT</th>
<th>CON</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-days</td>
<td>1.0 +/- 2.1</td>
<td>0.3 +/- 1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3-months</td>
<td>0.5 +/- 1.5</td>
<td>0.1 +/- 0.5</td>
<td>0.02</td>
</tr>
<tr>
<td>1-year</td>
<td>0.02 +/- 0.2</td>
<td>0.07 +/- 0.8</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Incidence and severity of infection. For severity of infection, the score ranges from 0-10 with a higher score being a more severe (see Methods section for details on the scoring).
Figure 2.2a: Consort Diagram – Surgical Arm

Assessed for eligibility (n=2722)

Excluded (n=2,472)
- Not meeting inclusion criteria (n=1,652)*
- Patient/Surgeon Refusal (n=483)
- Enrolled in another trial (n=92)
- Study personnel unavailable (n=241)
- Other (n=4)

Enrollment

Randomized (n=250)

Allocated to No-Touch Technique (n=127)
- Received allocated intervention (n=115)
- Did not receive allocated intervention
  - Unable to use saphenous vein (n=4)
  - Emergency scenarios (n=3)
  - Protocol violation (n=2)
  - Consent Withdrawn (n=2); Missing reason (n=1)

Allocation

Allocated to Conventional Technique (n=123)
- Received allocated intervention (n=120)
- Did not receive allocated intervention
  - No SVG used (n=2)
  - Surgeon error (n=1)

Follow-Up

Angiographic (n=105)
- Reasons for no angiography: Death (n=1), Patient/MD refusal (n=12), Medical reasons (n=8), No SVG used (n=1)
- 1-year Clinical follow-up (n=127)

Analysis

Analysed
- Primary outcome (n=127)
- Secondary angiographic outcomes (n=102)
  - 3 patients did not have study SVGs
- Secondary/tertiary clinical outcomes (n=127)

Analysed
- Primary outcome (n=123)
- Secondary angiographic outcomes (n=107)
- Secondary/tertiary clinical outcomes (n=123)

Figure 2.2a: Consort diagram of the surgical arm (No touch versus Conventional technique)
Assessed for eligibility (n=2722)

Excluded (n=2,472):
- Not meeting inclusion criteria (n=1,652)*
- Patient/Surgeon Refusal (n=483)
- Enrolled in another trial (n=92)
- Study personnel unavailable (n=241)
- Other (n=4)

Randomized (n=140)

Stoppage of Drug by Manufacturer (n=110)

Allocation

Allocated to Fish Oils (n=70)
- Received allocated intervention (n=70)
  - ConsentWithdrawn (n=1)

Allocated to Placebo (n=70)
- Received allocated intervention (n=70)

Follow-Up

Angiographic (n=60)
Reasons for no angiography: Death (n=2), Patient/MD refusal (n=5), Medical reasons (n=2), Withdrawn (n=1)

1-year Clinical Follow-up (n=69)
Reason for no 1-year follow-up: Withdrawal (n=1)

Analysis

Analysed
- Primary outcome (n=70)
- Secondary angiographic outcomes (n=60)
- Secondary/tertiary clinical outcomes (n=70)

Analysed
- Primary outcome (n=70)
- Secondary angiographic outcomes (n=59)
- Secondary/tertiary clinical outcomes (n=70)

Figure 2.2b: Consort diagram of the pharmacological arm (Fish oils versus Placebo)
Figure 2.3a: Kaplan Meier plot of the secondary outcome, MACCE (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the WHO definition, stroke, repeat revascularization), between the No Touch and Conventional groups. Comparison between the treatments were based on Cox proportion hazard model.
Figure 2.3b: Kaplan Meier plot of the tertiary outcome, MACCE-O (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the old definition, stroke, repeat revascularization), between the No Touch and Conventional groups. Comparison between the treatments were based on Cox proportion hazard model.
Figure 2.3c: Kaplan Meier plot of the secondary outcome, MACCE (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the WHO definition, stroke, repeat revascularization), between the Fish Oils and Placebo groups. Comparisons between the treatments were based on Cox proportion hazard model.
Figure 2.3d: Kaplan Meier plot of the tertiary outcome, MACCE-O (major adverse cardiac and cerebrovascular events (death, non-fatal myocardial infarction by the old definition, stroke, repeat revascularization), between the Fish Oils and Placebo groups. Comparison between treatments were based on Cox proportion hazard model.
Chapter 3

Long-Term Impact of Diabetes on Graft Patency after Coronary Artery Bypass Grafting Surgery: A Sub-study of the Multi-Centre Radial Artery Patency Study

Published in the Journal of Thoracic and Cardiovascular Surgery

3.1-Abstract

Objectives: To determine the impact of diabetes on radial artery and saphenous vein graft occlusion and clinical outcomes more than 5-years following coronary artery bypass surgery in the multi-centre Radial Artery Patency Study (NCT00187356).

Method: 529 patients less than 80-years of age with triple vessel disease undergoing coronary bypass surgery participated in this study. Angiographic follow-up occurred beyond 5-years after surgery with annual clinical follow-up. The primary objective was to compare the proportion of complete graft occlusion between radial and saphenous grafts among diabetics and non-diabetics. Additional objectives included determining predictors of complete graft occlusion and comparison of major adverse cardiac events defined by cardiac death, late myocardial infarction, and re-intervention.

Results: There were 148/529 patients (27.8%) with diabetes; 269 patients (83/269 (30.9%) diabetics) underwent late angiography at mean of 7.7 +/- 1.5 years after surgery. In diabetics, the proportion of complete graft occlusion was significantly lower in the radial 4/83 (4.8%) versus saphenous grafts 21/83 (25.3%), p=0.0004; this was similar in non-diabetics (p=0.19). Multivariate modeling showed that the use of radial artery and high grade target vessel stenosis were protective against late graft occlusion, whereas female gender, smoking history and elevated creatinine were associated with an increased risk; interaction between diabetic status and conduit type was also significant (p=0.02). Major adverse cardiac events were higher in diabetics (23/148 (15.5%) versus 35/381 (9.2%), p=0.04).
Conclusion: The use of the radial artery should be strongly considered in diabetic patients undergoing coronary bypass surgery especially with high grade target vessel stenosis.

3.2-Background
Diabetes Mellitus (DM) currently affects over 285 million adults in the world and is projected to increase to 439 million by 2030. A large portion of deaths in diabetics are associated with ischemic heart disease. Coronary artery bypass grafting surgery (CABG) is considered the standard of care in diabetics with advanced multi-vessel disease. This was confirmed in the international multi-centre randomized study (FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), which showed that in diabetics with multi-vessel disease, CABG resulted in a significantly reduced rate of major adverse cardiac events (all-cause death, non-fatal myocardial infarction (MI) and non-fatal stroke) compared to percutaneous coronary stenting (PCI) at 5 years (18.7% CABG versus 26.6% PCI, p=0.005); these findings were included in a recent systematic review which suggested that CABG should be revised to a Class I, Level A recommendation in diabetics with multi-vessel disease in both the American and European revascularization guidelines.

An important predictor of long-term success in CABG is graft patency. This is especially true in diabetics as they are prone to diffuse and rapidly progressive atherosclerosis. Due to the excellent long-term patency rates and resistance to atherosclerosis of internal mammary artery (IMA) grafts, surgeons have turned to the radial artery as another potential arterial conduit. A recent meta-analysis showed that radials were superior to SVGs
at mid-term angiographic follow-up.\textsuperscript{232} The Radial Artery Patency Study (RAPS) is a multi-centre randomized trial comparing the patency of the radial artery to the saphenous vein graft (SVG) (NCT00187356). The RAPS investigators reported that the proportion of radial arteries with complete graft occlusion was lower than SVG at 1-year (8.2\% versus 13.6\%, $p=0.009$)\textsuperscript{80} and beyond 5 years (8.9\% versus 18.6\%, $p=0.002$)\textsuperscript{79}. At 1-year, the radials were also superior to the SVGs in the diabetic cohort with respect to graft patency.\textsuperscript{106} We now report the long-term (beyond 5-years) impact of diabetic status on radial and saphenous graft patency. Specifically, the primary objective is to determine whether preoperative diabetic status differentially influences long-term complete occlusion between the radial and study SVG grafts. The secondary objective is to determine the potential predictors of long-term complete graft occlusion. The tertiary objective is to determine whether diabetic status influences long term event free survival after CABG.

3.3-METHODS

This is a secondary analysis of the RAPS study, which is a longitudinal multi-centre randomized controlled clinical trial (RCT) for which institutional research ethics approval was attained. All participants enrolled in the trial provided informed consent.

Population: Details of the RAPS protocol can be found elsewhere.\textsuperscript{233} Briefly, the RAPS study included patients less than 80-years of age with left ventricular ejection fraction (LVEF) greater than 35\% and triple vessel coronary disease undergoing non-emergent isolated CABG. Angiographic inclusion criteria were target vessel stenosis of $\geq 70\%$ to decrease the likelihood of competitive flow from the native circulation, vessel diameter of $\geq 1.5$mm and target vessel deemed to be of acceptable quality. Exclusion criteria were contra-indications to the use of the radial artery (i.e. positive Allen's test, abnormal arterial
upper limb duplex scan, and/or a history of vasculitis or Raynaud's syndrome) or the use of a saphenous vein (bilateral varicosities or vein stripping). Further exclusion criteria were factors limiting follow-up research angiography which included creatinine greater than 180 umol/L, severe peripheral vascular disease limiting femoral access, coagulopathy or obligatory use of anticoagulants, known allergy to radiographic contrast, pregnancy, and geographic inaccessibility.

**Randomization:** A within-patient randomization design was applied whereby the radial artery was randomized to either the inferior (right coronary artery, RCA) or lateral (circumflex artery, Cx) region of the heart. The study saphenous graft would then be placed to the opposing territory (Cx or the RCA). This technique allowed patients to receive both study grafts and serve as their own internal control. The IMA was used for the anterior wall (left anterior descending, LAD) distribution. The randomization schedule was obtained using a central computer random number sequence generator and was stratified by centre in randomly varying blocks of 4-6. Randomization was concealed in a sealed opaque envelope and was revealed to the surgeon only after the patient entered the operating room.

**Surgical Technique and Peri-operative Management:** Both the radial artery and saphenous vein were harvested using an open technique. The non-dominant hand was used to harvest the radial artery. All operations were performed on-pump using cardiopulmonary bypass. Grafts were performed with a single distal and proximal aorto-coronary anastomosis; sequential and/or composite grafts were not performed. Details of the harvesting technique are published elsewhere. Each participating surgeon partook in a 2-day workshop held in Toronto, Canada at the beginning of the study to learn the standard
radial artery harvesting technique and could recruit patients after performing the operation in 3 patients.

**Postoperative Management**

Patients received 325 mg of aspirin within six hours postoperatively and daily thereafter – a lower dose of aspirin was used long term according to institutional practice. Intravenous nitroglycerin was administered during the first 24-hours postoperatively and vasopressors were avoided. Oral calcium-channel blockade (long acting nifedipine 30 mg daily) was initiated on the first postoperative day and continued for at least six months. Other postoperative care was individualized according to the study centre's preference. Patients were interviewed by telephone at one month, three months, six months, and yearly thereafter for a maximum of 10-years postoperatively.

Patients had serial electrocardiograms (ECG), preoperatively and on the first and fifth postoperative day, which were stripped of patient identifiers and read centrally by a core ECG committee, consisting of three cardiologists not otherwise associated with the study. The ECGs were read centrally in a blinded fashion and without any details of the perioperative course of the patient. Perioperative cardiac enzymes were measured according to the routine institutional practice but the results were not reviewed by the ECG committee. A perioperative MI was diagnosed when persistent new pathological Q waves were present on the postoperative electrocardiograms. A diagnosis of a perioperative myocardial infarction required a decision of 2 of the 3 reviewing cardiologists.

**Follow-up**
Angiography: Patients were approached to undergo invasive angiography after at least 5-years following CABG. All participating sites acquired angiograms digitally and the image sequences were transferred to compact discs that were sent to the main study centre for centralized reading. Patients who declined invasive x-ray angiography were offered the option of computed tomography angiography (CTA). Details of the angiography protocol is explained elsewhere. All invasive and CT angiograms were read centrally. Each invasive angiogram was independently adjudicated in a blinded fashion by 2 invasive cardiologists, with a third review in the case of disagreement of the primary or secondary outcome. Each CT angiogram was reviewed by an imaging cardiologist and a thoracic radiologist.

Clinical: Patients were interviewed by telephone at one month, three months, six months, and yearly thereafter for a maximum of 10-years postoperatively. If the patient had been hospitalized for cardiac reasons between interviews, in-patient records were obtained. Data on death, cause of death, non-fatal myocardial infarction, and repeat revascularization were obtained at each interview. All clinical events were reviewed centrally in a blinded fashion by a committee consisting of 2 cardiologists and 1 cardiac surgeon.

Statistical Analysis
Baseline demographics were compared between diabetics and non-diabetics. A two-sample t-test and the Wilcoxon Rank Sum test was used for parametric and non-parametric continuous variables respectively. All categorical variables (reported as frequency and percentage) were compared between the diabetic and non-diabetic cohort using the chi-square test.

The primary objective was to determine the rate of complete graft occlusion beyond 5-years after surgery between the radial artery and SVG based on preoperative diabetic status.
Complete occlusion was defined by invasive angiography as a Thrombolysis in Myocardial Infarction (TIMI) score of 0, or occlusion according to CTA between diabetics and non-diabetics. In order to address the primary objective of determining whether diabetic status had a differential effect on radial and SVG graft occlusion, two types of univariate analysis were performed. The first analysis compared occlusion rates between the grafts (intergraft comparison of radial artery versus SVG) with respect to diabetic status; given the paired nature of this comparison, the McNemar test was performed as the test of significance. The second analysis compared occlusion rates within each graft type (intragraft comparison) with respect to diabetic status; the chi-square test was used due to testing of independent proportions.

The secondary objective was to determine potential predictors of complete graft occlusion. Given the paired nature of the study design, general estimation equation (GEE) model with a logit link function was chosen as the most appropriate. The a-priori potential variables that were tested in the model were baseline demographics including diabetic status, age, gender, hyperlipidemia, creatinine (10 umol/L increments), peripheral vascular disease, smoking status (any smoking history versus never smoked), and proximal native disease of target vessels (≥90% versus 70-89% stenosis), along with graft type (radial or SVG). The interaction term between diabetes and graft type was also tested (if the interaction term is not significant it should be removed and the final model rerun). Prior to modelling, the variables were assessed for multi-collinearity (tolerance statistic less than 0.4), and only one member of a correlated set of variables was retained for the final model. Because of the relatively small number of graft occlusions, bootstrapping was used to validate the model with 5000 iterations with replacement. The median odds ratio and its 95% confidence
interval (CI) of each of the prespecified covariates from the bootstrap were compared to the original model. The percentage of times the p-value was less than 0.05 during the 5000 iterations for each covariate was also determined.

The cumulative patency of the radial artery and the SVG were also compared, based on the early (1-year) and late angiography (beyond 5-years) after CABG. Each patient was right censored at their last angiogram if they did not have an event (i.e., complete occlusion). Cumulative patency curves for complete occlusion included any patient that had either early and/or late angiograms. The log-rank test was used to compare differences in the cumulative patency curves between diabetics and non-diabetics for each conduit.

The tertiary objective was to determine whether there was a difference in the proportion of major adverse cardiac events (MACE, defined as cardiac death, late MI, or repeat re-intervention) as well as the individual components of MACE in addition to all cause mortality between diabetics and non-diabetics. A chi-square test was used to compare these clinical events with respect to diabetic status. The log-rank test was used to compare differences in event-free survival time (i.e. free from MACE) between diabetic and non-diabetic patients.

For all statistical testing, a 2-tailed p-value less than 0.05 was considered significant. SAS version 9.4 (Cary NC, USA) was used for all analysis.

3.4-Results

Patient population: In the RAPS long-term study, 529 patients across 11 centres, underwent late clinical follow-up at a mean of 7.3 +/- 2.9 years, of which 148 (28.0%) were diabetics (114 (77.0%) non-insulin dependent diabetics (NIDDM), 34 (23.0%) insulin-
dependent diabetics (IDM)), at the time of CABG. Nine centres (n=510) participated in late angiographic follow-up; after excluding early deaths (n=18), protocol violations (n=16), both study graft occlusions at early angiography (n=3), new medical exclusions (n=64), excessive distance (n=8) and loss to follow-up (n=43), 358 patients were eligible for late angiographic analysis. After excluding late deaths (n=6) and patient refusal (n=83), 269 patients (75.1% of eligible patients, 83 (30.9%) diabetics) underwent late angiography (234 invasive x-ray angiography, 35 CTA) at a mean angiographic follow-up of 7.7 +/- 1.5 years after CABG. Of these, 25/269 were clinically directed and the remainder were mandated by the research protocol. As previously published, the non-angiographic cohort had a higher incidence of peripheral vascular disease compared to the angiographic cohort at baseline.79 Baseline demographics were generally similar between diabetics and non-diabetics for both the nested angiographic and larger late clinical follow-up cohort (Table 3.1). The proportion of female gender and hyperlipidemia were increased in the diabetics.

**Angiographic endpoints:** The proportion of completely occluded study grafts at angiography beyond 5-years after CABG (primary endpoint) was significantly lower in radial grafts 4/83 (4.8%) compared to SVG 21/83 (25.3%), p=0.0004 in diabetics (Table 3.2a). In non-diabetics, the proportion of completely occluded study grafts were similar (20/186 (10.8%) radials, 29/186 (15.6%) SVG, p=0.19). Within the graft subtypes, the proportion of completely occluded radial grafts were similar irrespective of diabetic status (4/83 (4.8%) DM versus 20/186 (10.8%) non-diabetics (Non-DM), p=0.11); however there was a trend towards a higher proportion of SVG occlusions in the diabetics (21/83 (25.3%) DM versus 29/186 (15.6%) Non-DM, p=0.06). (Table 3.2b) There were no significant differences in radial graft (p=1.0) and SVG occlusions (p=0.75) between insulin dependent
(n=16) and non-insulin dependent diabetics (n=67). The corresponding occlusion rate of the IMA graft to the LAD territory was 7.8% (DM) versus 5.1% (Non-DM), p=0.41. Radial versus SVG occlusion was proportionally similar between patients that underwent clinical and protocol directed angiograms.

GEE modeling was used to determine the predictors of late complete graft occlusion at the graft level (Table 3.3). There were no interactions between graft type and territory (p=0.54). The use of the radial artery (compared to the SVG) was found to be protective against long-term complete graft occlusion (odds ratio (OR) 0.43, 95% CI (0.25 – 0.75), p=0.003). In addition, having greater target native vessel stenosis at time of surgery (≥ 90% stenosis compared to less stenotic vessels of 70-89%) was also protective against complete occlusion (OR 0.59, 95% CI (0.35 – 0.97), p=0.04). Being female (OR 2.23, 95% CI (1.14 – 4.38), p=0.02) and having a smoking history (OR 1.49, 95% CI (1.01 - 2.21), p=0.047) were found to be positive predictors of complete graft occlusion along with an elevated creatinine (OR 1.17, 95% CI (1.02 – 1.35), p=0.03, per 10 umol/L increase). The overall protective effect of the radial graft was influenced by diabetic status (diabetes by graft type interaction p=0.02). To determine model fit, 5000 iterations were performed of the original model. The median OR and its 95% confidence interval were similar to the original model for all the prespecified covariates. With respect to the covariates that were significant predictors in the original model (female gender, the use of a radial graft, any smoking history, creatinine, and severity of proximal native disease), all with the exception of smoking history were significant more than 50% of times during the 5000 iterations;
smoking history was significant 47.3% of times. The remaining covariates were significant less than 11% in the 5000 iterations.

Cumulative patency curves were created based on 464 patients undergoing early and/or late angiography with complete occlusion being the failure event. Cumulative patency was similar for the radial artery irrespective of diabetic status (at 7.5 years, DM: 91.5 +/- 2.7% versus Non-DM: 90.3 +/- 2.0%, log-rank p = 0.51, Figure-3.1a); however for SVGs, cumulative patency curves were statistically different (at 7.5 years, DM: 79.7 +/- 3.9% versus Non-DM: 86.2 +/- 2.1%, log-rank p=0.03, Figure-3.1b). There were 236 patients that underwent serial early and late angiograms. Of the 227 (96.2%) non-occluded radials at early angiography, 12 (5.3%) became occluded by the second angiogram; for SVGs, of the 204 (86.4%) that were non-occluded, 11 (5.4%) became occluded.

**Clinical endpoints:** Of the 529 patients that underwent late clinical follow-up, the proportion of MACE defined as cardiac death, non-fatal late MI or coronary re-intervention (percutaneous intervention or repeat CABG) was significantly higher in diabetics (MACE: 23/148 (15.5%) DM, 35/381 (9.2%) Non-DM, p=0.04). Each of the individual components along with all-cause mortality trended to be higher in the diabetic group; all-cause death (19/148 (12.8%) DM versus 42/381 (11.0%) Non-DM, p=0.56), cardiac death (10/148 (6.8%) DM versus 16/381 (4.2%) Non-DM, p=0.22), late MI (5/148 (3.4%) DM versus 5/381 (1.3%) Non-DM, p=0.11), and re-intervention (11/148 (7.4%) DM, 16/381 (4.2%) Non-DM, p=0.13) (Table 3.4). Event free survival from MACE also trended to be lower in
diabetics (10 years: 72.8 +/- 6.1% DM versus 83.4% +/- 3.1% Non-DM, p=0.05, Figure-3.2).

3.5-Discussion
It is well known that diabetics have a higher propensity of rapidly progressive atherosclerosis, macrovascular disease, and higher mortality compared to non-diabetics.\textsuperscript{228} Consequently, issues of myocardial revascularization in these patients have received much attention favoring CABG over PCI especially in diabetics with advanced coronary disease.\textsuperscript{18,195,229,235} The long-term success of CABG is dependent on graft patency and appropriate conduit choice. The RAPS study is the first multi-centre within-patient randomized trial comparing the radial artery and SVG with patients undergoing late angiography at beyond 5 years after CABG.

The main finding of this substudy was that the SVGs compared to radial arteries had a higher proportion of complete graft occlusions beyond 5-years after CABG in diabetics. Compared to non-diabetics, SVG occlusions were also higher in diabetics. Furthermore, while the use of a radial artery along with a higher grade of target vessel stenosis was protective against late complete occlusion, female gender, a smoking history and elevated creatinine were predictors of complete occlusion. There was also an interaction between diabetes and the type of graft used. Finally, while univariate analysis showed that radials had a non-significantly higher occlusion rate in patients without diabetics (Table 3.2), the almost identical radial patency curves with respect to diabetic status were reassuring (Figure 3.1); the counter-intuitive univariate finding may have been due to low number of events. The graft occlusion findings in this study are consistent with our earlier publication
of 1 year angiography results which also showed that SVGs had a higher occlusion rate in diabetics versus non (19% versus 12%, p=0.04). At both early and late angiography, radial patency was statistically similar with respect to diabetic status and the use of the radial artery was protective against complete graft occlusion. Of the randomized trials comparing radial arteries to SVG to date, the Veterans Affairs Cooperatives Study Program (VA) was the only other study that reported potential influence of diabetes on radial and SVG patency; interestingly they found that radials had a lower patency compared to SVG in diabetics and the opposite was true for non-diabetics. This is in contrast to our findings and may have been due to their shorter follow-up period of 1-year. The lack of females, the possible differences with regards to target vessel stenosis, the surgeons’ discretion of target for the study conduit (as compared to the randomized targets in RAPS) may have also led to differential findings in the VA study. A recent study by Schwann et al., using propensity-matched analysis showed that the IMA and radial artery group conferred a significant late-survival advantage (16 years follow-up) in diabetics compared to IMA and SVG group (Hazard Ratio (HR) 0.78, 95% CI (0.65-0.95), p=0.012). Another propensity matched study by Tranbaugh and associates showed that diabetics who underwent CABG had a relative 57% increased 10-year mortality with saphenous vein grafting compared to radial artery grafting.

These findings are suggestive of SVGs doing poorly in diabetics compared to the radial artery. The phenomena of SVGs performing inferiorly to arterial grafts was seen in the Bypass Angioplasty Revascularization Investigation (BARI) which showed that CABG involving the use of the IMA had a substantial survival benefit in diabetics compared to
CABG involving only SVGs. Another recently published study using propensity scores showed that bilateral compared to single internal mammary artery utilization in diabetes was associated with a higher late survival (13.1 years versus 9.8 years, \( p=0.001 \)).\(^{238}\) Finally, the proportion of MACE was higher in diabetics compared to non-diabetics. While the individual components of MACE were all non-significantly higher in diabetics, the higher MACE in diabetics may have been driven by higher re-intervention rates, which had the highest absolute risk difference (3.2%). The difference in clinical event rates between diabetes and non-diabetes is likely underestimated in our study due to the within patient randomization design where each patient received both the radial and SVG biasing our findings towards the null.

**Limitations**

The RAPS study generally recruited low risk patients. Patients who underwent late angiography had lower incidence of hypertension and peripheral vascular disease compared to the cohort that did not undergo angiography. The utilization of within patient randomization allowed patients to serve as their own controls decreasing confounding bias; however this design did not allow for independent comparisons of clinical outcomes based on graft type. Furthermore, during follow-ups, there were no assessments of hemoglobin-A1c status therefore the severity or control of diabetes in these patients were not clear. In addition, while 75% of eligible patients underwent late angiography, the absolute number and the consequent event rates were small therefore the findings from this study should be considered hypothesis generating and further corroborated in larger studies. Finally and perhaps related to the small number of events is the unexpected finding of radial and SVG occlusions being qualitatively different (i.e. the proportion of radial occlusion was lower in
diabetics versus non-diabetics whereas for SVGs, it was higher in diabetics versus non-diabetics.

3.6-Conclusions
Radial arteries are associated with a lower proportion of late graft occlusion compared to SVG in diabetics. Furthermore, while severe target vessel stenosis (> 90%) is protective, female gender, smoking history and elevated creatinine are predictors of late graft occlusion. Finally, non-diabetics had a lower proportion of late major adverse cardiac events compared to diabetics. Our observational data from the prospectively randomized RAPS study support the utilization of the radial artery as a second conduit compared to the SVG is appropriate in diabetic patients.

3.7-Tables and Figures

Table 3.1: Baseline Characteristics of Patients With and Without Diabetes*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Late Clinical Follow-up Cohort (N=529)</th>
<th>P-value</th>
<th>Late Angiographic Cohort (N=269)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetics (N=148)</td>
<td>Non-Diabetics (N=381)</td>
<td></td>
<td>Diabetics (N=83)</td>
</tr>
<tr>
<td>Age – year (mean +/- SD)</td>
<td>59.9 +/- 7.7</td>
<td>60.8 +/- 8.7</td>
<td>0.17</td>
<td>59.4±7.6</td>
</tr>
<tr>
<td>Age &gt; 70 year – no. (%)</td>
<td>17 (11.5)</td>
<td>63 (16.5)</td>
<td>0.15</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Elective Surgery – no. (%)</td>
<td>93 (62.8)</td>
<td>251 (65.9)</td>
<td>0.51</td>
<td>54 (65.1)</td>
</tr>
<tr>
<td>Previous myocardial infarction – no. (%)</td>
<td>71 (48.0)</td>
<td>174 (45.7)</td>
<td>0.63</td>
<td>36 (43.4)</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>27 (18.2)</td>
<td>44 (11.6)</td>
<td>0.04</td>
<td>18 (21.7)</td>
</tr>
<tr>
<td>CCS class of angina – no. (%)</td>
<td>0.63</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (1.4)</td>
<td>8 (2.1)</td>
<td>2 (2.4)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>2</td>
<td>35 (23.7)</td>
<td>94 (24.7)</td>
<td>17 (20.5)</td>
<td>42 (22.6)</td>
</tr>
<tr>
<td>3</td>
<td>66 (44.6)</td>
<td>183 (48.0)</td>
<td>41 (49.4)</td>
<td>96 (51.6)</td>
</tr>
<tr>
<td>4</td>
<td>45 (30.4)</td>
<td>96 (25.2)</td>
<td>23 (27.7)</td>
<td>46 (24.7)</td>
</tr>
<tr>
<td>Congestive heart failure – no. (%)</td>
<td>9 (6.1)</td>
<td>7 (1.8)</td>
<td>2 (2.4)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Hypertension – no. (%)</td>
<td>82 (55.4)</td>
<td>178 (46.7)</td>
<td>39 (47.0)</td>
<td>82 (44.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia – no. (%)</td>
<td>109 (74.2)</td>
<td>240 (63.0)</td>
<td>64 (78.1)</td>
<td>125 (67.2)</td>
</tr>
<tr>
<td>Smoking history – no. (%)</td>
<td>111 (75.0)</td>
<td>267 (70.1)</td>
<td>61 (73.5)</td>
<td>131 (70.4)</td>
</tr>
<tr>
<td>Creatinine – µmol/L (mean +/- SD)</td>
<td>93.0 +/- 18.6</td>
<td>93.5 +/- 19.4</td>
<td>91.1±16.0</td>
<td>93.1±18.0</td>
</tr>
<tr>
<td>Peripheral vascular disease – no. (%)</td>
<td>13 (8.8)</td>
<td>33 (8.7)</td>
<td>5 (6.0)</td>
<td>11 (5.9)</td>
</tr>
<tr>
<td>Left ventricular grade – no. (%)</td>
<td>0.26</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>†</td>
<td>60 (40.5)</td>
<td>188 (49.3)</td>
<td>37 (44.6)</td>
<td>96 (51.6)</td>
</tr>
<tr>
<td>2</td>
<td>86 (58.1)</td>
<td>186 (48.8)</td>
<td>45 (54.2)</td>
<td>86 (46.2)</td>
</tr>
<tr>
<td>3</td>
<td>2 (1.4)</td>
<td>6 (1.6)</td>
<td>1 (1.2)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Target Vessel Stenosis – no. (%)</td>
<td>0.13</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Coronary Artery</td>
<td>0.61</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-89% Stenosis</td>
<td>44 (29.7)</td>
<td>122 (32.0)</td>
<td>24 (28.9)</td>
<td>60 (32.3)</td>
</tr>
<tr>
<td>&gt;90% Stenosis</td>
<td>104 (70.3)</td>
<td>259 (68.0)</td>
<td>59 (71.1)</td>
<td>126 (67.7)</td>
</tr>
<tr>
<td>Circumflex Artery</td>
<td>0.13</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-89% Stenosis</td>
<td>75 (50.7)</td>
<td>165 (43.3)</td>
<td>39 (47.0)</td>
<td>76 (40.9)</td>
</tr>
<tr>
<td>&gt;90% Stenosis</td>
<td>73 (49.3)</td>
<td>216 (56.7)</td>
<td>44 (53.0)</td>
<td>110 (59.1)</td>
</tr>
<tr>
<td>Radial-artery target vessel</td>
<td>0.13</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-89% Stenosis</td>
<td>67 (45.3)</td>
<td>145 (38.1)</td>
<td>34 (41.0)</td>
<td>71 (38.2)</td>
</tr>
<tr>
<td>&gt;90% Stenosis</td>
<td>81 (54.7)</td>
<td>236 (61.9)</td>
<td>49 (59.0)</td>
<td>115 (61.8)</td>
</tr>
<tr>
<td>Saphenous-vein target vessel</td>
<td>0.65</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-89% Stenosis</td>
<td>52 (35.1)</td>
<td>142 (37.3)</td>
<td>29 (35.0)</td>
<td>65 (35.0)</td>
</tr>
<tr>
<td>&gt;90% Stenosis</td>
<td>96 (64.9)</td>
<td>239 (62.7)</td>
<td>54 (65.1)</td>
<td>121 (65.1)</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± standard deviation (SD). CCS denotes Canadian Cardiovascular Society. †According to this scale, a grade of 1 indicates an estimated global left ventricular ejection fraction (LVEF) of 50 percent or more, a grade of 2 is LVEF of 35 to 49 percent, a grade of 3 is LVEF of 20 to 34 percent, and a grade of 4 is a LVEF of less than 20 percent.

Table 3.2a: Comparison of Complete Graft Occlusion Between the Radial Artery versus SVG by Diabetic Status

<table>
<thead>
<tr>
<th></th>
<th>Radial Artery Complete Occlusion n (%)</th>
<th>SVG Complete Occlusion n (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetics (n=83)</td>
<td>4 (4.8)</td>
<td>21 (25.3)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Non-Diabetics (N=186)</td>
<td>20 (10.8)</td>
<td>29 (15.6)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

P-values are based on a McNemar test and represent comparison of radial artery occlusion versus SVG occlusion for the respective diabetic status.

Table 3.2b: Comparison of Complete Graft Occlusion of the Same Conduit between Diabetics vs. Non-Diabetics

<table>
<thead>
<tr>
<th></th>
<th>Diabetics (N=83)</th>
<th>Non-Diabetics (N=186)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial Artery Complete Occlusion n (%)</td>
<td>4 (4.8)</td>
<td>20 (10.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Saphenous Vein Complete Occlusion n (%)</td>
<td>21 (25.3)</td>
<td>29 (15.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Radial and/or SVG Complete Occlusion n (%)</td>
<td>24 (28.9)</td>
<td>48 (25.8)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

P-values are based on chi-squares and represent the comparison of diabetics versus non-diabetics for the respective conduit (Radial or SVG) occlusion.

Table 3.3: Multivariable Predictors of Complete Graft Occlusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2.23</td>
<td>1.14 – 4.38</td>
<td>0.02</td>
</tr>
<tr>
<td>Radial graft</td>
<td>0.43</td>
<td>0.25 – 0.75</td>
<td>0.003</td>
</tr>
<tr>
<td>History of Smoking</td>
<td>1.49</td>
<td>1.01 – 2.21</td>
<td>0.047</td>
</tr>
<tr>
<td>Proximal Native Vessel Disease (≥90% versus 70-89% stenosis)</td>
<td>0.59</td>
<td>0.35 – 0.97</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Creatinine (per 10mol/L) | 1.17 | 1.02 – 1.35 | 0.03  
Diabetes | 1.10 | 0.65 – 1.86 | 0.72  
Diabetes * Graft type Interaction | | | 0.02  

Complete graft occlusion (either radial or SVG) is defined as Thrombolysis in Myocardial Infarction (TIMI) flow of 0 or non-patent as assessed by computed tomography angiography. Odds ratio less than 1 is protective against complete graft occlusion.

Table 3.4: Clinical endpoints between Diabetics vs. Non-Diabetics

<table>
<thead>
<tr>
<th>Clinical Endpoint</th>
<th>Diabetics (N=148)</th>
<th>Non-Diabetics (N=381)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiac events (%)</td>
<td>23 (15.5)</td>
<td>35 (9.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>All-cause death (%)</td>
<td>19 (12.8)</td>
<td>42 (11.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>10 (6.8)</td>
<td>16 (4.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Late Non-fatal MI (%)</td>
<td>5 (3.4)</td>
<td>5 (1.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Re-intervention (PCI or CABG)</td>
<td>11 (7.4)</td>
<td>16 (4.2)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

P-value compares the proportions of clinical events between diabetics and non-diabetics. Major adverse cardiac events is defined by cardiac death, late non-fatal myocardial infarction (MI) or re-intervention either by stent or redo CABG.
Figure 3.1a: Freedom from complete occlusion of the radial artery graft stratified by diabetic status. The log-rank p-value is testing for statistical significance between the radial artery graft patency curve of diabetics (DM) versus non-diabetics (Non-DM).
Figure 3.1b: Freedom from complete occlusion of the saphenous vein graft stratified by diabetic status. The log-rank p-value is testing for statistical significance between the saphenous vein graft patency curve of diabetics (DM) versus non-diabetics (Non-DM).
Figure 3.2: Major adverse cardiac event free survival (MACE) stratified by diabetic status. The log-rank p-value is testing for statistical significance between the MACE curves of diabetics (DM) versus non-diabetics (Non-DM). MACE is defined as cardiac death, or late myocardial infarction or repeat re-intervention of percutaneous coronary intervention or coronary artery bypass surgery.
Acknowledgements

The members of the Radial-Artery Patency Study Group are as follows: Executive Committee - S.E. Fremes, E.A. Cohen, R. Feder-Elituv, A. Laupacis; Manuscript Committee – S.E. Fremes, E.A. Cohen, S. Deb, A. Laupacis, S.K. Singh; Steering Committee - S.E. Fremes, E.A. Cohen, A. Laupacis, C. Buller, N.D. Desai, L. Errett, R. Feder-Elituv, J.F Morin, S. Deb, M.L. Myers, R. Novick, F.D. Rubens, S.K. Singh, T. Yau; Participating Cardiologists - D. Almond (Victoria Hospital, London, Ont.), C. Buller (University of British Columbia, Vancouver), E.A. Cohen (University of Toronto, Toronto), L. Dragatakis (McGill University, Montreal), L. Higginson (University of Ottawa Heart Institute, Ottawa), L. Schwartz (University of Toronto, Toronto), W. Tymchak (University of Alberta Hospital, Edmonton), R. Watson (University of Toronto, Toronto); Data Committee - M. Afshar, K. Algarni, S. Deb, R. Feder-Elituv, J. Sever, D. Une (all at University of Toronto, Toronto); Statisticians - M. Katik, A. Kiss (all at University of Toronto, Toronto); Angiographic Committee - E.A. Cohen, J. Dubbin, D. Ko, A. Moody, V. Pen, S. Radhakrishnan, L. Schwartz (all at the University of Toronto, Toronto); Clinical End-Points Committee - C. Joyner, F. Moussa, M. Myers (all at the University of Toronto, Toronto); Investigators - Health Sciences Centre, Winnipeg, Man.: D. Del Rizzo; Institute de Cardiologie de Montreal, Montreal: M. Carrier, R. Cartier, Y. Leclerc; London Health Sciences Center - University Campus, London, Ont.: D. Boyd, A. Menkis, R. Novick; London Health Sciences Center - Victoria Campus, London, Ont.: M.L. Myers; Montreal
Chapter 4

Impact of South Asian Ethnicity on Long-Term Outcomes after Coronary Artery Bypass Grafting Surgery: A Large Population-Based Propensity Matched Study

Published in the Journal of the American Heart Association

July 2016;5:e003941, pages 1-12
4.1-Abstract

**Background:** Ethnicity is an important predictor of coronary artery bypass grafting surgery (CABG) outcomes. South Asians-(SA), one of the largest ethnic groups with a high burden of cardiovascular disease, are hypothesized to have inferior outcomes after CABG compared to other ethnic groups. Given the paucity and controversy of literature in this area, the objective of this study was to examine the impact of SA versus the general population-(GP) on long-term outcomes following CABG.

**Method and Results:** Using administrative databases and a surname algorithm, 83,850-patients (SA:2,653, GP:81,197) who underwent isolated CABG in Ontario, Canada from 1996-to-2007 were identified; mean follow-up was 9.1±3.9 years. SA were younger (SA:61.7±9.4, GP:64.1±10.0 years, standardized-difference (STD)=0.25) with more cardiac risk-factors, including diabetes (SA:54.1%, GP:34.9%, STD=0.40). Propensity-score matching resulted in 2,473-matched pairs between SA and GP with all baseline covariates being balanced (STD<0.1). Being a SA compared to the GP, was protective against freedom from major adverse cardiac and cerebrovascular events (MACCE, defined by all-cause death, myocardial infarction (MI), stroke, or coronary reintervention): Adjusted Cox-proportional hazard ratio-(HR) 0.91, 95%-confidence interval (CI) 0.83-0.99, adjusted-p=0.04; this was also true for freedom from all-cause mortality: HR 0.81, 95% CI 0.72-0.91, adjusted-p=0.0004. The adjusted proportion of MACCE was lower in the SA (SA:34.7%, GP:37.8%, McNemar-p=0.03), driven largely by all-cause mortality (SA:20.4%, GA:24.3%, McNemar-p=0.001).
**Conclusions:** Contrary to existing notions, our study finds that being a South Asian is protective with respect to freedom from long-term MACCE and mortality after CABG. More studies are required to corroborate and explore causal factors of these findings.
4.2-Introduction
Ischemic heart disease is one of the leading causes of death worldwide.\(^{18,239}\) In North America, coronary revascularizations including coronary artery bypass grafting surgery (CABG) or percutaneous coronary intervention (PCI) are amongst the most common medical procedures performed.\(^{212}\) South Asians, comprising of people originating from India, Pakistan, Sri Lanka, Nepal and Bangladesh, represents one of the largest ethnic groups in the world;\(^{203}\) migration has resulted in significant number of this ethnic group settling in the western hemisphere, including Canada, the United States (US), and the United Kingdom (UK). In Canada, South Asians are the largest and most rapidly growing visible ethnic group;\(^{206}\) it is projected that by 2031, South Asians will continue to be the largest visible minority in Canada, growing to an estimated 3.2–4.1 million.\(^{204}\)

Several studies have shown that South Asians in North America have a higher burden of cardiovascular disease and cardiovascular deaths compared to Caucasians and other ethnic groups.\(^{202,205,206}\) Similar findings also exist in other developed regions of the world like the UK, where deaths related to coronary disease are higher in South Asians compared to Caucasians.\(^{240}\) Many factors have been postulated to be linked to these findings including a higher prevalence of diabetes, hypertension, increased small-sized low density lipoproteins (LDL), increased abdominal visceral fat, and increased prevalence of metabolic syndrome in South Asians compared to Caucasians.\(^{202,205,206,241}\) Moreover, it has also been shown that South Asians compared to other ethnic groups tend to have more extensive coronary disease including higher prevalence of three vessel and left main disease along with systolic dysfunction at time of initial angiography;\(^{208}\) there is also widespread belief that South Asians have smaller caliber coronary arteries.\(^{209}\)
CABG has become the standard of care for revascularizing patients with advanced severe coronary disease, especially in diabetics.\textsuperscript{18,38} A large study involving the Society of Thoracic Surgeons (STS) database showed that ethnicity (Caucasians versus Non-Caucasians) was an independent predictor of operative mortality after CABG.\textsuperscript{201} Quan et al.\textsuperscript{208} investigated the use of invasive cardiac procedures and suggested that physicians may consider patient ethnicity when recommending procedures including CABG or PCI. With respect to PCI, a recent large retrospective study in the UK (n=279,256) showed that ethnicity (South Asians versus Caucasians) was not an independent predictor of mortality (Adjusted Hazard Ratio (HR) 0.99; 95\% confidence interval (CI) 0.94 - 1.05, median follow-up 2.8 years);\textsuperscript{210} in CABG however, the evidence has been controversial with regards to whether being South Asian is an independent predictor of adverse outcomes after CABG.\textsuperscript{209,211,213,215} These studies are limited by small numbers, lack of adjustment of baseline differences or absence of long-term follow-up. Given that ethnicity maybe an important determinant of which procedure is recommended and the notion that South Asians may have worse outcomes after CABG given the size of their coronaries, it would be prudent to conduct a large robust study with long-term outcomes to determine whether South Asian ethnicity is truly associated with worse outcomes compared to Caucasians and other ethnic groups. Such evidence can further empower the multi-disciplinary heart team to decide whether PCI or CABG would be ideal particularly for individual South Asian patients.

The primary objective of this paper was therefore to determine whether South Asians (SA) compared to the General Population (GP) is an independent predictor of freedom from long-term major adverse cardiac and cerebrovascular events (MACCE) after undergoing
isolated CABG. The secondary objective was to determine whether being a South Asian is a predictor of all-cause mortality. Additional objectives included determining predictors of MACCE in both SAs and the GP along with comparing individual components of MACCE in the unadjusted and the matched cohorts.

4.3-Methods
This is a multi-centre retrospective propensity-score matched study using large administrative databases that prospectively collect patient data. These databases are held securely at the Institute of Clinical and Evaluative Sciences, which is a 'prescribed entity' under Ontario's health information privacy legislation which permits this study to be conducted under a waiver of informed consent. The study was approved by the institutional review boards of Sunnybrook Health Sciences Centre and the University of Toronto.

Study Population
All adult patients greater than 20 years of age who underwent isolated CABG across Ontario, Canada, between April 1, 1996 and March 31, 2007 were included using the Cardiac Care Network (CCN) Registry. The time period chosen was based on the earliest complete records of pertinent covariates in the CCN database and permitted acquisition of at least 5 years of follow-up for each patient. The data of the patients identified were then linked to three administrative databases through a unique encrypted patient identifier. These databases included the Ontario Registered Persons Database (RPDB), used to identify deaths; Office of the Registrar General, Deaths database (ORGD, used to identify cause of death); and the Canadian Institutes for Health Information Discharge Abstract Database (CIHI-DAD), used in concert with the CCN Registry to determine patient demographic
details at time of index CABG and patient outcomes including readmission for an MI, re-intervention, or stroke following the index surgery until June 2012.

**Ethnicity**

Each patient included in this study was categorized as being a member of the South Asian population or of the GP (composed of non-South Asians, predominantly Caucasians) using the Visible Minority surname list derived by Shah and Tu.²⁴² Briefly, building on a previously derived South Asian surname list using Canadian death certificate data,²⁴³ surnames from the community telephone directory and encyclopedia of surnames published by the Indian government were added.²⁴⁴ Each name was then reviewed by at least two researchers of South Asian origin. Surnames were excluded if they did not uniquely belong to SA (ie. surnames common to both SA and other ethnic groups, such as ‘Fernandes’). Disagreements between the two researchers were reviewed by a panel of five reviewers with South Asian origin to reach an agreement. The final list included only surnames that were uniquely South Asian. This list was applied to all members of the RPDB, a registry of all current and former residents of Ontario. This list was validated against the gold-standard self-reported ethnicity from the Canadian Community Health Survey (CCHS), a cross-sectional national telephone survey conducted by Statistics Canada. The specificity of the visible minority surname list for identifying SA ethnicity is 99.7%, sensitivity 50.4%, positive predictive value 89.3%, and negative predictive value 97.2%. The lower sensitivity is primarily a result of excluding surnames which may be common to multiple ethnic groups.²⁴²

**Statistical Analysis**
Propensity-score Analysis

A propensity-score matched analysis was used to adjust for anticipated baseline confounding variables. A propensity score was calculated for each patient using a logistic regression model to estimate the probability of being a South Asian. The variables included in this model were time of surgery (stratified into 3 periods of approximate equal intervals: April 1, 1996 to December 31, 1999, January 1, 2000 to December 31, 2003, and January 1, 2004 to March 31, 2007), age (years), creatinine (µmol/L), sex, Canadian Cardiovascular Society (CCS) Class, left ventricular ejection fraction (LVEF) grade (grade 1: ≥ 50%, grade 2: 35-49%, grade 3: 20-34%, grade 4: <20%), left main or multi-vessel disease (defined as left main disease with or without additional coronary disease, double or triple vessel coronary artery disease including the proximal left anterior descending (LAD) or 3 vessel disease without proximal LAD), history of diabetes mellitus, hypertension (HTN), acute myocardial infarction (AMI within 30 days prior to operation), any myocardial infarction, hyperlipidemia, smoking, cerebrovascular disease (CVD), congestive heart failure (CHF), chronic obstructive sleep apnea (COPD), dialysis, peripheral vascular disease (PVD), previous CABG, and previous PCI. Once the propensity scores were estimated for each patient, each SA patient was matched to one patient from the GP cohort in the institution at which the surgery was performed and on the logit of the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score. Matching was done without replacement, so that each patient occurred at most once in the matched sample.

Baseline Demographics
Balance of baseline characteristics between the SA and GP cohort were assessed using standardized differences (STD) of each covariate where a STD < 0.1 was considered a negligible difference in the mean or prevalence of a covariate between SA and the GP.247,248

Outcomes Analysis

The primary objective was to determine whether SA patients, following CABG, were at increased risk of long term MACCE compared to the GP (MACCE defined by: all-cause mortality, myocardial infarction (MI), coronary reintervention (PCI or re-CABG), or stroke). The secondary objective was to determine whether SA patients had worse survival (time to all-cause mortality) compared to GP patients after CABG.

For both of the above objectives, Cox proportional hazards models were fitted using a robust variance estimator in order to account for the matched nature of the sample.249 Effect estimates were presented using hazard ratios and their associated 95% confidence intervals. Kaplan-Meier curves were also estimated for both of the objectives. Differences between the survival curves for SA and the GP were tested using a stratified log-rank test accounting for the matched design; this analysis was also used to generate 30-day, 1-year, 5-year and 10-year estimates of freedom from MACCE and all-cause death stratified by ethnicity.

Given the lack of long-term data after CABG according to ethnic background, tertiary objectives were to determine the unadjusted crude proportions of MACCE between the SA and GP in addition to determining the predictors of MACCE for each of the original cohorts. For each cohort, a Cox proportional hazards model was used to identify significant predictors. The clinically relevant covariates selected a priori for the models were those
included in the propensity model in addition to urgency rating score (URS, a calculated score ranging from 0 to 6, with 0 being the most urgent and 6 being the least).250

Continuous variables were reported as mean ± standard deviation. Categorical variables were reported as frequencies and percentages. A two-tailed p-value less than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.2 (Cary, NC).

4.4-Results
Baseline Demographics

Between 1996 and 2006, 83,850 patients underwent isolated CABG across the province of Ontario. Of this cohort, 2,653 (3.2%) were SA and 81,197 (96.8%) were part of the GP. As anticipated, these two groups were significantly different from each other with respect to many of the baseline covariates at time of the index CABG (Table 1). SA were younger (SA: 61.7 ± 9.4, GP: 64.1 ± 10.0), and had a higher prevalence of cardiac risk factors including diabetes (SA: 1,435 (54.1%), GP: 28,332 (34.9%), STD=0.40). The prevalence of smoking was however lower in the SA group (SA: 718 (27.1%), GP: 48,138 (59.3%), STD=0.66). The use of propensity-score matching resulted in the formation of 2,473 matched pairs, each comprising one SA patient and one GP patient (Table 4.1). Good balance was observed for all the pertinent covariates, with the resulting STD being less than 0.10 for each variable.

Outcomes
The mean duration of follow-up was 9.1 ± 3.9 years for the overall unmatched cohort, and 9.3 ± 3.5 years for the matched cohort. There were no significant differences with respect to follow-up duration between the two ethnicity groups.

**Primary Outcome**

SA patients, compared to the GP, had a decreased rate of occurrence of MACCE (HR 0.91, 95% CI (0.83–0.99), p-value=0.04) (Table 4.2). The Kaplan-Meier (KM) curves were also statistically different with freedom from MACCE being higher in SA: 1-year SA: 93.9%, GP: 93.8%; 5-years – SA: 84.0%, GP: 83.5%; 10-years - SA: 67.6%, GP: 64.4%; stratified log-rank p-value=0.02 (Figure 4.1a,b).

**Secondary Outcome**

Being a South Asian was strongly associated with a decreased risk of all-cause mortality compared to the GP (HR 0.81, 95% CI (0.72 – 0.91), adjusted p-value = 0.0004) (Table 4.3). The adjusted KM-curves were strongly significantly different between the two groups: 1-year, SA: 97.3%, GP: 97.2%; 5-years, SA: 92.9%, GP: 92.2%; 10-years, SA: 83.0%, GP: 78.7%; stratified p-value = 0.003 (Figure 4.2a,b). Freedom from cardiac mortality between SA and GP was similar (HR 0.82, 95% CI (0.68-1.00), p=0.05).

**Predictors**

Predictors of freedom from MACCE (determined from the full unmatched cohort) were similar for both the SA and GP (Table 4.4). Being male was strongly protective in both cohorts (SA: HR 0.80, p=0.007; GP: HR 0.90, p<0.0001). Having diabetes (SA: HR 1.34,
p<0.0001; GP: HR 1.36, p<0.0001) and PVD (SA: HR 1.50, p=0.0002; GP: HR 1.39, p<0.0001) were amongst the strongest risk factors in both cohorts.

Additional Outcomes

Overall MACCE was substantially higher in the GP compared to SA in the unmatched cohorts (Unmatched SA: 942 (35.5%), GP: 38,288 (47.2%), p<0.001; Matched SA: 859 (34.7%), GP: 934 (37.8%), p=0.03) (Table 4.5). The relationship was similar for all-cause and cardiac mortality (All-cause mortality - Unmatched SA: 562 (21.2%), GP: 28,338 (34.9%), p<0.001; Matched SA: 505 (20.4%), GP: 600 (24.3%), p=0.001; Cardiac mortality – Unmatched SA: 193 (7.3%), GP: 10,059 (12.4%), p<0.001; Matched SA: 172 (7.0%), GP: 207 (8.4%), p=0.06). Proportion of re-intervention and stroke were similar between the two matched groups.

4.5-Discussion

It has been suggested that physicians consider ethnicity when recommending interventions.\textsuperscript{208} To our knowledge, the current study is one of the largest multicenter administrative database studies to report long-term results (mean of 9 years) after CABG, comparing SA, an ethnicity with a high burden of cardiovascular disease, to the GP in Canada. We report that SA patients had better long-term outcomes than the GP, including higher freedom from MACCE, which was driven predominantly by lower all-cause mortality.

We wanted to determine whether outcomes in SA patients were worse than the general population. Indeed, using the crude populations, they are better in the SA than the GP, which is probably the most important result in terms of public policy and healthcare
decision making. To reduce inherent biases due to baseline differences in the SA and GP, we performed propensity matching. Using the propensity matched patient groups, the SA still had lower MACCE, all-cause mortality and cardiac mortality. A limitation of this study in terms of generalizability is that the propensity-matched sample consisted of patients who resembled South Asians; however, they had much better outcomes than the crude GP patients, which further reinforces our conclusion.

The currently available evidence in this high-risk group following CABG is scarce, controversial, and mostly report early outcomes following surgery and not long-term outcomes, which was our primary objective. Brister\textsuperscript{211} performed a single-centre propensity score-matched analysis of 917 SA and Caucasians and reported that operative mortality was higher in the SA group (SA: 2.5\%, Caucasians: 1.1\%, \(p=0.02\)) and suggested that being a SA was an independent predictor of early mortality (OR 3.1, 95\% CI (1.4–6.8), \(p\)-value not reported). This study was performed from 1994–2003 in a single centre in Ontario; as such, we performed a sensitivity analysis which showed that the HR changed only slightly when excluding the centre in Brister’s study for mortality (HR 0.83, \(p=0.01\)). While some patients did overlap between our current study and that of Brister’s, our study reports a longer follow-up.

A study similar to Brister was performed in the UK by Zindrou\textsuperscript{214} (SA: \(n=436\), Caucasian: \(n=1,458\)) which reported that SA patients had almost twice the 30-day mortality rate than that of Caucasians. Another UK study by Goldsmith\textsuperscript{215} (SA: \(n=194\), Caucasian: \(n=190\)) showed similar in-hospital morbidity but higher in-hospital mortality in SA (SA: 6.7\%, Caucasians: 2.6\%, \(p=0.06\)). This study however, had a higher proportion of SA patients
undergoing non-elective surgery, and no difference in mortality was found when stratified by this co-variate; in our study, urgency of surgery (defined by an urgency rating score) was similar between the SA and GP cohort (Table 4.1). In contrast, another study by Elahi and colleagues 209 (SA: n=650, Caucasian n=7,226) found similar 30-day mortality (OR 1.07, p=0.59) and 6-month mortality (OR 1.1, p=0.31) and concluded that SA ethnicity did not appear to be a strong risk factor for adverse outcomes following CABG compared to Caucasians. The controversial results of early excess mortality in SA patients demonstrated in the previous studies may have resulted due to limited sample size, biases associated with single-centred practices, or lack of adjustment for baseline differences. In our present study, while the main objective was to assess long-term outcomes, we found that adjusted freedom from 30-day mortality was slightly worse with a strong overall p-value between SA and the GP in the matched cohorts (SA: 1.7%, GP: 1.4%, stratified log-rank p=0.003). A scale adjusted magnified view of the time to event analysis of event-free survival curve (figure 4.1b) and all-cause mortality (figure 4.2b) shows that SA do slightly worse in the early period. We performed a meta-analysis using the random effects model adding our crude non-adjusted data to the available literature (excluding Brister’s study to prevent double counting as it was a centre that was also included in our study) for 30-day mortality data and found that the odds of mortality was higher being a SA compared to the GP (Odds Ratio (OR) 1.36 95% CI (0.92-2.04), p=0.13, (Figure S1) for early mortality); although this did not reach statistical significance, the directionality of the OR seems to be consistent with that of our matched cohort (Table 4.3, 30-day mortality) and that of Brister’s study for the early period after CABG.
In addition to all-cause mortality, for the first time, we were able to assess cause of mortality (cardiac versus all-cause mortality). The proportion of cardiac related deaths compared to all-cause mortality was 34-35% in both the unmatched and matched GP and the unmatched and matched SA patient groups (Table 4.5). Cardiac mortality was greater in the unmatched (p<0.001) GP compared to the SA population. Although freedom from cardiac mortality had a protective HR for SA (HR 0.82), its 95% CI crossed one (0.68 – 1.00); while we can’t conclude that cardiac mortality is lower in the South Asians in the propensity matched groups, we can conclude that cardiac mortality is certainly not higher in the South Asians.

While we have shown that SA patients do well following CABG in the long-term, we do not yet know the underlying reasons for these findings. It has been suggested that SA compared to Caucasians have smaller coronary arteries therefore potentially resulting in poorer outcomes after CABG. However, a recent study using quantitative coronary angiography comparing SA and Caucasians contradicted this hypothesis by reporting similar proximal coronary artery sizes and severity of coronary disease; another study showed that adjusted coronary size based on body surface area was similar between the two ethnic groups. These findings could explain why, in our study, SA did not perform poorly after CABG compared to the GP. Alternatively, given the pre-existing notion that SA patients do poorly because of reduced caliber of coronary arteries, it is possible that SA patients in our study who were accepted for coronary surgery in Ontario were highly selected, and considered to be surgical candidates only if the target artery sizes were suitably large, resulting in better outcomes.
While speculative, there are several other factors that could potentially explain why long-term post-CABG outcomes for SA patients were better than those for the GP in our study. It has been reported that SAs tend to smoke tobacco less than Caucasians; females of SA origin seldom have a smoking history.\textsuperscript{202,206} A long-term study with a median follow-up of 20 years showed that persistent smokers had higher risks of all-cause death and repeat revascularization after CABG.\textsuperscript{252} While in our study, the higher proportion of smokers present in the GP cohort were adjusted for through matching, it may be possible that following CABG, more patients in the GP continued to smoke, explaining the better outcomes associated with SA patients. Medication adherence is another important factor for secondary prevention of cardiac events after CABG.\textsuperscript{253} In patients following an acute MI, it was shown that prescription of evidence-based therapies at 3 months were similar across SA, Caucasians and Chinese ethnicities.\textsuperscript{254} Adherence was similar between SA and non-SA for statins and calcium-channel blockers; SA were more likely to adhere to beta-blockers and less likely to ACE-inhibitors compared to their non-SA counterparts.\textsuperscript{254} Given the gap in the literature in medication practices specifically following CABG with respect to ethnicity, we can speculate that perhaps a higher medication adherence may be present in the SA compared to the GP following CABG. A third factor is cardiac rehabilitation, which has been associated with early physiologic benefits\textsuperscript{255}, decreased long-term mortality\textsuperscript{256} and reduced need for hospitalization following CABG.\textsuperscript{257} While literature investigating cultural influences in cardiac rehabilitation is scarce, a study by Banerjee\textsuperscript{258} showed that while SA patients were less likely to complete the entire 6-month rehabilitation program compared to Caucasians, they trended to a greater change in maximum metabolic equivalents, and more often reached at least 85% of their target heart rate. While important research has been
recently published in this area using qualitative studies identifying enabling and reinforcing factors such as flexible rehab programs and closer physician and family support, studies specifically evaluating cardiac rehabilitation practices following CABG are still lacking. Finally, dietary modifications have been shown to be effective, at least in the short-term, after CABG. While Chiu and colleagues, in a large cross-sectional study of Ontario residents, reported an increased prevalence in inadequate fruit and vegetable consumption along with obesity in SA, to our knowledge there are no studies specifically examining dietary changes following CABG in the context of ethnic differences. We can only speculate that, in parallel with medication adherence, SA patients may also be following a more heart-healthy diet following CABG.

The major strengths of this study are that it is multi-centre, the largest to date on this subject, and statistically robust. We performed a matched analysis using propensity scores which emulates, as closely as possible, a randomized controlled study design with the design phase being the matching process separated by the analysis phase. This method of propensity scoring compared to other propensity techniques has been shown to reduce a greater degree of bias due to observed confounding variables; the matching process was also ideal for this study as there were a large number of control subjects (GP) allowing us to match nearly all (93.2%) of the identified SA cohort.

There were also pertinent limitations in this study. This was an observational study using provincial and national administrative databases. Intraoperative data were largely unavailable in these databases and represents an important limitation. Bristers single-centred study using propensity analysis neutralized many of these factors, including cross-
clamp time, pump time and mean distal grafts. While we know that our match worked well, as the STD for all measured baseline variables were negligible (including proportion of left main and MVD), we still cannot be certain that intraoperative factors were balanced. Furthermore, while propensity matching performs well in balancing known confounders, it does not account for unknown confounders and treatment-selection bias which are inherent in observational studies. Similarly, these databases cannot accurately capture lifestyle factors including exercise, diet, smoking habits and medication compliance. As mentioned above, these components may help to explain why SA patients had better long-term outcomes than the GP, and therefore dedicated prospective studies in these areas are encouraged. Lastly, we used an ethnic surname list to differentiate SA patients from the GP. One limitation of such a list are those surnames obtained through marriage; however, it has been reported that South Asians are least likely to marry outside their ethnic group. Furthermore, while this list is highly specific, it has a moderate sensitivity due to exclusion of surnames that may be common to many ethnicities. While this may have resulted in some names that were misclassified as the GP, this does bias the results conservatively to the null, and therefore the outcome differences may actually be underestimated.

4.6-Conclusion
Contrary to the notion that South Asians have worse outcomes after CABG compared to other ethnic groups, our large propensity-matched study finds that South Asians actually do better than the General Population in the long-term after CABG with respect to freedom from MACCE and all-cause mortality in Ontario. The causes for these findings are likely multifactorial and warrant further investigation. Given that ethnicity may influence
physician recommendation for medical procedures, our study, while hypothesis generating, will contribute to this regard; further studies are however required to corroborate our findings.

Acknowledgements:

We are thankful to Ms. Julie Wang, Ms. Alice Chong, and Mr. Jiming Fang at the Institute of Clinical and Evaluative Sciences, Toronto Canada, for their assistance in obtaining the necessary dataset and guidance in the analysis. We are also grateful to Dr. Prateek Lala, from the Hospital for Sick Children, Toronto Canada, for editing our manuscript.

Funding:

This work was supported by the Vanier Canada Graduate Scholarship from the Canadian Institute of Health Research (Dr. Deb), Tier 1 Canada Research Chair in Health Services Research and an Eaton Scholar Award (Dr. Tu), Clinician Scientist Award from the Heart and Stroke Foundation, Ontario Provincial Office (Dr. Ko), Career Investigator Award from the Heart and Stroke Foundation, Ontario Provincial Office (Dr. Austin), and the Bernard S. Goldman Chair in Cardiovascular Surgery (Dr. Fremes).

Disclosures: None

4.7-Tables and Figures

Table 4.1: Baseline Demographics
<table>
<thead>
<tr>
<th>Co-variates</th>
<th>General Population (N=81,197)</th>
<th>South Asians (N=2653)</th>
<th>St.Diff</th>
<th>General Population (N=2473)</th>
<th>South Asians (N=2473)</th>
<th>St.Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.1 ± 10.0</td>
<td>61.7 ± 9.4</td>
<td>0.25</td>
<td>61.8 ± 10.2</td>
<td>61.6 ± 9.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine</td>
<td>97.3 ± 56.0</td>
<td>95.2 ± 55.3</td>
<td>0.04</td>
<td>95.6 ± 51.5</td>
<td>95.0 ± 55.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Urgency Rating Score</td>
<td>4.6 ± 1.2</td>
<td>4.7 ± 1.1</td>
<td>0.08</td>
<td>4.6 ± 1.1</td>
<td>4.7 ± 1.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>63,186 (77.8)</td>
<td>2,054 (77.4)</td>
<td>0.01</td>
<td>1,894 (76.6)</td>
<td>1,910 (77.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>28,332 (34.9)</td>
<td>1435 (54.1)</td>
<td>0.40</td>
<td>1,334 (53.9)</td>
<td>1,327 (53.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>HTN n (%)</td>
<td>58,772 (72.4)</td>
<td>2,063 (77.8)</td>
<td>0.12</td>
<td>1,982 (80.1)</td>
<td>1,919 (77.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>History of Smoking n (%)</td>
<td>48,138 (59.3)</td>
<td>718 (27.1)</td>
<td>0.66</td>
<td>695 (28.1)</td>
<td>673 (27.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia n (%)</td>
<td>42,369 (52.2)</td>
<td>1547 (58.3)</td>
<td>0.12</td>
<td>1,525 (61.7)</td>
<td>1,438 (58.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous MI n (%)</td>
<td>36,570 (45.0)</td>
<td>1181 (44.5)</td>
<td>0.01</td>
<td>1,068 (43.2)</td>
<td>1,108 (44.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Acute MI n (%)</td>
<td>18,730 (23.1)</td>
<td>662 (25.0)</td>
<td>0.04</td>
<td>619 (25.0)</td>
<td>623 (25.2)</td>
<td>0</td>
</tr>
<tr>
<td>CHF n (%)</td>
<td>11,517 (14.2)</td>
<td>352 (13.3)</td>
<td>0.03</td>
<td>334 (13.5)</td>
<td>326 (13.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>CVD n (%)</td>
<td>9,457 (11.6)</td>
<td>229 (8.6)</td>
<td>0.09</td>
<td>221 (8.9)</td>
<td>206 (8.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>PVD n (%)</td>
<td>12,110 (14.9)</td>
<td>205 (7.7)</td>
<td>0.20</td>
<td>185 (7.5)</td>
<td>189 (7.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>COPD n (%)</td>
<td>5,821 (7.2)</td>
<td>97 (3.7)</td>
<td>0.14</td>
<td>81 (3.3)</td>
<td>87 (3.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dialysis n (%)</td>
<td>943 (1.2)</td>
<td>31 (1.2)</td>
<td>0.06</td>
<td>30 (1.2)</td>
<td>24 (1.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous PCI n (%)</td>
<td>7,268 (9.0)</td>
<td>193 (7.3)</td>
<td>0.06</td>
<td>174 (7.0)</td>
<td>186 (7.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous CABG n (%)</td>
<td>2,359 (2.9)</td>
<td>40 (1.5)</td>
<td>0.08</td>
<td>37 (1.5)</td>
<td>34 (1.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Left Main Disease n (%)</td>
<td>19,745 (24.3)</td>
<td>486 (18.3)</td>
<td>0.14</td>
<td>532 (21.5)</td>
<td>458 (18.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>*MVD n (%)</td>
<td>62,922 (77.5)</td>
<td>2,085 (78.6)</td>
<td>0.03</td>
<td>1,945 (78.6)</td>
<td>1,954 (79.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>CCS Class n (%)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>1</td>
<td>3,604 (4.4)</td>
<td>139 (5.2)</td>
<td></td>
<td>131 (5.3)</td>
<td>130 (5.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12,365 (15.2)</td>
<td>451 (17.0)</td>
<td></td>
<td>432 (17.5)</td>
<td>428 (17.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25,600 (31.5)</td>
<td>754 (28.4)</td>
<td></td>
<td>642 (26.0)</td>
<td>705 (28.5)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>38,325 (47.2)</td>
<td>1283 (48.4)</td>
<td></td>
<td>1,268 (5)</td>
<td>1,210 (48.9)</td>
<td></td>
</tr>
<tr>
<td>LVEF grade n (%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>1</td>
<td>36,442 (44.9)</td>
<td>1,164 (43.9)</td>
<td></td>
<td>1,038 (42.0)</td>
<td>1,106 (44.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26,453 (32.6)</td>
<td>945 (35.6)</td>
<td></td>
<td>941 (38.1)</td>
<td>901 (36.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12,868 (15.8)</td>
<td>448 (16.9)</td>
<td></td>
<td>434 (17.9)</td>
<td>419 (16.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2,734 (3.4)</td>
<td>53 (2.0)</td>
<td></td>
<td>51 (2.1)</td>
<td>47 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: St.Diff = standardized difference (less than 0.1 is negligible), y = years, HTN = hypertension, Previous MI = previous myocardial infarction (any MI within 15 years prior to index CABG), Acute MI = any myocardial infarction within 30 days prior to
index CABG), CHF = congestive heart failure, CVD = cerebrovascular disease, PVD = peripheral vascular disease, COPD = chronic obstructive pulmonary disease. CCS = Canadian Cardiovascular Society Class, LVEF = left ventricular ejection function. *MVD = multivessel disease (defined as left main disease, double or triple vessel disease including the proximal left anterior descending artery (LAD), or 3-vessel disease without proximal LAD). Hyperlipidemia is defined as documented history of dyslipidemia diagnosed and/or treated by a physician.

Table 4.2: Time to Event Analysis for Freedom from Major Adverse Cardiac and Cerebrovascular Events after adjustment using Propensity Match Analysis (MACCE)

<table>
<thead>
<tr>
<th>Freedom from MACCE for South Asians Compared to the General Population</th>
<th>Hazard Ratio: 0.91, 95% CI (0.83–0.99), Adjusted p-value for paired Cox proportional hazard model = 0.04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from MACCE</td>
<td>General Population %, (95% CI)</td>
</tr>
<tr>
<td>30-day</td>
<td>98.1%, (97.6%–98.6%)</td>
</tr>
<tr>
<td>1-year</td>
<td>93.8%, (92.8%–94.7%)</td>
</tr>
<tr>
<td>5-years</td>
<td>83.5%, (82.0%–84.9%)</td>
</tr>
<tr>
<td>10-years</td>
<td>64.4%, (62.3%–66.5%)</td>
</tr>
</tbody>
</table>

Stratified log-rank p-value = 0.02

Abbreviations: CI = Confidence Interval

Table 4.3: Time to Event Analysis for Freedom from All-cause Mortality after adjustment using Propensity Match Analysis
Freedom from All-Cause Mortality for South Asians Compared to the General Population

<table>
<thead>
<tr>
<th>Freedom from All-cause Mortality</th>
<th>General Population %, (95% CI)</th>
<th>South Asians %, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day</td>
<td>98.6%, (98.1%-99.0%)</td>
<td>98.3%, (97.7%-98.7%)</td>
</tr>
<tr>
<td>1-year</td>
<td>97.2%, (96.5%-97.8%)</td>
<td>97.3%, (96.7%-97.9%)</td>
</tr>
<tr>
<td>5-years</td>
<td>92.2%, (91.0%-93.1%)</td>
<td>92.9%, (91.8%-93.8%)</td>
</tr>
<tr>
<td>10-years</td>
<td>78.7%, (76.8%-80.5%)</td>
<td>83.0%, (81.3%-84.6%)</td>
</tr>
</tbody>
</table>

Stratified log-rank p-value = 0.003

Abbreviations: CI = Confidence Interval

Table 4.4: Predictors of Freedom from Major Adverse Cardiac and Cerebrovascular Events (MACCE) After CABG in South Asians and the General Population

<table>
<thead>
<tr>
<th>Covariates</th>
<th>General Population (n=81,197)</th>
<th>South Asians (n=2653)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.03</td>
<td>1.03-1.04</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>1.00</td>
<td>1.00-1.00</td>
</tr>
<tr>
<td>URS</td>
<td>0.97</td>
<td>0.96-0.98</td>
</tr>
<tr>
<td>Male</td>
<td>0.90</td>
<td>0.88-0.93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.36</td>
<td>1.33-1.39</td>
</tr>
<tr>
<td>HTN</td>
<td>1.17</td>
<td>1.14-1.20</td>
</tr>
<tr>
<td>History of Smoking</td>
<td>1.16</td>
<td>1.13-1.19</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.91</td>
<td>0.89-0.93</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.17</td>
<td>1.14-1.20</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0.99</td>
<td>0.96-1.02</td>
</tr>
<tr>
<td>CHF</td>
<td>1.40</td>
<td>1.36-1.44</td>
</tr>
<tr>
<td>CVD</td>
<td>1.46</td>
<td>1.41-1.50</td>
</tr>
<tr>
<td>PVD</td>
<td>1.39</td>
<td>1.35-1.43</td>
</tr>
<tr>
<td>COPD</td>
<td>1.37</td>
<td>1.32-1.42</td>
</tr>
<tr>
<td>Dialysis</td>
<td>1.23</td>
<td>1.10-1.37</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1.19</td>
<td>1.14-1.23</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1.30</td>
<td>1.23-1.37</td>
</tr>
<tr>
<td>Left Main Disease</td>
<td>1.08</td>
<td>1.05-1.11</td>
</tr>
<tr>
<td>MVD</td>
<td>0.99</td>
<td>0.97-1.02</td>
</tr>
</tbody>
</table>
Abbreviations: Y = years, HTN = hypertension, Previous MI = previous myocardial infarction (any MI within 15 years prior to index CABG), Acute MI = any myocardial infarction within 30 days prior to index CABG), CHF = congestive heart failure, CVD = cerebrovascular disease, PVD = peripheral vascular disease, COPD = chronic obstructive pulmonary disease. MVD = multivessel disease (defined as left main disease or proximal left anterior descending artery and one or both of circumflex & right coronary or 3-vessel disease without proximal LAD)

Table 4.5: Overall Outcomes for Duration of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Unmatched</th>
<th>Matched</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General Population</td>
<td>South Asians</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>(N=81,197)</td>
<td>(N=2,653)</td>
<td></td>
</tr>
<tr>
<td>Mean Follow-Up</td>
<td>9.1 ± 3.9</td>
<td>9.3 ± 3.5</td>
<td></td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡MACCE</td>
<td>38,288 (47.2%)</td>
<td>942 (35.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>28,338 (34.9%)</td>
<td>562 (21.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac-cause mortality</td>
<td>10,059 (12.4%)</td>
<td>193 (7.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>7,275 (9.0%)</td>
<td>235 (8.9%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Stroke</td>
<td>6,080 (7.5%)</td>
<td>167 (6.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>$Re-intervention</td>
<td>8,280 (10.2%)</td>
<td>306 (11.5%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*P-value from a chi-square statistic for independent data. †P-value from a McNemar statistic for matched data. ‡MACCE is major adverse cardiac and cerebrovascular events defined by all-cause mortality, myocardial infarction, stroke or re-intervention following the index CABG. $Re-intervention is composed of repeat coronary artery bypass surgery and/or repeat percutaneous intervention.
Figure 4.1a: Freedom from MACCE. MACCE defined by all-cause mortality, myocardial infarction, stroke or re-intervention.

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>30-days</th>
<th>1-year</th>
<th>5-years</th>
<th>10-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asians</td>
<td>2411</td>
<td>2324</td>
<td>2078</td>
<td>854</td>
</tr>
<tr>
<td>General Population</td>
<td>2429</td>
<td>2321</td>
<td>2067</td>
<td>828</td>
</tr>
</tbody>
</table>

Stratified Log-rank p=0.02
Figure 4.1b: Freedom from MACCE, scale adjusted to highlight the first year. MACCE defined by all-cause mortality, myocardial infarction, stroke or re-intervention.
<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>30-days</th>
<th>1-year</th>
<th>5-years</th>
<th>10-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asians</td>
<td>2,431</td>
<td>2,408</td>
<td>2,298</td>
<td>1,064</td>
</tr>
<tr>
<td>General Population</td>
<td>2,440</td>
<td>2,405</td>
<td>2,280</td>
<td>1,003</td>
</tr>
</tbody>
</table>

Figure 4.2a: Freedom from all-cause mortality.
Figure 4.2b: Freedom from all-cause mortality, scale adjusted to highlight the first year. MACCE defined by all-cause mortality, myocardial infarction, stroke or re-intervention.
### Supplement Figure

Figure S1: Meta-analysis of in-hospital or 30-day mortality of South Asians and the General Population after coronary artery bypass grafting surgery excluding study by Brister et al.²⁰⁹,²¹¹-²¹⁵

<table>
<thead>
<tr>
<th>Study name</th>
<th>Publication Year</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldsmith</td>
<td>1999</td>
<td>2.657 (0.928-7.606)</td>
<td>1.822 0.069</td>
</tr>
<tr>
<td>Zindrou</td>
<td>2001</td>
<td>2.013 (1.202-3.371)</td>
<td>2.660 0.008</td>
</tr>
<tr>
<td>Eliahi</td>
<td>2006</td>
<td>1.072 (0.705-1.629)</td>
<td>0.324 0.746</td>
</tr>
<tr>
<td>Hadjinikolaou</td>
<td>2010</td>
<td>2.619 (1.126-6.090)</td>
<td>2.235 0.025</td>
</tr>
<tr>
<td>Gasevic</td>
<td>2013</td>
<td>0.522 (0.162-1.685)</td>
<td>-1.088 0.277</td>
</tr>
<tr>
<td>Deb</td>
<td>2016</td>
<td>0.963 (0.728-1.272)</td>
<td>-0.268 0.789</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.364 (0.915-2.035)</td>
<td>1.524 0.128</td>
</tr>
</tbody>
</table>

Favours South Asians Favours General Population
Chapter 5
General Discussion, Appraisal of Hypotheses and Conclusions
5.1-General Discussion
Since the first successful CABG performed by Dr. Robert Goetz in 1960, there have been significant advances in the management of coronary artery disease. In the era of advanced PCI and evolving drug eluting stents, the risk profile of cardiac surgical patients has increased (more patients > 80 years of age and frail – both factors associated with higher risk of adverse postoperative outcomes), along with cases becoming more complex; as such, appropriate patient selection and perioperative decision making has become paramount.

Moreover, while the volume of CABG has decreased due to broader application of PCI, it still remains the standard of care in certain patient populations including diabetics and advanced coronary disease. Achieving good short and long-term outcomes after CABG in such patients compared to young healthy patients with less complex coronary anatomy are both challenging and the ultimate goal. In order to achieve this, there are many aspects of CABG that have the potential to be optimized in order to improve short and long-term outcomes. Conduit selection is one of the most important predictors of CABG outcomes. While the evidence of arterial grafting is growing, long-term results in selected patient populations (including diabetics) are not known. This also speaks to the fact that patient factors are important components to revascularization outcomes (and therefore choice of intervention). Furthermore, despite growing evidence of arterial grafting, the use of multiarterial grafting in the surgical community remains low suggesting surgeons still prefer to use SVGs. As such, improving aspects of SVG use (including harvesting techniques) may further enhance CABG outcomes. Furthermore, similar to PCI where pharmacological agents have improved outcomes (especially with drug eluting stents),
perioperative pharmacological agents can be explored as well to potentially improve CABG outcomes.

In this thesis, we undertook investigations to determine whether certain surgical, patient and pharmacological factors can improve short and or long-term outcomes after CABG. To do this, we undertook 3 studies: Study 1) A multicentred 2x2 factorial RCT to determine whether a novel no-touch harvesting technique of the SVG compared to the conventional SVG harvesting technique along with fish-oil supplementation compared to placebo, can improve 1-year angiographic and CABG outcomes, Study 2) A secondary analysis from the multi-centre RAPS trial, to determine whether radial arteries are superior to SVG in diabetics long-term and Study 3) An administrative database study using propensity scores to determine whether a patient factor (South Asian ethnicity, generally deemed to be higher risk for CABG) does indeed result in worse outcomes compared to the general population in Ontario.

5.2-Appraisal of Hypothesis 1

Hypothesis: We hypothesize that the NT technique will result in superior angiographic patency and clinical outcomes at 1-year after CABG compared to patients receiving the CON technique.

The above hypothesis was tested using a multi-centre international 2x2 factorial design with a surgical arm (NT versus CON) and a pharmacological arm (FO versus P). With respect to the surgical arm, our data did not support the hypothesis in that we found that there was no significant difference between NT and CON with respect to complete study SVG occlusion or cardiovascular death at 1-year after CABG. With respect to secondary outcomes of study
SVG with significant (>50%) or complete occlusion, the CON group had almost 2x more events (NT 7.8% vs CON 15.4%), however, this was not significant. However, when analyzed as treated, this numerical difference was more pronounced (NT: 7.1%, CON: 15.3%, p=0.06). There was also no difference with respect to clinical outcomes between NT and CON.

Proposed mechanisms of SVG failure were described in the introductory chapter of this thesis. To summarize, endothelial injury which can occur during SVG harvesting has been associated with intimal hyperplasia which is an important component for the progression of atherosclerosis. To this end, the NT SVG taken with a pedicle and without mechanical distention (presumably less injurious to the endothelium) can minimize this risk. Multiple studies mainly from Sweden, led by Souza’s group, have shown biochemical superiority of NT versus CON. With regards to clinical studies, the Souza group has reported their 16-year outcomes which showed that NT was superior to CON with respect to graft patency (NT 83% vs CON 64%). Kim et al. reported an observational study from Seoul Korea that also showed that NT was superior to minimally manipulated SVG at 1-year.

There were some inherent methodological differences between our study and the two other clinical studies by Souza and Kim. Our study was a multi-centre RCT, while Souza’s was single-centred; this novel NT technique was essentially devised by Souza and taught to the other participating centres by Souza and Fremes; therefore certain centres that were part of our trial, may not have had the experience as that of Souza or Fremes or still in the learning curve for the technique. Furthermore, our CTA assessment of NT vs CON was
based on the study graft which was a-priori identified by the surgeon. This method was chosen in order to allow the surgeons freedom to use conventional SVG harvesting for other targets in the same patient if required. In contrast, each patient received one type of vein in the other two studies\textsuperscript{149,220} that allowed for a greater sample size of vein assessment at time of angiography. Lastly, Kim’s study\textsuperscript{220} was composed of composite vein grafting whereas ours and Souza’s\textsuperscript{149} were predominantly aortocoronary grafts.

It is also worth noting that our target sample size was 769 patients in each group and our anticipated event rate for NT was 14% and CON 20%. We were severely underpowered due to funding and our actual event rates were lower than anticipated (NT 5.5%, CON 10.6%). Such low event rates may be an important component of why we did not reach statistical significance.

Another reason for not seeing statistically significant differences at 1-year could be due to the fact that the NT technique is associated with slower progression of atherosclerosis\textsuperscript{147} which is a process that is known to start beyond 1 year after CABG;\textsuperscript{43} as such, perhaps the true effects will only be seen in longer term angiographic assessments. The finding of a more pronounced protective effect when assessing significant stenosis or occlusion (for the treatment received) for NT versus CON along with a stronger p-value is reassuring and consistent with what we had anticipated as well as other studies.\textsuperscript{147,149,151,152,218} Moreover, the magnitude of our results were consistent with the two other clinical studies mentioned above (Souza and Kim)\textsuperscript{149,220}; the unadjusted pooled estimate using a random model of the 3 studies for 1-year graft occlusion favored the use of NT (OR 0.44, 95% CI (0.25-0.76), p=0.00), Figure 5.1.
Figure 5.1 - Meta-analysis of early vein graft occlusion at 1 year. NT=no touch, CON=conventional.

While our data did not statistically support the hypothesis, it is encouraging that the patency rate favors the NT technique at least numerically. While the biggest benefit seems to be graft patency, one of the concerns however, associated with the NT technique, is leg infection. The incidence of leg infection at 30-days was significantly higher in the NT (NT 23.3% versus CON 9.5%, p<0.01); however, by 1-year, incidence of infection was similar between the 2 groups (NT 0.9% versus CON 0.9%). Similarly, the severity of infection was higher in the NT at 30-days (mean score NT 1.0 versus CON 0.3, p<0.01), however at 1-year, this was similar (NT 0.02 versus CON 0.07). With NT harvesting, the pedicle of the vein is harvested alongside the vein to avoid touching the vein directly. As mentioned in previous chapters, the pedicle contains vaso vasorum that supplies micronutrients and oxygen.\textsuperscript{152} As such, with the NT technique, the preservation of the pedicle with the vein has beneficial effects to the SVG,\textsuperscript{152} however, without a pedicle, the healing of the leg may become impaired perhaps due to disruption of lymphatics and microvessels as well as a
greater wound. This is likely the reason for higher incidence of leg infection with the NT, however, it is reassuring that the severity of infection is low and that it essentially resolves by 1 year. Preventative measures in this regard include avoiding this technique on patients with peripheral vascular disease, severe obesity, or uncontrolled diabetes. Furthermore, it is important to not create flaps while exposing the vein and to meticulously close in multiple layers to devoid any gaps.

Another limitation of the NT technique is that endoscopic vein harvesting is not yet possible. In our study, less than 5% of veins were harvested endoscopically. There have been numerous studies that examined open versus endoscopic vein harvesting including a meta-analysis of 267,525 patients that showed no difference in cardiovascular outcomes and graft occlusion at 2.6 years between the two techniques.\textsuperscript{114} Souza et al.,\textsuperscript{157} compared NT to endovein and found early patency to be significantly lower in the endovein (NT 94% versus endovein 27%, \( p < 0.02 \)), however, leg infection rate was higher in NT (NT 18% versus endovein 2%, \( p < 0.0001 \)). Perhaps as technology evolves, endoscopic harvesting will also evolve allowing for NT harvesting techniques.

Overall, this is the first multi-centre study to assess whether NT is superior to CON with respect to SVG patency. Improving SVG patency remains a challenging and important problem. While the data in this study did not support the hypothesis of superiority for the novel NT technique compared to CON, the results are nonetheless encouraging and warrants further examination longitudinally and in a bigger study.
5.3-Appraisal of Hypothesis 2
We hypothesize that patients who received fish-oils will have superior angiographic patency and clinical outcomes at 1-year compared to patients receiving a placebo.

Similar to hypothesis 1, the above hypothesis was tested in the same trial representing the pharmacological arm of a 2x2 factorial design. Our data did not support the hypothesis that fish-oils were associated with superior graft patency and clinical outcomes at 1-year. Moreover, the magnitude of the primary outcome (graft occlusion or cardiovascular death) was actually higher in the FO group compared to P (FO 30% versus P 20%, p=0.17); in addition, MACCE-O was significantly higher in FO (FO 17.1% versus P 4.3%, p=0.02).

There have been large trials that supports the notion that omega-3 fatty acids found in FO are beneficial in reducing cardiovascular events in patients who have had an MI or has documented coronary disease. While it is not clearly known how FO exert cardiovascular protection, potential mechanism include reduction in cardiac arrhythmia, antithrombogenic, and reduction in rate of atherosclerosis. Given the potential secondary prevention benefits of FO, the potential effects of FO after cardiac surgery is an area of interest and also controversial. There have been numerous trials that have investigated whether FO can reduce atrial fibrillation after cardiac surgery the results of which have largely been negative. To our knowledge, there is only one randomized study (n=610) that specifically assessed whether FO had protective effects on graft patency after CABG; this study showed that FO were associated with lower SVG occlusion compared to control (27% versus 33%). Another study by Bendetto et al. showed that patients on omega-3 fatty acid supplement had a lower rate of repeat revascularization and mortality especially in patients with poor ventricular function.
The findings of our study are different from the other 2 studies. This may be due to various factors that existed in our study. First, in addition to funding, we had issues with the manufacturer and therefore, only 140 patients were able to complete the pharmacological component of the study. Second, almost 50% of patients in the FO arm were non-compliant (defined as drug interrupted at any time for > 5 days), compared to 37% in the placebo group. In our study, we measured compliance at each of the clinical visit by counting the pills remaining against expected. In other drug studies, like the GISSI trial, compliance was measured similar to our trial assessing drug refill rates every 3 months; while they did not specifically state compliance rate in the manuscript, 1614/5666 (28.4%) patients discontinued n-3 fatty acids during the study. In the study by Eritsland et al.,189 (RCT comparing FO versus no FO) compliance was measured by counting pills as well as serum fatty acid measurements; 29 patients were defined as non-compliant and were excluded from their analysis. In the DART trial,184 compliance was a more difficult measure as the intervention was dietary; they measured compliance by questionnaires as well as objectively through serum fatty acid measurements; the authors in this study qualified compliance as ‘good’.184 In clinical practice, usually a third of patients completely comply, one third partially comply and the other third does not comply at all.270 Compliance (or lack thereof), represents a real-life phenomenon and therefore, is accounted for in trials using the intention to treat principle,271 as was done in our study. Such a low compliance rate, especially in a small sample size, could have resulted in the lack of angiographic difference between FO and P.

Furthermore, we did not anticipate a higher proportion of MACCE-O events in FO compared to P. We do not have a clear reasoning as to why there were higher events in
patients taking FO. In addition to these results being due to chance alone, one possibility is that the proportions of patients on aspirin at discharge and 1-year were lower in the FO cohort compared to P; this was also true for statins at 1-year. Both of these agents are recommended after CABG (Class I, Level A) and is associated with better patency.\textsuperscript{272,273}

The dose of FO (2g/day – 340mg EPA/170mg DHA per 1g) given in our study was similar to doses in the larger trials (DART – 500-800mg of omega-3 fatty acids/day, GISSI – 1g/day),\textsuperscript{177,184,185} and is similar to the AHA recommendation of 1g of EPA+DHA / day in patients with documented coronary disease.\textsuperscript{187} Despite the similarities in dosing, we may not have used the right preparation for the drug; perhaps our source was not ideal.

Finally, we initiated treatment early prior to surgery in ‘naïve’ patients – starting FO postoperatively or use of chronic FO prior to surgery maybe safe.

Overall, this is the first multi-centre RCT to determine whether FO supplementation is efficacious in reducing graft occlusion as well as cardiovascular events. Given one of the mechanisms of FO supplementation is reducing atherosclerosis (similar to NT), perhaps the effects of such an agent will also not be seen until later.

**Hypothesis 1 and 2: 2x2 Factorial Trial – The Major Points**

Given that both of the above hypotheses were tested using a 2x2 factorial design, the pertinent points of the trial as a whole will be discussed here. First, this is a multi-centre RCT and therefore important biases including allocation bias is reduced.\textsuperscript{274} Similarly, for the surgical arm, except the surgeon, all others involved were blinded; for the pharmacological arm, all were blinded except the pharmacist. Angiographic outcomes were assessed centrally by blinded chest radiologists and clinical outcomes were assessed by a
blinded adjudication committee. The multi-centre nature of this study strengthened its external validity.

We performed a 2x2 factorial study in order to minimize the patients needed while trying to answer 2 questions.\textsuperscript{275} Given this design, we focused on the marginal outcomes after we ensured that there were no significant interactions between the surgical and pharmacological arm for each of the major outcomes.\textsuperscript{275} Moreover, since the sample size of the surgical arm (n=250) was different from the pharmacological arm (n=140), the 2x2 tables could only be done on the 140 patients. As such, while we performed the statistical analysis of the surgical and pharmacological arm independently, we did present all of the data in a descriptive manner (within table data) for each of the major outcomes in table 5 (surgical outcomes) and 7 (pharmacological outcomes). Furthermore, factorial design studies are ideal for addressing 2 or more questions efficiently, especially when no interactions exist.\textsuperscript{275} However, there are costs for each intervention, and in this case there was a delay in the study start due to a prolonged review process with the Natural Health Products of Health Canada for approval of the fish oil intervention - this is particularly important for investigator initiated studies for which there is no industry support.

Finally, with regards to our outcomes, we elected to perform CTA to assess angiographic status. CTA has been shown to have high sensitivity (97.9\%) and specificity (100\%) for detecting graft patency;\textsuperscript{276} furthermore, given its non-invasive nature, we were able to obtain 84.8\% 1-year CTA completion. Furthermore, for the primary outcome, we included angiographic (graft occlusion) and clinical outcome (death), which allowed us to include all
patients in this outcome. We focused on 1 study SVG for angiographic outcomes in the surgical arm, however, the status of all grafts was assessed for the pharmacological arm.

**Relevance of Study**

While the above study did not provide conclusive evidence mainly due to being underpowered, it was nonetheless the first multi-centre trial to test a surgical intervention that could potentially address one of the biggest limitations in CABG surgery – ie. SVG patency. The surgical arm data, while not statistically significant, provided encouraging results favoring SVG patency using the NT technique; we are hopeful, that perhaps a longer follow-up of this study and perhaps a larger study will reveal the true efficacy of this technique. With respect to FO, this was again the first multi-centre study to test its efficacy on graft patency and we do not have convincing evidence to recommend this pharmacologic agent. In fact, given the findings of our data, we would not recommend its use in the manner we did until larger studies are performed.

**5.4-Appraisal of Hypothesis 3**

We hypothesize that radial artery patency will be significantly greater than SVG in both diabetics and non-diabetics. We also hypothesize that non-diabetic patients will have better late clinical outcomes compared to diabetics following CABG.

The above hypotheses were tested as part of secondary analysis from the multi-centre Radial Artery Patency Study. We found that in patients with diabetes, there were significantly higher proportions of SVG occlusion compared to radial arteries (RA 4.8% versus SVG 25.3%, p=0.0004), beyond 5-years after CABG. Moreover, while radial artery patency did not significantly differ with respect to diabetic status, SVGs performed poorly
in diabetic compared to non-diabetics (SVG occlusion: Diabetics 25.3% versus Non-diabetics 15.6%, p=0.06). We also found that MACE was higher in diabetics (15.5%) versus non-diabetics (9.2%).

Diabetes is a growing epidemic in the world; in general, compared to non-diabetics, diabetics do poorly after coronary revascularization (both PCI and CABG).\textsuperscript{193} Due to large studies like the FREEDOM\textsuperscript{194} and SYNTAX\textsuperscript{195} trials, there is now strong evidence that CABG, rather than PCI, should be the considered the standard of care in diabetics with advanced coronary disease. In CABG, approximately 25-40% of patients are usually diabetic.\textsuperscript{82,195,277} Although diabetics do better with CABG than PCI, BARI showed that compared to non-diabetics, diabetes is a poor predictor of clinical outcomes after CABG.\textsuperscript{278} Therefore, this represents another potential area where optimization of surgical factors can perhaps improve CABG outcomes.

The vasculature of patients with diabetes is different than non-diabetics.\textsuperscript{192} More specifically, diabetes has been associated with impaired endothelium dependent vasodilation,\textsuperscript{279} impaired cardiac function including increased LV mass and wall thickness, reduced myocardial function and increased arterial stiffness,\textsuperscript{280} and hyperthrombogenicity.\textsuperscript{281} Furthermore, diabetics are thought to be more susceptible to diffuse and rapidly growing progression of atherosclerosis.\textsuperscript{192} As such, optimizing graft patency in such patients becomes that much more imperative.

In our study, radial arteries were superior to SVGs in diabetics. Furthermore, SVG had better patency rates in non-diabetics than diabetics. These late results are consistent with our early 1-year results which also showed the superiority of radial arteries in diabetics.\textsuperscript{106}
As mentioned earlier, diabetics are more susceptible to atherosclerosis;\textsuperscript{192} furthermore, atherosclerosis is a major mechanism of failure in SVGs.\textsuperscript{43} With regards to radial arteries, histological studies have shown that radial arteries have one layer of elastic lamina with multiple fenestrations.\textsuperscript{89,282} While this makes them more susceptible to atherosclerosis compared to the internal mammary artery (which has fewer fenestrations),\textsuperscript{59} the incidence of atherosclerosis is still low compared to SVGs.\textsuperscript{89,282,283} This maybe one reason why meta-analyses comparing RA versus SVG have not shown a significant difference early on, however, the superior patency results have become evident beyond 4 years in the radial artery.\textsuperscript{111,232}

To our knowledge, our study is only one of two studies that have compared RA versus SVG as part of a RCT with respect to diabetic status. The other study is the VA trial\textsuperscript{82} that was mentioned in the first chapter, which randomized 757 patients (99% men, 42% diabetic) to RA versus SVG. Their findings at 1-year with respect to diabetic status was different from ours in that SVGs had better patency in patients with diabetes (95.2%) than patients without diabetes (84.8%) whereas the radial artery patency was similar in both cohorts (89%). There were some important differences between the VA and RAPS study: all of the VA patients were men (99%); the follow-up was short term; the targets were chosen by the surgeon as opposed to randomization as used in RAPS; and there may have been potential differences with regards to target vessel stenosis between the two studies.\textsuperscript{82,227} In contrast, Lin et al.,\textsuperscript{284} performed a propensity study with 260 matched pairs comparing RA to SVG with respect to 12-year survival and concluded that the RA provided superior long-term survival advantage especially in patients with diabetes (HR 0.59, 95% CI 0.41-0.85, \(p=0.005\)); no significant differences were evident in patients without diabetes. Moreover,
Schwann et al.,\textsuperscript{198} performed another observational study with 2281 diabetics patients who underwent CABG with 16-year follow-up; they used propensity analysis to match 578 patients to determine whether RA or SVG in addition to IMA was superior in this diabetic cohort. They concluded that late survival was superior with RA/IMA grafting (HR 0.78, 95\% CI 0.65-0.95), p=0.012) and that radial artery grafting should be used liberally in diabetic patients.\textsuperscript{198} Another observational study by Hoffman et al.,\textsuperscript{285} using a propensity matched analysis (409 matched pairs) comparing 15 year outcomes, concluded that RA use conferred a significant and sustained survival advantage compared to IMA/vein (HR 0.683, 95\% CI 0.51-0.92, p=0.01).

Although there is growing evidence for the use of radial arteries even in patients with diabetes, the selection of radial artery targets is an important factor that can affect radial artery patency. In our study, cumulative patency was higher in radial arteries when grafted to targets with \( \geq 90\% \) stenosis than if the target had a \(<90\%\);\textsuperscript{79} proximal native disease was a significant predictor of late graft occlusion and target of \( \geq 90\% \) was protective (OR 0.59, 95\% CI 0.35-0.97, p=0.04).\textsuperscript{227} The impaired patency of the radial artery when grafted to less diseased targets has also been reported by others.\textsuperscript{286} It is postulated that this phenomena is likely related to competitive flow in that competitive flow (through mechanisms not clearly understood) causes progressive auto-regulated narrowing of the radial artery which can ultimately lead to graft occlusion\textsuperscript{105}. Given that the media of the radial artery is thicker than the IMA with more smooth muscle cells along with the fact that radials are more reactive to vasoactive agents due to its receptors,\textsuperscript{89,286,287} the potential contractile force of this conduit is very high which can lead to graft dysfunction.\textsuperscript{105} Therefore, irrespective of diabetic status, radials should only be targeted to high grade proximal stenosis of \( \geq 90\% \).
It is also worth mentioning that our study further adds to the evidence of multi-arterial grafting in general. There is now growing evidence that multi-arterial grafting confers survival advantage in patients with diabetes. Tatoulis et al.,288 performed one of the largest administrative database studies from Australia with 34,181 patients undergoing first time isolated CABG of which 11,642 were diabetic (34.1%) comparing TAR versus non-TAR. They reported significantly lower late mortality with TAR in diabetics (TAR 10.2%, non-TAR 12.2%, p=0.04) with 10-year Kaplan Meier survival of 82.2% (TAR) versus 78.3% (non-TAR), log-rank p=0.036. Yamaguchi et al.,289 performed an observational study on 2618 patients comparing single arterial versus multi-arterial grafting in patients with diabetes versus patients who are non-diabetics; they concluded long-term survival advantage (12-years, multi-arterial grafting 64.9% versus single arterial grafting 58.8%, p=0.04) in diabetics; a benefit was also observed in non-diabetics (71.4% versus 63.8%, p=0.014, respectively).289 Gaudino et al.,290 performed a meta-analysis of 8 propensity studies of 10,287 patients, mean follow-up of 37.2 to 196.8 months, comparing 2 versus 3 arterial grafts, and concluded that three arterial grafts did not increase operative risk but was associated with superior long-term survival (HR 0.8, 95% CI 0.75-0.87, p<0.001) irrespective of diabetic status.

Although there is growing evidence of multi-arterial grafting, the concern by surgeons in diabetics is sternal wound infection, especially when bilateral internal mammary arteries are used. As mentioned in earlier chapters, there is now increasing support of use of BIMA in diabetics.62,71
Lastly, it is worth noting we reported that MACE was higher in patients with diabetes (15.5%) versus patients who were non-diabetic (9.2%). Our study design was such that we randomized the radial artery to either the right or left territory and a SVG went to the opposing territory and therefore, each patient received both grafts. While the strength of this design is that it allows us to assess both grafts at angiography, the limitation is that we cannot objectively attribute clinical events to a certain graft.

**Relevance of Study**

Diabetes is an important patient factor that has been shown to influence clinical outcomes after CABG. Optimizing conduit choice (an important surgical factor) in this high risk population can potentially improve CABG outcomes. Our secondary analysis from the RAPS trial shows that the radial artery is superior to SVG with respect to long-term angiographic patency in patients who are diabetic. As such, radial arteries should be used in this population. Furthermore, irrespective of diabetic status, when using the radial artery, our data continues to support the use of radial arteries for highly stenotic native vessels of 90% or more. Moreover, our study adds to the growing evidence and support of multi-arterial grafting.

**5.5-Appraisal of Hypothesis 4**

We hypothesize that being a South Asian compared to the general population will result in worse clinical outcomes following CABG.

The above hypothesis was tested using Ontario’s administrative databases. It was a retrospective study of 83,850 patients that underwent isolated CABG from 1996 to 2007; this population was stratified into SA versus the GP (mainly whites) based on a validated
surname algorithm to identify SA. In order to adjust for baseline differences, we matched using propensity scores. Our data does not support our hypothesis – our findings show that being SA actually had a protective effect with regards to long-term outcomes compared to the GP (event free survival from MACCE – adjusted HR 0.91, 95% CI 0.83-0.99, p=0.04 and survival from all-cause mortality – adjusted HR 0.81, 95% CI 0.72-0.91, p=0.0004).

Ethnicity is becoming an important recognized patient factor in coronary interventions. Numerous studies have recognized that different ethnic backgrounds have different outcomes with coronary heart disease. Furthermore, differential outcomes have been reported based on ethnicity and type of coronary intervention. As mentioned in previous chapters, South Asians, one of the largest visible minorities in Canada, are associated with a higher burden of cardiovascular disease than other ethnicities including Caucasians and Chinese. This ethnic group has also been shown to have an unique cardiovascular risk profile compared to Caucasians, including a higher prevalence of diabetes, higher abdominal obesity, and higher biochemical markers (lipoproteinA, homocysteine levels). With respect to CABG, while the literature is limited, a small number of studies have reported that SA in fact have worse clinical outcomes after CABG compared to Caucasians. It has been suggested that SA may have worse outcomes partly because of smaller coronaries compared to Caucasians. In contrast, a large study published in JACC Interventions of 279,256 patients, reported that SA was no worse than Caucasians in mid-term mortality after PCI. These findings become relevant in context of a population based study by Quan et al., which suggested that physicians may consider ethnicity when deciding which procedure to recommend.
Our findings agree with the smaller studies\textsuperscript{211,214} in that there seems to be a worse early mortality for SA (figure 1b, 2b, 3), however our data for long-term outcomes suggest that SA in fact have better event free survival from MACCE and all-cause mortality than the GP. While such findings are encouraging in this high risk ethnic group, we do not have clear mechanisms to explain them. We postulate that it is likely multi-factorial, including socioeconomic status, lifestyle factors\textsuperscript{261} including diet and exercise, adherence to medications\textsuperscript{254,293} and resources including cardiac rehabilitation which is associated with reduced mortality after CABG.\textsuperscript{294} A recent study by Beatty et al.,\textsuperscript{295} has shown that the strongest predictor of cardiac rehabilitation referral after a coronary procedure is the hospital performing this procedure. It is known that there are areas within major cities where certain ethnic groups may be a majority (ethnic enclaves)\textsuperscript{296}; as such, hospital differences in referrals may result in ethnic differences in cardiac rehab referrals. A limitation of our study is that we did not capture these factors.

**Relevance of Study**

This is the first multi-centre propensity matched observational study investigating long-term outcomes after CABG in the SA ethnic group in Ontario. Our findings suggest that SA actually do well in the long-term after CABG compared to the GP. There seems to be a notion that SA do poorly after CABG\textsuperscript{211,214} and given physicians may consider ethnicity as a patient factor when recommending cardiac procedures,\textsuperscript{208} our data adds important evidence to a limited pool of small scale studies in this topic. Furthermore, the mechanism for why we had these findings are unclear and therefore further studies, both qualitative and
quantitative, are needed to better understand the multitude of factors that may be involved between ethnic groups and cardiovascular outcomes.

5.6-Conclusions
We undertook 3 studies to determine certain surgical, pharmacological and patient factors that can potentially affect CABG outcomes. Study one was the international multi-centre 2x2 factorial trial (SUPERIOR SVG), did not show superiority of the novel NT SVG harvesting technique compared to CON with respect to 1-year angiographic patency or clinical outcomes, however the magnitude of the results were encouraging suggesting longer term follow-up and a bigger study. Our data also did not support the use of FO supplementation after CABG compared to P as there were no angiographic or clinical benefits associated with fish oil use. Study two was the secondary analysis from the multi-centre RAPS trial that supported the use of radial arteries over SVGs in diabetics and confirmed that when radials are used, they should be targeted to a native vessel that has a high grade proximal stenosis (>90%). Study three was a large retrospective administrative database study of patients that underwent CABG in Ontario and found that being SA is in fact protective against long-term MACCE and all-cause mortality compared to the GP; therefore if deemed appropriate, contrast to previous notions, being SA should not exclude patients from undergoing CABG.
6.0-References


249. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med 2014;33:1242-58.
262. Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. Med Decis Making 2009;29:661-77.


