THE RELATIONSHIP BETWEEN BODY MASS INDEX AND CORONARY ARTERY DISEASE IN NEWFOUNDLAND AND LABRADOR, CANADA

by

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Abstract

The focus of this master's research was two-fold. First, the relationship between body mass index (BMI) and severity of coronary artery disease (CAD) was examined in patients undergoing diagnostic coronary angiography (CA) for suspected CAD in Newfoundland and Labrador, Canada. The primary outcomes were 1-year all-cause and cardiac specific mortality. Second, in patients with established CAD and undergoing percutaneous coronary intervention (PCI) the relationship between BMI and short-term adverse events including vascular and non-vascular (i.e., in-lab and post-procedural) complications was investigated. This thesis is presented in manuscript form and consists of four chapters with the first being an introduction and the fourth, final chapter being a discussion. The second chapter focuses on the relationship between BMI and angiographic severity of CAD, while the third chapter focuses on the impact of BMI on vascular and non-vascular complications in patients undergoing PCI. This research failed to detect an association of BMI levels with 1-year mortality in patients with *suspected* CAD after adjustment for potential confounding variables. Further, overweight and obesity were not independent correlates of short-term complications among patients with *established* CAD who had a PCI.

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List of Abbreviations

ACS - Acute coronary syndromes

APPROACH – NL - Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease - Newfoundland and Labrador

ASA – Acetylsalicylic acid

BMI - Body mass index

CA – Coronary angiography

CABG - Coronary artery bypass grafting

CAD - Coronary artery disease

CARAT- Coronary Artery Reporting and Archiving Tool

CCS- Canadian Cardiovascular Society

CHD- Coronary heart disease

CHF – Congestive Heart Failure

CI – Confidence Interval

COPD- Chronic Obstructive Pulmonary Disease

CRF- Chronic Renal Failure

CV- Cardiovascular

CVD - Cardiovascular Disease

DJS - Duke Jeopardy Score

DVT – Deep Vein Thrombosis

EF - Ejection Fraction

HR – Hazard Ratio

HREA- Health Research Ethics Authority

HTN - Hypertension

GI – Gastrointestinal

GP - Glycoprotein

IABP –Intra-aortic balloon pump

LAD - Left anterior descending artery

LMCA - Left main coronary artery

LMWH – Low molecular weight heparin

LV - Left ventricular

MACCE – Major adverse cardiac and cerebrovascular events

MI – Myocardial infarction

NL – Newfoundland and Labrador

NLCHI – Newfoundland and Labrador Centre for Health Information

NW – Normal Weight

OB – Obese

OW - Overweight

OR – Odds Ratio

PCI - Percutaneous coronary intervention

PDA - Posterior descending coronary artery

PVD – Peripheral Vascular Disease

RCA - Right coronary artery

RR – Relative Risk

SD – Standard deviation

STEMI - ST elevation myocardial infarction

WHO – World Health Organization

List of Publications

The following papers have been derived from the work of this thesis.

Journal Papers

Gregory AB, Lester K, Gregory DM, Twells, LK, Midodzi WK, Pearce NJ. The relationship of body mass index to short-term clinical outcomes in patients undergoing percutaneous coronary intervention. *Cardiology Research and Practice* August 2016, http://dx/doi.org/10.1155/2016/7154267.

Gregory AB, Lester K, Gregory DM, Twells, LK, Midodzi WK, Pearce NJ. The relationship between body mass index and the severity of coronary artery disease in patients referred for coronary angiography in Newfoundland and Labrador, Canada. [Submitted for peer review to the *Journal of the American Medical Association* Cardiology August 2016]

Presented Abstracts

Impact of body mass index on in-hospital complications in patients undergoing percutaneous coronary intervention in Newfoundland and Labrador, Canada. First Place Award Post-Graduate Year 1 Internal Medicine [Oral Presentation] Internal Medicine Resident Research Days, Memorial University, The Dr. Grenfell Adams Medical Research Award. May, 2014. Monetary Award $500

Impact of body mass index on in-hospital complications in patients undergoing percutaneous coronary intervention in Newfoundland and Labrador, Canada. Update. Internal Medicine Resident Research Days, Memorial University. First Place Award - Post-Graduate Year 2 Internal Medicine [Oral Presentation], May, 2015. The Dr. Patrick Parfrey Internal Medicine Resident Research Award. First Place Overall. Monetary Award $500

Impact of body mass index on in-hospital complications in patients undergoing percutaneous coronary intervention from 2006-2013 in Newfoundland and Labrador, Canada. The Obesity Society, Obesity Week 2015, Los Angeles, California. [Poster Presentation] November, 2015.

The relationship between body mass index and severity of coronary artery disease. Post-Graduate Year 3 Internal Medicine [Oral Presentation] The Dr. Patrick Parfrey Internal Medicine Resident Research Award. First Place Overall, June, 2016. Monetary Award $650. Nominated for CSCI-CIHR Excellence in Resident Research Award, an annual award for the best resident research project conducted during the resident research training program at each Canadian medical school.

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Co-authorship Statement

Chapter 2

Dr. Anne Gregory, Dr. Deborah Gregory, Dr. Laurie Twells and Dr. Neil Pearce conceived and designed the study. Dr. Anne Gregory, Kendra Lester, Dr. Deborah Gregory, Dr. Laurie Twells, Dr. William Midodzi, and Dr. Neil Pearce were involved in data analysis and interpretation of the data. Dr. Anne Gregory and Dr. Deborah Gregory drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Chapter 3

Dr. Anne Gregory, Dr. Deborah Gregory, Dr. Laurie Twells and Dr. Neil Pearce conceived and designed the study. Dr. Anne Gregory, Kendra Lester, Dr. Deborah Gregory, Dr. Laurie Twells, Dr. William Midodzi, and Dr. Neil Pearce were involved in data analysis and interpretation of the data. Dr. Anne Gregory and Dr. Deborah Gregory drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Chapter 1 Introduction and Overview

1.1 Background and Rationale

1.1.1 *Epidemiology of obesity*

According to the World Health Organization (WHO), obesity, defined as abnormal or excessive fat accumulation that may impair health [1], is reaching epidemic proportions worldwide. Body mass index (BMI) is a method of classifying body weight according to health risk. It is calculated for the population aged 18 and over, excluding pregnant females and persons less than 3 feet (0.914 metres) tall or greater than 6 feet 11 inches (2.108 metres). [2] BMI is calculated as weight in kilograms divided by height in metres squared (kg/m^2). The BMI index is categorized in the following way: under 18.5 (underweight); BMI 18.5 to 24.9 (normal weight); BMI 25.0 to 29.9 (overweight); BMI 30.0 to 34.9 (obese-Class I); BMI 35.0 to 39.9 (obese-Class II); BMI 40 or greater (obese - Class III). [1-3]

In 2014, approximately 13% of adults 18 years of age and older, worldwide were obese (i.e., BMI $\geq 30 kg/m^2$) and 39% were overweight (i.e., 25.0 to 29.9 kg/m^2). Since the 1980s obesity has more than doubled. [1] Canada is no exception to this increasing trend among adults. The prevalence of obesity in Canada increased from 6.1% to 18.3%, (i.e., 200%) between 1985 and 2011, equating to more than 4.8 million adults .[4] Continued increases have been projected for all Canadian provinces up to 2019. [4] Newfoundland and Labrador (NL) has the highest rate of obesity in the country and

it is estimated that 71% of the province's population will be either overweight or obese by 2019. [4]

Alarmingly, the prevalence has increased substantially in children and adolescents in developed countries: 23.8% of boys and 22.6% of girls were overweight or obese. In developing countries, the prevalence of overweight and obesity has also increased in the last few decades in children and adolescents from 8.1% to 12.9% in boys and from 8.4% to 13.4 % in girls. [5]

1.1.2 *Obesity and health risk*

People are becoming overweight and obese at a younger age and are exposed to cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia and smoking [6] and are at greater risk to develop coronary artery disease (CAD). [7] Weight loss of 5-10% has been associated with improvement in pre-existing cardiovascular risk factors including hypertension, diabetes and dyslipidemia, improvement in clinical events, and outcome (i.e., mortality). [8-13]

According to WHO [1] and Health Canada guidelines [2], health risk levels are associated with each of the following BMI categories: normal weight = least health risk; underweight and overweight = increased health risk; obese class I = high health risk; obese class II = very high health risk; obese class III = extremely high health risk.

Obesity is an independent risk factor for cardiovascular disease [14-18], and patients with a high BMI are considered to be at high risk for cardiovascular disorders. It has

been associated with (1) advanced cardiovascular disease such as acute coronary syndrome (ACS) requiring procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), (2) reduction in life expectancy [19], and (3) a higher mortality rate [16, 20-21]. Because of the high prevalence of CAD, overweight and obese patients more frequently undergo revascularization procedures such as PCI and CABG. Population-based registries and databases have reported the prevalence of overweight and obesity to be as high as 70% to 80% among patients undergoing revascularization procedures. [22-25]

1.1.3 *Obesity paradox*

Cardiovascular disease with CAD is by far the most important cause of excess deaths in obese patients. [26] In the general population, overweight and obesity are associated with increased risk of cardiovascular disease and all-cause-mortality. [27-28] In the Prospective Studies Collaboration, based on 66,552 deaths among 894,576 participants in 57 prospective studies, the observed reduction in median survival was 0-2 years in overweight individuals, 2-4 years in obese individuals, and 8-10 years in very obese individuals. [29]

Research examining the number of deaths in Canada attributable to obesity found that almost 1 in 10 premature deaths among those 20-64 years of age were attributed to overweight and obesity. The proportion of all deaths among adults 20-64 years of age that could be attributed to overweight and obesity increased from 5.1% in 1985 to 9.3% in 2000. [30] A Canadian study involving 11,326 participants who were followed

for 12 years reported that compared with those in the normal weight category, even after adjustment for key sociodemographic factors and health behaviors, those in the underweight, class II or class III obesity categories had a significantly increased risk of all-cause mortality. In contrast, people who were overweight but not obese had a significantly lower risk than normal weight population. There was no significant difference in risk of mortality between obesity class I and normal weight respondents. [31] Higher mortality in the highest weight category and higher mortality in the lowest weight categories compared with those who are of normal weight has been described as a J- or U-shaped mortality curve. [32-33]

Although obesity is associated with higher overall mortality risk in the general population, several studies have suggested that obesity confers a survival advantage in a number of diseases. The phenomenon was first described in 2002 by Gruberg et al. [22] Consecutive patients undergoing PCI (N= 9,633) were categorized in groups: BMI < 24.9 kg/m^2 (n=1,923), BMI = 25-30 kg/m^2 (n=4,813), and BMI > 30 kg/m^2 (n=2,897). Normal weight patients had a higher incidence of major in-hospital complications, including cardiac death (1.0% vs. 0.7% vs. 0.4%; p = 0.001), than overweight or obese patients. At 1 year, mortality was significantly higher in normal BMI patients compared to overweight or obese patients (10.6% vs. 5.7% vs. 4.9%; p < 0.0001) and for cardiac mortality (4.8% vs. 3.3% vs. 2.5%; p < 0.0001), whereas rates of myocardial infarction and revascularization were similar despite a better baseline clinical profile of normal weight patients.

This unexpected and controversial finding, termed "obesity paradox", has been reported in patients with diabetes [34], end-stage renal disease [35], hypertension [36], heart failure [37], CAD [36, 38-40], CABG [38-41], PCI [38-40], stroke [42], peripheral vascular disease [43] and chronic obstructive pulmonary disease [44]. The mechanisms leading to this phenomenon are unclear.

Four meta-analyses focused on the CAD patient population have reported that being overweight or obese (BMI $\geq$ 25kg/m^2) is associated with greater survival in CAD patients, whereas a normal BMI confers higher all-cause and cardiovascular mortality. A large meta-analysis performed by Romero-Corral et al. in 2006 which included 250,152 patients with established CAD and a mean follow-up of 3.8 years reported that overweight and obese CAD patients have a lower risk for total and cardiovascular (CV) mortality after revascularization compared with underweight and normal-weight CAD patients. However, in patients with a BMI $\geq$35 kg/m^2, there was an excess risk for CV mortality without any increase in total mortality. [39] This meta-analysis demonstrated that moderately obese individuals (BMI 30-35 kg/m^2) and those who were severely obese (BMI $\geq$35 kg/m^2) do not have a significantly greater risk for total mortality (RR, 0.93, 95% CI, 0.85-1.03 and RR, 1.10, 95% CI, 0.87-1.41, respectively). However, although moderately obese patients had no increase in cardiovascular mortality (RR, 0.97, 95% CI, 0.82-1.15) compared with the normal-weight group, those with severe obesity had a greater risk, (RR, 1.88, 95% CI, 1.05-3.34). In addition, CV mortality was worse among the severely obese. In 2008, Oreopoulos et al. [38] compared the short- and long-term mortality in a large cohort of

patients with established CAD undergoing PCI and CABG. The findings suggest that the in-hospital and long-term mortality rates were similar or lower in obese patients compared to normal weight patients irrespective of initial treatment strategy. Patients with mild or moderate obesity treated with either revascularization or medical management were at lower adjusted risk of mortality when compared with patients with a normal BMI. [38] This meta-analysis included articles published 20 years ago, in the year 1996. A meta-analysis by Sharma et al. [45] in 2014 which included 36 studies with a mean follow-up period of 1.7 years reported higher total (RR, 2.59, 95% CI, 2.09-3.21) and CV (RR, 2.67, 95% CI, 1.63-4.39) mortality rates among the underweight patients. The risk of CV mortality was lowest among the overweight patients (RR, 0.81, 95% CI 0.68-0.95). A more recent meta-analysis published by Bundhan et al. in 2015 comprised of 22 studies conducted from 2000 to 2015 consisted of 242,377 patients (73,143 normal weight, 103,608 overweight, and 65,626 obese) undergoing PCI. They reported that in-hospital (RR, 0.62, 95% CI 0.55-0.71; RR, 0.57, 95% CI 0.52-0.63), 12 months (RR, 0.62, 95% CI 0.55-0.71; RR, 0.57, 95% CI 0.52-0.63) and ≥ 1-year (long-term) (RR, 0.62, 95% CI 0.55-0.71; RR, 0.57, 95% CI 0.52-0.63) mortality risks were significantly lower in the overweight and obese groups respectively. [46]

Although meta-analytic findings have reported improved clinical outcomes in overweight and obese patients treated for cardiovascular diseases compared to normal weight patients, suggesting a paradoxical survival benefit; other studies have shown an absence of this phenomenon. Uncertainty exists about the relationship between BMI

and mortality after PCI. For example, in a study of patients treated with drug-eluting stents in a routine clinical practice similar rates of all-cause death, and major adverse cardiac and cerebrovascular events defined as the composite of cardiac and noncardiac death, myocardial infarction, and stroke were observed between normal weight patients compared to overweight and obese individuals. [47] Akin et al. concluded that there was no evidence of an obesity paradox in a routine clinical practice of patients undergoing PCI with drug-eluting stents. In another German network registry analysis of 890 consecutive patients presenting with ST-segment elevation myocardial infarction (STEMI) including cardiogenic shock, normal weight patients and obese patients had similar rates of all-cause mortality even after risk-adjustment for baseline characteristics suggesting no evidence of an obesity paradox in the STEMI population including patients with cardiogenic shock. [48]

1.1.4 *The Relationship between BMI and severity of CAD in suspected, but not yet confirmed patients with CAD.*

The obesity paradox has also been reported in patients with suspected, but not yet confirmed, CAD. Coronary angiography (CA) can be used to in clinical practice and research to quantify CAD severity. [49] Historically CAD has been categorized as single, double, triple-vessel, and left main disease, with luminal stenosis of either ≥50% (left main) or ≥70% (other major epicardial vessels) used to define significance. [50] However, the perception that stratification of patients with risk level variation was limited, lead to the development of more meaningful scoring systems to determine the severity of CAD and prognosis. [51-53]

One such scoring system was developed by Dash et al. [52] The Duke Jeopardy Score (DJS) was used to predict mortality in patients undergoing CA for suspected but unconfirmed CAD. Dash et al. [52] developed the DJS, a prognostic tool predictive of 1-year mortality in patients with CAD, which was validated by Califf et al. [53] in 1985. The coronary tree is divided into 6 segments: the left anterior coronary artery (LAD), diagonal branches of the LAD, septal perforating branches, circumflex coronary artery, obtuse marginal branches, and posterior descending coronary artery. All segments with ≥75% stenosis, or ≥ 50% left main stenosis, are considered to be at risk. Each such segment is assigned 2 points. The maximum possible number of points is 12. A score from 0 to 12 is assigned to each CA based on the number of segments involved. In the study by Califf et al. [53] the authors reported an association between the DJS and 5-year survival. The 5-year survival was 97% in patients with a DJS of 2 and 95%, 85%, 78%, 75% and 56% for patients with DJS of 4, 6, 8, 10, and 12, respectively. [53] The prognostic value of the DJS was greater than the number of diseased vessels. Thus, patients with a score of ≥8 represented a different and more anatomically high-risk population than the multivessel CAD population, leading to a different relationship between the cardiovascular risk factors (i.e., diabetes, male sex, family history of CAD, hypertension, dyslipidemia, smoking and obesity) and CAD severity.

The DJS is the validated scoring system [52-55] used by APPROACH-NL to estimate the amount of myocardium at risk and was therefore used in the current study. It is a validate prognostication tool and an index of CAD burden predictive of 1-year

mortality in patients treated medically or with PCI. Detailed CA data are automatically populated from the Coronary Artery Reporting and Archiving Tool (CARAT), a graphic recording and communication application. [56] A PDF file is created containing the anatomy of the coronary arteries according to the DJS and becomes part of each patient's medical record.

As mentioned previously, obesity is an accepted risk factor for CAD; therefore, it could be assumed that obese patients have poorer outcomes than non-obese patients. [57] However, a number of studies have reported findings that contradict this supposition about the relationship between BMI and mortality in patients undergoing CA for suspected CAD. Studies that have focused on BMI and angiographically demonstrated CAD have found that obese patients tend to have less severe and extensive CAD than non-obese patients. Very few studies have examined the association of body mass index (BMI) and CAD in patients undergoing CA. In a study by Rubinshtein et al. [58] obese patients referred for CA were younger and had a lower prevalence of left main disease. Multivariate regression analysis showed advancing age, male gender, diabetes, and hyperlipidemia were independent predictors of high-risk anatomy, whereas obesity remained a significant negative independent predictor (p =0.02). Late mortally (30 to 36 months) was not different between obese (6.9%) and non-obese (8.2%) patients but was significantly higher in patients with high-risk coronary anatomy (12.4%) than in those without high-risk coronary anatomy (5.6%, p = 0.003). Niraj et al. [59] also found that obese patients from the U.S. (N=770) referred for CA were younger and had a lower burden for CAD; however, the authors

did not find obesity to be a significant predictor for severity of CAD after adjustment for confounders and suggested that younger age may have influenced the obesity paradox observed in their study. BMI was not a significant predictor of more severe coronary anatomy. In a 2011 study examining the influence of BMI on extent of coronary atherosclerosis and cardiac events in a cohort of patients at risk of CAD, Rossi et al. [60] found that BMI was not significantly associated with extent of coronary atherosclerosis and mortality confirming the earlier findings of others [56-57]. Parsa and Jahanshahi [61] also reported an inverse relationship between BMI and severity of CAD in a cross-sectional, prospective study of 414 patients with suspected CAD. No Canadian studies were identified that examined the relationship between BMI and severity of CAD in patients undergoing CA for suspected CAD.

1.1.4.1 Summary of gaps in the literature

Cardiac catheterization for coronary angiography is an invasive procedure with inherent risks. Several authors have suggested that, paradoxically, obese patients have a lower CAD burden (measured by the Duke Jeopardy Score [DJS]) and lower prevalence of high-risk coronary anatomy (significant left main or triple vessel disease) compared to non-obese patents despite a higher prevalence of diabetes, hypertension, and dyslipidemia. [59, 62-63]

The relationship between obesity and severity and extent of CAD remains controversial. The clinical implication of whether or not obesity is directly related to CAD prognosis is still subject to debate. Although obesity is clearly a risk factor for developing CAD, obesity itself may not necessarily expose patients undergoing

coronary CA to greater risk. A greater understanding of why obesity is associated with less angiographic CAD is necessary to prevent potentially unnecessary cardiac catheterizations from being done in this patient population. No Canadian studies were identified that examined the relationship between BMI and severity of CA in patients undergoing CA for suspected CAD. To the best of our knowledge this study which focused on the NL adult patient population will be the first Canadian study to investigate this issue.

1.1.5 *The Relationship between BMI and short-term outcomes (i.e., vascular and non-vascular in-lab/post-procedural) in patients with established CAD undergoing PCI*

Studies that have investigated the relationship between BMI and clinical outcome following PCI have reported contradictory findings. [22-25, 59, 64-77] Numerous studies and large meta-analyses have demonstrated an *"obesity paradox"* in which lean patients with established cardiovascular disease (CVD) have a worse clinical prognosis than do their more overweight/obese counterparts with the same CVD, including coronary heart disease (CHD). However, several studies suggest that obese patients within the higher classes of obesity do not have more favorable outcome. In a large systematic review of over 250,000 CHD patients in 40 cohort studies followed for 3.8 years, Romero-Corral et al. reported that overweight and obese CHD patients had a lower cardiovascular and total mortality compared to underweight and normal weight patients; however, patients with class II obesity (BMI >35 kg/m^2) were at greater risk of cardiovascular mortality but still no increase in total mortality. Das et al.

reported a U-shaped in hospital mortality curve in a very large cohort with ST-segment myocardial infarction. The normal BMI group had the highest unadjusted in hospital mortality. However, the patients with class III obesity (BMI ≥40 kg/m^2) had increased mortality in both unadjusted and adjusted models compared with the referent group (class I obesity). In a 2013 study by Angeräs et al. [78] of over 60,000 patients referred for CA, compared to the lean referent group (BMI 21.0-23.5 kg/m^2), the highest mortality occurred in the underweight group (BMI < 18.5 kg/m^2), the lowest mortality occurred in the modest overweight group (BMI 26.5-28.0 kg/m^2), whereas mortality remained lower for obesity up to 35 kg/m^2, and then increased.

The findings of Azimi et al. [79] from a large cohort of 35,573 patients with established CHD, who were followed for 11 years (median 3.2 years) demonstrated that the highest mortality occurred in underweight (BMI < 18.5 kg/m^2), followed by the class III group (BMI ≥ 40kg/m^2). Increased mortality risk was observed among the low normal BMI group (BMI < 18.5-23.0 kg/m^2), whereas the lowest mortality was in the pre-obese group (BMI 27.5-30 kg/m^2), followed by the mild overweight (BMI 25-27.5 kg/m^2). The authors suggest that the relationship between BMI and mortality in CHD might represent an "*overweight paradox*" rather than an "obesity paradox". In a 2013 systematic review and meta-analysis of 97 studies of more than 2.88 million individuals in the general population, Flegal et al. [21] found that the lowest mortality occurred in overweight (BMI 25-30 kg/m^2), followed by mild or class I obesity(BMI 30-35 kg/m^2). These findings lend support to the potential protective relationship of overweight in both the general population and in cohorts of patients with CHD.

Although the preceding studies and meta-analyses have focused primarily on mortality as a clinical outcome in patients with established CAD, many studies have also examined the association between BMI and clinical outcomes after PCI including in-hospital mortality, bleeding events (e.g., access site bleeding), vascular complications (e.g., pseudoaneurysm, arteriovenous fistula, vascular occlusion, retroperitoneal bleeding), stent thrombosis, major adverse cardiovascular (e.g., stroke) and cardiac events (e.g., myocardial infarction). As mentioned earlier, Gruberg et al. [22] first described an obesity paradox in 2002 in a study of consecutive patients undergoing PCI (N= 9,633) were categorized in groups: BMI < 24.9 kg/m^2 (n=1,923), BMI = 25-30 kg/m^2 (n=4,813), and BMI > 30 kg/m^2 (n=2,897). Normal weight patients had a higher incidence of major in-hospital complications, including cardiac death (1.0% vs. 0.7% vs. 0.4%; $p = 0.001$), than overweight or obese patients. At 1 year, normal BMI patients compared to overweight or obese patients mortality had significantly higher rates of all-cause mortality (10.6% vs. 5.7% vs. 4.9%; $p < 0.0001$) and cardiac mortality (4.8% vs. 3.3% vs. 2.5%; $p < 0.0001$), whereas rates of myocardial infarction and revascularization were similar despite a better baseline clinical profile of normal weight patients.

Findings from other studies also suggest that obesity may be associated with better short-term outcome (e.g., decreased risk of death, bleeding complications, vascular complications such as arteriovenous fistula, pseudoaneurysm, hematoma) in patients undergoing PCI [23-25, 64-66, 68, 71, 74, 77, 80]. For example, Mehta et al. studied 2,325 patients with acute myocardial infarction who received primary PCI and

reported that although obese patients (those with a BMI ≥ 30 kg/m^2) had more cardiovascular risk factors at baseline, they had fewer groin bleeds, shorter hospital stays, and fewer deaths in the hospital and at 12 months than did patients with a normal BMI. The authors suggested that the difference may have been due to the fact that obese patients were a mean of 6 years younger than the patients with normal BMI or because obesity is related to impaired fibrinolysis and increased platelet aggregation. [64] Gurm et al. [66] pooled data from 4 randomized controlled trials of platelet glycoprotein IIb/IIIa inhibitors in patients who underwent PCI and concluded that increased BMI was associated with a decreased risk of myocardial infarction, death, need for urgent revascularization, and hemorrhagic complications. The risk of major or minor bleeding and transfusion requirement was highest in lean patients (BMI < 18.5 kg/m^2) and lowest in obese patients (BMI ≥ 30 kg/m^2). Delhaye et al. [65] examined the role of BMI in records of 16,783 patients who underwent PCI. The patients were grouped according to six BMI categories: underweight (BMI, < 18.5), normal weight (BMI, 18.5-24.9), overweight (BMI, 25-29.9), class I obesity (BMI, 30-34.9), class II obesity (BMI, 35-39.9), class III obesity (BMI, ≥40). The incidence of major bleeding varied significantly ($p<0.001$) among BMI groups: underweight (5.6%), normal weight (2.5%), overweight (1.9%), class I obese (1.6%), class II obesity(2.1%), class III obesity (1.9%). Compared with normal weight patients, the risk of major bleeding was higher in underweight patients (OR, 2.29 [95% CI, 1.56-3.38]) and lower in Class I obese patients (OR, 0.65 [95% CI, 0.47-0.90]). In a retrospective review of 5,234 patients undergoing PCI, Cox et al. [68] reported that the rates of vascular complications was highest in extremely thin and morbidly obese

patients and lowest in moderately obese patients. In a study by Das et al. [74], after multivariate adjustment, extreme obesity (i.e., class III) was associated with increased in-hospital mortality (OR, 1.64, 95% CI, 1.32-2.03). Normal weight was associated with increased major bleeding (OR, 1.18, 95% CI, 1.08-1.30), while class III obesity was not (OR, 1.09, 95% CI, 0.94-1.26). Powell et al. found that compared to obese patients, underweight patients had higher rates of femoral bleeding, hematoma, and blood loss that required transfusion. [80]

In contrast to the observed overweight paradox and obesity paradox, recent studies found no association between BMI and 1-year mortality [72] following PCI or BMI and short-term complications [47-48]. In a 2010 study by Ndrepepa et al. [72] that investigated the impact of BMI on clinical outcome after adjustment for other cardiovascular risk factors in 9,146 patients with acute coronary syndromes (ACS) who underwent CA and PCI, BMI was not an independent correlate of 1-year mortality [HR, 1.25, 95% CI, 0.94-1.64, $p = 0.127$ for the 1^{st} vs 4^{th} BMI quartile]. In a 2012 study Akin et al. [47] compared the clinical outcomes among unselected patients stratified by BMI from the prospective multicenter German drug-eluting stent registry who underwent PCI. In-hospital and 1-year outcomes including the rate of major adverse cardiac and cerebrovascular events (MACCE) defined as a composite of death, myocardial infarction, and stroke and target vessel revascularization were examined. Baseline clinical characteristics were more severe for overweight and obese patients. After risk-adjustment, 1-year follow-up comparison between groups revealed similar rates of all-cause death (3.3% vs. 2.4% vs. 2.4%, p = 0.17), MACCE (7.1% vs. 5.6%

vs. 5.5%, p = 0.09) and target vessel revascularization in survivors (10.9% vs. 11.7% vs. 11.6%, p = 0.56) in normal weigh patients compared to overweight or obese individuals. No evidence of an obesity paradox was observed. In a 2015 study of 890 consecutive patients admitted and treated for STEMI including cardiogenic shock and cardiopulmonary resuscitation, Akin et al. [48] found that after risk-adjustment, 1-year follow-up comparison between groups revealed similar rates of all-cause death (9.13% vs. 8.3% vs. 6.2%, p = 0.50), MACCE (15.1% vs. 13.4% vs. 10.2%, p = 0.53) and target vessel revascularization in survivors (7.0% vs. 5.0% vs. 4.0%, p = 0.47) in normal weigh patients compared to overweight or obese individuals. Similar to the authors' study in 2012, the findings did not support the presence of an obesity paradox The authors suggested that the obesity paradox reported by others might be related to bias that could not be adjusted for using statistical methods.

1.1.5.1 Summary of gaps in the literature

A significant number of studies have investigated the impact of obesity on the clinical outcomes of patients undergoing PCI since the obesity paradox phenomenon was first described by Gruberg et al. in 2002. [22], but it remains a controversial issue. Many of these studies have suggested the existence of an obesity paradox, i.e., that despite being associated with increased risk of coronary artery disease, increased BMI predicts more favorable outcome after coronary revascularization. Other studies have shown contradictory effects of obesity on outcome after PCI. More recently researchers have suggested the existence of an overweight paradox rather than an obesity paradox. The issue of the existence of an obesity paradox remains controversial. A small number of

studies in recent years have found no support for the existence of a protective effect of overweight or obesity on clinical outcome following PCI. Given the global obesity trends and the association of obesity and CAD, the proportion of patients who undergo coronary revascularization who are obese is likely to increase. More research is required to address knowledge gaps and the contradictory findings that currently exist in the research literature.

1.2 Purpose

There is a paucity of data on the prevalence of obesity in patients undergoing CA and/or PCI in the province of NL and differences among BMI groups on demographic, clinical, and procedural findings. As well, the relationship between BMI and angiographically determined CAD severity requires further research to determine if obese patients are less likely to have severe CAD than non-obese patients. Further, the relationship between short-term clinical outcomes (vascular complications, non-vascular in-lab and post-procedural complications occurring within 48 hours) and BMI has not been examined.

The current study was performed for the following purposes (1) to examine the relationship between BMI and severity of CAD and its impact on mortality (i.e., 1-year all-cause and cardiac specific mortality) in the NL patient population referred for CA to a single tertiary care centre in the province, and (2) to determine the effect, if any, of BMI on short-term outcomes (24-48 hours) in patients who had a PCI.

1.3 Area of Investigation

Newfoundland and Labrador (NL) is a Canadian province situated on the eastern side of the country with a population of approximately 528,000. [81] The General Hospital, located at the Health Science Centre, in St. John's is the only diagnostic cardiac catheterization centre in the province.

Detailed demographic, clinical, and procedural data on all patients undergoing diagnostic cardiac catheterization, percutaneous coronary intervention, or CABG is collected by specially trained cardiac care nurses. Sociodemographic and clinical data such as age, sex, weight, height, current smoking status, family history of premature CAD, co-morbid conditions, medications, in-lab and post-procedural data, etc. is collected and entered into the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease –NL database. Data are collected for a 24-48 hour period (i.e., 24 hours for out-patients and 48 hours for in-patients).

1.4 Significance of the Study

Since the relationships between BMI and severity of CAD and BMI and clinical outcome following PCI remain poorly understood, two studies were conducted to address gaps in the research literature and advance current knowledge in this field. The first study specifically examined the relationship between BMI and severity of CAD in patients with suspected, but unconfirmed CAD, referred for CA in one Canadian province. The primary outcome was one-year all-cause and cardiac-specific mortality. The second study explored the relationship between BMI and short-term complications

in patients with established CAD undergoing PCI. The primary outcomes were vascular and in-lab/ post-procedural adverse events.

1.5 Program of Research for Thesis

This section is intended to provide the reader with details on this student's personal contribution to the program of research and a clear distinction between individual and team effort.

After completing Medical School in 2013, I worked on a small research project in my post-graduate year 1 of internal medicine under the supervision of Dr. Neil Pearce, an interventional cardiologist and director of APPROACH –NL at Eastern Health. My research initially focused on the impact of body mass index on in-hospital complications in patients undergoing diagnostic cardiac catheterization and/or percutaneous coronary intervention from 2006 to 2010 in NL. I was the principal investigator on an application to the Health Research Ethics Authority (HREA) and responsible for the development of the proposal for ethics review and data analysis. After obtaining permission from Ms. Cathy Burke, Regional Director, Cardiac Care Program at Eastern Health to access de-identified data, I worked with Jennifer Matthews, Project Coordinator of APPROACH-NL to access the necessary data to conduct my data analysis. I subsequently presented my research findings as an oral presentation at Internal Medicine Resident Research Days in May 2014.

Prior to this I enrolled as a graduate student in the Clinical Epidemiology program at Memorial University in the fall of 2013 under the co-supervision of Dr. Laurie Twells

and Dr. Neil Pearce. As part of my thesis work I was to continue with my resident research topic i.e., the impact of body mass index on in-hospital complications in patients undergoing diagnostic cardiac catheterization and/or percutaneous coronary intervention but to expand on the number of years (i.e., 2006 to 2013). An amendment to my original application to the HREA was made requesting ethical approval to obtain additional years of de-identified data. I analyzed the additional data and provided an update at Internal Medicine Resident Research Days, Memorial University in my second year of residency.

In addition to this work, in August 2015 I was to investigate the issue of BMI and severity of coronary artery disease in patients undergoing CA. This required obtaining additional data, more specifically, Duke Jeopardy Scores and 1-year all-cause and cardiac-specific mortality data on all patients undergoing CA from 2006 to 2013. Ethical approval was given to obtain this data and to conduct a secondary analysis of the de-identified APPROACH-NL data. The findings were presented at Internal Medicine Resident Research Days, Memorial University in my third year of residency.

After completion of my data analysis I was primarily responsible for drafting two papers as part of my thesis. I am first author on both manuscripts - one has been published and the other is under review. The preparation of the manuscripts has been a team effort, but as part of that effort I have been involved with the study concept and design, statistical analysis and interpretation of the data, drafting of the manuscripts, and critical revision of the manuscripts for important intellectual content.

1.6 Research Objectives

The specific research objectives guiding this master's work were as follows:

1. To identify all patients who underwent a diagnostic coronary angiography (CA) from May 1st, 2006 to December 31st, 2013 enrolled in the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease - Newfoundland and Labrador (APPROACH - NL) database.
2. To examine the relationship between BMI and severity of CAD and its impact on short-term outcomes (i.e. 1 year all-cause and cardiac-specific mortality) in in the NL patient population referred for CA for suspected CAD at a single tertiary care centre in the province.
3. To identify all patients who underwent PCI from May 1st 2006 to December 31st, 2013 enrolled in the APPROACH - NL database.
4. To investigate the effect of BMI on short-term outcomes (vascular complications, in-lab non-vascular complications, post procedural adverse events occurring within 24 hours (out-patients) to 48 hours (in-hospital patients)).

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Chapter 2 Research Paper #1

The relationship between body mass index and the severity of coronary artery disease in patients referred for coronary angiography

A version of this chapter has been submitted for publication to the *Journal of the American Medical Association Cardiology*.

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2.1 Abstract

Objective: To examine the relationship between body mass index [BMI (kg/m^2)] and angiographic severity of coronary artery disease (CAD).

Background: Obesity is associated with increased risk of cardiovascular disease and may be associated with more severe CAD; however, the relationship between BMI and severity of CAD is uncertain and remains a controversial topic.

Methods: 8,079 patients undergoing coronary angiography (CA) for suspected CAD were identified in the APPROACH Newfoundland and Labrador (NL) database. Duke Jeopardy Score (DJS), a prognostic tool predictive of 1-year mortality in CAD, was assigned to angiographic data. Patients were grouped into 3 BMI categories: normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese ($\geq$ 30 kg/m^2) and multivariable adjusted hazard ratios for 1-year all-cause and cardiac-specific mortality calculated.

Results: 84% of the cohort was overweight or obese. Cardiac risk factor prevalence significantly increased with increasing BMI. BMI was inversely proportional to DJS, indicative of less severe CAD in patients with higher BMI. 199 deaths (2.5%) including 99 cardiac specific occurred with a significantly higher proportion of deaths occurring in normal weight patients despite more favourable baseline characteristics ($p < 0.001$). Mortality tended to rise with incremental increases in DJS.

Conclusions: Obesity was associated with less severe CAD as evidenced by CA, suggesting obese patients are more likely to be referred early for CA based on the

prevalence of cardiovascular risk factors. This study failed to detect an association of BMI with 1-year mortality after adjustment for potential confounding variables.

2.2 Introduction

Overweight and obesity are defined as "abnormal or excessive fat accumulation that may impair health". [1] In 2014, approximately 39% of adults worldwide were overweight and 13% were obese. Obesity has more than doubled since the 1980s. [1] Between 1985 and 2011, the prevalence of obesity in Canada increased 200% from 6.1% to 18.3% equating to more than 4.8 million adults, with continued increases expected. [2] Newfoundland and Labrador (NL), a Canadian province, has the highest rate of obesity in the country and it is estimated that 71% of the province's population will be either overweight or obese by 2019. [2]

Obesity is an independent risk factor for cardiovascular disease [3-7], and is associated with advanced cardiovascular disease requiring procedures such as percutaneous coronary intervention (PCI), reduction in life expectancy [8], and a higher mortality rate [5, 9, 10]. Weight loss has been associated with improvement in pre-existing cardiovascular risk factors including hypertension, diabetes and dyslipidemia and mortality. [11-14] Despite these findings, other studies have reported improved clinical outcomes in overweight and obese patients treated for cardiovascular diseases compared to normal weight patients, suggesting a paradoxical survival benefit. This "reverse epidemiology" or counter-intuitive outcome has been reported in patients with diabetes [15], end-stage renal disease [16], hypertension [17] and multiple other conditions traditionally associated with poorer outcomes [18-25]. The mechanisms leading to this phenomenon, termed "obesity paradox", are unclear.

The quantification of CAD severity for clinical practice and research purposes can be captured using coronary angiography (CA). [26] Historically CAD has been categorized as single, double, triple-vessel, and left main disease, with luminal stenosis of either ≥50% (left main) or ≥70% (other major epicardial vessels) used to define significance. [27] However, stratification of patients with risk level variation was perceived to be limited using this approach. As a result, more meaningful scoring systems to determine the severity of CAD and prognosis were developed. [28-30]

Very few studies have examined the association of body mass index (BMI) and CAD in patients undergoing CA. In a study by Rubinshtein et al. [31] patients with obesity referred for CA were younger and had a lower prevalence of left main disease. Niraj et al. [32] also found that obese patients referred for CA were younger and had a lower burden for CAD; however, the authors did not find obesity to be a significant predictor for severity of CAD after adjustment for confounders suggesting that younger age may influence the obesity paradox. Parsa and Jahanshahi [33] also reported an inverse relationship between BMI and severity of CAD in a cross-sectional, prospective study of 414 patients with suspected CAD.

Obesity is an accepted risk factor for CAD; therefore, it may be assumed that obese patients have poorer outcomes than non-obese patients. [34] However, a number of studies report findings that contradict this supposition about the relationship between BMI and mortality in patients undergoing CA for suspected CAD. In a 2011 study examining the influence of BMI on extent of coronary atherosclerosis and cardiac events in a cohort of patients at risk of CAD, Rossi et al. [35] found that BMI was not

significantly associated with extent of coronary atherosclerosis and mortality confirming the findings of others [31,36, 37].

The aim of the current study was to examine the relationship between BMI and severity of CAD and its impact on 1-year mortality in the NL patient population referred for CA at a single tertiary care centre.

2.3 Methods

2.3.1 Setting

The health care needs of approximately 528,000 residents [38] of NL, Canada are the responsibility of four integrated health authorities. The largest authority, Eastern Health, has the only CA laboratory located at the Health Sciences Centre, a tertiary care centre which performs all CA referrals from four health authorities.

2.3.2 Study design and data collection

Secondary analysis of de-identified data for all adult patients 18 years of age and older who had CA between May 1st, 2006 and December 31st, 2013 was conducted using a large population-based clinical database. Eastern Health uses a clinical software application (i.e., Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease [APPROACH]) to prospectively collect detailed demographic, clinical and procedural data on all patients referred for CA, undergoing CA procedures, PCI, and coronary artery bypass graft (CABG). Details of the database and methods of collection have been previously described. [39]

Patients undergoing CA were identified from the cardiac care program's clinical database. There were 21,886 diagnostic CAs performed from May 1st 2006 to December 31st , 2013. Eligible subjects included all residents of NL over the age of 18 years with a BMI ≥18.5 kg/m^2. The index CA and DJS were used; therefore, duplicate cases (n = 3,369) of patients with more than one CA during the observation period were excluded. The following patients were also excluded from the study: undergone CA during a period of time DJS's were not collected (i.e., 1,871 and 2,750 patients in 2006 and 2007, respectively); all patients who had a procedure performed in 2013 due to the unavailability of 1-year mortality data (n = 2,336); missing BMI data (n = 119 or 1.0%) or underweight (n = 66 or 0.6%); had history of CABG (n = 776), PCI (n = 749), or myocardial infarction (n= 1,538); less than 18 years of age (n = 2); missing DJS data (n = 110 or 1.2%); missing indication code for CA or if the CA was performed for any reason other than the following: acute coronary syndrome, stable angina, unstable angina, atypical pain, serious arrhythmia or presenting with cardiovascular symptoms not matching the above-mentioned common diagnostic categories. After exclusion criteria were applied to the population of patients undergoing CA since the inception of the cohort on May 1st 2006, a final study sample of 8,079 patients having a first CA for suspected, but not yet confirmed, CAD was identified.

Weight and height were measured and documented by a nurse at the time of CA. If patients were unstable, self-reported weight and height were collected and BMI calculated. Patients were grouped according to three BMI categories using the World

Health Organization classification system: normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese class >30 kg/m^2. [40] These categorizations reflect relative levels of risk to health. [41] It has been demonstrated that obese patients are much more likely to die from cardiac causes and lean patients are much more likely to die from non-cardiac causes over a 10-year period following index myocardial infarction. [42] In the current study, the underweight BMI category (BMI < 18.5 kg/m^2) was excluded because of the potential impact of comorbid conditions (e.g., advanced heart failure, cachexia) on outcome, conditions which are not captured in APPROACH.

CA data were obtained from the Coronary Artery Reporting and Archiving Tool (CARAT), a graphic recording and communication application. [43] Detailed angiographic findings of all patients undergoing CA are automatically populated in APPROACH and a PDF file is created containing the anatomy of the coronary arteries according to the DJS [29] and becomes part of each patient's medical record. In the current study, severity and extent of obstructive CAD is based on the DJS. Dash et al. [29] developed the DJS, a prognostic tool predictive of 1-year mortality in patients with CAD, which was validated by Califf et al. [30] in 1985. The coronary tree is divided into 6 segments: the left anterior coronary artery (LAD), diagonal branches of the LAD, septal perforating branches, circumflex coronary artery, obtuse marginal branches, and posterior descending coronary artery. All segments with ≥75% stenosis, or ≥ 50% left main stenosis, are considered to be at risk. Each such segment is assigned 2 points. The maximum possible number of points is 12. A score from 0 to 12 is assigned to each CA based on the number of segments involved and automatically populated in APPROACH.

The usefulness of the DJS as a simple score that is easy to use clinically as a prognostic tool has been confirmed in a large Canadian population cohort of > 20,000 patients undergoing PCI or CABG. [44] Following PCI, there was no difference between DJSs 0 and 2; however, a stepwise increase in 1-year mortality with a DJS of >2 was found.

Mortality data stored in the NL Centre for Health Information (NLCHI) Mortality System was provided to Eastern Health's cardiac care program via a data linkage. The primary outcomes of the current study were all-cause and cardiac-specific mortality at 1-year.

All patients who had a CA during the time period under examination gave written, informed consent to the cardiac care program for data collection and follow-up observation after CA. The study protocol received ethical approval from the Health Research Ethics Authority of Memorial University and Eastern Health.

2.3.3 Data analysis

Analyses are based on 8,079 patients with a BMI $\geq$ 18.5 kg/m^2 undergoing CA for the first time. Continuous variables are reported as mean ± standard deviation and were compared using ANOVA. Categorical variables are reported as number (%) and were compared using chi-square tests. Fisher exact tests were used when the expected number was less than 5, if necessary. After the assumptions of survival analysis were met, time-to-event outcomes were analyzed using Kaplan-Meier survival techniques. The final enrollment date was December 31st, 2012 and patients without events were censored on December 31st, 2013, the final date for which mortality data was available. Patients who died within one year of the procedure were identified and their time to death was

determined as the difference between the date of death and date of procedure. Patients who did not die within one year were assigned a survival time of 12 months. Survival curves were compared using the log-rank test. All factors that could potentially influence survival were included (see characteristics in Table 2.1) in addition to BMI and DJS. Assumptions of proportionality in Cox regression hazard were tested and met. Univariate and multivariate adjusted Cox regression models were performed to identify predictors of 1-year mortality and compute crude and multivariate-adjusted hazards ratios and 95% confidence intervals as a measure of the relative risk of death at one year for increasing BMI categories. Normal weight was the referent group (18.5-24.9 kg/m^2). Covariates included BMI, DJS, age, sex, hypertension, diabetes, hyperlipidemia, smoking history, family history of premature CAD, left ventricular (LV) grade, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), renal insufficiency, dialysis, chronic renal failure (CRF), congestive heart failure (CHF) and malignancy. A two-sided p-value <0.05 was considered statistically significant. In the model all independent variables were dichotomous with the exception of age and BMI. BMI was included both as a continuous variable [45] and an ordinal variable. Obesity was defined as a BMI ≥ 30 kg/m^2. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp.

2.4 Results

Baseline characteristics are presented in Table 2.1. Among 8,079 patients approximately 84% were overweight or obese: 1,297 (16.1%) had a normal BMI, 3,072 (38%) had a BMI indicating overweight, 3,710 (45.9%) were classified as obese. The average weight

in kilograms for the entire sample was 85.2±17.8 and the average BMI was 30.3 ±5.7. There were significant differences among BMI categories in terms of age, sex, presence of hypertension, diabetes, hyperlipidemia, and family history of cardiovascular disease, COPD, PVD and LV grade. Significantly higher proportions of males compared to females comprised all BMI categories. As expected, the prevalence of hypertension, hyperlipidemia and diabetes significantly increased with increasing BMI. Patients with obesity were significantly younger and had a higher rate of a family history of CAD and COPD. Normal weight patients had a higher rate of PVD, renal insufficiency, dialysis, and LV Grades III and IV. BMI groups did not differ significantly with regards to smoking history, CRF, CVD, malignancy, or CHF. A greater proportion of patients with angina categorized according to the Canadian Cardiovascular Society as class II-IIII was noted in obese; whereas a greater proportion of normal weight patients experienced class IV.

Table 2.1

Baseline characteristics of study subjects undergoing coronary angiography in relation to BMI category (N= 8079)

Variable	Normal	Overweight	Obese	p-value*
Male sex	57.4% 744/1297	67.7% 2081/3072	60.6% 2249/3710	.000
Weight (kgs ± SD)	64.7±8.8	78.8±9.3	97.7±16.0	.000
BMI (mean ± SD)	22.9 ±1.6	27.6±1.4	35.0±4.7	.000
Age, years	63.4 ± 11.3	62.1 ± 10.6	59.7 ± 10.2	.000
HTN	56.7% 735/1297	60.9% 1870/3069	71.0% 2629/3704	.000
Hyperlipidemia	76.4% 991/1297	79.3% 2433/3068	81.5% 3022/3706	.000
Family history of premature CAD∓	56.4% 730/1295	62.8% 1925/3063	65.5% 2421/3695	.000
Current/Former Smoker	68.6% 889/1295	68.8% 2105/3060	69.2% 2557/3693	.890
Diabetes	15.7% 203/1297	20.8% 638/3069	34.5% 1279/3708	.000
Renal Insufficiency	5.2% 67/1296	4.0% 124/3069	3.5% 130/3705	.030
Dialysis	1.2% 16/1296	0.5% 15/3069	0.5% 19/3705	.009
CRF	2.9% 38/1296	2.2% 69/3069	2.0% 75/3705	.166
Malignancy	5.2% 67/1296	4.3% 132/3069	4.1% 153/3705	.282
COPD	16.2% 210/1297	13.0% 398/3069	18.8% 697/3705	.000
PVD	7.0% 91/1297	4.3% 131/3069	3.8% 139/3705	.000
CHF	1.9% 25/1296	1.8% 54/3069	2.2% 81/3705	.450
CVD	6.9% 90/1296	5.3% 163/3069	5.5% 204/3705	.088
CCS Angina Grading Scale				
No angina or atypical symptoms	14.2% 184/1296	11.2% 343/3072	12.5% 463/3708	.000
Class 1	2.1% 27/1296	2.6% 80/3072	2.5% 94/3708	
Class 2	15.2% 197/1296	24.3% 746/3072	28.4% 1053/3708	
Class 3	3.6% 47/1296	6.3% 195/3072	7.9% 292/3708	
Class 4	64.9% 841/1296	55.6% 1708/3072	48.7% 1806/3708	

Variable	Normal	Overweight	Obese	p-value*
LV Grade				
I (>50%)	83.0% 1067/1286	84.3% 2557/3033	86.0% 3154/3668	.003
II (35-50%)	10.6% 136/1286	11.0% 334/3033	9.6% 353/3668	
III (20-34%)	4.0% 52/1286	3.6% 110/3033	3.0% 110/3668	
IV (<20%)	2.4% 31/1286	1.1% 32/3033	1.4% 51/3668	

Values are means ± SD or % (n/N).

Note. CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVD = cerebrovascular disease; HTN = hypertension; PVD = peripheral vascular disease.

ǂ Family history of CAD is positive if the patient has/had any direct blood relative (parent, siblings, children) who have been diagnosed with angina, MI or sudden cardiac death before age 55 years.

*p value for chi square for categorical variables or ANOVA for continuous variables

DJSs calculated during CA by BMI category are presented in Table 2.2. A score of 0, indicative of a normal angiogram or non-critical (< 70%) stenosis in any of the coronary arteries, was assigned to 526 (40.6%) normal weight patients, 1,197 (39.0%) overweight patients, 1,687 (45.5%) obese patients. Differences were observed among BMI categories and all DJS levels ($p < 0.001$), with the exception of DJS ≥ 10. Patients in the obese group tended to have lower scores indicating less CAD severity.

Table 2.2

Duke Jeopardy Score (DJS) based on coronary angiographic findings in relation to BMI category (N= 8079)

Score	**Normal Weight (n=1297)**	**Overweight (n=3072)**	**Obese (n=3710)**	**p value**
≥ 2	771 (59.4)	1875 (61.0)	2023 (54.5)	.000
≥ 4	542 (41.8)	1229 (40.0)	1303 (35.1)	.000
≥ 6	424 (32.7)	966 (31.4)	992 (26.7)	.000
≥ 8	248 (19.1)	568 (18.5)	593 (16.0)	.006
≥10	162 (12.5)	369 (12.0)	395 (10.6)	.096
12	91 (7.0)	198 (6.4)	188 (5.1)	.010

Note. DJS –Duke Jeopardy Score is a score from 0 to 12 which estimates the amount of myocardium at risk on the basis of particular location of stenosis. A score of 0 is indicative of a normal angiogram or non-critical (< 70%) stenosis in any of the coronary arteries. A score of 0 was assigned to 526 (40.6%) normal weight patients, 1197 (39.0%) overweight patients, 1687 (45.5%) obese patients.

Values are numbers of patients (percentage)

*p value for chi square for categorical variables

p <.0.001 for overall difference between groups

Within the first year of undergoing CA there were 199 deaths (2.5%) among 8,079 patients, of which 99 (1.2%) were cardiac-specific. A significantly higher proportion of deaths occurred in patients with normal BMI compared to overweight or obese patients, despite more favourable baseline characteristics among the normal weight group ($p < 0.001$). There were no statistically significant differences observed for cardiac-specific mortality among BMI categories (Figure 2.1a). Mortality tended to rise with incremental increases in DJS scores, with the exception of DJS 6 ($p < 0.001$) (Figure 2.1b).

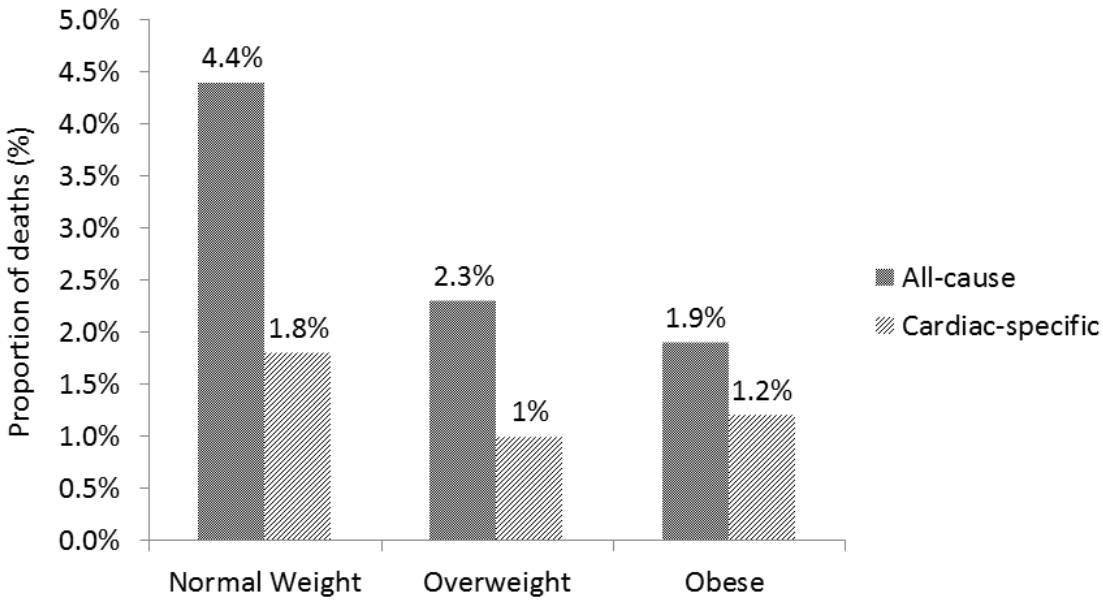
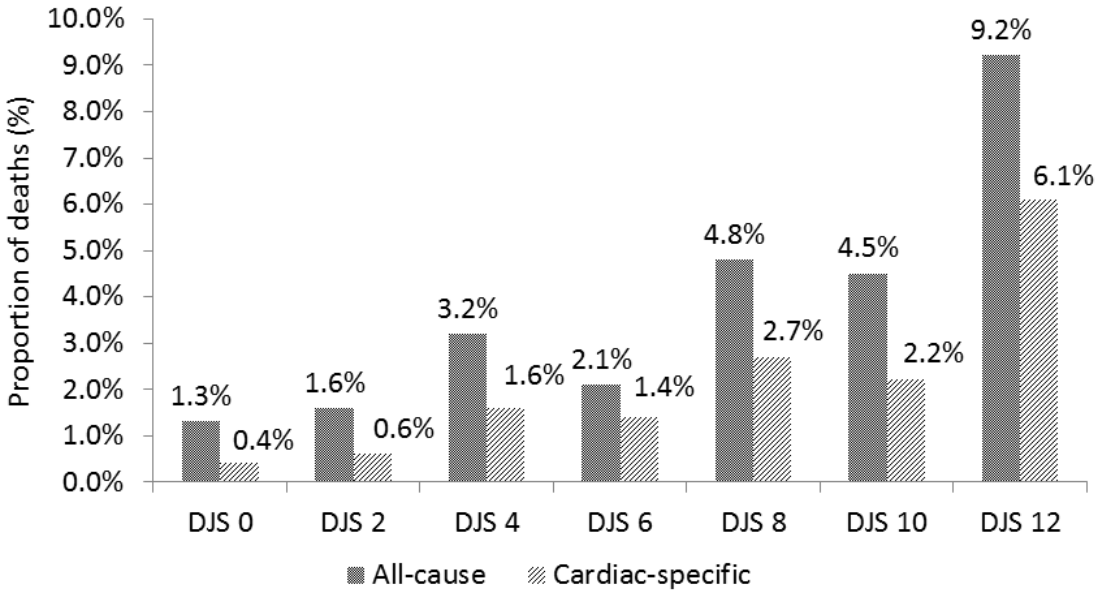


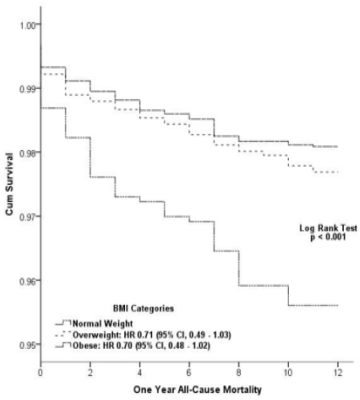
Figure 2.1a. **Unadjusted 1-year all-cause and cardiac-specific mortality according to BMI.**



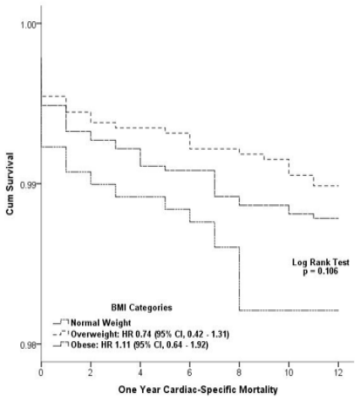
Note: DJS –Duke Jeopardy Score (0 to 12) estimates the amount of myocardium at risk on the basis of particular location of stenosis. A score of 0 is indicative of a normal angiogram or non-critical (< 70%) stenosis in any of the coronary arteries.
All-cause mortality p<.001; Cardiac-specific mortality p<.001

Figure 2.1b. **Unadjusted 1-year all-cause and cardiac-specific mortality according to Duke Jeopardy Score.**

The unadjusted one-year all-cause survival rates of normal weight, overweight and obese groups indicated that survival rates were highest for the obese and overweight groups and lowest for the normal weight group (p <0 .001) (Figure 2.2a). There were no significant differences among the BMI categories for cardiac-specific mortality (p = 0.106) (Figure 2.2b).



BMI Category	Time (Months)	Number of Deaths	Number Censored	Number at Risk
Normal Weight	0-2	23	0	1274
	2-4	12	0	1262
	4-6	4	0	1258
	6-8	7	0	1251
	8-10	7	0	1244
	10-12	4	0	1240
Overweight	0-2	34	0	3038
	2-4	7	0	3031
	4-6	7	0	3024
	6-8	10	0	3014
	8-10	5	0	3009
	10-12	8	0	3001
Obese	0-2	33	0	3677
	2-4	11	0	3666
	4-6	8	0	3658
	6-8	13	0	3645
	8-10	3	0	3642
	10-12	3	0	3639



BMI Category	Time (Months)	Number Deaths	Number Censored	Number at Risk
Normal Weight	0-2	12	11	1274
	2-4	2	10	1262
	4-6	1	3	1258
	6-8	3	4	1251
	8-10	5	2	1244
	10-12	0	4	1240
Overweight	0-2	17	17	3038
	2-4	3	4	3031
	4-6	1	6	3024
	6-8	3	7	3014
	8-10	2	3	3009
	10-12	5	3	3001
Obese	0-2	25	8	3677
	2-4	4	7	3666
	4-6	5	3	3658
	6-8	6	7	3645
	8-10	2	1	3642
	10-12	3	0	3639

Figure 2.2a (Left). **Unadjusted Kaplan Meier and 1-year all-cause mortality in patients undergoing coronary angiography by BMI; *Figure 2.2b (Right).* Unadjusted Kaplan Meier and 1-year cardiac-specific mortality in patients undergoing coronary angiography by BMI.**

The following variables emerged as significant factors associated with 1-year all-cause mortality during univariate analyses: age, hypertension, diabetes, family history of premature CAD, CHF, PVD, CVD, COPD, malignancy, renal insufficiency, CRF, dialysis, DJS and BMI both as a categorical and continuous variable. The variables gender and hyperlipidemia were not significant. All statistically and clinically significant

variables with *p* values < 0.20 were included in multivariate Cox proportional regression analysis. Multivariate regression analysis showed age, diabetes, PVD, COPD, malignancy, renal insufficiency, DJS 8, 10 and 12, LV Grades III and IV as significant correlates of 1-year all-cause mortality. BMI was not a statistically significant correlate of all-cause mortality; however the hazards ratios and 95% CIs for the overweight (HR, 0.71; 95%, CI 0.49-1.03) and obese (HR, 0.70; 95% CI, 0.48-1.03) showed a trend toward a protective effect when compared to the normal weight category (Table 2.3). Cox regression analysis was also performed using BMI as a continuous variable; however, it was not a significant factor associated with 1-year all-cause mortality (data not shown).

Table 2.3

Correlates of 1-year all-cause mortality calculated by Cox proportional hazards multiple regression analysis

	Overall n=8079	**B**	**S.E.**	**Wald**	**P value**	**HR**	**95% CI**
Age	61.2 ± 10.6	.044	.008	26.802	.000	1.04	1.03-1.06
Hypertension	5234 (64.9%)	-.040	.179	.050	.823	.96	.68-1.37
Diabetes	342 (36.9%)	.175	.161	1.18	.277	1.19	.87-1.63
Family history of premature CAD	5076 (63.0%)	-.170	.155	1.19	.274	.84	.62-1.14
CHF	160 (2.0%)	.384	.259	2.193	.139	1.47	.88-2.44
PVD	361 (4.5%)	.517	.223	5.361	.021	1.68	1.08-2.60
CVD	457 (5.7%)	-.041	.232	.032	.859	.96	.61-1.51
COPD	1305 (16.2%)	.585	.166	12.379	.000	1.79	1.29-2.49
Malignancy	352 (4.4)	.559	.238	5.522	.019	1.75	1.10-2.79
Renal insufficiency	321 (4.0%)	.666	.305	4.75	.029	1.95	1.07-3.54
CRF	182	.355	.375	.898	.343	1.43	0.89-4.28

	Overall n=8079	B	S.E.	Wald	P value	HR	95% CI
	(2.3)						
Dialysis	50 (0.6)	.665	.402	2.738	.098	1.95	0.68-2.97
Current/former smoker	5551 (69.0%)	.196	.174	1.26	.262	1.22	.86-1.71
DJS							
0 (referent category)	3410 (42.2%)			28.637	.000		
2	1595 (19.7%)	-.021	.253	.007	.932	.98	.60-1.61
4	692 (8.6%)	.296	.277	1.14	.286	1.35	.78-2.31
6	973 (12.0%)	-.017	.286	.003	.953	.98	.56-1.72
8	483 (6.0%)	.761	.268	8.088	.004	2.14	1.27-3.62
10	449 (5.6%)	.662	.282	5.501	.019	1.94	1.12-3.37
12	198 (6.4%)	.998	.239	17.415	.000	2.71	1.70-4.33
LV Grade							
Grade I (Referent category)	6778 (84.9)			50.146	.000		
Grade II	823 (10.3)	.309	.216	2.038	.153	1.36	.89-2.08
Grade III	272 (3.4)	1.226	.222	30.423	.000	3.41	2.20-5.27
Grade IV	114 (1.4)	1.568	.280	31.337	.000	4.80	2.77-8.31
BMI Category							
Normal Weight	1297 (16.1)			4.213	.122		
Overweight	3072 (38)	-.341	.189	3.255	.071	.71	.49-1.03
Obese	3710 (45.9)	-.356	.194	3.37	.066	.70	.48-1.02

Note. BMI = Body mass index; CHF = congestive heart failure; CI= Confidence Interval; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVD = cerebrovascular disease; DJS=Duke Jeopardy Score; HR = Hazard ratio; LV = left ventricular; PVD = peripheral vascular disease; S.E. indicates standard error.

Multivariate regression analysis examining cardiac-specific mortality showed age, CHF, DJSs 4 to 12, LV Grades III and IV as significant correlates of 1-year cardiac-specific mortality but not BMI (Table 2.4).

Table 2.4

Correlates of 1-year cardiac-specific mortality calculated by Cox proportional hazards multiple regression analysis

	Overall n=8079	**B**	**S.E.**	**Wald**	**P value**	**HR**	**95% CI**
Age	61.2 ± 10.6	.046	.012	14.646	.000	1.05	1.02-1.07
Hypertension	5234 (64.9%)	.112	.274	.167	.682	1.12	.65-1.91
Diabetes	342 (36.9%)	.312	.225	1.93	.165	1.37	.88-2.12
Family history of premature CAD	5076 (63.0%)	-.098	.222	.196	.658	.91	.59-1.40
CHF	160 (2.0%)	.725	.340	4.56	.033	2.07	1.06-4.02
PVD	361 (4.5%)	.510	.322	2.512	.113	1.67	.89-3.13
CVD	457 (5.7%)	-.027	.329	.007	.935	.97	.51-1.89
COPD	1305 (16.2%)	.275	.247	1.238	.266	1.32	.81-2.14
Malignancy	352 (4.4)	-1.88	1.01	3.491	.062	.15	.02-1.10
Renal insufficiency	321 (4.0%)	.466	.448	1.085	.298	1.59	.66-3.83
CRF	182 (2.3)	.2925	.544	.288	.591	1.34	.46-3.89
Dialysis	50 (0.6)	.422	.636	.440	.507	1.53	.44-5.31
Current/former smoker	5551 (69.0%)	.272	.255	1.14	.286	1.31	.86-1.71
DJS							
0 (referent category)	3410 (42.2%)			30.545	.000		
2	1595 (19.7%)	.242	.436	.307	.579	1.27	.54-3.00
4	692 (8.6%)	1.012	.421	5.763	.016	2.75	1.20-6.28

	Overall n=8079	B	S.E.	Wald	P value	HR	95% CI
6	973 (12.0%)	.941	.401	5.513	.019	2.56	1.17-5.62
8	483 (6.0%)	1.46	.407	12.854	.000	4.31	1.94-9.57
10	449 (5.6%)	1.245	.432	8.317	.004	3.47	1.49-8.09
12	198 (6.4%)	1.762	.367	23.023	.000	5.83	2.84-11.99
LV Grade							
Grade I (Referent category)	6778 (84.9)			37.607	.000		
Grade II	823 (10.3)	.239	.320	.559	.455	1.27	.68-2.38
Grade III	272 (3.4)	1.154	.320	12.987	.000	3.17	1.69-5.94
Grade IV	114 (1.4)	1.98	.348	32.352	.000	7.24	3.66-14.33
BMI Category							
Normal Weight	1297 (16.1)			2.72	.257		
Overweight	3072 (38)	-.305	.293	1.083	.298	.74	.42-1.31
Obese	3710 (45.9)	.100	.284	.126	.722	1.11	.64-1.92

Note. BMI = Body mass index; CHF = congestive heart failure; CI= Confidence Interval; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVD = cerebrovascular disease; DJS=Duke Jeopardy Score; HR =Hazard ratio; LV = left ventricular; PVD = peripheral vascular disease; S.E. indicates standard error.

2.5 Discussion

Our study examined the relationship between BMI and CAD and 1-year mortality in a large cohort of patients undergoing CA for suspected, but not yet confirmed CAD. 84% of patients were overweight and obese. It was hypothesized that overweight patients, particularly those in the higher BMI categories, would have more severe CAD and be at greater risk of death at 1-year compared to normal weight patients. Contrary to our hypothesis, we found that normal weight patients had higher unadjusted 1-year all-cause mortality than overweight and obese patients despite having more favorable baseline characteristics but more severe disease. Obese patients presented with less severe CAD based on DJSs despite having a higher prevalence of recognized risk factors including hypertension, hyperlipidemia, and diabetes. In the current study, we found differences in the average age of obese and non-obese patients, with obese patients being significantly younger than their non-obese counterparts. We did not observe a difference in unadjusted cardiac-specific mortality across BMI categories.

In patients with established CAD a reverse J-shaped relationship between all-cause mortality and cardiovascular mortality and BMI has been reported in three meta-analyses. [19, 20, 46] However, very few studies have examined the association of BMI and CAD in patients undergoing CA for suspected, but not yet confirmed CAD. The current study findings support the paradoxical findings of Rubinshtein et al. [31] and Niraj et al. [32]. In a study by Rubinshtein et al. [31] on 928 patients with CAD, the authors reported an inverse relationship between BMI and severity of CAD. Other risk factors such as diabetes, hyperlipidemia, and male gender were correlated with severity of CAD. Niraj et

al. [32] investigated the relationship between severity of CAD and BMI according to the DJS in a sample of 770 patients from the US including 212 Caucasians and 428 African-Americans. The authors' also reported a paradoxical relationship. In both studies, the obese patients were significantly younger than the normal weight and overweight patients, leading to the conclusion that this association could be partly or completely explained by the increased likelihood of early physician referral of obese patients for cardiac catheterization and therefore at an earlier stage of CAD. The inverse relationship between BMI and severity of CAD was also reported most recently by Parsa and Jahanshahi [33] in a cross-sectional prospective study performed between September 2009 and March 2011 among 414 patients with suspected CAD undergoing CA.

We did not observe a significant relationship between BMI and 1-year all-cause or cardiac-specific mortality. After controlling for potential confounders such as other cardiovascular risk factors and comorbidities in our analyses, BMI did not emerge as an independent factor significantly associated with either all-cause or cardiac-specific mortality. The statistically insignificant but clinically relevant odds ratios and confidence intervals for both the overweight and obese categories were consistent with a 51% and 52% reduction in risk of all-cause mortality for overweight and obese patients, respectively.

It is important to note that in the current study, significant proportions of overweight (39%) and obese (45.5%) patients who underwent CA did not have CAD based on angiographic generated DJSs. We were unable to examine the relationship between BMI and mortality in patients who had a CA but were not diagnosed with CAD due to the low

event rates of 45 all-cause and 13 cardiac-specific deaths. In a study conducted by Oreopolous et al. [21], the authors reported an obesity paradox in patients who had CA with no CAD. The authors offered two explanations for the unexpected finding (1) other cardiac risk factors could classify these patients as having "pre-clinical" disease and that a higher BMI was protective, and (2) referral and treatment bias in CAD since obesity is a "visible" risk factor that may predispose physicians to refer obese patients for CA earlier than those with a normal BMI. Niraj et al. [32] also suggested that the trend of normal or minimal change angiography in obese patients in their 2006 study may have been due to a tendency of bias of physicians to refer obese patients for earlier angiography. Rubinshtein et al. [31] suggested that a younger age could be associated with a lower prevalence of high-risk coronary anatomy compared with non-obese older patients. This could partially explain the findings of the current study as well. Patients of normal weight were significantly older than their obese counterparts and had more angiographic severe CAD according to their DJSs.

Although the mechanism for the potential protective effect of obesity among patients with CAD remains unclear, a number of potential mechanisms have been proposed: greater metabolic reserves, less cachexia, younger presenting age, more aggressive medical therapy, more aggressive diagnostic and revascularization procedures, increased muscle mass and strength, possible improved cardiorespiratory fitness despite obesity, diminished hormonal response including the renin-angiotensin-aldosterone system, and unmeasured confounders, including selection bias. [47]

Our study has a number of strengths. We report on a large population-based cohort of consecutive patients undergoing CA at a single tertiary cardiac centre using APPROACH-NL prospectively collected data. Data quality assurance indicated that the amount of missing data was minimal (1.2%). Actual measures of height and weight were taken at the time of CA, unless the patients were unstable. We were able to assess the effect of BMI on 1-year all-cause and cardiac-specific mortality in patients with and without CAD using data linkage to up-to-date mortality data from the NL Vital Statistics Division.

This study also has limitations. First, our study is an observational non-randomized cohort study and therefore provides evidence of association not causation. Second, patients with missing BMI data were excluded (n = 119), although this accounted for only 1.0%. Third, BMI has been criticized as an inaccurate method to investigate body fatness because it is not as well correlated to cardiovascular disease and death as other measures of obesity including waist circumference and waist-to-hip ratio [47], data that were unavailable in the APPROACH clinical database. Fourth, BMI was collected at the time of the index CA only and potential changes in BMI were not accessed. Finally subgroups of obese patients could not be analyzed due to small numbers.

2.6 Conclusions

Obesity was associated with less severe CAD as evidenced by CA, suggesting obese patients are more likely to be referred early for CA based on the prevalence of cardiovascular risk factors including hypertension, hyperlipidemia and diabetes. This

study failed to detect an association of BMI with 1-year mortality after adjustment for potential confounding variables.

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Chapter 3 Research Paper #2

Impact of Body Mass Index on Short-term Outcomes in Patients Undergoing Percutaneous Coronary Intervention in Newfoundland and Labrador, Canada

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3.1 Abstract

Background and Aim: Obesity (BMI $\geq$ 30kg/m^2) is associated with advanced cardiovascular disease requiring procedures such as percutaneous coronary intervention (PCI). Studies report better outcomes in obese patients having these procedures but results are conflicting or inconsistent. Newfoundland and Labrador (NL) has the highest rate of obesity in Canada. The aim of the study was to examine the relationship between BMI and vascular and non-vascular complications in patients undergoing PCI in NL.

Methods: We studied 6,473 patients identified in the APPROACH-NL database who underwent PCI from May 1st 2006 to December 31st 2013. BMI categories included: normal, 18.5 $\leq$ BMI < 25.0 (n=1073); overweight, 25.0 $\leq$ BMI < 30 (n=2608); and obese, BMI $\geq$ 30.0 (n=2792).

Results: Patients with obesity were younger, had a higher incidence of diabetes, hypertension, and family history of cardiac disease. Obese patients experienced less vascular complications: (normal, overweight, obese: 8.2%, 7.2%, 5.3%, p =0.001). No significant differences were observed for in-lab (4.0%, 3.3%, 3.1%, p =0.386) or post-procedural (1.0%, 0.8%, 0.9%, p =0.725) non-vascular complications. After adjusting for covariates, BMI was not a significant factor associated with adverse outcomes.

Conclusion: Obesity was not an independent correlate of short-term vascular and non-vascular complications among patients undergoing PCI.

3.2 Introduction

Obesity is an independent risk factor for cardiovascular disease [1-5], and is associated with advanced cardiovascular disease requiring procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass surgery, reduction in life expectancy [6], and a higher mortality rate [3,7-8]. A number of observational studies have reported improved clinical outcomes (i.e., increased survival benefit) in overweight and obese patients treated for cardiovascular diseases compared to normal weight patients, a phenomenon commonly referred to as "obesity paradox". [9-14] This phenomenon is considered to be counter-intuitive, referred to as "reverse epidemiology", and reported in patients with hypertension [15], heart failure [16], coronary artery disease (CAD) [15, 17-19], coronary artery bypass surgery [17-20], and PCI [17-19]. Inconsistent results have been reported regarding the association between BMI and short-term clinical outcomes (i.e., vascular complications, non-vascular in-lab and post procedural complications) and/or mortality in patients undergoing PCI [9-10,13, 21-27]; therefore, it is not entirely clear whether an obesity paradox exists.

Obesity is a common and rapidly growing public health concern. Between 1985 and 2011 the prevalence of this disease in Canada increased 200% from 6.1% to 18.3% equating to more than 4.8 million adults, with continued increases projected. [28] Newfoundland and Labrador (NL) has the highest rate of obesity in Canada. It is estimated that 71% of the province's population will be either overweight or obese by 2019. [28] There is a paucity of data on the prevalence of obesity in patients undergoing PCI in the province. Furthermore, the relationship between short-term clinical outcomes and BMI has not been

examined in patients undergoing PCI in NL. In the present study, we examine (1) the prevalence of obesity among patients undergoing PCI and the differences among BMI groups on demographic, clinical and procedural findings, and (2) examine the association between the most commonly used anthropometric parameter to assess adiposity (i.e., BMI) and short-term outcomes (vascular complications, non-vascular in-lab and post-procedural complications occurring within 48 hours).

3.3 Methods

3.3.1 Study Design

We performed a retrospective analysis of prospectively collected de-identified data for all patients 18 years of age and older who had a PCI between May 1st , 2006 and December 31st , 2013 in the province of NL, Canada using a well-established clinical database (i.e., Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease [APPROACH- Newfoundland and Labrador (NL)]. Detailed prospective demographic, clinical and procedural data on all patients undergoing diagnostic cardiac catheterization and/or percutaneous coronary intervention (PCI) and cardiac surgery since 2006 is collected by specifically trained clinical cardiac catheterization database nurses. Nurses collect and record on an abstraction sheet patient data provided by nurses responsible for the care of the patient which includes examination and assessment of the access site for potential vascular complications. The attending physician also examined the vascular access site. All data are verified by chart review until hospital discharge by these nurses. Prospectively collected data on each consecutive patient is entered into the APPROACH-NL clinical database. A research nurse is responsible for the management of the database

including completeness of data entry and quality assurance activities. Details of the database and methods of collection have been previously described. [29] If patients are not hospitalized, they remain in the local area for 24 hours and are advised to return to the emergency department (ER) if they encounter any problems. ER admissions are audited by a clerk in the cardiac catheterization laboratory in the event a patient returns to the ER.

3.3.2 Study Population

For the current study, all consecutive PCIs (N =6633) performed on patients 18 years of age and older between May 1st, 2006 and December 31st, 2013 at the Health Science Centre, Eastern Health, NL were enrolled. PCI procedures performed on underweight (BMI < 18.5kg/m^2) individuals (n=47) or those with missing BMI data or unlikely valid BMI levels of >70 or <11kg/m^2 (n= 113) were excluded. The remaining patients comprised the study cohort. Based on these selection criteria, 6,473 patients were included in the final analysis.

Weight and height were measured and documented by a nurse at the time of PCI. If patients were unstable, self-reported weight and height were collected and BMI calculated. Patients were grouped according to three BMI categories using the World Health Organization classification system: normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese (>30 kg/m^2). [30] These categorizations reflect relative increasing levels of risk to health. [31]

3.3.3 Clinical Outcomes and Definitions

The *primary outcome* was short-term complications occurring within 48 hours after the intervention. *Vascular access complications* were defined as hematoma (> 5cm), pseudoaneurysm, arteriovenous fistula, vascular occlusion, access site bleeding, retroperitoneal bleed, and loss of distal pulse or occlusion. *Non-vascular complications* included in-lab events (abrupt coronary closure, emergency coronary artery bypass surgery (CABG), access site complications, death, ventricular tachycardia/ventricular fibrillation, pulmonary edema, shock, and dissection) and *post-procedural complications* (death, myocardial infarction, emergency CABG, abrupt coronary closure, hemorrhagic or ischemic CVA, and GI bleed). Each of the outcomes was a composite of the individual outcomes defined in each category.

3.3.4 Ethical Considerations

All patients who had a PCI during the time period under examination gave written, informed consent to the cardiac care program for data collection and follow-up observation after PCI. The study protocol was approved by the Health Research Ethics Authority of Memorial University and Eastern Health.

3.3.5 Data Analysis

Demographic characteristics, clinical and procedural related variables were summarized. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using ANOVA, and the differences between categorical variables were examined using the χ^2 test and, where appropriate, the Fisher exact test is reported. All p

values were two-tailed, with statistical significance defined by a p value < 0.05. Comparisons were performed for a trend in increasing BMI categories using χ^2 test for trends. Univariate logistic regression analysis was performed to determine the odds ratio for vascular complications and non-vascular complications occurring in the cardiac care laboratory identified within 24-48 hours post PCI. Multivariate logistic regression analysis was used to examine independent predictors for each of the patient outcomes. Due to the low non-vascular post-procedural complication event rate regression analyses were not performed. Variables identified in Tables 3.1 through 3.3 were selected for these models based on univariate p values <0.20 and overall clinical significance. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. [32]

3.4 Results

A cohort of 6,473 patients was identified from the population of patients who had a PCI during the time period under examination. BMI for normal weight, overweight and obese patients from 2006 to 2013 are presented in Figure 3.1. Tables 3.1 through 3.3 show the baseline characteristics of patients according to categories of BMI, medications at time of referral, and admitting clinical, angiographic and procedural data.

Baseline Characteristics

Of the 6,473 patients 16.6% were normal weight (n= 1073), 40.3% were overweight (n = 2608) and 43.1% were obese (n=2792). In each of the years examined less than 19% of patients who had a PCI were of normal weight (Table 3.1 and Figure 3.1). The baseline

characteristics of the study patients according to the three BMI categories are presented in Table 3.1. There were statistically significant differences between the groups on a number of characteristics. A higher proportion of overweight patients were male. Patients with obesity were younger, had a higher incidence of coronary risk factors such as diabetes mellitus and hypertension, and had a family history of cardiovascular disease. Patients with a higher BMI were also more likely to have COPD, whereas normal weight patients were more likely to have PVD. No significant differences were observed in smoking status.

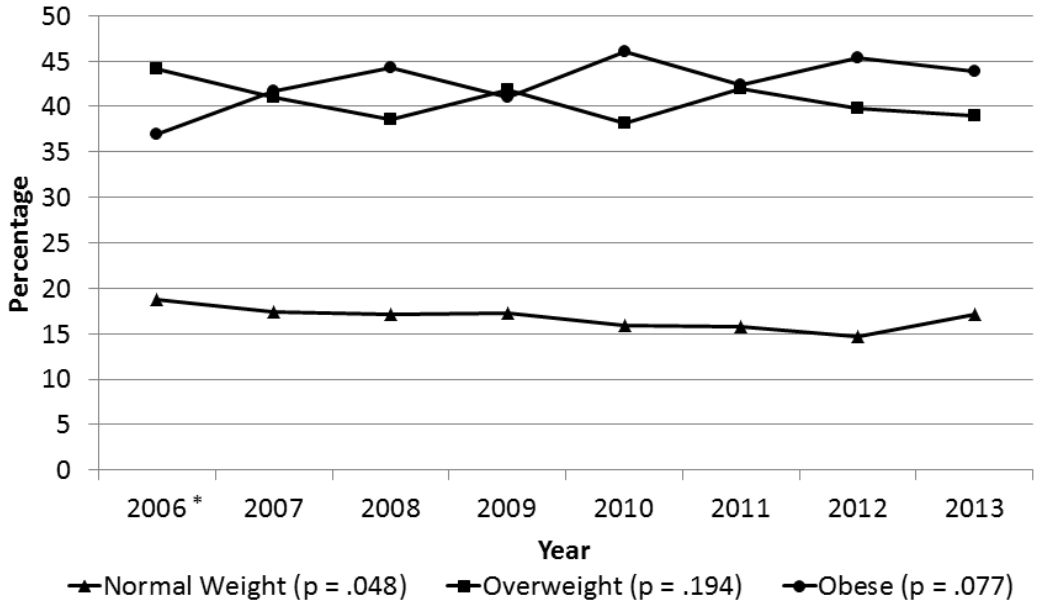
Table 3.1 *Baseline characteristics of patients according to categories of BMI*

Variable	Total N	NW	OW	OB	*p* value*
Number of patients	6473	1073	2608	2792	
Age, years	6473	65.1 ± 11.1	63.1 ± 10.5	60.7 ± 10.1	p<.001
Male sex	6473	695 (64.8)	1975 (75.7)	1945 (69.7)	p<.001
Cardiovascular risk factors					
HTN	6462	658(61.4)	1661(63.8)	2066 (74.1)	p<.001
Hyperlipidemia	6462	905 (84.4)	2241 (86.1)	2434 (87.4)	p= .050
Diabetes	6464	226 (21.1)	637 (24.5)	1040 (37.3)	p<.001
Family history	6440	622 (58.3)	1627 (62.7)	1822 (65.5)	p<.001
Smoking status	6421				
Never	1719	298 (28.1)	698 (27.0)	723 (26.1)	p= .441
Smoking history	4702	763 (71.9)	1891 (73.0)	2048 (73.9)	
PVD	6460	91 (8.5)	172 (6.6)	156 (5.6)	p=.005
COPD	6459	156 (14.6)	335 (12.9)	479 (17.2)	p<.001

Values are presented as n (%) or mean ± SD, as indicated.

**p* values for chi-squared or ANOVA tests.

Note. BMI =body mass index; COPD = Chronic obstructive pulmonary disease; NW = normal weight; OB = obese; OW = overweight; PCI = percutaneous coronary intervention; HTN = hypertension; MI = myocardial infarction; PVD = peripheral vascular disease.



*Period from May 1st to December 31st, all other years are reported as calendar years.

Note: Chi square trend test p values reported for BMI categories.

Figure 3.1. **BMI trends for normal weight, overweight and obese patients who had a PCI from 2006 to 2013.**

Medications at the time of referral for PCI were examined. The details regarding the use of medications prior to PCI are presented in Table 3.2. No significant differences were found in the use of acetylsalicylic acid (ASA), warfarin, pre-procedural GP IIb/IIIa inhibitors, beta blockers, low molecular weight heparin (LMWH), IV heparin, IV nitrates, or statin therapy between the groups. Patients with obesity were less likely to receive a thienopyridine antiplatelet medication (ticlopidine/clopidogrel), but were more likely to receive an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blockers and long acting nitrates.

Table 3.2

Medications at time of referral for PCI by BMI category

	Total N	**NW**	**OW**	**OB**	***p* value***
Number of patients	6473	1073	2608	2792	
Beta blockers	6431	863 (81.2)	2154 (83.1)	2318 (83.5)	p =.220
ACE inhibitors	6429	510 (48.0)	1296 (50.0)	1476 (53.2)	p =.006
ARB antagonist	6428	104 (9.8)	305 (11.8)	431 (15.5)	p < .001
CCB	6430	173 (16.3)	433 (16.7)	596 (21.5)	p < .001
LA nitrates	6430	307 (28.9)	729 (28.1)	869 (31.3)	p =.032
Statin therapy	6427	874 (82.3)	2199 (84.9)	2345 (84.5)	p =.134
ASA	6432	983 (92.5)	2402 (92.6)	2612 (94.1)	p =.058
Ticlopidine/Clopidogrel	6432	806 (75.8)	1846 (71.2)	1925 (69.3)	p < .001
Warfarin	6429	15 (1.4)	47 (1.8)	59 (2.1)	p =.329
GP IIb/IIIa inhibitors	6437	5 (0.5)	14 (0.5)	13 (0.5)	p =.924
LMWH	6439	428 (40.2)	971 (37.4)	1003 (36.1)	p =.068
IV heparin	6439	220 (20.6)	497 (19.1)	579 (20.8)	p =.268
IV nitrates	6430	141 (13.3)	313 (12.1)	307 (11.1)	p =.149

Values are presented as n (%).

**p* values for chi-squared tests.

Note. ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI =body mass index; CCB = calcium channel blockers; LA nitrates = long-acting nitrates; LMWH=low molecular weight heparin; NW = normal weight; OB = obese; OW = overweight; PCI = percutaneous coronary intervention.

Angiographic and Procedural Data

Admitting clinical, angiographic and procedural data are shown in Table 3.3. Normal weight patients were significantly less likely to require a closure device ($p < 0.001$) compared to other BMI groups. However, there were no significant differences among the BMI categories in the prevalence of prior PCI, prior CABG, prior HF, prior MI, pulmonary embolism, thromboembolic history, deep vein thrombosis, same sitting angioplasty, intra-aortic balloon pump (IABP) use at time of referral or during the

procedure /cardiogenic shock at time of procedure, use of GP IIb/IIIa inhibitors, access site, and choice of sheath size. A greater proportion of normal weight patients presented as emergency/urgent cases, whereas more elective procedures were performed in overweight and obese patients. A greater proportion of obese patients presented with unstable angina, whereas a much lower proportion presented with a STEMI. A greater proportion of patients with angina categorized according to the Canadian Cardiovascular Society as class II-IIII was noted in obese; whereas a greater proportion of normal weight patients experienced class IV.

Table 3.3
Admitting clinical, angiographic and procedural data for patients undergoing PCI according to BMI category

	Total N	**NW**	**OW**	**OB**	**p value***
Number of Patients	6473	n= 1073	n = 2608	n = 2792	
Cardiovascular history					
Prior PCI	6462	226 (21.1)	543 (20.9)	627 (22.5)	p =.318
Prior CABG	6462	129 (12.0)	298 (11.5)	289 (10.4)	p =.247
Prior HF	6462	52 (4.9)	83 (3.2)	106 (3.8)	p =.052
Prior MI	6462	212 (19.8)	527 (20.3)	581 (20.8)	p =.734
CVD	6450	89 (8.3)	160 (6.2)	174 (6.3)	p =.041
Same sitting angioplasty	6473	864 (80.5)	2138 (82.0)	2321 (83.1)	p =.149
IABP/Cardiogenic shock	6461	7 (0.7)	16 (0.6)	31 (1.1)	p =.104
Priority	6466				
Low risk	1861	220 (20.5)	783 (30.0)	858 (30.7)	
Emergency	397	72 (6.7)	170 (6.5)	155 (5.6)	
Urgent	4208	780 (72.7)	1654 (63.4)	1774 (63.5)	p < .001
PE	6216	8 (0.8)	13 (0.5)	15 (0.6)	p = .641
Thromboembolic history	6218	5 (0.5)	12 (0.5)	10 (0.4)	p = .797
DVT	6219	16 (1.6)	32 (1.3)	32 (1.2)	p = .663
CCS Angina Grading Scale	6469	1071	2606	2791	

No pain or atypical symptoms		69 (6.4)	123 (4.7)	128 (4.6)	
Class 1		11(1.0)	43 (1.7)	35 (1.3)	
Class 2		108 (10.1)	434 (16.7)	463 (16.6)	
Class 3		90 (8.4)	270 (10.4)	326 (11.7)	
Class 4		794 (74.1)	1736 (66.6)	1839(65.9)	p < .001
Stable angina	1748	202 (18.9)	731 (28.1)	815 (29.3)	p < .001
ACS	4341	n=791	n=1724	n=1825	
STEMI	1227	251 (31.7)	501 (29.1)	475 (26.0)	
Non-STEMI	1939	349 (44.1)	787 (45.6)	803 (44.0)	
Unstable angina	1174	191 (24.1)	436 (25.3)	547 (30.0)	p = .001
Thrombolytics contraindicated	4143	11 (1.5)	27 (1.6)	24 (1.4)	p = .831
Failed thrombolysis	4274	26 (3.4)	77 (4.5)	59 (3.3)	p =.122
Access site					
Radial/Brachial	1172	193(18.0)	468(17.9)	511(18.3)	
Femoral	5301	880 (82.0)	2140 (82.1)	2282 (81.7)	p=.938
Sheath size					
Sheath size 5 Fr	924	160 (14.9)	393 (15.1)	371 (13.3)	
Sheath size 6 Fr	5432	893 (83.2)	2171 (83.3)	2368 (84.9)	
Sheath size 7/8 Fr	114	20 (1.9)	43 (1.6)	51 (1.8)	p =.386
Closure device	6470	484 (45.1)	1359 (52.1)	1506 (54.0)	p < .001
GP IIb/IIIa inhibitors	6471	134 (12.5)	338 (13.0)	351 (12.6)	p =.889

Values are presented as n (%).

*p values for chi-squared tests.

Note. BMI =body mass index; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CVD = cerebrovascular disease; HF = heart failure; IABP = intra-aortic balloon pump; MI = myocardial infarction; NW = normal weight; OB = obese; OW = Overweight; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PVD = peripheral vascular disease; STEMI = ST elevation myocardial infarction.

Complications occurring with 24 to 48 hours of PCI according to BMI

Complications occurring with 24 to 48 hours of PCI according to BMI category are presented in Table 3.4 and Figure 2.2. Obese subjects experienced a lower proportion of vascular complications: (normal, overweight, obese: 8.2%, 7.2%, 5.3%, $p = 0.001$). No significant differences were observed for non-vascular complications either in-lab (4.0%, 3.3%, 3.1%, $p = 0.386$) or post-procedural (1.0%, 0.8%, 0.9%, $p = 0.725$).

Table 3.4

Vascular and non-vascular complications occurring within 24 to 48 hours in patients undergoing PCI according to BMI category

	NW (n=1073)	**OW (n =2608)**	**OB (n =2792)**	***p* value***
Vascular complications	88 (8.2)	187 (7.2)	149 (5.3)	0.001
Non-vascular in-lab complications	43 (4.0)	87 (3.3)	87 (3.1)	0.386
Non-vascular post-procedural complications	11 (1.0)	20 (0.8)	25 (0.9)	0.725

Values are presented as n (%).

Note. BMI = body mass index; NW = Normal Weight; OW = Overweight; OB = Obese; PCI= percutaneous coronary intervention

**p* values for chi-squared tests.

Vascular complications were defined as hematoma (> 5cm), pseudoaneurysm, arteriovenous fistula, vascular occlusion, access site bleeding, retroperitoneal bleed, loss of distal pulse or occlusion.

Non-vascular complications occurring in-lab included abrupt coronary closure, emergency coronary artery bypass surgery (CABG), access site complications, death, ventricular tachycardia/ventricular fibrillation, pulmonary edema, shock, and dissection.

Non-vascular post-procedural complications included death, myocardial infarction, emergency CABG, abrupt coronary closure, hemorrhagic or ischemic CVA, and GI bleed.

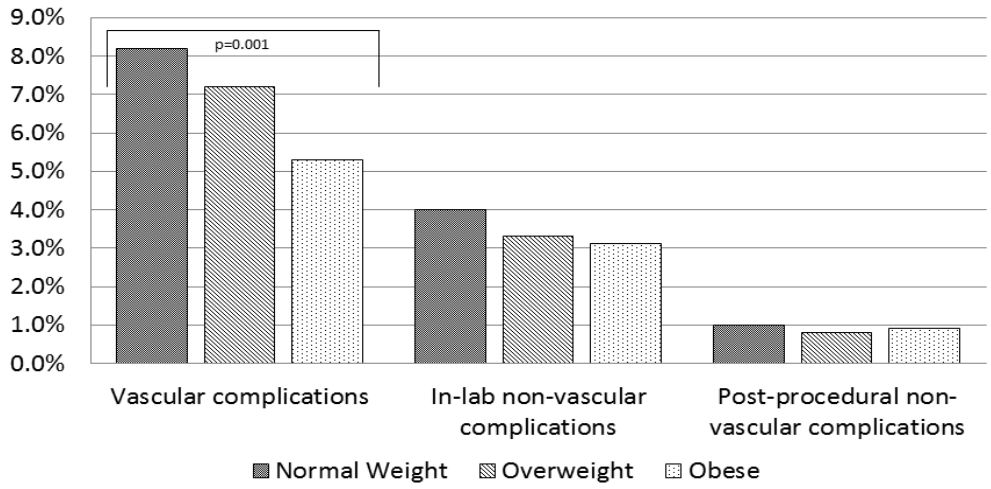


Figure 3.2. **Prevalence of vascular and non-vascular complications (in-lab and post-procedural) by BMI category.**

We performed multivariate analyses to adjust for clinical and procedural characteristics. Independent factors associated with the primary outcomes of vascular complications and non-vascular in-lab complications are shown in Tables 3.5 and 3.6. Increasing age, GP IIb/IIIa inhibitor and LMWH use during the procedure, and the utilization of a femoral access site approach were significant factors associated with the occurrence of vascular complications. Males, patients with diabetes and patients who had a closure device, and PCIs performed in 2010 were less likely to have vascular complications. GI/liver disease, warfarin use, utilization of GP IIb/IIIa inhibitors or IV Heparin during PCI, and older age were significant factors associated with the occurrence of non-vascular in-lab complications. Male sex and the use of a closure device were protective factors associated

with a less likelihood of non-vascular in-lab complications. BMI *was not* a significant factor associated with either vascular or non-vascular in-lab complications (Tables 3.5 and 3.6).

Table 3.5

Multivariate adjusted OR for vascular complications in patients undergoing PCI

	OR	**95% CI**	***p* value**
Age	1.02	1.01-1.03	0.001
Male	0.69	0.55-0.86	0.001
Diabetes	0.65	0.51-0.84	0.001
Sheath size 5Fr	0.42	0.20-0.85	0.016
Procedural GP IIb/IIIa inhibitors	1.95	1.50-2.54	0.000
Pre-procedural LMWH	1.29	1.03-1.61	0.029
Closure device	0.54	0.43-0.68	0.000
Femoral Access	2.98	2.00-4.45	0.000
Year, 2010	0.49	0.30-0.80	0.005
BMI (Referent category is normal weight)			
Overweight	1.01	0.76-1.33	.967
Obese	0.83	0.62-1.11	.219

Adjusted for access site, age, ASA, BMI, closure device, diabetes, gender, GI/liver disease, LMWH in-lab, LMWH pre-procedural, GP IIb/IIIa inhibitors in-lab, GP IIb/IIIa inhibitors pre-procedural, pre-procedural IV Heparin, prior CVD, prior HF, prior PCI, sheath size, smoking status, Ticlopidine/Clopidogrel, year.

Note. BMI =body mass index; CVD = cardiovascular disease; GP = glycoprotein; HF = heart failure; LMWH=low molecular weight heparin; PCI = percutaneous coronary intervention.

Table 3.6

Multivariate adjusted OR for non-vascular in-lab complications in patients undergoing PCI

	OR	**95% CI**	***P* value**
Age	1.02	1.001-1.03	0.039
Male	0.64	0.47-0.87	0.005
GI/Liver disease	1.53	1.02-2.27	0.038
GP IIb/IIIa inhibitors in-lab	4.99	3.65-6.81	0.000
IV Heparin in-lab	1.70	1.14-2.52	0.009
Warfarin	2.38	1.14-4.98	0.021
Closure Device	0.28	0.19-.040	0.000
BMI (Referent category is normal weight)			
Overweight	0.93	0.62-1.38	0.705
Obese	0.54	0.58-1.32	0.879

Adjusted for age, BMI, closure device, diabetes, dvt, family history of premature CAD, GP IIb/IIIa inhibitors in-lab, gender, GI/liver disease, hypertension, IV Heparin in-lab, LMWH in-lab, prior CABG, prior COPD, prior CVD, prior HF, prior PCI, prior PVD, pulmonary embolism, sheath size, warfarin, year.

Note. BMI =body mass index; CAD = coronary artery disease; CABG = coronary artery bypass surgery; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; GP = glycoprotein; HF = heart failure; LMWH=low molecular weight heparin; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease.

3.5 Discussion

The present study examined all adult patients who had a PCI procedure performed between 2006 and 2013 in one Canadian province to determine the prevalence of obesity in this patient population and trend in rates over time. A second objective was to examine the relationship between BMI and short-term vascular and non-vascular complications occurring within 48 hours and compare outcomes among three BMI categories (normal weight, overweight and obese). The majority of patients (84.3%) were either overweight or obese. Our study findings are comparable to other studies that have used PCI registries. [10-11, 26] In the current study we found that over time there was a significant trend of decreasing prevalence for the normal weight category of patients undergoing PCI (p = 0.048). Similar to previous studies, the current study demonstrates that obese patients presented with more risk factors for CAD than overweight or normal weight patients. Obese patients were younger, diabetic, and hypertensive and had higher rates of hyperlipidemia and family history of CAD.

We hypothesized BMI was an independent correlate of outcome in patients undergoing PCI, more specifically, obese patients would experience worse outcomes compared to normal and overweight patients. The obese patients in the present study were significantly younger and had higher incidence of coronary risk factors such as diabetes mellitus and hypertension, and had a family history of cardiovascular disease, but based on the findings of the univariate analyses had a significantly lower rate of vascular complications (hematoma (> 5cm), pseudoaneurysm, arteriovenous fistula, vascular occlusion, access site bleeding, retroperitoneal bleed, loss of distal pulse or occlusion)

than their normal weight and overweight counterparts. There were no significant differences in the rates of nonvascular in-lab (acute coronary closure, emergency CABG, access site complications, death, ventricular tachycardia/ventricular fibrillation, pulmonary edema, shock, and dissection) and post procedural complications (death, myocardial infarction, emergency CABG, abrupt coronary closure, hemorrhagic or ischemic CVA, and GI bleed) among the BMI categories.

After multiple logistic regression analysis, BMI was not a significant predictor of short-term outcomes (vascular complications or in-lab non-vascular complications). Our data regarding BMI in NL patients is consistent with one previous Canadian study, but is contradictory to the findings of a 2009 study conducted by Byrne et al [24]. Similar to our findings, Shubair et al [10] evaluated the effect of BMI on in-hospital outcomes in a consecutive series of coronary artery disease patients undergoing PCI enrolled in a clinical database at the Hamilton Health Sciences in Ontario Canada. The authors found that obesity was not associated with in-hospital post-procedural death, myocardial infarction, repeat PCI, CABG, or major adverse cardiac event defined as a composite of death, myocardial infarction, repeat PCI, and CABG. Using a large Canadian provincial registry, Byrne et al [24] investigated the relationship between BMI, bleeding, and outcome (i.e., 1- year mortality) after PCI. The authors reported that lower BMI ($\leq$ 18.5 kg/m^2) and higher BMI ($\geq$ 40 kg/m^2) patients were at greater risk of bleeding and death after PCI. Other studies conducted in Western society have reported underweight [9, 21, 24], normal weight [9, 21] and extremely obese patients [25-27] are at greater risk for adverse outcomes after PCI. Cox et al [9] reported that the rate of vascular complications

was highest in extremely thin and morbidly obese patients and lowest in moderately obese patients. In a study by Gruberg et al [21], the authors reported normal weight patients were at the highest risk for in-hospital complications (i.e., major bleeding, vascular complications, emergency CABG, and myocardial infarction) and cardiac death compared to overweight and obese patients. Two studies by Gurm et al. [22-23] suggested that being moderately obese conferred a protective effect, referred to as an "obesity paradox", in relation to vascular complications and major adverse outcomes after PCI, a finding consistent with that reported by Cox et al. [9]

In other studies that have focused primarily on the comparison of normal weight and extremely obese (≥ 40 kg/m^2) patients undergoing PCI, researchers have reported that extremely obese patients have increased vascular complications [26] compared to normal weight individuals and higher rates of in-hospital mortality [25-27] compared to overweight individuals. In the current study, we were unable to examine the various classes of obesity due to the small numbers in each category.

Our study has a number of strengths. We report on a large population-based cohort of patients undergoing PCI at a single tertiary cardiac centre using APPROACH-NL prospectively collected data. Data quality assurance indicated that the amount of missing data was minimal (1.7%). Actual measures of height and weight were taken at the time of the procedure unless the patients were unstable.

This study also has a number of limitations. Our study is an observational non-randomized cohort study with retrospective analysis. The current study design can only

establish association and not causation. We used data from a clinical database and as such cannot account for confounders not captured in the database. The study population was heterogeneous (i.e., included patients with variable levels of coronary artery disease severity ranging from acute coronary syndrome with cardiogenic shock to stable angina). Patients with missing BMI data were excluded (n = 113) which may contribute to selection bias, but as missing data only accounted for 1.7% this is unlikely. Despite its widespread use, the use of BMI in terms of its accuracy to define obesity is controversial. [33-35] BMI is not as well correlated to cardiovascular disease and death as other measures including waist circumference and waist-to-hip ratio [36], data that were unavailable in the clinical database. A lack of underweight and severely obese patients meant that comparisons in our study were made between only three BMI groups: normal weight, overweight, and obese.

3.6 Conclusion

Obesity was not an independent predictor of short-term outcomes (vascular or non-vascular complications occurring within 24 to 48 hours) in patients undergoing PCI at our institution.

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Chapter 4 Summary

This program of research was designed to investigate associations between BMI and clinical outcomes in patients with *suspected* as well as *documented* CAD. This final chapter provides a summary discussion of the findings, the strengths and limitations of the studies, the clinical implications of the findings, plans for knowledge translation, identification of future research, and conclusions of this study. The *first* section includes a summary of the findings. The *second* section provides a description and discussion of the strengths and limitations of the studies. The *third* section outlines the clinical implications and knowledge translation. Topics within this section include knowledge translation of the findings arising from this research to date and planned translational activities. The *fourth* section describes potential areas for future research in this area. The *final* section includes a summary of the conclusions of this research.

4.1 Summary of the Current Research Findings

This research contributes new evidence from Canada to the debate surrounding the associations between BMI and clinical outcomes in patients with suspected as well as documented CAD. Despite the known adverse effects of obesity on the development, severity and progression of CAD, a number of studies have provided evidence of the existence of an "overweight paradox" and/or an "obesity paradox" after CA and/or PCI; while, fewer studies have not provided support for this phenomenon. Our findings contradict the findings of the majority of studies that have investigated this issue and suggested that a protective effect on clinical outcomes exists in overweight and/or obese

individuals. Our findings are consistent with the findings reported by several researchers who found no evidence of an obesity paradox after PCI. [1-5]

The **first** paper in Chapter 2 focused on the relationship between BMI and severity of CAD in patients referred for and undergoing diagnostic CA for suspected CAD in NL, Canada. The primary outcome of the research was 1-year all-cause and cardiac-specific mortality. This study failed to detect an association of BMI with 1-year mortality after adjustment for potential confounding variables. The findings did suggest that obesity was associated with less severe CAD as evidenced by CA, suggesting obese patients are potentially more likely to be referred early for CA based on the prevalence of cardiovascular risk factors including hypertension, hyperlipidemia and diabetes. Previous studies have suggested that the presence of comorbid conditions in obese and overweight younger patients usually leads to more aggressive therapy of cardiovascular risk factors which likely leads to improve outcomes despite obesity. [4-9] For example, in a study of 130,139 patients hospitalized for CAD, higher BMI was associated with increased use of standard medical therapies such as ASA, beta-blockers, renin-angiotensin inhibitors, and lipid lowering therapy and increased likelihood of undergoing CA and revascularization. [7-8] Younger age may also be associated with lower CAD burden with a lower prevalence of high-risk coronary anatomy compared with non-obese patients. [8-10] Despite this it has been reported that obese patients undergo more diagnostic and revascularization procedures than patients with low or normal weight. [4]

The **second** paper in Chapter 3 focused on the relationship between BMI and short-term adverse events including vascular and non-vascular (i.e., in-lab and post-procedural)

complications in patients with established coronary artery disease who were undergoing PCI. The findings suggested that obesity was not an independent predictor of short-term outcomes (vascular or non-vascular complications occurring within 24 to 48 hours) in patients undergoing PCI at our institution. Similar findings have been reported by others [2, 4, 11] but are in contrast with previous reports showing more positive clinical outcomes in overweight and/or obese patients [12-17].

It has been proposed that the apparent paradox that has been observed by other researchers may be the result of collider stratification, a source of selection bias that is common in epidemiology research. [18] According to Banack and Kaufman [19] the typical demonstration of this bias results from conditioning on a variable affected by exposure with the outcome (referred to as a collider). Distortion of the association between exposure and outcome as a result of this conditioning on a collider can therefore produce a spurious protective association between obesity and mortality in disease groups. [19]

Other potential mechanisms through which an obesity paradox could arise have been offered including greater metabolic reserves, less cachexia, younger presenting age, more aggressive medical therapy, more aggressive diagnostic and revascularization procedures, increased muscle mass and strength, possible improved cardiorespiratory fitness despite obesity, attenuated hormonal response including renin-angiotensin-aldosterone system, unmeasured confounders, including selection bias. [20] Other researchers have specifically addressed the issue of bias and the obesity paradox proposing that the obesity paradox may be associated with biases such as lead time bias, confounding bias, and

publication bias [21], biases that cannot be completely corrected for by statistical means [3]. Lead time bias occurs when early detection of the disease is confused with prolonged survival. Obese individuals have an increased pre-test probability for CHD which could lead to earlier testing, and early diagnosis could result in increased survival. In contrast, lean individuals have a lower pretest probability, and consequently present with more advanced disease, and thus a worse subsequent prognosis. The authors also suggest that there is a potential for confounding bias, for example, smoking and lower BMI have been associated with mortality. The authors also suggest that the findings of decreased survival among obese individuals might not be considered new research resulting in negative studies being less likely to be published than positive studies resulting in publication bias. [21]

4.2 Strengths and Limitations

This study has both strengths and limitations. Selection bias was limited with the use of a large population-based cohort of patients undergoing diagnostic cardiac catheterization and PCI at a single tertiary cardiac centre using APPROACH-NL prospectively collected data. Data quality assurance indicated that the amount of missing data was minimal (1.7%). Actual measures of height and weight were taken at the time of the procedure unless the patients were unstable.

This study also has a number of limitations mostly linked to the retrospective nature of the analysis and to the lack of ability to adjust for confounding variables. The design of the study was an observational non-randomized cohort study with retrospective analysis. Therefore, only association and not causation can be established. In an attempt to adjust

for a large number of risk factors (i.e., potential confounders) and a small number of events per variable, we summarized covariate information into a propensity score for inclusion in the outcome model; however, this analytical method was not feasible. Data from a clinical database was used and as such cannot account for confounders not captured in the database. The study population was heterogeneous (i.e., included patients with variable levels of coronary artery disease severity ranging from acute coronary syndrome with cardiogenic shock to stable angina).

Patients with missing BMI data were excluded (n = 113) which may contribute to selection bias, but as missing data only accounted for 1.7% this is unlikely. Despite its widespread use, the use of BMI in terms of its accuracy to define obesity is controversial given its inability to differentiate lean mass and body fat. [21-24] BMI is not as well correlated to cardiovascular disease and death as other measures including waist circumference and waist-to-hip ratio [21], data that were unavailable in the clinical database. It is well documented that respondents have a tendency to underestimate their weight and/or overestimate their height. [25] However, self-reported height and weight are considered valid for identifying relationships in epidemiologic studies [26], with self-reported values being strongly correlated with measured values [27-28]. This research examined BMI at an initial point in time and related it to mortality a 1-year. A lack of underweight and severely obese patients meant that comparisons were limited to three BMI groups: normal weight, overweight, and obese. A number of researchers had reported that severely obese (BMI $\geq$40 kg/m^2) individuals have more vascular complications compared to normal weight individuals and higher rates of in-hospital

mortality [29-31]; however, the relatively small sample size for patients in the extreme ends of BMI classification limited the statistical power and did not yield an adequate number of observations for multivariate regression analyses of infrequent adverse events.

4.3 Clinical Implications and Knowledge Translation

The clinical implications of whether or not obesity is directly associated with adverse outcomes such as 1-year mortality in patients referred for CA for suspected CAD is still subject to debate. This is also the case for patients undergoing PCI as a treatment option for CAD. Referral bias may partially explain the finding of the absence of significant CAD in obese patients in the current research. Obese and overweight patients may have been referred for cardiac catheterization at an earlier stage of coronary involvement. Patients may have experienced more severe symptoms (e.g., chest pain, shortness of breath, increased blood pressure) or disability suggestive of symptomatic CAD leading to an increased likelihood of referral for CA.

Knowledge Translation

The results of this study have been presented locally and internationally. Research findings were disseminated on a local level via oral presentations at the Resident Research Days in the years 2014 through 2016. Finally, this research was disseminated at the international level at The Obesity Society - Obesity 2015 - Annual Scientific Meeting in Los Angeles, California.

Two manuscripts were prepared and submitted for publication. The first manuscript has been published in the journal *Cardiology Research and Practice*. The second manuscript

arising from this research has been submitted for peer review to the *Journal of the American Medical Association Cardiology*. Planned future translational activities include presentations at the Clinical Epidemiology Seminar Series, Memorial University and to the Cardiac Care Program at Eastern Health.

4.4 Future research

The findings of the current research indicate that obesity and overweight were not associated with worse short-term outcome in patients undergoing CA or PCI. These are invasive procedures with inherent risk associated with each. Determining the accuracy of referral patterns for cardiac catheterization was beyond the scope of the current research but given the findings of less severe disease in the obese and overweight classes of BMI, future clinical investigation focusing on referral patterns may be worthwhile. In addition, prospective evaluation of obesity as a risk factor for adverse events after PCI requires data from multiple cardiac centres in order to provide satisfactory power to detect increased risk for infrequent adverse events among all BMI groups. Finally, it has been suggested that future analyses should correct for survivor selection with probabilistic bias analysis techniques or inverse probability-of-censoring weights. [19]

4.5 Conclusions

In summary, the findings of the current research did not support the existence of either an overweight or obesity paradox. BMI was not associated with increased mortality and severity of CAD in patients referred for suspected CAD or with short-term clinical outcomes following PCI. It is important to emphasize that despite the negative findings associated with the two current studies, obesity is an independent risk factor of advanced

cardiovascular disease and mortality. An overweight or obesity paradox may indeed exist but physicians should be aware that patients with an increased BMI remain at high risk for the development of CAD and poor outcomes over the long-term. [6]

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normal-weight patients. Findings from the NCDR (National Cardiovascular Data Registry). *J Am Coll Cardiol* 2013; 62:692-696.

Appendix A

Letter Request for APPROACH-NL Data and Approval

Eastern Health

July 3, 2014

Ms. Cathy Burke
Regional Director, Cardiac Care Program, Eastern Health
300 Prince Philip Drive
St. John's, NL
Canada A1B 3V6

Dear Ms. Burke:

I am first year internal medicine resident at Eastern Health and a graduate student enrolled in the Faculty of Medicine's Clinical Epidemiology Program at Memorial University. The Health Research Ethics Authority granted ethical approval to conduct a research study to examine the relationship of body mass index with in-hospital outcomes (procedural complications, vascular complications, and mortality) of adult patients >19 years of age undergoing following diagnostic cardiac catheterization and percutaneous coronary intervention. The research will be conducted under the supervision of Dr. Neil Pearce, Director, APPROACH.

The objectives of the proposed observational study are (1) to examine the prevalence of obesity among patients undergoing cardiac catheterization and/or percutaneous coronary intervention from May 1st 2006 to December 31, 2013, (2) to examine short-term in-hospital and out-patient outcomes (procedural complications, vascular complications, and mortality) following these cardiac procedures, and (3) to examine long-term survival.

To achieve the objectives of the research requires the secondary analysis of de-identified cases contained in the APPROACH database. Therefore, I am requesting your permission for the release of a de-identified SPSS electronic file containing the following:

1. Demographic data (e.g., age, sex, current smoker).
2. Historical data at the point in time of the procedure (e.g., hypertension, diabetes, dyslipidemia, peripheral vascular disease, congestive heart failure, prior infarction, renal dysfunction, prior stroke, prior CABG, prior PTCA)
3. Presenting data at the point in time of the procedure (myocardial infarction present (< 7days prior), acute myocardial infarction (< 24 hours prior), cardiogenic shock, cardiac arrest, ventricular tachycardia/fibrillation).
4. Diagnostic data (e.g. ejection fraction, left main stenosis > 70%)
5. Procedural data including type of procedure conducted e.g., (access site (i.e., transfemoral access, transradial access), sheath size, date of procedure, type of bleeding avoidance strategy used post-procedure (i.e., vascular closure device, manual compression).
6. Outcome data including complications reported (vascular complications such as retroperitoneal bleed events, access site bleeding events, pseudoaneurysm, arteriovenous

Eastern
Health

7. fistula, hematoma, occlusion, dissection, loss of distal pulse, and other complications including infection within 48 hours of the procedure).
8. Pre-procedural medication (Aspirin, Clopidogrel, statins, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker, oral nitrate, heparin, low molecular weight heparin, thrombolytic, bivalirudin)
9. Laboratory data (e.g., baseline hemoglobin, post-procedural hemoglobin)
10. In-lab procedural data (e.g., medications, treatments provided, adverse events)
11. Post-procedural medication (Aspirin, Clopidogrel, statins, beta blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker, oral nitrate, heparin, warfarin)

The outcomes to be examined include the following:

Primary outcomes: in-hospital and out-patient outcomes (procedural complications, vascular complications and death) within 48 hours.

Secondary outcomes: (1) change in prevalence of morbidly obese patients from 2006 to 2013, and (2) comparison of long-term survival between moderate and severe obese and normal weight patients using all-cause mortality.

If you require further information about the study, please contact me at 765-7893.

Sincerely

Anne Gregory, MD
PYG1-Internal Medicine
Eastern Health
16 Dick's Square, St. John's, NL
Canada A1B 4A6

Dr. Neil Pearce,
Director, APROACH
Cardiology Consultants
99 Airport Road,St. John's, NL
Canada A1A 4Y3

Appendix B

Health Research Ethics Authority Letter of Approval

Health Research Ethics Authority

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

April 15, 2014

Anne Gregory
16 Dick's Square
St. John's, NL
A1C 4A6

Dear Dr Gregory

Reference #14.074

Re: **What is the relationship of body mass index to in-hospital outcomes (procedural complications, vascular complications, and mortality) of adults ≥ 19 years of age undergoing following diagnostic cardiac catheterization and percutaneous coronary intervention?**

Your application received an expedited review by a Sub-Committee of the Health Research Ethics Board and **full approval** was granted effective **April 15, 2014.**

This approval will lapse on April 15, 2015. **It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HREB office prior to the renewal date; you may not receive a reminder, therefore the ultimate responsibility is with you as the Principle Investigator.** *The information provided in this form must be **current to the time of submission** and submitted to the HREB **not less than 30 nor more than 45 days** of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HREB website http://www.hrea.ca.

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

- Application, approved
- Letter requesting de-identified electronic file, approved
-

The Health Research Ethics Board advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

email: info@hrea.ca Phone: 777-8949 FAX: 777-8776

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

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

It is **your responsibility to seek the necessary approval from the Regional Health Authority or other organization as appropriate. You are also solely responsible for providing a copy of this letter, along with your application form, to the Office of Research Services should your research depend on funding administered through that office.**

Modifications of the protocol/consent are not permitted without prior approval from the Health Research Ethics Board. Implementing changes in the protocol/consent without HREB approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HREB website) and submitted to the HREB for review. This research ethics board (the HREB) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; ICH Guidance E6: Good Clinical Practice* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by *Health Canada Food and Drug Regulations Division 5; Part C*
Notwithstanding the approval of the HREB, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

Dr Fern Brunger, PhD (Chair Non-Clinical Trials)
Ms. P. Grainger, (Vice-Chair Non-Clinical Trials)
Health Research Ethics Board

For Office Use only: April 17, 2014

email: info@hrea.ca Phone: 777-8949 FAX: 777-8776

Health Research Ethics Board
777 6974 (Phone)
777-8776 (Fax)

Version June 2013

RECEIVED JUL 1 1 2014

Request for Amendment to an Approved Application

HREB #: 14.074	Current Date: July 3, 2014

Title of study: Include protocol number, if any.

What is the relationship of body mass index to in-hospital outcomes (procedural complications, vascular complications, and mortality) of adult patients ≥ 19 years of age undergoing following diagnostic cardiac catheterization and percutaneous coronary intervention?	
Amendment Date: June 23, 2014	**Version # (If applicable):#1**

Are these changes editorial and/or administrative?	Yes x	No
Will there be any increase in risk, discomfort or inconvenience to the participants?	Yes (Specify below)	No x
Are there changes to inclusion or exclusion criteria?	Yes (Specify below) x	No
Is a modification to the consent form required?	Yes (Append form)	No x

Summarize the significant changes being requested. It is not necessary to itemize editorial, administrative and similar changes.

We are currently conducting a secondary analysis of de-identified data on all consented patients from May 2006 to December 31, 2010. The database consists of all consenting patients from May 2006 to December 31, 2010. However to capture the incidence and prevalence of severe obesity in patients undergoing diagnostic cardiac catheterization in NL we require additional years of data on all consented patients between 19 years of age and older who had diagnostic cardiac catheterization and/or percutaneous coronary intervention between January 1st, 2011 to December 31, 2013 at the Health Sciences Centre, Eastern Health.

What is the rationale for the amendment(s)?

Since the prevalence of obesity, particularly the higher classes of obesity, continues to rise in Canada, in general, and more specifically in Newfoundland and Labrador [1], the likelihood of at-risk obese patients requiring invasive cardiac procedures will increase over time. The data we currently have in a de-identified database captures the years 2006 to 2010, however to capture comprehensive up to date information on patients presenting for cardiac procedures we require additional years (2011 to 2013).

Other pertinent information – List ALL documents, including version dates, to be reviewed:

Anne Gregory — Printed Name of Principal Investigator

Signature of Principal Investigator

July 4/14 — Date

HREB #:	Amendment Date:	Version:

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

This Health Research Ethics Board (the HREB) has reviewed the amendment as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to Tri-Council Policy Statement (TCPS2) and applicable laws and regulations. The membership of this research ethics board complies with the membership requirements for research ethics boards defined in TCPS2.

Full Board Review and Approval granted at _____ *Meeting*

_____ _____
Signature Chair (Dr. Fern Brunger) *Date*

_____ _____
Signature Vice-Chair (Patricia Grainger) *Date*

OR

Reported to Full Committee at July 24, 2014 *Meeting*
Approved by:

_____ _____
Signature Chair (Dr. Fern Brunger) *Date*

Patricia Grainger APPROVED JUL 11 2014
Signature Vice-Chair (Patricia Grainger) *Date*

*Attach additional documentation if necessary

HREB #:	Amendment Date:	Version:

RECEIVED AUG 2 4 2015

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

Version January 2018

Request for Amendment to an Approved Application

HREB #: #14.074	Current Date: August 10, 2015

Title of study: Include protocol number, if any.

What is the relationship of body mass index to in-hospital outcomes (procedural complications, vascular complications, and mortality) of adult patients ≥ 19 years of age undergoing diagnostic cardiac catheterization and percutaneous coronary intervention?

Amendment Date: August 10, 2015	Version # (if applicable): #3

Are these changes editorial and/or administrative?	Yes x	No
Will there be any increase in risk, discomfort or inconvenience to the participants?	Yes (Specify below)	No x
Are there changes to inclusion or exclusion criteria?	Yes (Specify below)	No x
Are participants enrolled in the study?	Yes	No x
Is a modification to the consent form required?	Yes (Attach revised ICF)	No x
Is a consent addendum required? (*If participants are enrolled in the study and the proposed changes affect them, a consent addendum must be submitted*)	Yes (Attach consent addendum)	No x

Summarize the significant changes being requested. It is not necessary to itemize editorial, administrative and similar changes.

We are requesting an additional variable be extracted from the APPROACH database. The variable is the Duke Myocardial Jeopardy Score for each patient. The score is a prognostic tool predictive of 1-year mortality in coronary artery disease patients which is assigned to angiographic data.

What is the rationale for the amendment(s)?

To examine the severity of coronary artery disease in patients with obesity undergoing diagnostic cardiac catheterization and/or percutaneous coronary intervention and 1-year predictive mortality after these cardiac procedures.

Other pertinent information – List ALL documents, including version dates, to be reviewed:

Printed Name of Principal Investigator | Signature of Principal Investigator | Date: AUG 10/15

HREB #:	Amendment Date:	Version:

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

This Health Research Ethics Board (the HREB) has reviewed the amendment as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to Tri-Council Policy Statement (TCPS2) and applicable laws and regulations. The membership of this research ethics board complies with the membership requirements for research ethics boards defined in TCPS2.

***Full Board** Review and Approval granted at* _____ *Meeting*

_____ _____
Signature Chair (Dr. Fern Brunger) *Date*

_____ _____
Signature Vice-Chair (Patricia Grainger) *Date*

OR

***Reported** to Full Committee at* Sept 3, 2015 *Meeting*

Approved by:

_____ _____
Signature Chair (Dr. Fern Brunger) *Date*

Patricia Grainger _____
Signature Vice-Chair (Patricia Grainger) *Date* APPROVED AUG 2 / 2015

*Attach additional documentation if necessary

HREB #:	Amendment Date:	Version:

Appendix C

Research Proposals Approval Committee – Eastern Health

Eastern Health

Department of Research
5TH Floor, Janeway Hostel
Health Sciences Centre
300 Prince Philip Drive
St. John's, NL A1B 3V6
Tel: (709) 752-4636 Fax (709) 752-3391

August 14, 2014

Dr. Anne Gregory
16 Dick's Square
St. John's, NL
A1C 4A6

Dear Dr. Gregory:

Your research proposal *HREA Reference #14.074 "What is the Relationship of Body Mass Index to In-hospital Outcomes (procedurka complications, vascular complications, and mortality) of Adults ≥ 19 Years of Age Undergoing Diagnostic Cardiac Catherization and/or Percutaneous Coronary Intervention?"* was reviewed by the Research Proposals Approval Committee (RPAC) of Eastern Health at a meeting dated August 12th, 2014 and we are pleased to inform you that the proposal has been approved.

The approval of this project is subject to the following conditions:

- The project is conducted as outlined in the HREA approved protocol;
- Adequate funding is secured to support the project;
- In the case of Health Records, efforts will be made to accommodate requests based upon available resources. If you require access to records that cannot be accommodated, then additional fees may be levied to cover the cost;
- A progress report being provided upon request.

If you have any questions or comments, please contact Sharon Newman, Manager of the Patient Research Centre, at 777-7283 or by E-mail at sharon.newman@easternhealth.ca.

Sincerely,

Mike Doyle, PhD
Director of Research
Chair, RPAC