Optimizing the Pre-Operative Risk Profile of Older Adults Undergoing Elective Cardiac Surgery: A Randomized Controlled Trial

by

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Abstract

This study determined whether pre-operative exercise and education (PREHAB) improves the frailty status and physical activity behaviour of older adults undergoing elective cardiac surgery, more than standard care (StanC). Using a subset of patients from a multi-centre trial (NCT02219815), twenty-six patients over the age of sixty were randomized to receive StanC (n=12) or PREHAB (n=14). Blinded research assistants collected data at baseline prior to randomization and one week pre-operatively. Changes in frailty were assessed using a 30-item functional frailty index (FFI); whereas, changes in physical activity behaviour were assessed using accelerometers. Baseline data was not different between groups. Frailty status improved by 17%, 5% and 35% amongst StanC, PREHAB "non-completers" and PREHAB "completers", respectively. No changes in moderate to vigorous physical activity were found pre-operatively. These data suggest that the PREHAB intervention is feasible to implement and may result in improved frailty status amongst frail older adults awaiting elective cardiac surgery.

Dedication

I would like to dedicate this work to the individuals that have supported me throughout my life, specifically my mother and father. This thesis is a culmination of hard work, dedication, sacrifice and is a testament to the work ethic that my parents instilled in me from a young age. To my mother, I am truly grateful for all of the sacrifices that you have made to support my academic and career aspirations. To my father, I know that you would be proud of what I have achieved today and my memories of you continue to inspire me to achieve greater levels of success. I am grateful for the sacrifices that my parents have made to afford me the unique training opportunity that graduate school presents and aspire to continuously strive for excellence to honour this commitment.

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Abbreviations

ACE – Angiotensin Converting Enzyme

ADL – Activities of Daily Living

ARB – Angiotensin Receptor Blocker

AUC – Area Under the Curve

BMI – Body Mass Index

BP – Blood Pressure

CABG – Coronary Artery Bypass Graft Surgery

CACPR – Canadian Association of Cardiovascular Prevention and Rehabilitation

CAD – Coronary Artery Disease

CCB – Calcium Channel Blocker

CCS – Canadian Cardiovascular Society

CFS – Clinical Frailty Scale

CHF – Congestive Heart Failure

CI – Confidence Interval

CKD – Chronic Kidney Disease

COPD – Chronic Obstructive Pulmonary Disease

CPAG – Canadian Physical Activity Guidelines

CR – Cardiac Rehabilitation

CVD – Cerebrovascular Disease

EuroSCORE – European System for Cardiac Risk of Mortality

EXERT – Exercise Rehabilitation Trial

FFI – Functional Frailty Index

FIT – Frailty Intervention Trial

HF-ACTION – Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training

HR – Hazard Ratio

HRQoL – Health-Related Quality of Life

ICU – Intensive Care Unit

LIFE-P – Lifestyle Interventions and Independence for Elders Pilot

LOS – Length of Stay

METs – Metabolic Equivalents

MI – Myocardial Infarction

MVPA – Moderate to Vigorous Intensity Physical Activity

OR – Odds Ratio

PASE – Physical Activity Scale for the Elderly

PREHAB – Pre-Operative Rehabilitation for Reduction of Hospitalization After Coronary Artery Bypass and Valvular Surgery

PVD – Peripheral Vascular DiseaseRR – Risk Ratio

SD – Standard Deviation

SPPB – Short Physical Performance Battery

StanC – Standard of Care

STS-PROM – Society of Thoracic Surgeons Predicted Risk of Mortality

VO_{2max} – Maximal Oxygen Consumption

VO_{2peak} – Peak Oxygen Consumption

WBC – White Blood Cell

WRHA – Winnipeg Regional Health Authority

6MWT – 6-Minute Walk Test

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Chapter 1: Introduction

Cardiovascular disease is the number one cause of mortality worldwide, accounting for up to 30% of deaths globally and nearly 17% of total hospitalizations in Canada.[1,2] Collectively, the term cardiovascular disease comprises a group of disorders originating in the heart and blood vessels, which includes coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral vascular disease (PVD), among others. The economic impact of cardiovascular disease in Canada is estimated to be in excess of $20.9 billion annually.[2] This statistic is troubling, as it is estimated that up to 80% of cardiovascular disease can be prevented by modifiable risk factors, including physical activity, tobacco usage and dietary choices.[1]

Treatment strategies for patients with cardiovascular disease typically include lifestyle modification and a variety of pharmacological interventions, which, when combined have demonstrated increased efficacy beyond monotherapy alone.[3] However, in patients with severe cardiovascular disease, surgical intervention is often necessary. Among the most common cardiac surgical procedures are coronary artery bypass graft (CABG) surgery and valve repair/replacement, as well as less invasive, non-surgical interventions such as percutaneous coronary intervention and transcatheter procedures. Cardiac surgery has been demonstrated to reduce long-term morbidity and mortality when compared to medical therapy alone, particularly in high-risk patients with cardiovascular disease.[4] A meta-analyses combining observational study data from 205,717 patients undergoing isolated CABG surgery reported in-hospital mortality to be 1.7% and the incidence of non-fatal myocardial infarction (MI) to be 2.4%,[5] while long-term survival following CABG is reported to be 89% and 80% at 5- and 8-years post-operatively, respectively.[6] However, due to an aging demographic and advances in surgical procedures, older patients with multiple comorbidities, previously believed to be unsuitable for a

surgical intervention, are now frequently being referred for cardiac surgery. For example, the proportion of patients aged 75 years of age and older undergoing cardiac procedures increased from 16% in 1990 up to 25% in recent estimates made in 2012.[7] These patients have the potential for higher rates of perioperative complication and often experience prolonged recovery periods.[8] While chronological age has been demonstrated to be associated with poor outcomes after surgery,[9–11] emerging evidence has identified several non-traditional, modifiable risk factors, including frailty,[12] physical activity behaviour[13–21] and aerobic capacity[22,23] as equally important prognostic indicators of surgical success.

Despite the Canadian Physical Activity Guidelines (CPAG)[24] and the Canadian Cardiovascular Society (CCS) Heart Failure Management Guidelines[25] recommending moderate to vigorous intensity physical activity (MVPA) to improve cardiovascular health, it has been documented that cardiac patients accumulate insufficient physical activity prior to their surgical procedure.[15,18,20,26,27] Based on the structure of the modern health care system resulting in "wait lists" prior to elective surgery and the data indicating that cardiac patients are often inactive, there is a strong rationale to investigate strategies for pre-operative risk factor optimization, particularly in an already deconditioned cohort of frail, older adults. Furthermore, since the phenotype of frailty is characterized by reductions in muscle mass, strength and physical activity levels, cardiac rehabilitation (CR) may be a suitable intervention to counteract these impairments and optimize risk pre-operatively.[28] Traditional CR is an interdisciplinary program prescribed to post-operative cardiac surgery patients that has been demonstrated to be safe in older adults[13,29–31] and result in robust reductions in mortality and major morbidity.[32–36] However, few studies have investigated the utility of implementing CR programming during the pre-operative period as an optimization strategy prior to surgery. The following literature review will introduce the

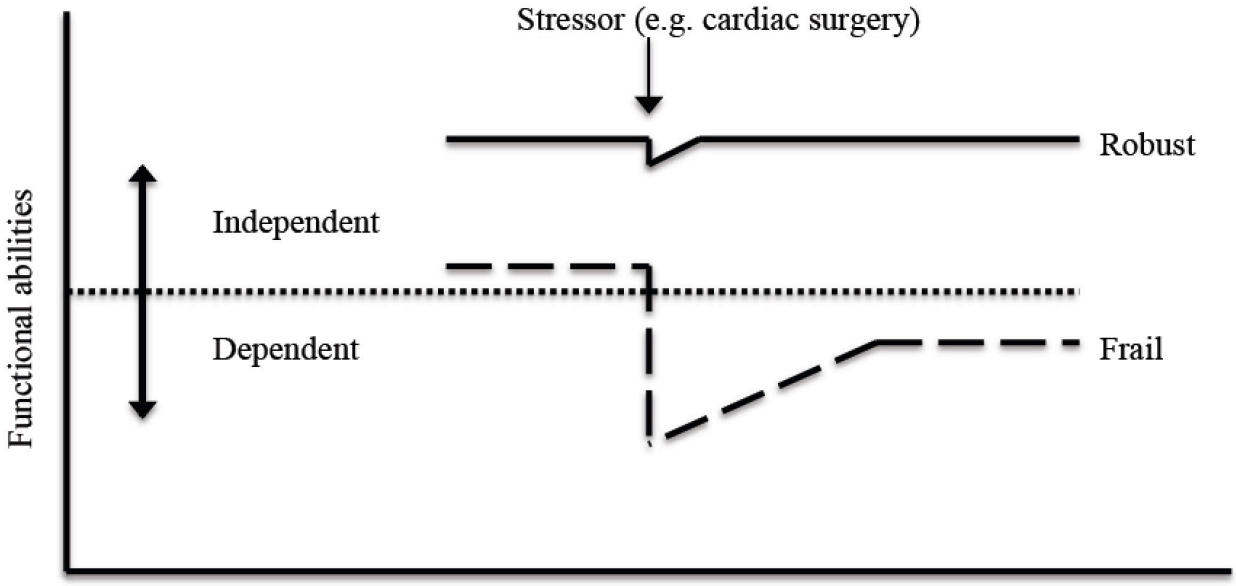
concept of frailty in the context of the modern surgical patient and evaluate the importance of physical activity in patients with established or unrepaired cardiovascular disease. This literature review will also highlight the efficacy of CR and provide a rationale for implementing a "pre-habilitation" program prior to elective cardiac surgery to optimize pre-operative risk factors in a frail cohort of older adults.

Chapter 2: Review of Literature

Defining the Concept of Frailty

Frailty is a syndrome characterized by decreased physiologic reserve and is defined by an increased vulnerability to stressors (Figure 1).[28,37] The term is often used to describe a vulnerable subset of the population that is at a high risk for adverse health outcomes, including falls, admission to long-term care facilities and mortality.[37] While frailty is not necessarily synonymous with age, it is more prevalent among older adults and is also more common in women and in patients with cardiovascular disease.[28]

Figure 1. Diagrammatic Representation of Frailty



The top line represents a robust individual that, following a stressor (e.g. cardiac surgery, infection) has a minor deterioration in functional status and then returns to baseline levels quickly thereafter. The bottom line represents a frail individual that experiences a disproportionate deterioration in functional status following a stressor event and subsequently does not regain baseline functioning.

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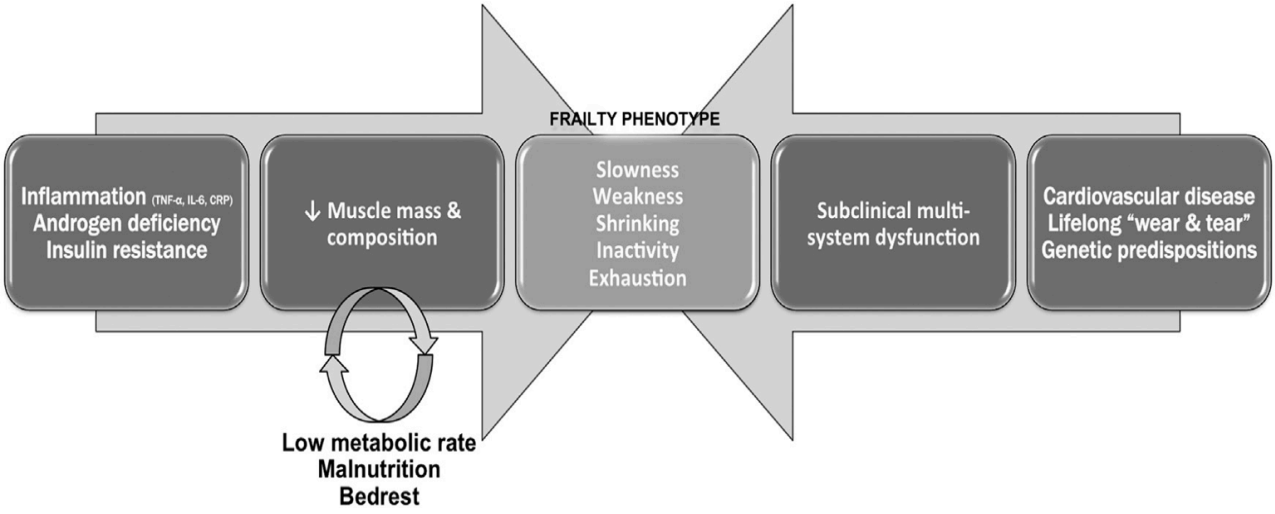
The precise physiological underpinnings leading to the progression of frailty have yet to be fully elucidated. It is generally accepted, however, that the frailty syndrome results from several sub-threshold decrements to interrelated physiological systems, including the development of cardiovascular disease, sarcopenia and insulin resistance (Figure 2). Under normal circumstances, redundancies exist in organ systems to compensate for age-related declines and perturbations to homeostasis that commonly occur with disease and other physiological stressors.[38] For example, more neurons in the brain and excess myocytes in skeletal muscle are present than are adequately required for survival.[39] However, the accumulation of widespread cellular damage in frail individuals results in a loss of redundancy and an inability to overcome small disturbances in health status that may occur with disease or an acute stressor such as cardiac surgery.

Data collected from epidemiologic studies support the notion that frailty involves dysregulation across interrelated physiological systems. In the Women's Health and Aging Studies I and II, several systemic abnormalities were investigated, including inflammation, hormonal dysregulation, adiposity, neuromuscular and micronutrients.[40] Interestingly, study authors reported that the mean number of impaired systems nonlinearly predicted frailty status; one to two systems (OR: 4.8 95% CI 1.1-21.1), three to four systems (OR: 11.0 95% CI 2.5-47.9) and five ore more systems (OR: 26.0 95% CI 3.7-183.3). Additionally, the mean number of impaired systems increased progressively in non-frail (1.3 impaired systems 95% CI 1.1-1.4), pre-frail (1.8 impaired systems 95% CI 1.7-1.9) and frail (2.7 impaired systems 95% CI 2.4-3.0) individuals. The most frequent combination of disease states in frail patients include cardiovascular disease, chronic kidney disease (CKD), pulmonary disease, anemia and depressive symptoms.[41] Collectively, this data suggests that the number of systems, not the

individual system itself, is predictive of frailty status and this results in an impaired ability to respond appropriately to homeostatic perturbations. One proposed physiological mechanism leading to dysregulation of interrelated physiologic systems involves chronic inflammation.[42] In fact, compared to middle quartiles, individuals in the lowest quartile of basal Interleukin 6 (OR: 0.48 95% CI 0.31-0.74) and tumor necrosis factor alpha (OR: 0.59 95% CI 0.38-0.90) were less likely to be classified as frail.[42] Additionally, high levels of C-reactive protein have been associated with an increased risk of frailty (OR: 1.82 95% CI 1.19-2.80) in cross-sectional studies of community-dwelling older adults, as have increased levels of the glycoproteins transferrin and fibrinogen.[43] Although the precise physiologic milieu leading to the progression of frailty has yet to be discovered, it appears that chronic inflammation may contribute to the general dysfunction associated with the frailty syndrome.

Figure 2. Pathophysiology of the Frailty Syndrome



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Recent literature has also examined the intricate relationship between frailty and impaired cognitive function, defining the term "cognitive frailty" as being the simultaneous occurrence of physical frailty and impaired cognition, in the absence of diagnosed dementia.[44,45] Interestingly, results from the longitudinal Gait and Brain Study indicate that frail individuals over the age 65 are more likely to experience cognitive decline when compared to non-frail peers (77% vs. 54%, p=0.02).[46] Additionally, results from this observational study identified a unique manifestation of cognitive-frailty, such that individuals with slow gait speed and cognitive impairment had the highest risk for progression to dementia over a 5-year follow-up (HR: 35.9 95% CI 4.0-319.2). Several cross-sectional studies have also demonstrated elevated rates of cognitive impairment amongst frail individuals, where up to 22% of community-dwelling frail individuals meet the criteria for cognitive impairment, compared to just 12% and 10% in the pre-frail and non-frail groups, respectively ($p<0.001$).[47] A recent narrative review suggested a causal mechanistic link between cognitive impairment and frailty, such that chronic inflammation, androgen imbalances, cardiovascular disease and the presence of neurofibrillary tangles and plaques may underlie the development of the cognitive-frailty syndrome.[48] Even so, authors of this review acknowledge the lack of quality experimental evidence examining the possible pathophysiologic pathways leading to the progression of frailty.

Measuring Frailty

Currently, there does not exist a universally accepted definition of frailty, which is likely a result of the substantial overlap that exists between the interrelated concepts of disability, comorbidity and sarcopenia. For example, comorbidity is defined by the presence of two or more diagnosed diseases in an individual, which coincides with many of the characteristics of frailty.[37] In fact, in 2576 community dwelling adults from the Cardiovascular Health Study over the age of

65 with 2 or more diagnosed diseases, 249 (9.6%) were also considered frail.[37] Moreover, the phenotype of frailty is characterized by reductions in muscle mass, strength, endurance and activity level,[28] which encompasses the progressive loss of skeletal muscle mass in patients with sarcopenia.[28,49] Thus, frailty and sarcopenia are not mutually exclusive, which makes it challenging to distinguish the frailty syndrome from several interrelated concepts in the literature. There are two dominant methods of assessing frailty in the literature: (1) the phenotype model proposed by Fried and colleagues;[28] and, (2) the accumulation of deficits model originally proposed by Rockwood and colleagues.[50] The following sections will review the phenotype model and the accumulation of deficits model, in addition to introducing two emerging tools; the Clinical Frailty Scale (CFS; originally based on the frailty index model)[51] and the Short Physical Performance Battery (SPPB).[52,53] These tools are becoming increasingly relevant frailty assessments due to their ease of implementation in a clinical setting.

The Phenotype Model

In a seminal study, Fried and colleagues prospectively examined data from 5317 community-dwelling men and women enrolled in the Cardiovascular Health Study.[28] Demographically, participants were 65 years of age and older, and frailty was defined by the presence of three or more of the following characteristics: 1) unintentional weight loss (i.e. 10 lbs in past year); 2) exhaustion (i.e. self-report); 3) weakness (i.e. grip strength in lowest 20% for gender and body mass index); 4) slow walking speed (i.e. slowest 20% on time to walk 15 feet); and 5) low physical activity (i.e. lowest quintile of kilocalories expended per week). Notably, the prevalence of frailty was up to two-fold higher in women compared to men and prevalence increased progressively with each 5-year age category. Participants who were defined as frail also had higher rates of comorbidities, including cardiovascular disease, pulmonary disease and diabetes.

Furthermore, intermediate frailty (i.e. pre-frail patients), defined as possessing one or two frailty characteristics, conferred an increased risk of becoming frail over a 4-year follow up period (OR: 2.63 95% CI 1.94-3.56), compared to those individuals classified as robust at study entry. Patients who were frail also reported difficultly in mobility tasks (71.7% in frail vs. 16.0% in non-frail) and instrumental activities of daily living (59.7% in frail vs. 13.5% in non-frail). Collectively, this data suggests that disability is an outcome of frailty, while the presence of comorbidities such as cardiovascular disease confers an increased risk of developing frailty. The phenotype model provides a standardized definition of frailty amongst community-dwelling older adults with established predictive validity (see *Frailty Confers an Increased Risk of Mortality* below*)*. Major limitations of the phenotype definition of frailty include the feasibility of implementation in a clinical setting and the exclusion of certain characteristics that may contribute to frailty, such as cognitive dysfunction or mental health disorders. Furthermore, the phenotype definition of frailty may experience a ceiling effect in severely frail patients presenting with all five characteristics.

The Accumulation of Deficits Model

The accumulation of deficits model, originally proposed by Rockwood and colleagues, provides a quantitative measure of frailty and can be used to stratify a heterogeneous population of older adults on a continuous scale.[50] To develop the original 92-item frailty index, Mitnitski et al. obtained prospective data from 10,263 men and women over the age of 65 enrolled in the Canadian Study of Health and Aging. Study authors developed an index of frailty by dividing the number of deficits present by the total number of deficits in the index. Thus, an individual with few deficits was classified as robust; whereas, an individual with many deficits was classified as frail. Notably, the cut-point of 0.25 has been used previously in the literature to classify an

individual as frail,[54] while an index of 0.67 is generally the highest frailty index observed in any setting and indicates imminent risk of death.[55] The frailty index model has been proposed as a broad indicator of aging and can be adapted to include many different variables, provided that the variables are deficits associated with health status, generally increase in prevalence with age and the index must contain a minimum of 30 total deficits.[56] This makes the accumulation of deficits model attractive for implementation in research and clinical settings, as the variables that comprise an index can be modified to include measures collected as part of routine clinical care. In fact, Rockwood and colleagues reported that 1000 iterations of the frailty index using a random sample of 50-75% of 91 total variables (i.e. both self-report and clinical measures) collected as part of the Canadian Study of Health and Aging showed little overlap between frailty quartiles in both men and women.[57] This suggests that the frailty index is a robust and replicable strategy for assessing frailty and that the individual variables included within an index can be flexibly adapted to include a range of clinical and self-report characteristics.

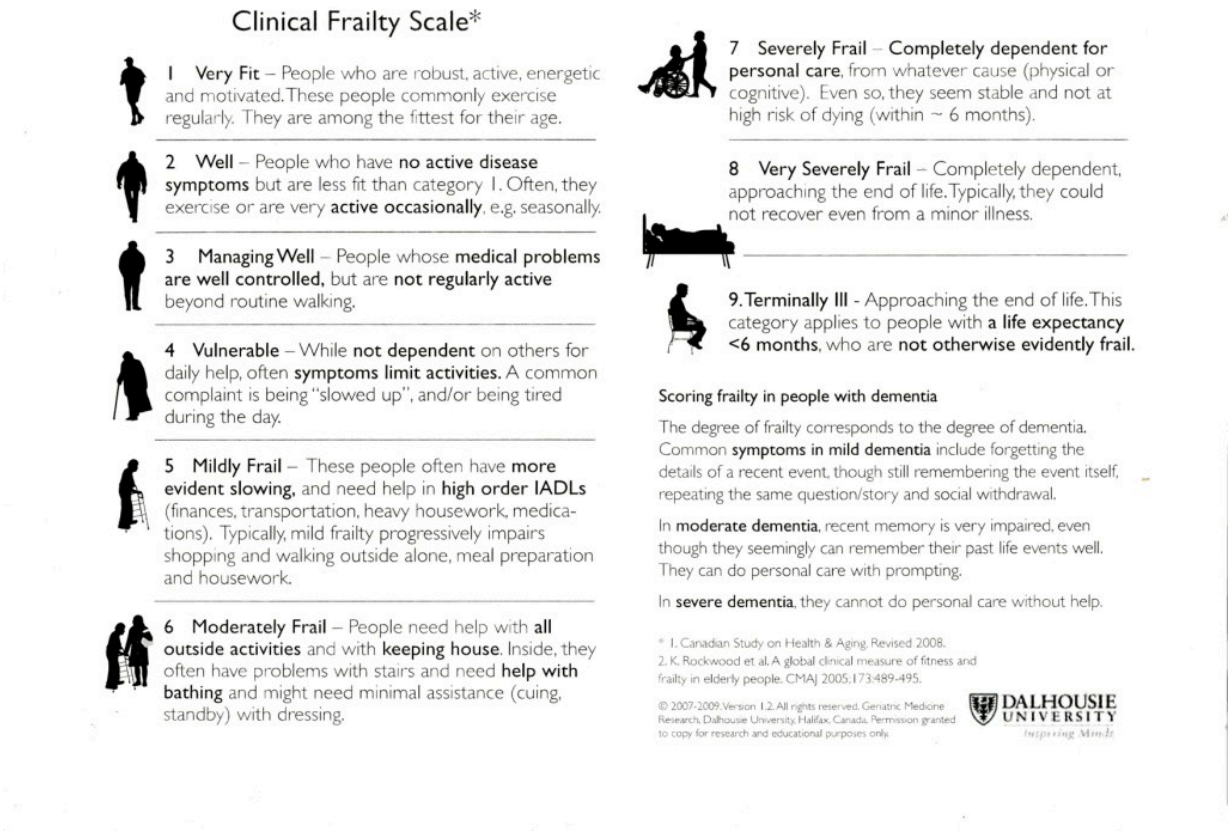
The phenotype model and the accumulation of deficits model demonstrate a moderately strong correlation (r=0.65), with frailty index scores, increasing progressively in robust individuals with no phenotype characteristics (Average Frailty Index=0.12), pre-frail individuals with one or two characteristics (Average Frailty Index=0.30) and frail individuals with three or more characteristic (Average Frailty Index=0.44).[54] Both measures demonstrate exponential increases with age, increased prevalence in women and associations with poor self-reported health status.[58] The primary advantage of the accumulation of deficits model is that the index covers a range of characteristics related to aging and physiological decline and as such, may be more accurate in predicting adverse health outcomes when compared to other models of frailty. In fact, data from the Cardiovascular Health Study revealed that in frail individuals, the phenotype model

underestimated the risk of death by 67%; whereas, the accumulation of deficits model underestimated the risk of death in just 12% of participants.[59] Even so, the accumulation of deficits model is burdensome to implement in a clinical setting due to the number of variables that must be collected and may be less effective in identifying individuals with activities of daily living (ADL) limitations. A cross-sectional analysis of 4096 adults over the age of 50 enrolled in the National Health and Nutrition Examination Survey identified that 97.8% of individuals classified as frail by the phenotype model and 56.6% of frail individuals according to the index also had an ADL disability.[58] Thus, there are practical limitations to both of the frailty models described above and to feasibly implement frailty screening in routine clinical practice, new tools must be developed.

The Clinical Frailty Scale (CFS)

The 7-point CFS was originally developed by Rockwood and colleagues in 2305 patients enrolled in the Canadian Study of Health and Aging II as a predictive tool to evaluate frailty in a clinical setting.[51] Physicians subjectively assign patients a score ranging from 1 (i.e. Very Fit) to 7 (i.e. Severely Frail), with each incremental increase in CFS score being associated with an increased 70-month mortality (~0.8 for a score of 1-3, ~0.6 for a score of 4, ~0.45 for a score of 5 and ~0.4 for a score of 6-7). The CFS is highly correlated with the frailty index (R=0.80) and also incrementally predicts admission to institutional care. Thus, the CFS presents a promising screening tool that can be feasibly implemented in a clinical setting and may be predictive of long-term adverse health outcomes. Recent modifications to the CFS have added two additional categories of frailty (i.e. very severely frail and terminally ill) to the original 7-point scale to accommodate for the ceiling effect often observed in severely frail patients (9-point scale shown in Figure 3).

Figure 3. Clinical Frailty Scale



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging. Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Inspiring Minds

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The Short Physical Performance Battery (SPPB)

The SPPB includes a series of physical performance tests that assess lower extremity function and disability, not frailty specifically.[52] However, the SPPB has been increasingly used as a practical indicator of frailty in the literature.[60,61] The test itself includes three physical performance measures: 1) balance test (side-by-side, semi-tandem and tandem stances); 2) time to walk 8 feet; and 3) time to rise from a chair and return to a seated position 5 times. Each measure is scored out of 4, with 0 indicating an inability to complete the task and 4 indicating completion within the allotted time, for a cumulative total of 12 points. Notably, the SPPB is moderately correlated (r=0.33) with the Fried criteria, while a cut-off score of 9 on the SPPB demonstrated good sensitivity (92%) and specificity (80%) in identifying frailty in a cohort of 60 Canadians aged 65 to 74 (AUC=0.81).[61] Major limitations of the SPPB include the ceiling effect that occurs in robust individuals and an emphasis on lower body functional ability to the exclusion of cognitive function, upper body function and several other aspects of physiological decline that contribute to the development of the frailty syndrome.

Prevalence, Risk Factors and the Health Impacts of Frailty

Patients who are classified as frail are at an increased risk of adverse health outcomes, including mortality, major morbidity, falls and institutionalization. The following section will outline the prevalence and health impacts of frailty in addition to investigating the association between cardiovascular disease and frailty.

Prevalence of Frailty

The prevalence of frailty varies based upon the definition and the specific population that is investigated. For example, in a cross-sectional analysis of 18,227 community-dwelling adults over the age of 50 enrolled in the Cardiovascular Health Study, 4.1% were classified as frail

according to the phenotype criteria and 37.4% were classified as pre-frail (i.e. 1 or 2 criteria).[62] This prospective study of older adults also revealed that women (5.2%) were more frequently frail than men (2.9%), and in the 7510 individuals over the age of 65, 17% were classified as being frail. Thus, the prevalence of frailty appears to increase with age and is more commonly diagnosed in women.[63,64] Shamliyan and colleagues recently conducted a systematic review compiling 24 population-based studies examining frailty in community-dwelling adults over the age of 65 and reported the pooled prevalence of frailty to be 14% according to the phenotype criteria,[63] which is consistent with other reports.[64] Interestingly, when the accumulation of deficits model was used, the prevalence of frailty in the pooled population increased to 24%. Prevalence of frailty also increased with age (age 65-70, 3%-6% phenotype, 5%-15% accumulation of deficits; age 70-80, 5%-12% phenotype, 8%-17% accumulation of deficits) with individuals over the age of 85 having the highest prevalence of frailty (26% phenotype, 50%-56% accumulation of deficits). These data demonstrate that the prevalence of frailty increases with age, while the accumulation of deficits model appears to estimate the prevalence of frailty to be slightly higher than the phenotype model. This discrepancy is likely a result of the breadth of variables collected by the accumulation of deficits model compared to the five specific markers evaluated by the phenotype criteria.

Frailty Confers an Increased Risk for Mortality

Literature suggests that patients who are classified as frail are at an increased risk of mortality and major morbidity compared to non-frail peers. In Shamliyan et al.'s systematic review compiling data from 92,813 community-dwelling older adults, compared to non-frail peers, frailty as defined by the phenotype model increased mortality by 50%; whereas, frailty defined by the accumulation of deficits increased mortality by 15%.[63] Evidence from the Population

Health Survey of Canada also suggests that increases in frailty, defined by the accumulation of deficits model incrementally predicts mortality, suggesting a dose-response relationship. For example, individuals over the age of 65 with a frailty index of 0.25 or greater have a 10-year survival probability of 27%, compared to 70% in individuals with a frailty index less than 0.08.[65] The association between frailty and impaired survival remains significant in both men and women and the association is strongest over a 4-year follow-up period.[63]

Cardiovascular Disease as a Risk Factor for Frailty

In the context of cardiovascular disease, frailty is more prevalent in patients with established heart disease. For example, in 223 patients (mean age 71) with heart failure, 21% were classified as frail according to the phenotype criteria and 48% were considered pre-frail,[66] which is higher than prevalence estimates in the general population of older adults.[63] In 4735 community-dwelling older adults enrolled in the Cardiovascular Health Study, cardiovascular disease was associated with an approximately 3-fold increase in the prevalence of frailty (OR: 2.79 95% CI 2.12 to 3.67).[67] However, both of these studies failed to investigate the temporal sequence of frailty and cardiovascular disease. More simply stated, it is not well understood whether frailty precedes the development of cardiovascular disease, or the reverse, if cardiovascular disease leads to the progression of the frailty syndrome. The Women's Health Initiative Observational Study was the first to suggest that cardiovascular disease preceded the development of frailty.[68] In fact, in 28,181 women between the ages of 65 and 79 who were not classified as frail at baseline, CAD (OR: 1.47 95% CI 1.25-1.73), stroke (OR: 1.71 95% CI 1.24-2.36) and hypertension (OR: 1.18 95% CI 1.08-1.29) were predictive of frailty over a 3-year follow-up period. Thus, it appears that cardiovascular disease may be a pre-cursor to the development of frailty in older adults. A recent systematic review conducted by Afilalo and colleagues

established the association between frailty and cardiovascular disease by compiling 9 studies and data from 54,250 participants.[69] Study authors reported that cardiovascular disease was associated with an increased risk of prevalent (i.e. total number of frail patients; OR: 2.7-4.1) and incident frailty (i.e. number of newly diagnosed frail patients; OR: 1.5). Results from the Cardiovascular Health Study also support the role of cardiovascular disease as a pre-cursor to the development of frailty.[67] In this study, participants with cardiovascular disease were 2.8-fold more likely to be classified as frail compared to those without cardiovascular disease, with congestive heart failure (CHF) being the strongest predictor of frailty status (OR 7.51 95% CI 4.66-12.12). Furthermore, after adjusting for age, gender and race, individuals with systolic blood pressure (BP) ≥125 mmHg (OR: 1.15 95% CI 1.05-1.26), ankle-arm index <0.8 (OR: 3.56 95% CI 2.03-6.24), major electrocardiography abnormalities (OR: 1.58 95% CI 1.10-2.26) and left ventricular mass ≥ 140 grams (OR: 1.16 95% CI 1.03-1.31) were more likely to be frail. Thus, subclinical cardiovascular disease is predictive of frailty status, presenting an opportunity for early intervention strategies in this population.

Pre-Frailty as a Risk Factor for Cardiovascular Disease

Recent evidence from the Progetto Vento Anziani population-based prospective cohort study conducted in two separate geographic regions of Italy suggests that frailty is also a risk factor for the subsequent development of cardiovascular disease.[70] In this study, a sample of 1,567 study participants aged 65 years and older without frailty (i.e. robust or pre-frail) at baseline were followed longitudinally for a period of 4.4 years. Study authors reported that pre-frailty (i.e. defined as having one or two characteristics of the Fried phenotype criteria), was significantly associated with the subsequent development of cardiovascular disease. Individuals expressing one frailty characteristic (HR: 1.25 95% CI 1.05-1.64) and two frailty characteristics (HR: 1.79

95% CI 1.27-2.52) were more likely to experience hospitalization for MI, CVD or heart failure compared to individuals expressing no frailty characteristics. This study is in contrast to previous literature presented in this review suggesting that subclinical cardiovascular disease is a pre-cursor to the development of the frailty syndrome.[67,68] Taken together, the literature likely suggests that a bi-directional relationship exists between frailty and cardiovascular disease, such that both syndromes exacerbate simultaneously or have synergistic effects within vulnerable individuals.

Frailty is a Risk Factor for Adverse Outcomes Following Cardiac Surgery

Markers of decreased physiologic reserve have also been investigated as risk indicators in patients undergoing cardiac procedures, where up to 54.1% of patients can be classified as frail.[69,71] The first study to demonstrate an association between frailty and adverse post-operative outcomes was conducted by Lee and colleagues, which retrospectively evaluated frailty in 3826 patients undergoing cardiac surgery.[72] Study authors reported that frail patients had a 1.5-fold greater risk of all-cause mortality, and frailty status (i.e. defined as an impairment in ADL, ambulation or documented history of dementia) was an independent predictor of in-hospital mortality (OR: 1.8 95% CI 1.1-3.0) and institutional discharge post-operatively (OR: 6.3 95% CI 4.2-9.4). While many studies have used composite definitions of frailty, Afilalo and colleagues demonstrated the singular measure of gait speed as an independent predictor of major morbidity and mortality (OR: 3.05 95% CI 1.23-7.54) and discharge to a health care facility (OR: 3.19 95% CI 1.40-8.41) following coronary artery bypass graft (CABG) or valve replacement surgery in patients over the age of 70.[73] This study is highly pragmatic in that the single measure of gait speed could be routinely implemented in clinical practice with limited burden on health care resources. Frailty status has also been associated with longer post-surgical hospital length of stay

(LOS; 9 ± 6 days in frail vs. 6 ± 5 days in non-frail) and is independently associated with 1-year mortality (HR: 3.5 95% CI 1.4-8.5) following transcatheter aortic valve replacement (TAVR) surgery.[74] While risk stratifying tools such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE)[75] and Society of Thoracic Surgeons Predicted Risk of Morality (STS-PROM)[76–78] are used routinely in clinical practice, incorporating a frailty screening tool may be beneficial in stratifying a patient's risk profile prior to cardiac surgery. In fact, the addition of frailty to the STS-PROM (AUC 0.73-0.76) as a risk stratification tool in older adults over the age of 70 provides incremental value and improved model discrimination compared to using the STS-PROM alone (AUC 0.68-0.72).[7] This is supported by results from a recent systematic review conducted by Sepehri and colleagues, which suggests that frailty status, defined using multiple criteria, had a strong positive relationship with the risk of cardiac and cerebrovascular events following cardiac surgery (OR: 4.89 95% CI 1.64-14.60).[12] Another review conducted by Beggs et al. confirms this association between frailty and an increased likelihood of adverse perioperative outcomes in a variety of surgical populations, including cardiac, vascular, abdominal and orthopedic procedures.[79] For an overview of studies specific to cardiac surgery compiled by Sepehri et al.,[12] refer to Table 1.[7,72,74,80–82]

Table 1. Frailty and Post-Operative Outcomes

Study	Population	Frailty Measure	Outcomes Measured	Association
Lee (2011)[72]	Patients undergoing cardiac surgery (n=3826)	Katz Index of Activities of Daily Living, independence in ambulation and dementia	In-hospital mortality, midterm all-cause mortality, discharge to institution, in-hospital outcomes	Frailty associated with increased in-hospital mortality (OR: 1.8 95% CI 1.1-3.0, p=0.03), prolonged institutional care (OR: 6.3 95% CI 4.2-9.4, p=0.0001) and increased midterm mortality (HR: 1.5 95% CI 1.1-2.2, p=0.01)
Sundermann (2011)[80]	Patients ≥ 74 years undergoing cardiac surgery (n=400)	Comprehensive Assessment of Frailty	1-year all-cause mortality, major adverse cardiac and cerebrovascular events	Frailty associated with increased 1-year mortality (OR: 1.11 95% CI 1.05-1.17, p<0.001)
Afilalo (2012)[7]	Patients ≥ 70 years undergoing CABG or valvular surgery (n=152)	5-item Cardiovascular Health Study Frailty Scale, 7-item Cardiovascular Health Study Frailty Scale, Gait Speed, 4-item MacArthur Successful Aging	Post-operative mortality, major morbidity	Gait speed associated with increased mortality or major morbidity (OR: 2.63 95% CI 1.2-5.9, p<0.05)
Green (2012)[74]	Patients ≥ 60 years undergoing transcatheter aortic valve replacement (n=159)	Modified Fried Criteria	All-cause mortality, procedural outcomes	Frailty associated with increased 1-year mortality (HR: 3.16 95% CI 1.3-7.5, p=0.009)
Stortecky (2012)[81]	Patients ≥ 70 years undergoing transcatheter aortic valve implantation (n=100)	Modified Multi-dimensional Geriatric Assessment	All-cause mortality, major adverse cardiac and cerebrovascular events	Frailty associated with increased 1-year mortality (OR: 3.68 95% CI 1.2-11.2, p=0.02) and increased major adverse cardiac and cerebrovascular events (OR: 4.89 95% CI 1.6-14.6, p=0.003)
Schoenenberger (2013)[82]	Patients ≥ 70 years undergoing transcatheter aortic valve implantation (n=119)	Modified Geriatric Baseline Examination	Functional decline, mortality	Frailty associated with functional decline or death (OR: 4.46 95% CI 1.9-10.8, p=0.001)

Modifying Frailty with Exercise

It has been estimated that up to 5% of deaths in older adults could be delayed by preventing the onset of frailty.[63] While the efficacy of exercise at preventing adverse outcomes such as falls[83] and cognitive decline[84] have been previously reported in systematic reviews, the precise role of exercise in preventing or reversing frailty has yet to be fully elucidated. A systematic review examining exercise interventions and frailty conducted by Theou and colleagues concluded that multi-modal exercise interventions of longer duration (i.e. >5 months) performed 3 times per week provided superior results in the management of frailty.[85] However, definitions used to evaluate frailty in many of the 47 studies identified by this systematic review were inconsistent. Only three of the included studies cited utilized validated measures of frailty. Thus, more quality research is needed in this area.

Faber and colleagues conducted a multi-centre, randomized controlled trial of moderate intensity exercise in older adults and used the Fried phenotype criteria to evaluate frailty.[86] Specifically, the trial evaluated two exercise programs: (1) the first program focused on developing balance and mobility (n=54); and, (2) the second program utilized Tai Chi to improve balance, coordination and muscular strength (n=70). Both programs were delivered once per week for four weeks, followed by twice-weekly exercise sessions for 16-weeks thereafter. Although study authors did not evaluate the effect of the program on frailty status directly, they did report that falls risk in the pre-frail subgroup decreased by 61%; whereas, the intervention increased the risk of falls in the frail subgroup (HR: 2.95 95% CI 1.64-5.32). Paradoxically, this study indicates that pre-frail patients may derive the most benefit from an exercise intervention compared to those at the extreme continuum of frailty. A study by Peterson and colleagues evaluated the effectiveness of a 6-month telephone counseling intervention, consisting of

behaviour change techniques and goal setting activities, in frail patients and reported that the intervention group had an 18% reduction ($p = 0.08$) in the proportion of frail to non-frail participants at a 6-month follow up, as defined by the Fried criteria.[87] However, this study combined both frail and pre-frail individuals into a single category; therefore, the intervention is difficult to generalize to the frail population specifically.

Recently, the multi-centre Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) randomized controlled trial investigated a 12-month physical activity intervention in 424 community dwelling older adults (ages 70-89) at risk for mobility disability.[88–90] The 12-month, progressive intervention consisted of aerobic, strength, flexibility and balance components combining both centre-based and home-based sessions. In contrast, individuals randomized to the control arm were provided weekly health education sessions for 26 weeks, followed by monthly education sessions for the remainder of the 12-month study. Study authors reported the baseline prevalence of frailty to be approximately 23% as defined by the Fried phenotype criteria.[90] Interestingly, the 12-month physical activity intervention was found to improve physical performance,[88] attenuate the incidence of major mobility disability[89] and reduce the prevalence of frailty in the intervention group (10% 95% CI 6.5-15.1%) relative to controls (19.1% 95% CI 13.9-15.6%).[90] Furthermore, differences in the mean number of frailty criteria between the intervention and control groups existed at the 6-month (-0.23 95% CI -0.42 to -0.04) and 12-month assessments (-0.27 95% CI -0.47 to -0.06).[90] Thus, evidence from the LIFE-P trial indicates that the frailty syndrome is modifiable through an interdisciplinary, progressive physical activity intervention.

Perhaps the most rigorous study evaluating the effectiveness of exercise in modifying frailty status comes from Cameron and colleagues.[91,92] In the single centre Frailty Intervention Trial

(FIT), 216 participants were randomized to a 1-year interdisciplinary, individualized health intervention including nutrition, social engagement, physiotherapy and exercise components. The control arm received standard care, including consultations with a general practitioner or medical specialist as required, with no specific exercise prescription. Although no differences in frailty were identified at the 3-month assessment, study authors reported a lower prevalence of frailty, as defined by the phenotype criteria, in the intervention group compared to controls (absolute difference 14.7% 95% CI 2.4-27.0%) at a 12-month follow-up. Furthermore, scores on the SPPB declined in the control group by an average of 0.98 over 12-months; whereas, SPPB scores increased in the intervention group by an average of 0.52 (between group difference 1.44 95% CI 0.80-2.07). However, due to the multidisciplinary nature of the intervention, it is difficult to attribute these improvements in frailty status and physical function to the exercise program specifically. Even so, this trial supports the results of the multi-centre LIFE-P study, suggesting that frailty status is indeed modifiable following a 12-month, interdisciplinary intervention. Further research is needed to determine if intensive exercise interventions of shorter duration may have a similar influence on frailty status in various clinical populations, including those with cardiovascular disease.

Physical Activity, Exercise Capacity and Cardiovascular Disease

Regular physical activity confers an array of cardiovascular benefits, is an established characteristic in the phenotype model of frailty[28] and is recommended as a strategy in both the primary and secondary prevention of CAD.[93] In a meta-analysis conducted by Sofi and colleagues combining results from 26 studies and 513, 472 patients, high (RR: 0.73 95% CI 0.66-0.8) and moderate levels (RR: 0.88 95% CI 0.83-0.93) of leisure time physical activity conferred a cardio-protective effect against the subsequent development of CAD.[94] Specific to

secondary prevention, leisure-time physical activity has been demonstrated to be an independent predictor of survival in patients with CAD, where sedentary individuals with CAD have a 1.6-fold greater risk of long-term mortality (HR: 1.63 95% CI 1.34-1.97) compared to active counterparts.[95] In apparently healthy subjects, physical activity is associated with a risk reduction of 35% (95% CI 30-40%) in relation to cardiovascular mortality and 33% (95% CI 28-37%) in all-cause mortality;[96] this association remains significant even in older adults accumulating low doses (RR: 0.78 95% CI 0.71-0.87) and in older adults adhering to recommended physical activity guidelines (RR: 0.72 95% CI 0.65-0.80).[97] While even modest amounts of physical activity can confer health benefits, there appears to be a dose-response relationship relating to physical activity and cardiovascular disease risk. In patients with established cardiovascular disease, an energy expenditure of 1600 kcal per week has been demonstrated to be effective in halting the progression of CAD; whereas, an energy expenditure of 2200 kcal per week is associated with plaque reduction.[98] Further evidence of a dose-response relationship comes from a meta-analysis conducted by Williams, which reported that with each percentile increase in physical activity, there is an associated -0.0031% reduction in relative risk of developing CAD.[93]

Related to the accumulation of physical activity, exercise capacity has also been demonstrated as an important prognostic indicator of long-term adverse health outcomes in apparently healthy individuals[99] and in patients with cardiovascular disease.[100] For example, in 6213 men referred for exercise testing, every 1-Metabolic Equivalent of Task (MET) increase in exercise capacity was associated with a 9% improvement in survival (HR: 0.91 95% CI 0.88-0.94 for each 1-MET increment) over a mean follow-up period of 6.2 years.[99] Additionally, Kavanagh and colleagues conducted an observational study of 12,169 men referred for CR and reported that maximal oxygen uptake (VO_{2max}) was a predictor of cardiac mortality, where individuals with a VO_{2max} of

15 to 22 and >22 mLO_2/kg/minute had 38% and 61% reductions in the risk of cardiac death, respectively, compared to individuals with a VO_{2max} under 15 mLO_2/kg/minute.[100] Thus, interventions aimed at increasing the accumulation of physical activity and improving physical fitness amongst patients with cardiovascular disease are warranted.

Cardiac Rehabilitation

More than a half century ago, patients who suffered from an acute coronary event were restricted to eight weeks of bed rest to prevent the occurrence of another MI.[101] This dogma persisted until the 1950's, when it was discovered that patients with cardiovascular disease experienced significant deconditioning by remaining sedentary,[102] leading to the initiation of several studies in the 1960's investigating the therapeutic potential of exercise following major cardiac events.[103,104] Today, CR has developed into a formal, interdisciplinary, medically supervised program for post-surgical and post-MI patients combining exercise, education and counseling components. Collectively, these secondary prevention programs aim to prevent future hospitalization and cardiac mortality through the modification of behavioural and biological risk factors. Since the frailty phenotype is characterized by reductions in muscle mass, strength, endurance and activity levels, CR is ideally suited to counteract these impairments and improve frailty status.[28] In fact, a recent narrative review of randomized trials concluded that interdisciplinary programs such as CR are a promising therapeutic strategy for frail older adults;[85] however, none of the trials included in this review targeted pre-operative cardiac patients. As such, the utility of CR programming in the pre-operative setting warrants further investigation.

Health Benefits of Cardiac Rehabilitation

Attendance at CR confers an array of cardiovascular benefits, including improvements in aerobic capacity, BP and blood lipid levels. For example, a systematic review conducted by Taylor and colleagues revealed that compared to usual care, CR resulted in reductions in total cholesterol (-0.37 mmol/L 95% CI -0.63 to -0.11 mmol/L), systolic BP (-3.2 mm Hg 95% CI -5.4 to -0.9 mm Hg) and self-reported smoking (OR: 0.64 95% CI 0.50-0.83).[32] These results have also been confirmed in patients with chronic heart failure. In fact, the Exercise Rehabilitation Trial (EXERT) compared standard care with a 12-month exercise program in 181 patients with heart failure.[105] The intervention consisted of 3-months of supervised aerobic exercise, prescribed at 60-70% of maximum heart rate, followed by home-based exercise to be completed 3-times per week for the duration of the 12-month study. Study authors reported that exercise training resulted in significant improvements in peak oxygen uptake compared to the control group at 3-months (0.104 ± 0.026 vs. 0.025 ± 0.023 L/min) and 12-months (0.154 ± 0.074 vs. 0.024 ± 0.027 L/min). Similar results were obtained by Lavie and colleagues in a prospective analysis of 92 older adults (mean age 70.1 years) attending CR.[106] Notably, attendance at CR resulted in significant improvements in aerobic capacity (+1.9 METs), body mass index (BMI; -0.4 kg/m^2), percent body fat (-1.5%) and high-density lipoprotein cholesterol (+2.6 mg/dl), compared to baseline values.

While the benefits of traditional, moderate intensity exercise have been well-documented, recent evidence suggests that high-intensity interval training may confer a superior cardiovascular benefit in patients with CAD. In fact, a systematic review conducted by Cornish and colleagues reported that interval training increases aerobic capacity, endothelial function and ejection fraction to a greater extent than moderate intensity, continuous aerobic training in

patients with established CAD.[107] More specifically, a study conducted by Rognmo and colleagues reported that 10-weeks of supervised treadmill exercise at 80-90% of VO_{2peak} resulted in a 17.9% ($p= 0.012$) increase in aerobic capacity; whereas, cardiac patients training at 50-60% of VO_{2peak} increased their aerobic capacity by 7.9% ($p=0.038$).[108] The adaptation to training was significantly greater in the CAD patients performing high intensity exercise ($p=0.011$). In a seminal study, Wisløff and colleagues randomized 27 post-infarction heart failure patients (mean age 75.5 ± 11.1 years) to either moderate continuous training (i.e. 70% peak heart rate) or aerobic interval training (i.e. 95% peak heart rate) three times per week for a period of 12-weeks.[109] Maximal aerobic capacity increased to a greater extent in the interval training group compared to patients in the moderate intensity group (46% vs. 14%, $p < 0.001$), increasing from a baseline of 13.0 mL/kg/min to 19.0 mL/kg/min. Furthermore, interval training resulted in a 47% increase in vastus lateralis peroxisome proliferator-activated receptor gamma coactivator 1-alpha protein content ($p < 0.01$), increased maximal calcium reuptake into the sarcoplasmic reticulum by 60% ($p < 0.01$), induced reverse left ventricular remodeling, increased relative ejection fraction by 35% ($p < 0.01$) and increased stroke volume by 17% ($p < 0.01$). Collectively, this data indicates that participation in CR reduces several common risk factors associated with cardiovascular disease and significantly improves maximal aerobic capacity. Furthermore, incorporating high intensity interval training may result in superior improvements in aerobic capacity and cardiac function compared to moderate intensity continuous training in patients with established CAD.

Mental Health Benefits of Cardiac Rehabilitation

Literature investigating the influence of CR programming on health-related quality of life (HRQoL) and mental health has been largely inconclusive, however several studies indicate a

potential benefit. Notably, Duarte Freitas and colleagues conducted a prospective analysis of 101 patients (mean age 65 ± 12 years) participating in a short, 4-week intensive CR program completed five days per week.[110] Following completion of the program, study authors reported a 25% improvement in quality of sleep as assessed by the Pittsburgh Sleep Quality Index, a 14% improvement in mental health score ($p < 0.0001$) on the Short Form-36 Quality of Life questionnaire, a 32% decrease in depression ($p < 0.0001$) and a 29% decrease in anxiety ($p < 0.0001$) as assessed by the Hospital Anxiety and Depression Scale. Similarly, Milani and Lavie retrospectively assessed symptoms of depression in 522 coronary patients enrolled in CR and in a control group consisting of 179 patients who entered CR, but dropped out within 2 weeks.[111] Notably, 17% of all patients identified depressive symptoms upon entry into CR, as assessed by the 92-item Kellner Symptoms Questionnaire. Interestingly, the prevalence of depressive symptoms was decreased by 63% (from 17% to 6%, $p < 0.0001$) following attendance at CR; however, this study failed to report changes in depressive symptoms in the control group and thus, it is difficult to determine if CR program attendance was responsible for the observed improvement in mental health status. A meta-analysis conducted by Rutledge and colleagues confirmed a small to moderate effect size ($d = 0.23$ 95% CI 0.10-0.35) in relation to CR programming and subsequent improvement in the severity of depressive symptoms.[112] The efficacy of CR in reducing depression severity was irrespective of program duration, suggesting that indeed, CR programming may have beneficial effects on the mental health status of patients with CAD.

Cardiac Rehabilitation Reduces Mortality and Major Morbidity

Several clinical trials, cohort studies and meta-analyses have demonstrated that CR reduces rates of mortality and morbidity after major cardiac events. In fact, a meta-analysis of

randomized controlled trials conducted by Taylor and colleagues reported that patients attending CR have a 20% and 26% relative reduction in all-cause mortality and cardiac mortality, respectively, as compared to patients not attending CR.[32] Similarly, a Cochrane review conducted by Joliffe and colleagues reported a 27% reduction in all-cause mortality and a 36% reduction in major cardiac events in patients attending CR, compared to those not attending CR.[33] The benefits of CR have also been demonstrated in patients undergoing surgical and non-surgical procedures, such as percutaneous coronary intervention. In a secondary analysis of 2395 patients undergoing percutaneous coronary intervention, participation in CR resulted in a 46% relative reduction in in all-cause mortality (HR: 0.54 95% CI 0.41-0.71) over a median follow up of 6.3 years, compared to patients not attending CR.[34] The protective effect of CR on mortality has also been confirmed in patients undergoing combined heart valve and CABG procedures, where all-cause mortality over a 6.8 ± 2.8 year follow-up is reduced by 52% (HR: 0.48 95% CI 0.27-0.83) in patients attending CR programming.[113] Thus, it is well established that CR programs result in improved rates of survival after major cardiac events and following acute surgical interventions.

Long-term benefits of CR programming on mortality have also been demonstrated in patients with chronic heart failure. Belardinelli and colleagues were the first to establish the benefits of moderate intensity exercise training in patients with chronic heart failure, demonstrating reductions in mortality (RR: 0.37 95% CI 0.17-0.84) and hospital readmission (RR: 0.29 95% CI 0.11-0.88) following 12-months of CR programming.[35] More recently, the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial was a multi-centre, randomized controlled trial of aerobic exercise conducted in 2331 medically stable patients (median age 59 years) with heart failure.[36] The intervention consisted of 3-months of

supervised aerobic exercise at an intensity corresponding to 60-70% of heart rate reserve performed 3-times per week. Following the supervised exercise program, patients were provided with home exercise equipment, heart rate monitors and were instructed to exercise 5-times per week for 40 minutes. In contrast, participants in the usual care group were not provided with a formal exercise prescription, however they were provided with educational material on physical activity. Interestingly, participation in the aerobic exercise intervention resulted in an 11% reduction in all-cause mortality or hospitalization (HR: 0.89 95% CI 0.81-0.99) and a 15% reduction in cardiovascular mortality or heart failure hospitalization (HR: 0.85 95% CI 0.74-0.99) over a median follow-up 30-months, after adjusting for baseline characteristics. Thus, it appears that patients with heart failure may also derive significant long-term benefits from participating in formal CR programs.

Cardiac Rehabilitation Reduces Mortality in Older Adults

The majority of studies investigating the efficacy of CR programs have been conducted in low-risk, middle-aged patients, excluding older adults from the study population. Despite this literature gap, several studies have demonstrated CR to be effective in older patients as well. In fact, a longitudinal study conducted by Onishi and colleagues evaluated the long-term effects over a 10-year follow-up of CR in patients over the age of 65.[29] Notably, all-cause mortality was attenuated in patients attending CR compared to the control group not attending CR (14% vs. 28%) and the incidence of a major cardiovascular event was also reduced (HR: 0.43 95% CI 0.20-0.91). Another retrospective study conducted by Suaya and colleagues investigated five year mortality rates in 601,099 patients over the age of 65 that were hospitalized for coronary conditions or cardiac revascularization.[30] Study authors reported a 58% relative reduction in 1-year mortality and a 34% reduction in 5-year mortality amongst patients attending CR compared

to patients not attending CR. This study also demonstrated a significant dose-response relationship in older adults attending CR. In fact, patients attending greater than 25 CR sessions were 19% less likely to die over a period of 5-years compared to CR users attending 24 or fewer sessions. Data from Suaya et al.[30] and and Onishi et al.[29] indicate that older patients with cardiovascular disease derive similar benefits from CR programs as middle-aged participants. Furthermore, there may be a dose-response relationship governing improved clinical outcomes in this population, with 25 sessions representing a benchmark for attendance.

Aerobic Capacity Prior to Surgery is Associated with Improved Outcomes

The pre-operative functional capacity of patients undergoing cardiac surgery has been demonstrated to influence post-operative outcomes. For example, Cook and colleagues evaluated four components of fitness, including aerobic capacity, grip strength, elbow flexion strength and body fat percentage in 200 patients prior to CABG surgery using the Veterans Specific Activity Questionnaire, a dynamometer and skin-fold assessments, respectively.[22] A composite fitness score of zero to four was developed for each individual patient by assigning a value of one to represent normal function and zero to represent a deficiency in that particular parameter. Patients with a high body fat percentage (i.e. men > 26%, women > 33%), low grip strength (i.e. men < 32 kg, women < 20.5 kg) and low aerobic capacity (i.e. < 5 METs) experienced a longer hospital LOS post-operatively (mean ± SD 13.4 ± 15.9 days vs. 5.8 ± 2.5 days, $p = 0.001$) and were also more likely to suffer from at least one serious complication (52.4% vs. 31.4%, $p = 0.017$; defined as re-operation, deep sternal infection, stroke, ventilation > 1 day, renal failure, arrhythmia, multi-system organ failure, readmission within 30-days), as compared to patients with low body fat percentages, normal grip strength and a high aerobic capacity. Similarly, Smith and colleagues conducted a retrospective analysis of 596 patients (mean age 62.8 ± 10 years)

undergoing an isolated CABG procedure and reported an inverse relation between cardiopulmonary fitness and short-term complications after surgical intervention.[23] Using a multivariate analysis, study authors reported that patients achieving < 5 METs (n=78) on a symptom-limited exercise test were more likely to experience prolonged ventilation beyond 48 hours (OR: 2.13 95% CI 1.01-4.55), operative mortality (OR: 6.75 95% CI 1.73-26.4) and 30-day mortality (OR: 5.60 95% CI 1.50-20.8) compared to patients achieving ≥ 5 METs (n=518). Despite the limitations of retrospective data collection and potential underestimation of aerobic capacity in patients that terminated the test prematurely, Smith and colleagues provide robust evidence suggesting an independent association between pre-operative aerobic capacity and post-operative outcomes. This finding is consistent with other studies identifying pre-operative cardiorespiratory fitness as being predictive of short-term perioperative health outcomes in patients undergoing abdominal aortic aneurysm repair, bariatric surgery, non-cardiopulmonary surgery, liver transplantation and in older adults undergoing intra-abdominal surgery.[114–119]

Pre-Operative Physical Activity Behaviour is Associated with Improved Outcomes

Evidence from several observational studies indicates that pre-operative physical activity behaviour influences post-operative outcomes in patients undergoing CABG surgery. For example, in a prospective analysis of 202 patients undergoing CABG surgery, Nery and Barbisan investigated the effects of pre-operative leisure time physical activity on hospital LOS and subsequent risk of major cardiovascular events.[15] Patients were assigned to either active (i.e. 33% of participants) or sedentary (i.e. 67% of participants) groups based on data from the Baecke Usual Physical Activity Questionnaire. Notably, individuals who self-reported engaging in 30 minutes or more of physical activity, 3-4 times per week experienced a 33% reduction in hospital LOS post-operatively (HR: 0.67 95% CI 0.49-0.93), compared to individuals classified

as sedentary. Furthermore, active individuals were less likely to suffer a major cardiovascular event (OR: 0.22 95% CI 0.09-0.51), defined as death, acute MI or re-operation. Similarly, a study conducted by Rengo and colleagues in 683 older adults (>70 years) undergoing CABG reported 60-month survival rates to be 65% and 96% (log rank = 49.460, $p < 0.0001$) in less active and active groups, respectively, as assessed by the Physical Activity Scale for the Elderly.[13] A cox survival analysis also demonstrated a significant, nonlinear association between increasing physical activity scores and survival (PASE Score 40, HR: 3.13 95% CI 3.03-3.32; PASE Score 50, HR: 2.83 95% CI 2.74-3.01; PASE Score 60, HR 2.32 95% CI 2.24-2.49; PASE Score 70, HR: 1.96 95% CI 1.89-2.10; PASE Score 80, HR: 1.73 95% CI 1.67-1.85; PASE Score 90, HR: 1.57 95% CI 1.51-1.67; PASE Score 100, HR: 1.45 95% CI 1.41-1.54). While Rengo et al. provide the strongest evidence for an association between pre-operative physical activity and long-term survival, study results may have been influenced by a selection bias, as patients with severe physical limitations and medical comorbidities were excluded from the analysis.

Noyez and colleagues also investigated the role of sedentary behaviour in predicting rates of in-hospital and early mortality after cardiac surgery using the Coronary Surgery Radboud Hospital Database.[18] Of the 3150 patients undergoing elective cardiac surgery, 58% were classified as active; whereas, 42% were classified as sedentary according to the criteria of the Corpus Christi Heart Project. Specifically, this project characterized five levels of physical activity, ranging from sedentary (i.e. no physical activity above minimum demands of daily living) to vigorous (i.e. ≥1 dynamic activities performed 3 times/week, 20 minutes/session, hard exertion). The first two categories (i.e. sedentary and minimal) were classified as sedentary, while the upper three categories were classified as active (i.e. mild, moderate and vigorous) for the purposes of dichotomizing the exposure variable in the study. Interestingly, in-hospital

mortality (1.1 vs. 0.4%, p=0.014) and 30-day mortality (1.5 vs. 0.6%, p=0.006) were significantly higher in the sedentary group compared to those classified as active; however, sedentary lifestyle was not identified as an independent predictor of hospital or 30-day mortality following logistic regression analysis. Low-self reported physical activity has also been associated with post-operative complications such as atrial fibrillation,[20] renal insufficiency,[18] sternal wound problems,[18] perioperative MI,[19] prolonged intensive care unit (ICU) stay,[14,18] prolonged hospital stay[15,16] and re-operation[15]. However, conflicting results[17,19] and design limitations of research in this field make it challenging to confirm an association, as many studies have failed to statistically control for confounders such as age and disease severity in active and inactive groups. Furthermore, the use of self-report tools to quantify physical activity behaviour in these populations may be inappropriate, as a previous reports indicate no correlation between self-report and objectively measured physical activity levels.[120,121] A recent systematic review conducted by Kehler and colleagues (unpublished) highlighted the inconsistent associations between pre-operative physical activity and perioperative health outcomes in adults undergoing cardiac surgery; for an overview of studies compiled in this systematic review, refer to Table 2. [13–19]

Table 2. Pre-Operative Physical Activity and Post-Operative Outcomes

Outcome Measured	First author, year	Association	Number of events per group	Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI)
Major adverse cardiac and cerebrovascular events (MACCE)	Nery (2007)[15]	Physical activity is associated with reduced MACCE 2 years postoperatively	Active: 8/25 (31%); Inactive: 17/30 (57%), p=0.04	NR
	Martini (2010)[16]	Physical activity is not associated with mortality, re-hospitalization, cerebrovascular events, or MI (combined events) 2 years postoperatively	Active: 9/66 (14%); Inactive: 31/119 (26%), p=0.18	NR
	Rengo (2010)[12]	Physical activity is associated with a reduction in all-cause and cardiac and mortality 5 years postoperatively	NR	Adjusted Multivariable Cox proportional hazard for all-cause mortality: Exp(B) 0.248 (95% CI 0.141-0.434), p<0.001 Adjusted Multivariable Cox proportional hazard for cardiac-related mortality: Exp(B) 0.272 (0.133-0.555), p<0.001
30 day morbidity/Mortality	Markou (2007)[18]	Physical activity is associated with peri-operative MI, but not reoperation or other postoperative events (wound infection, renal, neurological, pulmonary, gastrointestinal)	Perioperative MI: Active: 4/226 (2%); Inactive: 11/202 (5%), p=0.03 Reoperation: Active: 15/226 (7%); Inactive: 9/202 (5%), p=0.32 Wound infection: Active: 3/226 (1%); Inactive: 7/202, p=0.14 Renal: Active: 3/226; Inactive: 7/202, p=0.14 Neurological: Active: 3/226 (1%); Inactive: 0/202 (0%) Pulmonary: Active 13/226 (6%); Inactive: 13/202 (6%), p=0.76 Gastrointestinal: Active: 4/226 (2%); Inactive: 3/202 (2%), p=0.81	NR
	Nery (2010)[14]	Physical activity is associated with a	Mortality:	Univariate OR for being active:

		reduction in 30 day morbidity and mortality	Active: 0/66 (0%); Inactive: 7/136 (5%), p=0.098 MI: Active: 1/66 (2%); Inactive: 6/136 (4%), p=0.431 Reoperation: Active: 0/66 (0%); Inactive: 1/136 (0.5%), p=1.0	NR Multivariate OR for being active: 0.22 (95% CI 0.09-0.51, p=0.001)
	Noyez (2013)[17]	Physical activity is associated with 30 day morbidity and mortality, but after adjustment, PA is no longer associated with hospital mortality or 30 day mortality	Hospital mortality: Active: 7/1815 (0.4%); Inactive: 15/1335 (1.1%), p=0.014 30 day mortality: Active: 10/1815 (0.6%); Inactive: 20/1335 (1.5%), p=0.007 Reoperation: Active: 105/1815 (5.8%); Inactive: 68/1335 (5%), p=0.40 Stroke: Active: 9/1815 (0.5%); Inactive: 12/1335 (0.9%), p=0.17 Renal insufficiency: Active: 32/1815 (1.8%); Inactive: 39/1335 (2.9%), p=0.03 Sternal wound: Active: 10/1815 (0.6%); Inactive: 17/1335 (1.3%), p=0.03 Ventilation >2 days: Active: 31/1815 (1.7%); Inactive: 54/1335 (4.0%), p=0.001	Univariate OR for being inactive: NR Hospital mortality multivariate OR for being inactive: 1.20 (95% CI 0.4-3.5, p=0.617) 30 day mortality multivariate OR for being inactive: 1.10 (95% CI 0.5-2.7, p=0.70)
Length of Hospital Stay	Markou (2007)[18]	Physical activity is not associated with a reduced post-operative hospital LOS	Active: 6.9 ± 8.2 days; Inactive: 7.3 ± 7.1 days, p=0.6	NR
	Nery (2007)[15]	Physical activity is associated with a reduced post-operative hospital LOS	Active: 12 ± 5 days, median 9 days (IQR 8-	NR

			15); Inactive: 15 ± 8 days, median 12 (IQR 9-19), p=0.03	
	Nery (2010)[14]	Physical activity is associated with a reduced post-operative hospital LOS	NR	HR: 0.67 (95% CI 0.49-0.93, p=0.018)
Intensive Care Unit Length of Stay	Markou (2007)[18]	Physical activity is not associated with a reduced ICU LOS	Active: 2.2 ± 5.3 days; Inactive: 2.1 ± 3.5 days, p=0.76	NR
	Cacciatore (2012)[13]	Physical activity is associated with a reduced proportion of patients requiring a prolonged ICU LOS (i.e. ICU stay > 3 days)	NR	Univariate OR: 0.984 (95% CI 0.977-0.992, p<0.001) Multivariate OR: 0.992 (95% CI 0.983-1.000, p=0.042)
	Noyez (2013)[17]	Physical activity is associated with a reduced ICU LOS and a reduced proportion of patients requiring a prolonged ICU LOS (i.e. ICU stay > 5 days)	Active: 1.3 ± 1.9 days; Inactive 3.0 ± 41.8 days, p=0.001 ICU > 5 days: Active: 19/1815 (1.0%); Inactive: 46/1335 (3.4%), p=0.001	NR

NR, not reported; MI, myocardial infarction; PA, physical activity; LOS, length of stay; IQR, interquartile range; ICU, intensive care unit

Surgical Wait List Times Increase Mortality and Negatively Influence Quality of Life

Due to a high volume of patients and modern medical systems mandating wait lists for elective procedures, individuals undergoing non-urgent cardiac surgery are often placed on waiting lists for extended periods of time. Based on the severity of symptoms, and the structural/functional abnormalities present in the coronary anatomy, patients are classified as either: (1) Urgent and Emergent; (2) Semi-Urgent; or, (3) Elective. Typically, urgent cases receive surgical intervention within hours; whereas semi-urgent cases are placed on a wait-list for approximately one month. In contrast, elective cases are placed on a waiting list ranging from 43 to 180 days in most cases, as locally defined by the Winnipeg Regional Health Authority Cardiac Sciences Program. Interestingly, extended wait-list times have been demonstrated to increase rates of mortality in patients undergoing cardiac surgery. In a prospective analysis of 8966 patients undergoing semi-urgent or elective CABG surgery, the odds of death were 64% greater in patients with a wait-list time of greater than one month (OR: 1.64 95% CI 1.02-2.63) compared to patients waiting less than one month.[122] It has also been demonstrated that the risk of death in patients waiting for CABG increases by approximately 11% every month, with patients waiting for 3-months experiencing a 37% increased risk of mortality while on the wait-list compared to the time they were accepted for surgery.[123] In a population-based registry study, Sobolev and colleagues examined in-hospital mortality in 9593 patients undergoing coronary revascularization in British Columbia using the Canadian Institute for Health Information Discharge Abstract Database.[124] Interestingly, this study utilized two pre-specified targets for surgical intervention: (1) as published by the CCS Access to Care Working Group,[125] where patients requiring revascularization should wait no longer than 2 weeks for semi-urgent procedures and 6 weeks for elective procedures; and, (2) provincial guidelines mandating semi-urgent procedures be

completed within 6 weeks and elective procedures within 12 weeks. After adjusting for pre-operative risk score in a logistic regression model, it was reported that individuals classified as having short delays (i.e. meeting CCS guidelines) were 68% less likely to experience in-hospital death (OR: 0.32 95% CI 0.20-0.51); whereas, individuals experiencing prolonged delays (i.e. meeting provincial guidelines, but not CCS targets) were just as likely (OR: 0.78 95% CI 0.38-1.63) to die in-hospital as individuals having an excessive delay (i.e. not meeting provincial guidelines). Collectively, this evidence indicates that extended waiting lists for cardiac procedures result in an increased risk of perioperative mortality. This is likely a result of the deconditioning that patients experience during the pre-operative period, as it has been documented both objectively and anecdotally that patients are inactive during this period of time.[13,18,27,120,121] While this evidence would appear to promote more rapid surgical procedures, waiting lists for elective procedures are often required due to resource constraints and to ensure more urgent cases are managed in a timely fashion. As such, strategies to optimize risk during the waiting period experienced by elective patients are warranted.

Surgical wait-list times also negatively influence HRQoL in patients requiring surgical revascularization. For example, patients waiting for CABG surgery for a period exceeding 97 days experience reduced physical functioning, social functioning and mental health as assessed by the Short Form-36 Quality of Life questionnaire, compared to patients waiting less than 97 days.[126] Given that modern health care systems are moving towards extended waiting lists for elective procedures, it is imperative that the health care team identifies novel strategies to maintain the cardiovascular and mental health status of patients while on the wait-list for cardiac surgery.

How Active are Patients while on the Wait-List?

There is a paucity of published literature examining the pre-operative physical activity behaviour of patients undergoing cardiac procedures, with most studies employing self-report methods to quantify physical activity accumulation.[15,18] A study by Nery and Barbisan classified physical activity behaviour according to the Baecke Usual Physical Activity Questionnaire, which investigates physical activity during the past 12 months.[15] Study authors classified 33% of participants as active, reporting leisure time physical activity three or more times per week for 30-minutes or more; whereas, the other 67% of participants were classified as sedentary. Similarly, Noyez and colleagues classified 58% of elective cardiac patients as active according to criteria used in the Corpus Christi Heart Project, which classifies five categories of physical activity ranging from sedentary to vigorous.[18] However, both of these studies utilized self-report to quantify physical activity behaviour, which is a method susceptible to recall bias. In fact, self-reporting physical activity has been demonstrated to over estimate aerobic physical activity accumulation by as much as 300%.[127] In contrast to the self-report methods referenced in the studies above, Kehler utilized accelerometers to quantify MVPA in elective CABG patients on the wait-list for surgery.[128] In this pilot randomized controlled trial, it was reported that patients on the wait-list accumulate a mean ± Standard Error of 46 ± 26 minutes of MVPA per week (i.e. 6.6 minutes per day), accumulated in bouts of 10 minutes or more. This result is slightly higher than reference values for MVPA in older adults aged 60-69 (mean ± Standard Error for males 6.5 ± 1.1, females 5.8 ± 0.9 min/day),[129] but remained considerably less than the 150 minutes of MVPA per week recommended by the CPAG for older adults.[24] The paucity of literature in this area represents a significant knowledge gap requiring further investigation.

Utilization of Pre-operative Interventions in Various Surgical Populations

Despite evidence indicating that pre-operative fitness and physical activity promotes positive health outcomes in cardiac patients, there are few published studies examining the effects of exercise interventions for improving physical fitness or function prior to cardiac surgery.[26,130–132] Even so, pre-operative exercise interventions have demonstrated efficacy in patients undergoing orthopaedic, thoracic and abdominal surgeries, which is supported by results from various systematic reviews.[133–135] This section will review the use of pre-operative exercise interventions in various surgical populations, followed by a review of studies investigating pre-operative interventions in cardiac surgery.

Exercise therapy prior to orthopaedic surgery appears to promote improvements in functional capacity and patient health. For example, a study by Rooks and colleagues investigated the effectiveness of a 6-week pre-operative exercise intervention in 108 patients undergoing hip and knee arthroplasty.[136] The intervention consisted of 3-weeks of resistance training followed by 3-weeks of cardiovascular, strength and flexibility exercises administered by a physical therapist. Study authors reported that participation in the pre-operative exercise intervention 3-times per week increased muscular strength by up to 20% pre-operatively, compared to no change in the control group. Furthermore, participation in exercise pre-operatively reduced the risk of discharge to a rehabilitation facility (OR: 0.27 95% CI 0.074-0.998) post-operatively; however, no persistent changes in functional outcomes were reported at 8 and 26-week follow-up time points. In contrast, Topp and colleagues investigated pre-operative resistance training and flexibility exercises in 54 patients undergoing total knee arthroplasty using a combination of hospital-based and home-based sessions. It was reported that attendance at a pre-operative exercise intervention 3-times per week improved sit-to-stand performance 1-month post-

operatively and also increased performance on several functional tasks 3-months post-operatively.[137] Although both of these studies used small sample sizes, results indicate that pre-operative exercise interventions in patients undergoing orthopaedic surgery may result in improved clinical outcomes after surgery.

In a study conducted by Bobbio and colleagues, authors investigated the effectiveness of a pre-operative cardiopulmonary rehabilitation intervention in 12 patients undergoing thoracic surgery for lung cancer.[138] The 4-week interdisciplinary intervention consisted of inspiratory muscle training, aerobic cycle training at up to 80% of maximal work rate, smoking cessation and optimization of pharmacological treatment. Notably, VO_{2max} was increased by a mean of 2.8 mLO_2/kg/min (from 13.5 ± 1.3 to 16.3 ± 1.9 mLO_2/kg/min). In addition to reaching statistical significance, this was considered to be a clinically meaningful improvement, as the study reported that all patients with a pre-operative VO_{2max} under 15 mLO_2/kg/min also experienced a post-operative cardiopulmonary complication. Jones and colleagues also conducted a study of pre-operative aerobic cycle exercise in patients undergoing thoracic surgery and found evidence for a dose-response relationship.[139] Notably, in patients who achieved greater than 80% adherence to the intervention, VO_{2peak} increased 3.3 mLO_2/kg/min (95% CI 1.1-5.4 mLO_2/kg/min), compared to no change in patients achieving less than 80% adherence.

Further evidence of pre-operative exercise interventions in the literature comes from patients undergoing abdominal surgery. Dronkers and colleagues investigated a 4-week therapeutic exercise program combining resistance training, inspiratory muscle training, aerobic exercise (55-75% of maximum heart rate) and functional activities in 42 older adult patients undergoing elective abdominal surgery.[140] Compared to the control group, which received exercise advice but no formal exercise programming, intervention participants improved respiratory muscle

endurance. However, no changes in hospital LOS or functional capacity were observed between groups following surgery. This study highlights the importance of designing pre-operative interventions that are of sufficient duration to bring about clinically meaningful improvements in exercise capacity and functional ability.

Utilization of Pre-operative Interventions in Cardiac Surgery Patients

Patients undergoing cardiac procedures may experience anxiety prior to their surgery and are often sedentary and at a heightened risk of cardiovascular deconditioning.[27] As such, interventions aimed at promoting physical activity and improving cardiovascular fitness during the pre-operative period are warranted. Despite this, few clinical trials have evaluated pre-operative exercise interventions in patients undergoing cardiac procedures. Herdy and colleagues conducted a randomized controlled trial in 56 patients undergoing CABG, where participants randomized to a cardiopulmonary rehabilitation group (n=29) received a minimum 5-day pre-operative and 5-day post-operative progressive exercise program.[130] Exercise was initially prescribed to elicit an energy expenditure of 2 METS and was progressively increased to 4 METS. Notably, participants randomized to the intervention group presented with attenuations in atelectasis (RR: 0.15 95% CI 0.03-0.8), atrial fibrillation (RR: 0.2 95% CI 0.05-0.8) and reduced their average post-operative hospital LOS (5.9 $\pm$ 1.1 vs. 10.3 $\pm$ 4.6 days). Although it is difficult to determine the effect of pre-operative exercise in isolation in this study design, it appears that perioperative exercise interventions may be a viable and safe approach to promote improved clinical outcomes in patients undergoing cardiac procedures.

Several studies have investigated the efficacy of inspiratory muscle training and breathing exercises in patients undergoing cardiac procedures, although none were conducted in the frail, older adult population. A Cochrane review conducted by Hulzebos and colleagues compiled

results from eight randomized controlled trials of pre-operative physical therapy in 856 patients undergoing cardiac procedures.[131] Notably, five of the studies utilized interventions consisting of inspiratory muscle training and three studies implemented a multi-modal intervention combining aerobic and breathing exercises. Results of the systematic review demonstrated that patients receiving pre-operative physical therapy have a reduced risk of post-operative atelectasis (RR: 0.52 95% CI 0.32-0.87) and pneumonia (RR: 0.45 95% CI 0.24-0.83), but no changes in rates of post-operative mortality. Furthermore, patients receiving pre-operative physical therapy also experience reductions in hospital LOS post-operatively (-3.21 days, 95% CI -5.73 to -0.69). Thus, evidence suggests that pre-operative physical therapy in the form of breathing exercises may contribute to a reduced risk of post-operative pulmonary complications and prolonged hospital LOS following cardiac surgery.

Perhaps the strongest evidence supporting pre-operative exercise interventions in patients undergoing cardiac surgery comes from a randomized trial conducted by Arthur et al., which investigated an 8-week supervised exercise program in 249 low-risk patients undergoing CABG.[132] The intervention consisted of individualized aerobic exercise training (prescribed at 40-70% of functional capacity) twice-weekly, in addition to education on risk factor modification and monthly telephone calls for support. In contrast, individuals randomized to the usual care group did not receive formal exercise programming. The primary outcome of the study investigated post-operative hospital LOS, while secondary outcomes examined exercise capacity, HRQoL and anxiety levels. Notably, patients randomized to the intervention group reduced their hospital LOS by a median of one day (95% CI 0 .0 to 1.0 day, p=0.002) and spent an average of 2.1 less hours (95% CI -1.2 to 16 hours, p=0.0001) in the ICU. Furthermore, participation in the intervention resulted in improvements in HRQoL at 6-months post-

operatively and more patients from the intervention group elected to participate in post-operative CR compared to control group (70% vs. 57%). The study also included a brief economic analysis, reporting that the pre-operative intervention resulted in a net cost savings of approximately $133 dollars per patient, per day. The trial by Arthur et al. provides quality evidence that pre-operative exercise interventions are well tolerated and can result in cost-savings through a reduction in hospital LOS. However, this study did not report on exercise capacity, physical activity behaviour and was also conducted in a relatively low-risk population undergoing CABG surgery, making it difficult to generalize to the contemporary, older adult cardiac patient. A recent study conducted by Rideout and colleagues examined 12-year health outcomes in elective CABG patients randomized to either a pre-surgical nurse-led CR program or standard care.[141] The intervention consisted of monthly health education and motivational interviewing, which was demonstrated in the initial study to result in improvements in BMI, systolic BP, diastolic BP and HRQoL.[142] Although at a 12-year follow-up there was residual survival benefit resulting from the intervention, the sample size was determined to be insufficient to demonstrate a statistically significant effect.[141] Even though the result did not reach statistical significance, a positive signal suggests that the benefits of pre-operative interventions in cardiac surgery patients may be extend beyond the immediate post-operative time period.

In a pilot study of pre-operative rehabilitation conducted at the St. Boniface Hospital, Kehler and colleagues randomized 17 elective CABG patients to standard care (n=9) or intervention (n=8), consisting of individualized aerobic (prescribed at 85% of VO_{2max}) and resistance exercise twice a week for a minimum of 4-weeks.[26] Additionally, participants randomized to the intervention group attended 12 education sessions on healthy lifestyle choices and cardiovascular risk factor reduction. Standard care consisted of a single, 3-hour cardiac pre-assessment

appointment, where patients were counseled on healthy lifestyle behaviours by an anesthesiologist and nurse. Data was collected at baseline, 1-week pre-operatively and 3-months post-operatively. Walking distance on a 6-minute walk test (6MWT) remained unchanged in the standard care group; whereas, intervention participants walked +132 and +145 meters more than baseline at the pre-operative and 3-month post-operative assessments, respectively. Additionally, 5-metre gait speed improved by 27% pre-operatively and 33% 3-months post-operatively, with no concurrent change in the standard care group. However, no statistically significant changes were observed in MVPA as assessed objectively by accelerometers from baseline to pre-operatively or 3-months post-operatively.[26,128] This non-significant result in MVPA between groups was likely a result of the small sample size, as pre-operative accelerometer data was available in just four participants in the intervention arm. Even so, this novel pilot data from demonstrates the feasibility and potential functional benefit of pre-operative rehabilitation in elective CABG patients.

Literature Knowledge Gap and Study Justification

Based on the evidence presented in this literature review, pre-operative fitness[22,23] and physical activity behaviour[13–19] are predictive of adverse post-operative outcomes in patients undergoing cardiac surgery. A review of literature also reveals that patients that are frail pre-operatively are at an increased risk of mortality and major morbidity after cardiac surgery,[7,12,72–74,80–82] which is a characteristic that may be modified by structured exercise interventions.[86,87,90,91] Since the phenotype of frailty is characterized by reductions in muscle mass, strength and endurance,[28] interdisciplinary CR programming is ideally suited to counteract these impairments and improve an individual's pre-operative frailty status. While several studies utilizing pre-operative exercise interventions in cardiac patients have demonstrated reductions in hospital LOS[130,132] and

improvements in functional capacity,[26] there is a paucity of literature examining pre-operative frailty status and physical activity behaviour in patients on the wait-list for elective cardiac surgery. Furthermore, studies employing pre-operative exercise interventions in cardiac patients have been conducted in relatively young, low-risk patients and have excluded frail, older adults.[26,132] Given that the demographic of patients undergoing cardiac surgery is shifting to include more older adults,[7,143] we will address a gap in the literature and determine if attendance at an interdisciplinary exercise and education intervention: (1) decreases the severity of frailty; (2) increases the amount of physical activity accumulated; and, (3) increases the functional walking ability of frail, older adults waiting for elective cardiac surgery. We anticipate that the results of this trial will challenge dogma and stimulate a significant change in practice by providing a strategy to optimize pre-operative risk factors in the modern cardiac surgery patient.

Chapter 3: Study Design

Rationale, Objectives and Hypotheses

Based on the review of literature presented, there exists a novel opportunity to implement an exercise and education rehabilitation intervention in frail patients awaiting elective cardiac surgery. To date, no high quality study has prospectively examined the impact of pre-operative CR in the frail, older adult population undergoing cardiac surgery. There is also a paucity of literature examining interventions targeting the modification of frailty and physical activity behaviour in patients undergoing elective cardiac surgery. Thus, the Pre-operative Rehabilitation for Reduction of Hospitalization After Coronary Bypass and Valvular Surgery (PREHAB) study (Clinical Trials Registry Number: NCT02219815) was a randomized controlled trial comparing a pre-operative, interdisciplinary, exercise intervention to current standard of care (StanC).[144] The PREHAB trial was a multi-centre, randomized controlled trial using assessor blinding and intention-to-treat analysis. The trial was conducted at two academic hospitals (i.e. St. Boniface Hospital Winnipeg, MB and Queen Elizabeth II Health Sciences Centre Halifax, NS) and one non-academic hospital (i.e. Saint John Regional Hospital Saint John, NB) that perform cardiac surgery. Additionally, each of these hospitals are partnered with a community-based CR facility, which provided the infrastructure and programming expertise necessary to deliver the intervention. The primary objectives of the trial were:

1. To determine if the PREHAB intervention decreases the severity of frailty, from baseline to pre-operatively, as assessed by a 30-item Functional Frailty Index (FFI).
2. To determine if the PREHAB intervention increases the amount of objectively accumulated MVPA in bouts of 10-minutes or more, from baseline to pre-operatively. Additionally, we characterized changes in total physical activity in 10-minute bouts,

light physical activity in 10-minute bouts, sporadic MVPA, sporadic total physical activity and sporadic light physical activity from baseline to pre-operatively. We also examined changes in sedentary time from baseline to pre-operatively in both PREHAB and StanC groups.

3. To determine if the PREHAB intervention influences functional walking ability, as assessed by a 6MWT and muscular strength/physical function as assessed by the SPPB.

We hypothesized that patients attending the PREHAB intervention would decrease their continuous FFI score and increase their accumulation of MVPA in 10-minute bouts significantly more than patients receiving StanC. Additionally, we hypothesized that the PREHAB intervention would: (1) increase total physical activity in 10-minute bouts; (2) increase light physical activity in 10-minute bouts; (3) increase sporadic MVPA; (4) increase sporadic total physical activity; (5) increase sporadic light physical activity; (6) decrease sedentary time; (7) improve functional walking ability; and, (8) increase muscular strength/physical function, more than patients receiving StanC. Note that the larger PREHAB trial (NCT02219815) is ongoing and will seek to investigate the effect of a pre-operative exercise and education program on hospital LOS; whereas, the present dissertation specifically investigated the effect of the intervention on the above noted primary and secondary outcomes. The results of the trial were reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials.[145]

Ethics Approval

The study protocol was reviewed and approved by the appropriate institutional review board or ethics committee for each participating centre. Locally, the University of Manitoba Health Research Ethics Board (H2014:208, Appendix A) and the St. Boniface Hospital Research

Review Committee (RRC/2014/1413, Appendix B) reviewed and approved the study protocol and participant information forms.

Recruitment, Eligibility Criteria and Screening

We began recruiting for this study in March of 2015 at the St. Boniface Hospital (Winnipeg, MB), Saint John Regional Hospital (Saint John, NB) and the Queen Elizabeth II Health Sciences Centre (Halifax, NS). From March 2015 to January 2016, we recruited 26 patients that were scheduled to undergo elective CABG, valve repair/replacement or combined procedures. While 1192 patients underwent elective cardiac surgery during the study recruitment period, a total of 199 patients were eligible for enrollment in the study. Note that the PREHAB randomized controlled trial is actively recruiting patients and will target a final sample size of 244 elective cardiac surgery patients; however, this dissertation will examine the first 26 patients enrolled in the trial. Refer to Figures 4 and 5 for an overview of the study design and for a flow of patient recruitment.

The inclusion criteria for the study was as follows:

1) Patients, aged 60 years or older, undergoing elective isolated CABG, aortic valve repair/replacement for moderate aortic stenosis or severe regurgitation, mitral valve repair/replacement for moderate stenosis or severe regurgitation or combined/valve procedures.

2) Patients with a CFS ≥3 (managing well) and < 7 (8 = very severely frail, approaching end-of-life or 9 = terminally ill) at time of acceptance for cardiac surgery.

3) Patients with an estimated ≥ 4-week surgical waitlist time.

The following patients were excluded from participating in the study:

1) Patients with unstable or recent unstable cardiac syndrome as defined by:

a. Severe heart failure (New York Heart Association Class IV) or angina (CCS Class IV) symptoms.
b. Critical left main coronary disease.
c. Hospitalization for arrhythmias, CHF or acute coronary syndrome prior to randomization.

2) Patients with severe left ventricular obstructive disease as defined by:

a. Severe aortic or mitral stenosis (aortic or mitral valve area <1.0cm^2 or mean gradient > 40 mmHg or > 10mmHg respectively).
b. Dynamic left ventricular outflow obstruction.

3) Patients demonstrating exercise induced ventricular arrhythmias or having experienced a recent hospitalization for arrhythmias.

4) Patients who had cognitive deficits that would preclude rehabilitation.

5) Patients with physical limitations that would preclude rehabilitation.

6) Patients that were unable to attend the PREHAB program.

Patient eligibility for the study was determined by reviewing hospital medical charts prior to the patient arriving in clinic. During an initial meeting with a cardiac surgeon, eligible and interested patients were approached by a research assistant who provided the patient with further details of the study. The patient was informed of the trial by the research assistant and was provided with a copy of the patient information and consent form at this time. Patients were provided with an adequate amount of time to consider their participation in the trial and were given an opportunity to ask questions. All patients enrolled in the study provided written informed consent prior to the baseline assessment and randomization. The patient information and consent form can be viewed in Appendix C.

Our strategy for rapid screening of frailty in incoming surgical patient consults utilized the 9-point CFS (Figure 3).[51] We defined a CFS score of greater than or equal to 3 (classified as "managing well") as an initial indication of frailty. Following training, clinicians completed a CFS score for every new cardiac surgery consult at each of the participating study sites. Patients with a CFS of 3 to 6 were eligible for enrollment in the trial. We excluded severely frail patients with a CFS greater than or equal to 7 due to physical limitations that would preclude participation in an exercise program. Following this initial indication of frailty, patients were subject to further frailty testing using a modified version of the Fried phenotype criteria[28] to ensure final eligibility for the study. Namely, a patient was deemed frail and thus eligible for the study if they met greater than 3 of the following 7 criteria: (1) slowness based on a 5-metre gait speed test[73]; (2) weakness assessed by grip strength[146,147]; (3) self-reported weight loss; (4) Exhaustion based on the two-item Center for Epidemiologic Studies Depression Index; (5) Depression assessed using the 5-Point Geriatric Depression Scale[148,149]; (6) Low physical activity assessed by the Paffenbarger Physical Activity Index[150]; and, (7) Cognitive impairment using the Montreal Cognitive Assessment[151,152].

Data Collection Schedule

All participants met with research staff at three time points during the course of the study: twice at the time of enrollment (i.e. baseline assessment, safety assessment/randomization) after the patient was referred for their surgical procedure and once approximately 1-week pre-operatively. At these time points, participants were provided with an accelerometer, instructions on how to use the device, underwent several physical performance tests and completed a written questionnaire package. In an attempt to avoid missing accelerometer data in patients that were called for their surgical procedure prior to their anticipated date, we also provided participants

with an accelerometer 4-weeks following initial randomization. This 4-week accelerometer data was only included in the analysis if pre-operative data was missing/unavailable. Demographic data collection occurred from both written and electronic medical record sources (i.e. patient information systems). Existing surgical and hospital databases were queried to capture patient demographics (i.e. age, gender, comorbidities and medications), physical measures and procedural urgency.

Figure 4. Overview of Study Design

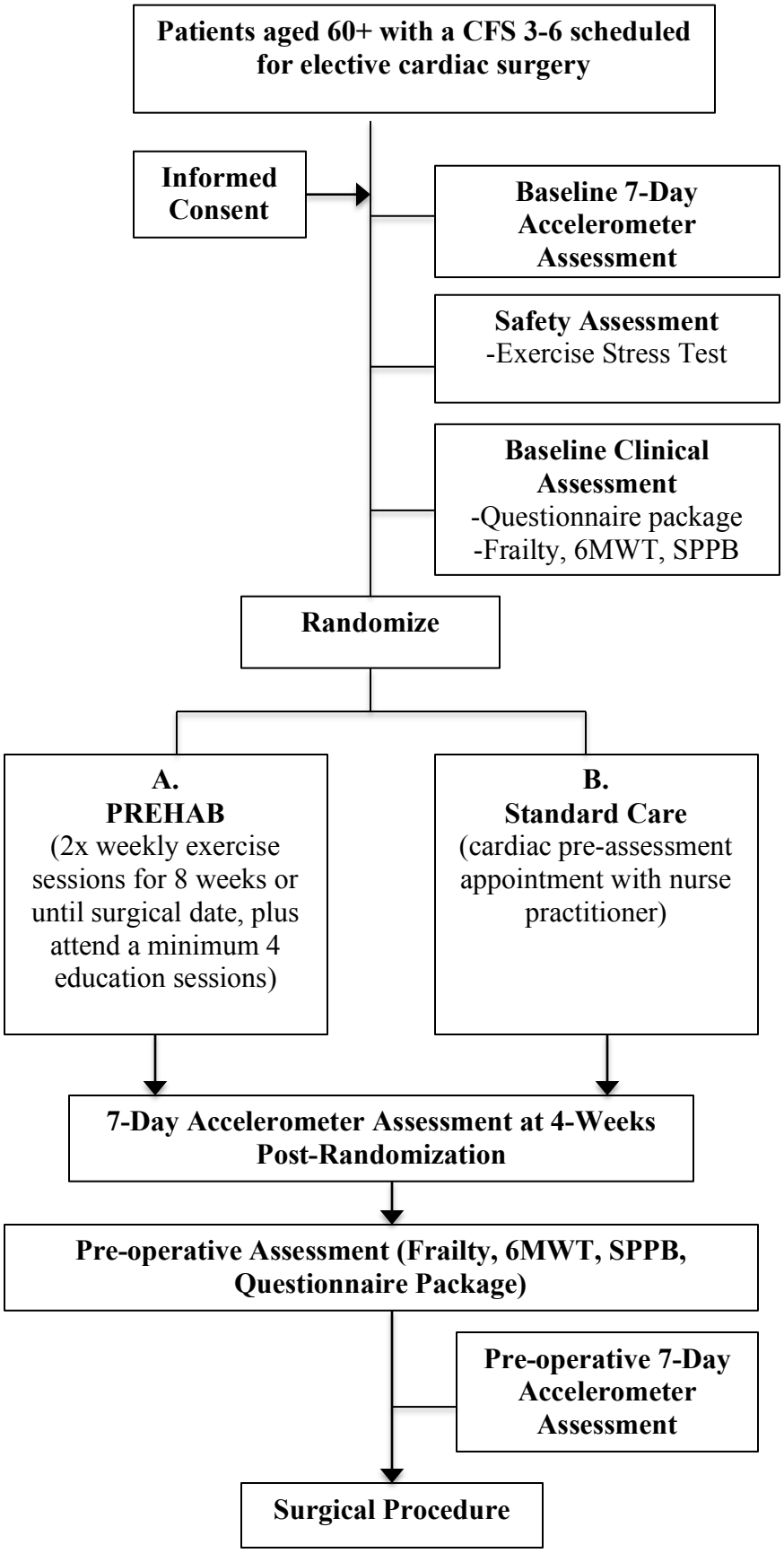
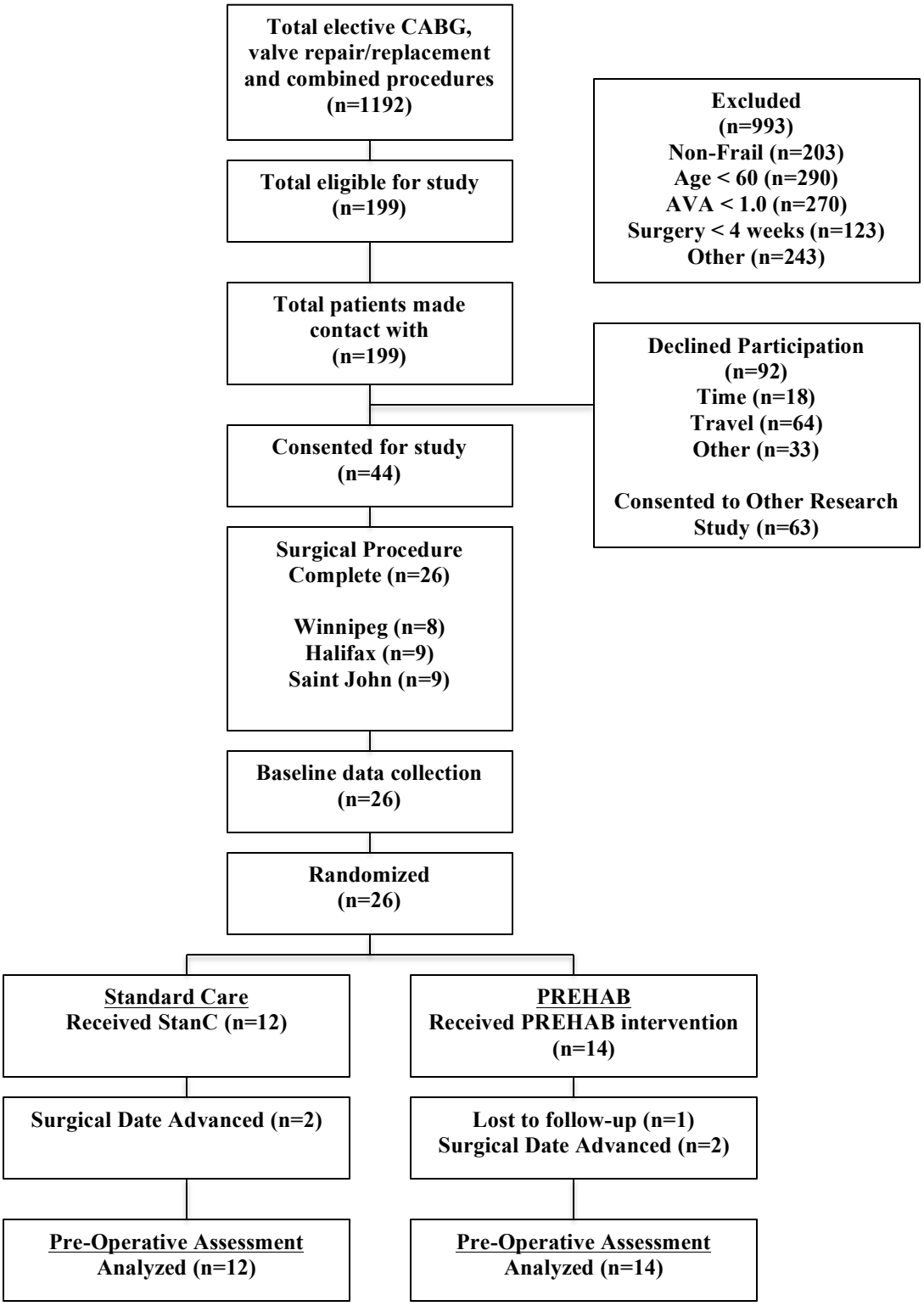


Figure 5. Patient Flow of Recruitment



Intervention vs. Standard Care

Randomization

After the consent process and baseline safety assessment, randomization (with concealed allocation) to study arms occurred on a 1:1 basis in permuted blocks via a pre-prepared, computer generated, randomized number. An independent biostatistician at the George and Fay Yee Centre for Healthcare Innovation (Winnipeg, MB) developed the randomization scheme, while a research assistant that was independent from the PREHAB study and not involved in data collection prepared opaque envelopes. All participants were free to withdraw from the study at any time without prejudice to future medical treatment.

Standard Care Arm (StanC)

The twelve patients randomized to the StanC arm received a standard, three-hour cardiac pre-assessment prior to their surgery, where a nurse practitioner and anesthetist individually assessed each patient's risk profile and cardiac status. Advice provided by the cardiac surgeon at the consult visit varied, however the majority of patients were advised to rest and participate in minimal amounts of light intensity physical activity prior to their surgery.

Intervention Arm

The fourteen patients randomized to the intervention group received, in addition to the above StanC, a four- to eight-week interdisciplinary, exercise and education program at a community-based CR facility. Adherence to the intervention was monitored by a swipe card system. For data collection purposes, completion of a minimum 8 sessions over 4-weeks was required to be categorized as completing the intervention. This pre-defined intervention length was based on pilot data indicating significant functional benefit (+174 meters, 43% improvement on 6MWT) after just four weeks of CR programming in a pilot study of pre-operative exercise and education

conducted at the St. Boniface Hospital.[128] Furthermore, the intervention was designed to include intensive exercise therapy and education within the first four weeks, followed by less-structured programming for the remaining four weeks to promote maintenance and sustained behaviour change. Thus, it was determined that that patients would likely derive significant health benefits from participating in the intervention for a period of four weeks.

All enrolled participants (i.e. intervention and StanC) were required to complete an intake health status assessment by the CR team at their respective site and complete a symptom-limited, graded exercise stress test supervised by a cardiologist using the modified Bruce protocol.[153] This intake assessment established the participant's safety to engage in physical activity and provided the basis for exercise prescription, which included an individualized, symptom-limited exercise program. Patients randomized to the intervention were required to complete a minimum of two sessions of supervised exercise per week for a period of four- to eight-weeks. Participants completed a warm-up program of approximately 15 minutes at the beginning of each session. Subsequently, aerobic exercise was prescribed at 40-60% of heart rate reserve (i.e. Karvonen Formula) based on baseline exercise stress test performance.[154] Aerobic exercise was prescribed for approximately 10-30 minutes, depending on individual tolerance and level of conditioning. Aerobic prescription was subsequently progressed to high intensity exercise in the context of symptom-limited, interval training up to 85% of maximal aerobic capacity based upon recommendations by a cardiologist, CR staff and individual tolerance.[155] All individual exercise sessions were concluded with a 10-minute cool down period. In addition to the prescribed exercise program, patients were required to attend and participate in 4 educational sessions tailored to self-management for CR and healthy living practices. These education sessions were designed to be directly relevant to the study population and covered a range of topics, including

risk factor reduction, medication use, cardiovascular physiology, smoking cessation, healthy eating, stress management and promotion of self-managed care.

Risks Associated with the Intervention

The project was designed in consultation with experts from the Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR), the Winnipeg Regional Health Authority (WRHA), the Reh-Fit Centre, the Wellness Institute, the Cardiac Sciences Program at the St. Boniface Hospital and the Cardiovascular Health Research in Manitoba group. Based on prior studies,[26,132] we determined that an exercise therapy program would likely decrease a patients' overall surgical risk and improve post-operative outcomes. Indeed, previous literature has confirmed the safety of CR outpatient programs, reporting the incidence of MI to be one per 293,990 patient hours and one per 783,972 patient-hours for fatalities.[156] Even so, participants were informed of the risks associated with participation in any exercise program, including the described PREHAB intervention. However, these risks were mitigated by the exclusion of participants with exercise-induced arrhythmias, unstable cardiac syndrome, severe left ventricular obstructive disease and any other physical limitations that would preclude participation in physical activity. All participants underwent a baseline exercise stress test supervised by a cardiologist, which was used to identify exercise-induced arrhythmias or other adverse symptoms occurring in response to physical activity. Furthermore, all exercise classes were supervised by qualified instructors at local CR sites, which were staffed by medical professionals to ensure safety of participants (e.g. nurses, physicians, dietitians, exercise specialists).

During the consent process and at any point during the conduct of the study, patients had the right to refuse participation. All potential subjects were encouraged to read through the consent

forms thoroughly prior to agreeing to participate in the study. Additionally, patients were excluded from the study if medical staff at either the local CR site or the participant's treating hospital determined that study participation could adversely influence their health status.

Compensation

All procedures performed as part of this study were provided at no cost to the participant. Patients randomized to the intervention arm were provided with parking passes (if required at the local site) at their respective CR facilities to minimize the burden of participating in the intervention.

Primary Outcome Variable

The study contained co-primary outcomes, including: (1) a change in frailty from baseline to pre-operatively; and, (2) a change in MVPA accumulated in 10-minute bouts, from baseline to pre-operatively.

Change in Frailty

Changes in frailty were assessed using a 30-item FFI that was developed utilizing the original model proposed by Rockwood and colleagues.[56,157] A frailty index was chosen over a frailty phenotype in the present study, as the frailty phenotype was hypothesized to be less sensitive to change in response to an exercise intervention. Briefly, the FFI in the present study was comprised of 30 variables, spanning a broad range of health indicators, including physical competency, self-reported ADL's, mood status and cognitive function. Variables were eligible for inclusion in the index if they were measured at both baseline and pre-operative assessments, and were selected for inclusion based on the criteria recommended by Searle et al.[56] Namely, variables included in the FFI were determined to be associated with health status, covered a

range of physiologic systems, generally increased in prevalence with age and did not saturate early. Recoding of individual variables within the index was conducted for categorical, ordinal and interval data such that variables could be scored from 0-1, where 0 represents absence of a deficit and 1 indicates full expression of a deficit. Several variables were coded using cut-points previously established in the literature where applicable; whereas, others were intuitively coded based on the number of possible responses to a question. Previous literature has confirmed that the specific composition of variables included within a frailty index does not influence its validity,[57] provided that the variables are related to health status, cover a range of domains, increase in prevalence with age and do not saturate early.[56] Additionally, all variables included in the present FFI have been used in previously published variations of the frailty index.[56,58,71] In a secondary analysis of three diverse longitudinal studies of community-dwelling adults (i.e. Nova Scotia Health Survey, Survey of Health, Aging and Retirement in Europe and the Yale Precipitating Events Project), Peña and colleagues also confirmed that variables within a frailty index can be coded as either dichotomous or continuous with negligible impact on the tool's ability to predict mortality.[158] For an overview of the variables included in the FFI, refer to Appendix D.

To establish the concurrent validity of the present FFI, we compared baseline frailty using both the current 30-item variation and a previously published index.[71] Notably, the index used to established concurrent validity has previously been demonstrated to be predictive of post-operative delirium, a transient state of severe confusion resulting from rapid changes in brain function. In a prospective cohort study of elective cardiac surgery patients conducted at the St. Boniface Hospital, frailty scores ≥ 0.3 were associated with a 3-fold increased risk of post-operative delirium (OR: 3.72 95% CI 1.39-9.92). Therefore, we used this previously published

frailty index as a comparator to establish the concurrent validity of the present tool. To further investigate the concurrent validity of the FFI developed as part of this dissertation, we also examined the agreement and association between the FFI and the well-established phenotype model of frailty.[28]

Change in Physical Activity Behaviour

Multi-directional accelerometers, considered the gold standard for assessing physical activity behaviour,[159] were used to objectively assess physical activity intensity and duration over a period of seven consecutive days at both baseline and pre-operative time points. Specifically, we used Actical accelerometers (Phillips – Respironics, Oregon, USA), which are highly accurate in assessing the duration and intensity of physical activity, have been validated in both children and adults,[160] and have demonstrated superior reliability compared to other common accelerometer models.[161] These devices utilize a piezo-electric accelerometer to detect motion in three directions, converting accelerations in the range of 0.05 to 2.0 G into an electrical charge and summing the counts over a specified time interval, commonly referred to as an epoch.[162] As such, accelerometers classify intensity based on the number of counts occurring within a given time period.

The cut points used in this project to identify MVPA were based on the work of Hooker and colleagues, who conducted an accelerometer cut-point validation study in community-dwelling middle-age (i.e. 45-64 years) and older adults (i.e. over 65 years).[163] Specifically, accelerometer data was analyzed in 10-minute intervals over 30-second epochs, using a cut point of 532.5 counts per 30-seconds. Patients were asked to wear the accelerometer over their right hip on an elasticized belt during waking hours for a period of 7-consecutive days. A valid file for data analysis was defined as including a minimum of 4 days with at least 10 hours per day of wear

time, as previously published in the literature.[164] Non-wear time was defined as at least 120 consecutive minutes of sedentary time (0 to 49.5 counts per 30-seconds).[165] Wear time was calculated by subtracting non-wear time from 24 hours.

The MVPA cut point of 532.5 counts per 30-seconds was chosen based on the similarities of the present study to the participant population and accelerometer model used by Hooker et al.[163] While a higher cut point (i.e. 1535 counts per minute)[166] was used to analyze MVPA in the Canadian Health Measures Survey,[164] their study population was considerably younger (ages 20-79) and healthier than the population investigated in the present study. A recent systematic review conducted by Gorman et al. highlights the importance of utilizing population-specific cut points in accelerometer studies, suggesting that due to age-related declines in physical fitness, lower MVPA cut points are required for studies investigating older adults.[167] Notably, study authors have reported MVPA cut points ranging from 574 to 3250 counts per minute in the literature, with the most commonly utilized cut point being 1952 counts per minute. Even so, we selected the cut point of 1065 counts per minute (i.e. 532.5 counts per 30-seconds) due its validation in community-dwelling adults over the age of 65.[163] Additionally, we decided to use the cut point proposed by Hooker and colleagues[163] instead of the cut point proposed by Copeland and colleagues[168] due to its validation in the Actical accelerometer model, which is the model that was used in the present study. A summary of accelerometer calibration studies in adults, using both the Actical and ActiGraph (Pensacola, Florida, USA) models can be viewed in Table 3.

Table 3. Examples of Accelerometer Cut Point Calibration Studies in Adults

Study	Accelerometer Model	Study Population	MVPA Cut Point (counts/min)
Hooker (2011)[163]	Actical	Ages 45-84 (n=73)	1065
Colley (2011)[166]	Actical	Age 18+ (n=26)	1535
Giffuni (2012) [169]	Actical	Ages 18-63 (n=29)	1726
Heil (2006)[160]	Actical	Mean age 37 (n=24)	1200
Welk (2004)[170]	Actical	College age (n=38)	1969
Swartz (2000)[171]	ActiGraph	Ages 19-74 (n=70)	574
Copeland (2009)[168]	ActiGraph	Ages 64-77 (n=38)	1041
Freedson (1998)[172]	ActiGraph	Ages 18+ (n=50)	1952
Yngve (2003) [173]	ActiGraph	Ages 18+ (n=28)	2260
Lopes (2009)[174]	ActiGraph	Mean age 63 (n=26)	2400

Secondary Outcome Variables

Other Assessments of Physical Activity

Additional accelerometer data parameters assessed included ten-minute bouts of total physical activity ($TotalPA_{10min}$), light physical activity in 10-minute bouts ($LightPA_{10min}$), sporadic MVPA ($MVPA_{spor}$), sporadic total physical activity ($TotalPA_{spor}$), sporadic light physical activity ($LightPA_{spor}$) and sedentary time. Sedentary time was defined as 0 to 49.5 counts per 30-seconds; whereas, light physical activity was classified based on the MVPA cut-point described in the primary outcome variable, namely, activity between 49.5 and 532.5 counts per 30-seconds. Sporadic physical activity was assessed in bouts of 30 seconds or greater, as this is the minimum bout for data collection purposes using a 30-second epoch length. In addition to accelerometer parameters, all participants randomized to the intervention arm maintained a standard exercise log monitoring intensity, duration and modality of both aerobic and resistance exercise programming.

Phenotype Frailty

As an additional marker of frailty, we also investigated changes in the Fried phenotype criteria[28] from baseline to pre-operatively in both intervention and StanC groups. Cut-offs for individual variables within the criteria have been previously published,[28,37] and individuals were classified as frail if they possessed at least three of the following seven criteria: (1) Shrinking; (2) Weakness; (3) Exhaustion; (4) Slowness; (5) Low Physical Activity; (6) Depression; and, (7) Cognitive Impairment. Standardized questionnaires, including the Paffenbarger Physical Activity Index[150] and the two-item Center for Epidemiologic Studies Depression index were used to assess physical activity behaviour and exhaustion, respectively. Weight loss over the past year was assessed via self-report; whereas, slowness and weakness were assessed objectively using the 5-metre gait speed test[73] and a grip strength dynamometer[146,147]. To measure grip strength, a calibrated, Jamar hand dynamometer (Lafayette Instrument Company, USA) was used. Participants were asked to position their elbows in 90-degree flexion and their hand in a semi-pronated position. The participant was then instructed to squeeze with as much force as possible for two to three seconds, or until the needle stopped rising, and the research assistant then recorded this value to the nearest kilogram. The best result of three trials with either the dominant or non-dominant hand was used for data analysis purposes. To assess normal walking speed, three separate trials of the 5-metre gait test were administered to each patient, with the average of the three trials being used for data analysis purposes. Patients were instructed to walk "at a comfortable pace" while a research assistant began timing at the first footfall following the 0-metre line. The timer was subsequently stopped at the first footfall after the 5-metre line and the final time was recorded in seconds. Depression and cognitive impairment were assessed

using standardized questionnaires, including the Geriatric Depression Scale (GDS-5)[148,149] and the Montreal Cognitive Assessment (MoCA), respectively.[151,152]

Functional Walking Ability

Changes in functional walking ability from baseline to pre-operatively were assessed using a standard 6MWT. All patients enrolled in the study performed the 6MWT indoors on a flat surface. The test was conducted in accordance with the guidelines provided by the American Thoracic Society, where participants were instructed to cover as much distance as possible during the six-minute time interval without running or jogging.[175] Study patients were permitted to use their walking aid if the aid was being used as part of everyday living. Additionally, patients were informed that they could stop and rest or terminate the test at any time throughout the assessment. Research assistants did not provide verbal encouragement and patients were only provided with the elapsed time of the test at 1-minute intervals. Total distance covered was recorded in meters.

The 6MWT has been used previously in patients with heart failure,[176,177] pulmonary disease,[178,179] and a variety of cardiac populations.[180,181] Notably, cardiac patients who walk less than 300 meters on a 6MWT are at a 3.7-fold increased risk of dying compared to those who walk greater than 450 meters,[182] while an improvement of 50 meters is generally considered to be a clinically relevant change in physical performance.[183] Furthermore, Ross and colleagues evaluated the ability of the 6MWT to predict VO_{2peak} in cardiopulmonary patients and reported a high correlation (R=0.82) between a maximal graded treadmill test and 6MWT results.[184] The 6MWT has also been used previously to evaluate changes in physical fitness following pre-operative exercise interventions in elective CABG patients.[26]

Physical Function and Muscular Strength

Changes in physical function and muscular strength from baseline to pre-operatively were assessed using the SPPB (Appendix E). The SPPB is a composite score combing results from a balance test, gait speed assessment and chair stand test. Scores range from 0 (i.e. worst) to 12 (i.e. best), and participants can be classified as having severe (0-3), moderate (4-6), mild (7-9) or minimal (10-12) limitations in physical function based on their final composite score.[52] Notably, there is a stepwise decline in the age and sex-adjusted rates of mortality and nursing home admission associated with increasing scores on the SPPB.[52] Furthermore, a 0.3 to 0.8 point change on the SPPB has been deemed to be a small, but clinically relevant change in physical performance.[183,185]

Physical Measures

The research staff collected the following physical measures at the baseline assessment in all study patients: resting BP, resting heart rate, height and weight.

Statistical Analysis and Sample Size Calculation

Descriptive statistics, including mean ± standard deviation for continuous variables and percentages for dichotomized variables, were computed to characterize baseline demographics and surgical parameters. Group comparisons at baseline for continuous variables were compared using an independent t-test or Mann-Whitney U-test for parametric and non-parametric data, respectively. Categorical variables were compared using chi-square or Fisher exact tests. The primary outcomes of frailty and MVPA in 10-minute bouts were analyzed using a two-way ANOVA with one repeated measure (i.e. time) and one between group comparison (i.e. control or intervention arm). If the statistical analysis returned a significant value ($p \leq 0.05$), a Newman-Keuls method post hoc analysis was performed to identify significant differences between

specific means. To examine longitudinal changes in binary variables over time, a generalized estimating equation was used. Time points for the study included baseline and pre-operative assessments, with an intent-to-treat analysis being utilized to handle drop-outs/missing data points. Patients randomized to the PREHAB arm were considered to have completed the intervention if they attended a minimum of 8 sessions over a period of at least four-weeks. To compare the concurrent validity of the FFI and a previously published frailty index at baseline,[71] a Bland-Altman plot was used to visually analyze the observed agreement between the two measurement approaches.[186,187] A Cohen's kappa coefficient[188] was also calculated to establish agreement between the two measurement approaches using the dichotomous frailty cut-off of 0.25 to distinguish frail and non-frail individuals.[54] We also utilized a Cohen's kappa coefficient and Spearman correlation to examine the strength of agreement between the FFI and the phenotype frailty criteria. All study participants that were randomized to the intervention or StanC arms were included in the final analyses, according to an intention-to-treat approach. All statistical analyses were conducted using Statistica software (StatSoft Inc., Dell Software, Tulsa, USA) and SPSS version 17.0 (IBM Corp., Armonk, USA).

Preliminary data demonstrated that in 4 PREHAB patients, the amount of MVPA accumulated in 10-minute bouts increased by 107 minutes from baseline to pre-operatively.[128] Based on this pilot data, a sample size of 10 individuals (i.e. 5 per study arm) would be required to detect a statistically significant change. However, based on the Physical Activity Guidelines Advisory Committee Report[189] an increase of 56 minutes of MVPA per week (i.e. 8 minutes per day) in previously sedentary individuals decreases the risk of mortality by 9%. Therefore, we decided to use this value as a minimal clinically important difference. Thus, a sample size of 30 individuals (i.e. 15 per study arm) were determined to be required for a two-tailed alpha test of 0.05 and a

power of 80% to detect a change of 56 minutes per week between groups. Based on the work of Arthur et al.,[132] we anticipated a 20% dropout rate and intended to recruit 36 patients (i.e. 18 in each study arm) to achieve an eventual sample size of 30 after dropout. Since the present study contained co-primary outcomes, we also conducted a sample size calculation to determine the anticipated sample size required to detect a statistically significant change in the FFI between intervention and StanC groups. To our knowledge, there is no existing literature that has examined the magnitude of change in the frailty index following an exercise intervention; however, many studies have previously suggested that deficits accumulate at a rate of 0.03 per year.[56,157,190] Based on this information and the literature suggesting that the "cut-off" distinguishing frail patients from non-frail patients is 0.25 (i.e. 7.5 deficits out of 30), we decided to use an absolute difference of 0.03 in the FFI as a clinically relevant change in frailty status following an exercise intervention. A sample size of 36 patients (i.e. 18 per study arm) was determined to be required for a two-tailed alpha test of 0.05 and a power of 80% to detect an absolute change of 0.03 in the FFI. Due to a slower than expected rate of recruitment, we analyzed data from the first 26 patients enrolled in the larger PREHAB randomized controlled trial. Based on our sample size calculations, we acknowledge that it is possible that our small sample size would not have the statistical power to provide insights about the effectiveness of the PREHAB intervention. Nonetheless, we determined that an interim analysis of the first 26 patients would provide valuable insight related to the effectiveness of the intervention and provide preliminary evidence to guide future program initiatives.

Chapter 4: Results

Baseline Characteristics

Medical chart reviews were conducted for all study participants to collect baseline demographics and relevant personal characteristics, including cardiovascular risk factors, medication usage, lab values and comorbidities (Table 4). Basic patient demographics, including age, gender, BMI, CFS, education level and smoking status did not differ between StanC and PREHAB groups. Relevant risk factors for cardiovascular disease and other comorbidities were also similar in both experimental groups. These risk factors included ejection fraction, BP, CCS Class, previous MI, diabetes, CVD, PVD, hypertension, dyslipidemia and cognitive impairment. Additionally, medication usage did not differ between groups, including the prescription of nitrates, beta-blockers, anti-platelet agents, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), statins and anticoagulants. Values for serum albumin were significantly higher in the PREHAB group compared to the StanC group (36.6 g/L vs. 30.2 g/L; $p<0.05$); in fact, StanC group patients had slightly lower serum albumin concentrations than what is considered normal (i.e. 35 to 50 g/L), which may be an indicator of overall nutritional status, liver or kidney damage. However, other lab values did not differ between groups, including hemoglobin, glycated hemoglobin, white blood cell (WBC) count, platelet count and creatinine. The study population achieved a baseline MET level of 5.3 ± 2.7 and 5.4 ± 1.9 on a stress test in StanC and PREHAB groups, respectively. While these values are considerably lower than reference values for Canadian adults over the age of 60,[191] the average aerobic capacity of patients in our cohort is consistent with data from Kavanagh et al. who previously reported an average of 5.5 ± 1.3 METs amongst CABG patients.[100]

Table 4. Comparison of Baseline Characteristics Between StanC and PREHAB Patients.

	StanC (n=12)	PREHAB (n=14)	p-value
Demographics			
Age (years)	70.3 ± 5.4	72.8 ± 7.1	0.32
Gender (% female)	3 (25.0%)	3 (21.4%)	1.00
Height (cm)	171.3 ± 7.1	170.4 ± 11.6	0.82
Weight (kg)	89.2 ± 14.4	85.7 ± 18.4	0.61
BMI	30.6 ± 6.7	29.3 ± 4.7	0.56
MET Level	5.3 ± 2.7	5.4 ± 1.9	0.89
CFS	4.0 ± 0.9	3.3 ± 0.7	0.06
Education (% College)	3 (25.0%)	8 (61.5%)	0.11
Current Smoker	2 (16.7%)	0 (0%)	0.16
Smoking History	5 (41.7%)	10 (71.4%)	0.16
Cardiac Status			
Ejection Fraction (%)	57.5 ± 8.9	54.0 ± 16.5	0.59
CCS Class	2.7 ± 0.5	2.4 ± 0.5	0.43
Resting Diastolic BP	73.5 ± 10.8	72.3 ± 16.3	0.86
Resting Systolic BP	132.1 ± 14.0	138.6 ± 21.5	0.46
Resting Heart Rate	68.8 ± 15.4	70.7 ± 17.0	0.80
CHF	4 (33.3%)	3 (25.0%)	1.00
Previous MI	4 (33.3%)	3 (25.0%)	1.00
Atrial Fibrillation	2 (16.7%)	0 (0%)	0.48
Prior Angioplasty or Stent	3 (25.0%)	2 (16.7%)	1.00
Pacemaker	0 (0%)	0 (0%)	1.00
Defibrillator	0 (0%)	0 (0%)	1.00
Cardiogenic Shock	0 (0%)	0 (0%)	1.00
Endocarditis	0 (0%)	0 (0%)	1.00
Comorbidities			
Diabetes Mellitus	6 (50.0%)	7 (53.8%)	1.00
CVD	3 (25.0%)	0 (0%)	0.09
PVD	0 (0%)	1 (7.7%)	1.00
COPD	0 (0%)	2 (15.4%)	0.48
Asthma	1 (8.3%)	0 (0%)	0.48
Arthritis	3 (25.0%)	5 (38.5%)	0.67
CKD	1 (8.3%)	0 (0%)	0.48
Dialysis	0 (0%)	0 (0%)	1.00
GI Disease	0 (0%)	3 (23.1%)	0.22
Dyslipidemia	11 (91.7%)	7 (53.8%)	0.07
Pulmonary Hypertension	0 (0%)	3 (23.1%)	0.22
Hypertension	10 (83.3%)	10 (76.9%)	1.00
Visual Impairment	4 (33.3%)	5 (38.5%)	1.00
Hearing Impairment	0 (0%)	2 (15.4%)	0.48
Liver Disease	0 (0%)	0 (0%)	1.00
Cirrhosis	0 (0%)	0 (0%)	1.00

Cancer	1 (8.3%)	1 (7.7%)	1.00
Dementia	0 (0%)	0 (0%)	1.00
Cognitive Impairment	1 (8.3%)	0 (0%)	0.48
Clinical Depression	1 (8.3%)	1 (7.7%)	1.00
Anxiety/Panic Attacks	0 (0%)	1 (7.7%)	1.00
Lab Values			
Hemoglobin (g/L)	127.2 ± 13.0	125.6 ± 20.5	0.83
HbA1c (%)	6.6 ± 1.2	6.7 ± 1.5	0.94
WBC Count (billion cells/L)	7.4 ± 1.6	9.8 ± 4.2	0.10
Platelet Count (billion/L)	202.3 ± 57.2	192.6 ± 61.0	0.71
Creatinine (μmol/L)	89.1 ± 26.5	67.8 ± 35.6	0.14
Albumin (g/L)	30.2 ± 3.7	36.6 ± 3.2	**0.02**
Medications			
Nitrate	9 (75.0%)	10 (71.4%)	1.00
Acetylsalicylic Acid	9 (75.0%)	9 (64.3%)	0.68
Anti-Platelet	4 (33.3%)	5 (35.7%)	1.00
Beta-Blocker	8 (66.7%)	9 (64.3%)	1.00
ACE Inhibitor	5 (41.7%)	5 (35.7%)	1.00
ARB	2 (16.7%)	5 (35.7%)	1.00
CCB	7 (58.3%)	6 (42.9%)	0.70
Statin	7 (58.3%)	6 (42.9%)	0.70
Anticoagulant	3 (25.0%)	5 (35.7%)	0.68
Benzodiazepine	2 (16.7%)	4 (28.6%)	0.65
Anti-depressant	2 (16.7%)	4 (28.6%)	0.65
Anti-arrhythmic	2 (16.7%)	4 (28.6%)	0.65
Diuretic	5 (41.7%)	6 (42.9%)	1.00
Steroid	2 (16.7%)	4 (28.6%)	0.65
Insulin	4 (33.3%)	5 (35.7%)	1.00
Proton Pump Inhibitor	2 (16.7%)	4 (28.6%)	0.65
Antibiotic	3 (25.0%)	4 (28.6%)	1.00

Continuous variables expressed as mean ± standard deviation. Categorical variables expressed in frequencies (percentage of group). Statistical comparisons were calculated using χ^2 or Fisher exact test for categorical variables and t test for continuous variables. BMI, body mass index; MET, Metabolic Equivalent of Task; CFS, Clinical Frailty Scale; CCS, Canadian cardiovascular society angina score; BP, blood pressure; CHF, congestive heart failure; MI, myocardial infarction; CVD, cerebrovascular disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; GI, gastrointestinal; HbA1c, glycated hemoglobin; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Surgical Parameters

Table 5 presents data collected for relevant surgical parameters. Although the intent of this dissertation was to investigate pre-operative risk factors, several surgical parameters were compared to establish that experimental groups were indeed similar with respect to the operative procedure itself. Time on wait list, procedural type, ICU LOS and hospital LOS did not differ between StanC and PREHAB groups. Patients enrolled in the study experienced a median (IQR) procedural wait time of 55 (39.8-81.3) and 60 (47.5-71.5) days in StanC and PREHAB groups, respectively. These average wait times are representative of the elective patient population in Manitoba, where wait times range from 43 to 180 days. The majority of study patients (i.e. 60% StanC, 58.3% PREHAB) underwent isolated CABG procedures, whereas a small number of patients underwent isolated valve (i.e. 0% StanC, 25% PREHAB) and combined procedures (i.e. 40% StanC, 16.7% PREHAB). Operative complications in the StanC group included four distinct incidents of atrial fibrillation, two occurrences of prolonged ventilation (i.e. ventilation > 24 hours), and one occurrence of stroke, gastrointestinal event, conduction disturbance and re-operation. Similarly, the PREHAB group experienced six individual occurrences of atrial fibrillation as well as one patient that experienced pneumonia, minor acute kidney injury and a gastrointestinal event. There were no differences in the number of patients experiencing operative complications between StanC and PREHAB groups.

Table 5. Comparison of Surgical Parameters for StanC and PREHAB Patients.

	StanC (n=12)	PREHAB (n=14)	p-value
Surgical Characteristics			
Time on Wait List (days)	55.0 (39.8-81.3)	60.0 (47.5-71.5)	0.83
Procedural Type			0.17
Isolated CABG	6 (60%)	7 (58.3%)	
Isolated Valve	0 (0%)	3 (25%)	
CABG + Valve	4 (40%)	2 (16.7%)	
Operative Complications	8 (66.7%)	7 (50%)	0.45
ICU Length of Stay (hours)	32.8 (19.9-82.6)	21.9 (19.4-42.5)	0.42
Length of Hospital Stay (days)	8.0 (5.3-19.5)	7.0 (6.5-8.5)	0.62

Continuous variables expressed as median (interquartile range). Categorical variables expressed in frequencies (percentage of group). Statistical comparisons were calculated using χ^2 or Fisher exact test for categorical variables and Mann-Whitney test for continuous variables. CABG, coronary artery bypass graft; ICU, intensive care unit.

Cardiac Rehab Attendance Data

Intervention attendance was monitored via a patient specific swipe card system at each individual study location and was collected in all patients randomized to the PREHAB intervention (n=14; Table 6). PREHAB patients were enrolled in the intervention for an average of 7.7 ± 5.5 weeks, accumulating a mean 6.7 ± 6.0 sessions over this period. Based on a previous pilot study[128] indicating significant functional benefit following an intervention duration of four-weeks, we defined intervention completion as consisting of attendance at eight sessions (i.e. two per week) over a minimum of four-weeks. Using this definition of intervention completion, 28.6% of PREHAB patients completed the interdisciplinary CR program. Additionally, using the patient's time on the wait-list and assuming two sessions per week as a target attendance rate, we determined that 28.6% of patients achieved at least 50% attendance, while 57.1% of patients attended 25% of total possible PREHAB sessions.

Table 6. PREHAB Intervention Attendance Data.

	PREHAB (n=14)
Attendance Data	
Mean time in Intervention (weeks)	7.7 ± 5.5
Sessions Attended	6.7 ± 6.0
Completed Intervention	4 (28.6%)
75% Completion	4 (28.6%)
50% Completion	4 (28.6%)
25% Completion	8 (57.1%)

Continuous variables expressed as mean ± standard deviation. Categorical variables expressed in frequencies (percentage of group). Intervention completion defined as attending PREHAB for a minimum 8 sessions for a period of 4 weeks or more. Percentage completion determined by the following equation ((Actual Attended Sessions/Expected Attendance)*100).

Patient Safety and Adverse Events

Overall, the exercise intervention was well tolerated with few incidences of adverse events. Our cohort experienced a total of four adverse events, however, these events were determined to be unrelated to the exercise intervention itself. In the PREHAB group, two patients were hospitalized for serious adverse events, including one occurrence of unstable angina and one incidence of post-operative stroke. It should be noted that the patient hospitalized for unstable angina had attended a PREHAB session more than 72 hours prior to the occurrence of the event. As such, an independent data safety monitoring board determined that this event did not occur as a result of the intervention. The occurrence of stroke in a patient randomized to the PREHAB group was also determined to be unrelated to the exercise intervention by an independent data safety monitoring board, as the incident occurred post-operatively. In the StanC group, two patients were hospitalized for serious adverse events, with one patient experiencing a post-operative stroke and another patient suffering worsening angina. As these patients were randomized to the StanC arm, an independent data safety monitoring board determined that neither adverse event occurred as a result of their enrollment in the study. Of the 26 patients

enrolled in the study, two StanC and two PREHAB patients had their surgical procedure advanced due to worsening symptoms experienced while on the wait list.

Changes in Frailty

Concurrent Validity of the Functional Frailty Index

As described previously, the FFI was specifically developed as part of this dissertation to provide a measure of frailty that would be both sensitive to change and also appropriately represent the frailty status of an individual patient. To establish the concurrent validity of the FFI, we compared baseline frailty to a previously published index developed by Jung and colleagues.[71] Note that the previously published index by Jung and colleagues could not be used as a marker of changes in frailty in the present study, as not all variables were collected at both pre- and post-operative time points. Using a cut-off of 0.25 to distinguish frail and non-frail patients,[54] the observed agreement was 88% with a kappa statistic of 0.75, which is classified as a moderately strong level of agreement.[192] This level of agreement can be observed visually in the Bland-Altman plot illustrated in Figure 6, where all but one data point falls within two standard deviations of the mean. We also demonstrated a significant association ($r=0.80$; $p<0.05$) between the FFI developed for the present study and the Jung frailty index using a Pearson correlation (Figure 7, Panel A). To further establish the concurrent validity of the FFI, we compared our frailty tool to the well-established frailty phenotype criteria using both a Cohen's kappa coefficient and a Pearson correlation. Although the kappa statistic of 0.24 indicated a minimally strong level of agreement, we demonstrated a significant correlation ($r=0.84$; $p<0.05$) between the FFI and the phenotype frailty criteria (Figure 7, Panel B).

Figure 6. Bland-Altman Plot Representing the Visual Agreement Between Functional Frailty Index and Jung Frailty Index at Baseline.

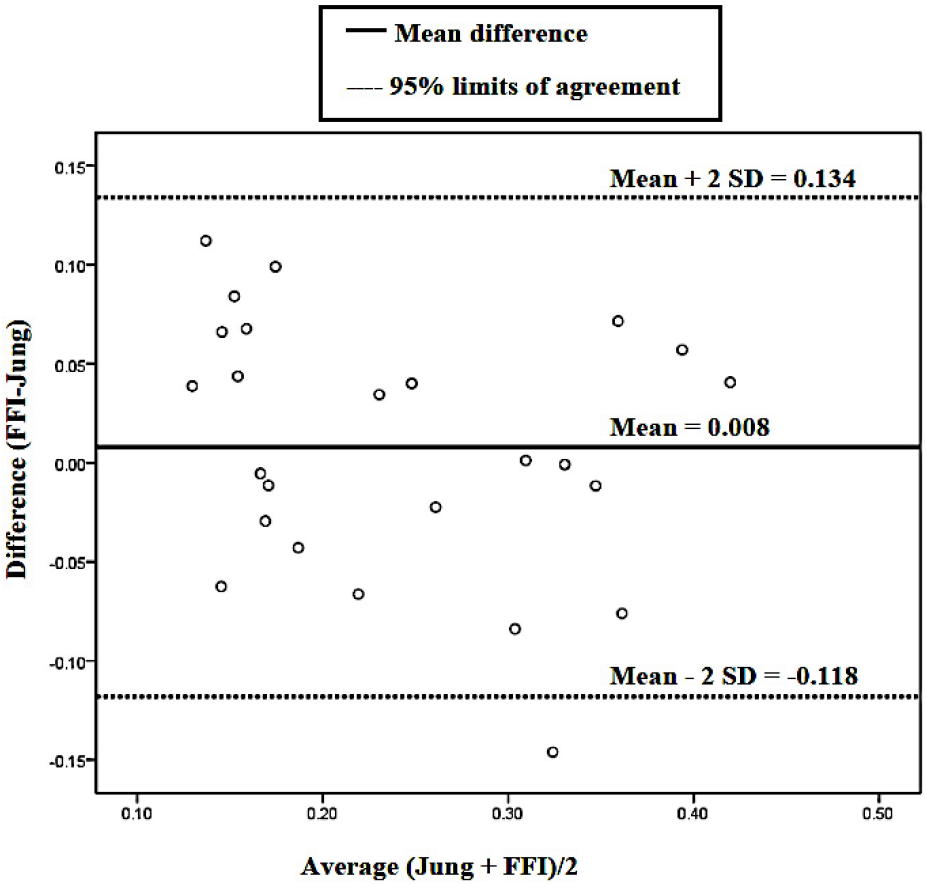
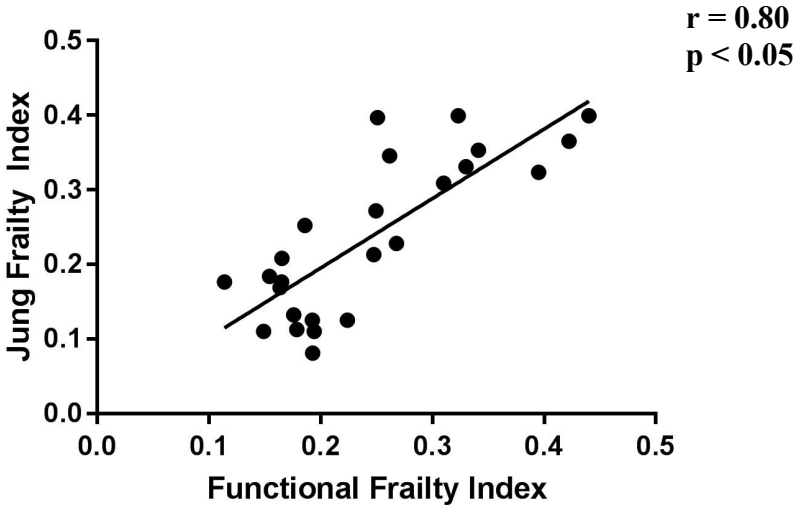
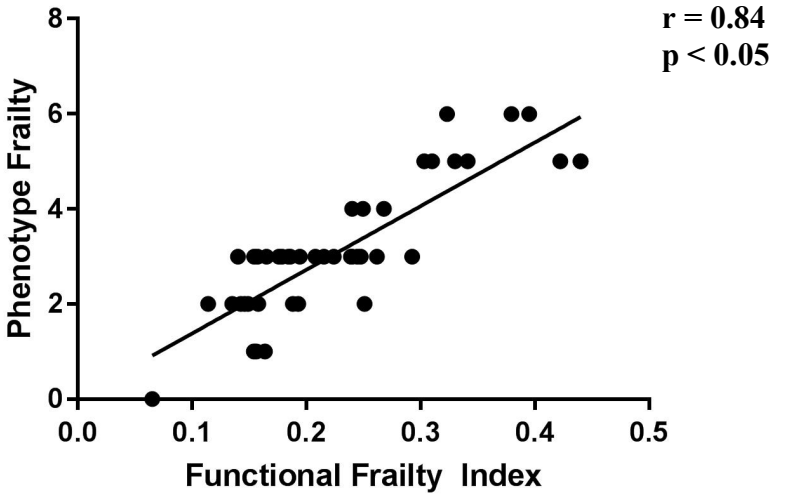


Figure 7. Associations Between Functional Frailty Index, Jung Frailty Index and Phenotype Frailty. Functional Frailty Index and Jung Frailty Index at Baseline (n=26; Panel A). Functional Frailty Index and Phenotype Frailty (n=52; Panel B). Significant associations for and Jung Frailty Index (p=0.0001) and Phenotype Frailty (p=0.0001).

A. Jung Frailty Index



B. Phenotype Frailty



Functional Frailty Index and Phenotype Frailty

Patients enrolled in the study had average baseline FFI scores of 0.27 ± 0.09 and 0.22 ± 0.08 in PREHAB and StanC groups, respectively. We also assessed frailty using the well-established phenotype model. Patients randomized to the StanC group expressed an average of 3.6 ± 1.2 deficits, whereas patients in the PREHAB group expressed 3.3 ± 1.5 deficits at baseline. No differences were observed for either the FFI or the phenotype frailty criteria at baseline (Table 7). Similarly, StanC and PREHAB were not different when FFI was analyzed pre-operatively; however, there was a significant improvement in FFI from baseline to pre-operatively when both StanC and PREHAB groups were combined (main effect of time; $p < 0.05$). A main effect of time ($p<0.05$), such that Pre-Operative < Baseline was also observed for phenotype frailty. To further examine the effect of the PREHAB intervention in specific cohorts of patients, we dichotomized patients at different FFI cut-offs (i.e. ≥ 0.2, ≥ 0.25, ≥ 0.3). There were no significant differences in the proportion of patients classified as frail by any cut-off at any time point; however, there was a trend ($p=0.07$) towards a significant reduction in the proportion of patients with an FFI ≥ 0.25 in the PREHAB group pre-operatively.

To examine which specific variables within the FFI were modified from baseline to pre-operatively in StanC and PREHAB groups, we developed an absolute measure of percentage change in all variables included in the index (Table 8). Variables representing the largest absolute improvement in the StanC group included the repeated chair stand test (19.6%), self-reported physical activity (20.0%), help with housework (18.3%), as well as both parameters related to self-reported exhaustion (35.6%, 26.7%). In contrast, PREHAB patients demonstrated a larger absolute improvement in gait speed (15.7%), 6MWT distance walked (12.9%), self-report physical activity (7.1%) and cognition (35.7%). Absolute percentage improvements in the

StanC group ranged from -10.0% to 35.6% in StanC; whereas, percentage improvements in PREHAB variables ranged from -15.4% to 35.7%.

Table 7. Comparison of Frailty Parameters Between StanC and PREHAB Patients at Baseline and Pre-Operatively.

	Baseline	Pre-Operative
Functional Frailty Index		
Continuous FFI		
StanC	0.27 ± 0.09	0.22 ± 0.10
PREHAB	0.22 ± 0.08	0.19 ± 0.06
FFI ≥ 0.2		
StanC	8 (66.7%)	5 (41.7%)
PREHAB	5 (38.5%)	6 (46.2%)
FFI ≥ 0.25		
StanC	6 (50%)	4 (33.3%)
PREHAB	4 (30.8%)	1 (7.7%)
FFI ≥ 0.3		
StanC	4 (33.3%)	2 (16.7%)
PREHAB	3 (23.1%)	1 (7.7%)
Improved FFI		
StanC		7 (58.3%)
PREHAB		5 (38.4%)
Fried Phenotype Frailty		
Continuous Phenotype		
StanC	3.6 ± 1.2	2.9 ± 1.4
PREHAB	3.3 ± 1.5	2.5 ± 1.3

Continuous variables expressed as mean ± standard deviation. Categorical variables expressed in frequencies (percentage of group). Statistical comparisons were calculated using two-way ANOVA and Newman-Keuls method post hoc test for continuous variables and generalized estimating equation and Fisher exact test for categorical variables. Improvement in FFI defined as a decrease of ≥ 0.03 from baseline to pre-operatively. Time effect for Continuous FFI and Continuous Phenotype where Pre-Operative < Baseline ($p<0.05$). FFI, functional frailty index.

Table 8. Percentage Improvement in Functional Frailty Index Variables from Baseline to Pre-Operatively in StanC and PREHAB Patients.

	Standard Care			PREHAB		
	Baseline	**Pre-Op**	**Absolute % Change**	**Baseline**	**Pre-Op**	**Absolute % Change**
SPPB Balance	13.8%	10%	3.8%	4.7%	3.3%	1.4%
Handgrip Strength	50.0%	60.0%	-10.0%	57.1%	50.0%	7.1%
Chair Stand	52.1%	32.5%	19.6%	48.2%	45.0%	3.2%
Gait Speed	41.7%	50.0%	-8.3%	35.7%	20.0%	15.7%
6MWT	56.3%	50.0%	6.3%	55.4%	42.5%	12.9%
Self-Report PA	50.0%	30.0%	20.0%	7.1%	0%	7.1%
Help Eating	0%	0%	0%	0%	0%	0%
Help Dressing	4.2%	0%	4.2%	0%	0%	0%
Help Grooming	4.2%	0%	4.2%	0%	0%	0%
Help Walking	0%	0%	0%	0%	0%	0%
Help Getting In/Out of Bed	4.2%	0%	4.2%	0%	0%	0%
Help Bathing	4.2%	0%	4.2%	0%	5.0%	-5.0%
Help Using Telephone	0%	0%	0%	0%	0%	0%
Help Transportation	8.3%	5.0%	3.3%	3.6%	5.0%	-1.4%
Help Shopping	16.7%	10.0%	6.7%	3.6%	0%	3.6%
Help Cooking	8.3%	0%	8.3%	0%	0%	0%
Help Housework	33.3%	15.0%	18.3%	7.1%	20%	-12.9%
Help Medication	4.2%	5.0%	-0.8%	0%	0%	0%
Help Finances	0%	0%	0%	0%	0%	0%
Feel Everything an Effort	72.3%	36.7%	35.6%	57.2%	50.0%	7.2%
Trouble Getting Going	50.0%	23.3%	26.7%	33.3%	40.0%	-6.7%
Unintentional Weight Loss	25.0%	0%	25%	28.6%	40.0%	-11.4%
Weight Loss Conclusion	25.0%	0%	25%	21.4%	10.0%	11.4%
Decline Food Intake	33.3%	20.0%	13.3%	21.4%	30.0%	-8.6%
BMI	66.7%	65.0%	1.7%	71.4%	65.0%	6.4%
Pain/Discomfort	29.2%	25.0%	4.2%	16.1%	22.5%	-6.4%
HRQoL	40.6%	44.5%	-3.9%	40.0%	36.0%	4.0%
Depression	25.0%	20.0%	5%	28.6%	44.0%	-15.4%
Anxiety	11.1%	16.6%	-5.5%	19.1%	20.0%	-0.9%
Cognition	83.3%	80.0%	3.3%	85.7%	50.0%	35.7%

Variables expressed as percentage of total group deficit, calculated by the equation ((total group deficit sum/sample size)*100). SPPB, Short Physical Performance Battery; 6MWT, 6-Minute Walk Test; PA, physical activity; BMI, body mass index; HRQoL, health-related quality of life.

Objectively Measured Physical Activity Behaviour

Physical activity was assessed objectively by accelerometer and the various parameters are displayed in Table 9. Physical activity was analyzed in bouts of 10-minutes or longer as well as in sporadic bouts of activity (i.e. accumulated activity in bouts of 30 seconds or longer). To be considered a valid accelerometer file for the purposes of data analysis, a minimum 10 hours per day of wear time across four days was required. Due to this restriction, valid accelerometer data was available in 12 PREHAB patients and 11 StanC patients.

When accelerometer data was analyzed in 10-minute bouts (i.e. $LightPA_{10min}$, $MVPA_{10min}$, $TotalPA_{10min}$), there were no differences between baseline and pre-operative time points at any intensity. StanC group patients accumulated an average of 29 ± 87 minutes of bouted MVPA at baseline, whereas PREHAB patients achieved 6 ± 12 minutes. These data are comparable to previous reports of objectively measured activity in cardiac surgery patients[120,128] and older adults with cardiovascular disease;[29] however, it remains substantially lower than recommended levels of physical activity for the apparently healthy Canadian adult population.[24]

When accelerometer physical activity was assessed using sporadic bouts of 30-seconds or longer, there were no differences in $LightPA_{spor}$ or $MVPA_{spor}$ at any time. When valid files were analyzed for $TotalPA_{spor}$, a main group effect ($p<0.05$) was found, such that PREHAB patients accumulated significantly more activity than StanC. Notably, patients in the PREHAB group accumulated 726 ± 268 minutes and 828 ± 320 minutes of $TotalPA_{spor}$ at baseline and pre-operative time points, respectively. In contrast, patients randomized to StanC accumulated 716 ± 326 minutes of $TotalPA_{spor}$ at baseline and 693 ± 301 minutes pre-operatively.

We also analyzed sedentary activity in sporadic bouts and in bouts of at least 10-minutes. A main group effect was observed for both $Sedentary_{10min}$ and $Sedentary_{spor}$, where StanC <

PREHAB ($p<0.05$), but this effect did not change over time. Patients enrolled in the study were sedentary for a mean 514 ± 72 minutes per day, equating to nearly 8.6 hours of sitting.

Table 9. Comparison of Accelerometer Physical Activity Between StanC and PREHAB Patients at Baseline and Pre-Operatively.

	Baseline	Pre-Operative
10-Minute Bouts (min/week)		
$LightPA_{10min}$		
StanC	34 ± 48	21 ± 30
PREHAB	11 ± 14	23 ± 43
$MVPA_{10min}$		
StanC	29 ± 87	31 ± 67
PREHAB	6 ± 12	10 ± 14
$TotalPA_{10min}$		
StanC	63 ± 90	52 ± 73
PREHAB	18 ± 17	34 ± 42
Sporadic Bouts (min/week)		
$LightPA_{spor}$		
StanC	635 ± 307	609 ± 268
PREHAB	661 ± 239	740 ± 288
$MVPA_{spor}$		
StanC	81 ± 108	85 ± 77
PREHAB	65 ± 40	88 ± 48
$TotalPA_{spor}$		
StanC	716 ± 326	693 ± 301
PREHAB	726 ± 268	828 ± 320
Sedentary Time (min/day)		
$Sedentary_{10min}$		
StanC	396 ± 49	480 ± 34
PREHAB	443 ± 67	537 ± 81
$Sedentary_{spor}$		
StanC	491 ± 40	480 ± 34
PREHAB	535 ± 89	537 ± 81

Values are means ± standard deviation. Statistical comparisons were calculated using two-way ANOVA and Newman-Keuls method post hoc test. Main group effect for $Sedentary_{spor}$ and $Sedentary_{10min}$ where StanC < PREHAB ($p<0.05$). Main group effect for $TotalPA_{spor}$ where StanC < PREHAB ($p<0.05$). PA, physical activity; MVPA, moderate to vigorous physical activity.

Functional Walking Ability

Patients in the StanC group walked an average of 297.7 ± 87.0 meters at baseline and 302.3 ± 82.7 meters pre-operatively. PREHAB patients walked an average of 332.2 ± 51.1 meters at baseline and 366.4 ± 57.7 pre-operatively, representing a 10.3% improvement in functional walking ability. No differences were observed for total distance walked on the 6MWT between StanC and PREHAB at any time point (Table 10).

Table 10. Comparison of Functional Walking Ability Between StanC and PREHAB Patients at Baseline and Pre-Operatively.

	Baseline	Pre-Operative
6-Minute Walk Test (m)		
StanC	297.7 ± 87.0	302.3 ± 82.7
PREHAB	332.2 ± 51.1	366.4 ± 57.7

Values are means ± standard deviation. Statistical comparisons were calculated using two-way ANOVA and Newman-Keuls method post hoc test.

Physical Function and Muscular Strength

There were no differences between PREHAB and StanC groups in physical function, as assessed by the SPPB, across any time point (Table 11). The average SPPB score at baseline was 7.3 ± 1.9 and 7.7 ± 1.7 in StanC and PREHAB groups, respectively. These values fall below the summary score of 10 previously established in the literature as a marker of impaired physical function amongst older adults.[52,193] We utilized this cut-point to examine changes in the proportion of patients with a summary SPPB score ≤ 9 at baseline and pre-operatively. However, there were no significant changes in the proportion of physically impaired patients over time.

Table 11. Comparison of Physical Function Between StanC and PREHAB Patients at Baseline and Pre-Operatively.

	Baseline	Pre-Operative
Short Physical Performance Battery		
Continuous SPPB		
StanC	7.3 ± 1.9	7.8 ± 1.9
PREHAB	7.7 ± 1.7	8.0 ± 1.7
SPPB Score ≤ 9		
StanC	11 (91.7%)	8 (66.7%)
PREHAB	10 (71.4%)	10 (71.4%)

Continuous variables expressed as mean ± standard deviation. Categorical variables expressed in frequencies (percentage of group). Statistical comparisons were calculated using two-way ANOVA and Newman-Keuls method post hoc test for continuous variables and generalized estimating equation for categorical variables. SPPB, short physical performance battery.

Sub-Analysis of PREHAB Completers and Non-Completers

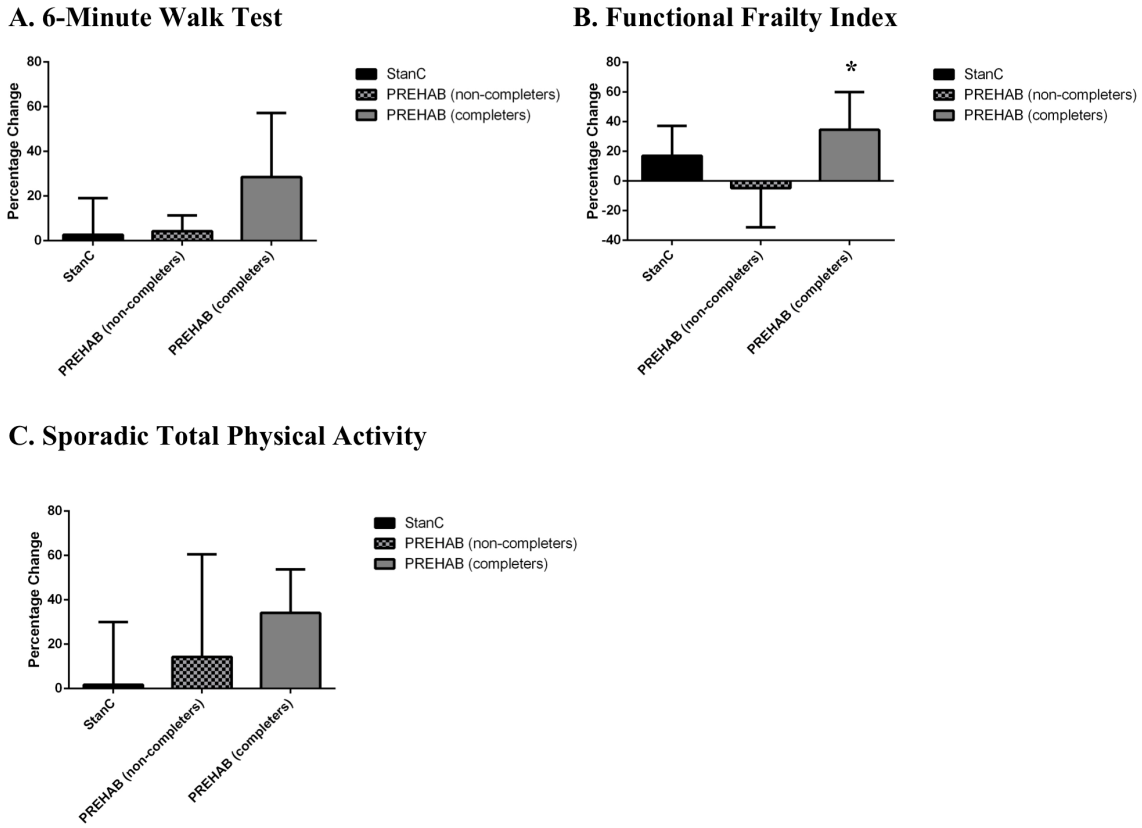
We conducted a sub-analysis of four PREHAB patients that completed the intervention (i.e. PREHAB Completers) and the ten participants classified as non-completers (Table 12). Statistically, we analyzed the data as an average percent change from baseline to pre-operatively to create a more intuitive interpretation of the results (Figure 8). While there were no significant differences in percent change from baseline to pre-operatively in 6MWT or $TotalPA_{spor}$, we found a significant difference between PREHAB completers and non-completers with respect to percentage change in FFI. Notably, PREHAB completers improved their FFI by 34.6 ± 25.4%; whereas, patients that did not complete the PREHAB intervention as intended experienced an average FFI decline of 4.8 ± 26.5% from baseline to pre-operatively ($p < 0.05$). Even so, the percentage improvement in FFI amongst PREHAB completers was not statistically different than that observed in the StanC group (i.e. 17.1 ± 20.1%).

Table 12. Sub-Analysis of Select Parameters in PREHAB Completers and Non-Completers at Baseline and Pre-Operatively.

	Baseline	Pre-Operative
Functional Frailty Index		
Continuous FFI		
StanC	0.27 ± 0.09	0.22 ± 0.10 *
PREHAB (non-completers)	0.19 ± 0.07 #	0.19 ± 0.06
PREHAB (completers)	0.28 ± 0.09 Ŧ	0.19 ± 0.08 *
Functional Walking Ability		
6 Minute Walk Test		
StanC	297.7 ± 87.0	302.3 ± 82.7
PREHAB (non-completers)	344.4 ± 41.6	358.9 ± 45.0
PREHAB (completers)	304.8 ± 66.0	383.3 ± 85.9
Physical Activity Behaviour		
$MVPA_{10min}$		
StanC	29.3 ± 87.0	30.5 ± 67.0
PREHAB (non-completers)	9.1 ± 14.2	12.6 ± 15.5
PREHAB (completers)	0 ± 0	5.9 ± 11.8
$TotalPA_{spor}$		
StanC	716.2 ± 326.4	693.2 ± 300.8
PREHAB (non-completers)	779.2 ± 301.1	832.1 ± 376.3
PREHAB (completers)	618.6 ± 170.4	820.1 ± 209.2

Continuous variables expressed as mean ± standard deviation. FFI, functional frailty index; StanC, standard care; MVPA, moderate to vigorous physical activity. StanC n=12; PREHAB Non-Completers n=10; PREHAB Completers n=4. * = different from baseline ($p<0.05$). # = different from StanC ($p<0.05$). Ŧ = different from PREHAB Non-Completers ($p<0.05$). Time effect for 6MWT where Baseline < Pre-Operative ($p<0.05$).

Figure 8. Comparison of Percentage Change in Select Parameters between Baseline and Pre-Operatively in StanC, PREHAB Non-Completers and PREHAB Completers. Values are mean percentage change ± standard deviation. StanC n=12; PREHAB Non-Completers n=10; PREHAB Completers n=4. Statistical comparisons were calculated using Kruskal-Wallis ANOVA and Mann-Whitney test. Percentage Change in 6-Minute Walk Test (Panel A). Percentage Change in FFI (Panel B). Percentage Change in Total Sporadic Physical Activity (Panel C). * = different from PREHAB non-completers ($p < 0.05$).



Correlations Between Frailty, Functional Walking Ability and Objectively Measured Physical Activity Behaviour

We utilized Pearson correlations to examine associations between primary and secondary outcomes, including frailty, physical activity behaviour and functional walking ability (Table 13, Table 14, Figure 9, Table 15 and Table 16). A significant ($p<0.05$) association between pre-operative functional walking ability, as assessed by the 6MWT, and $LightPA_{spor}$ ($r=0.44$) and $TotalPA_{spor}$ ($r=0.41$) was detected. Other physical activity parameters, including $LightPA_{10min}$, $MVPA_{spor}$, $MVPA_{10min}$ and $TotalPA_{10min}$ were not significantly associated with 6MWT results (Table 13). In contrast, a negative association was found between functional walking ability and pre-operative FFI score (Figure 9; $r=-0.40$, $p<0.05$), such that as an individual's distance walked on the 6MWT was higher, their continuous frailty index score was lower (i.e. less frail; Figure 9). Additionally, we found a significant ($p<0.05$) negative association between FFI score and $MVPA_{spor}$ ($r=-0.41$) and $TotalPA_{spor}$ ($r=-0.41$; Table 14). We also found significant associations between baseline FFI score and change in FFI score (Table 15) in the entire cohort ($r=-0.48$, $p<0.05$) and in the PREHAB group specifically ($r=-0.67$, $p<0.05$). When changes from baseline to pre-operatively in select parameters were computed, no significant associations were detected between $\Delta MVPA_{10min}$, $\Delta TotalPA_{spor}$, Δ6MWT and ΔFFI (Table 16). Even so, we did observe a trend ($r=0.38$, $p=0.06$) towards a significant association between $\Delta MVPA10_{min}$ and $\Delta TotalPA_{spor}$.

Table 13. Association Between Pre-Operative Functional Walking Ability (6MWT) and Objectively Quantified, Pre-Operative Physical Activity Parameters.

	Pearson Correlation	p-value
$LightPA_{spor}$	0.44	**0.02**
$LightPA_{10min}$	0.23	0.26
$MVPA_{spor}$	0.10	0.63
$MVPA_{10min}$	-0.29	0.15
$TotalPA_{spor}$	0.41	**0.04**
$TotalPA_{10min}$	-0.09	0.66

Pearson correlations and p-values shown. PA, physical activity; MVPA, moderate to vigorous physical activity.

Table 14. Association Between Pre-Operative Functional Frailty Index Score and Objectively Quantified, Pre-Operative Physical Activity Parameters.

	Pearson Correlation	p-value
$LightPA_{spor}$	-0.36	0.07
Light PA_{10min}	-0.21	0.30
$MVPA_{spor}$	-0.41	**0.04**
$MVPA_{10min}$	-0.18	0.38
$TotalPA_{spor}$	-0.41	**0.04**
$TotalPA_{10min}$	-0.28	0.17

Pearson correlations and p-values shown. PA, physical activity; MVPA, moderate to vigorous physical activity.

Figure 9. Association Between Pre-Operative Functional Frailty Index Score and Functional Walking Ability (6MWT). Functional Frailty Index and Functional Walking Ability (n=26). Significant association for Functional Walking Ability (p=0.04).

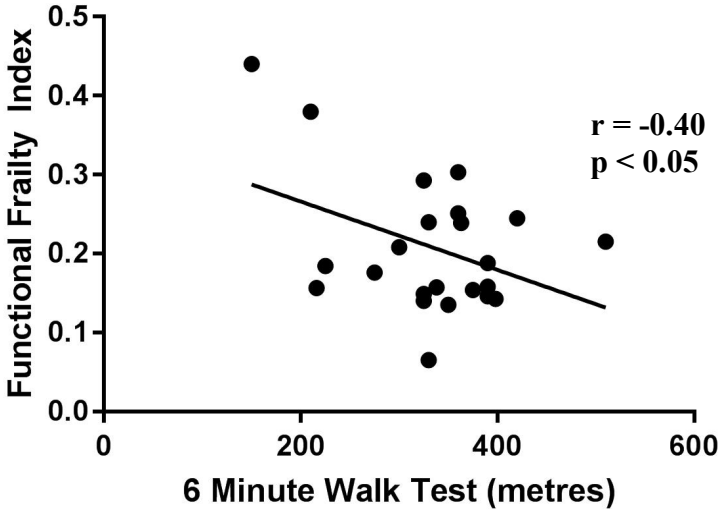


Table 15. Association Between Baseline Functional Frailty Index Score and Changes in Select Parameters in the Entire Cohort, PREHAB and Standard Care Groups.

	Whole Cohort	PREHAB	StanC
$\Delta MVPA_{10min}$	r=0.01	r=0.04	r=0.03
$\Delta TotalPA_{spor}$	r=-0.25	r=-0.37	r=0.07
Δ6MWT	r=0.13	r=0.46	r=0.01
ΔFFI	**r=-0.48***	**r=-0.68***	r=-0.22

Pearson correlations are shown. *=p<0.05. MVPA, moderate to vigorous physical activity; 6MWT, 6-Minute Walk Test; FFI, functional frailty index.

Table 16. Association Between Changes in Physical Activity Parameters, Functional Walking Ability and Functional Frailty Index Score.

	$\Delta MVPA_{10min}$	$\Delta TotalPA_{spor}$	Δ6MWT	ΔFFI
$\Delta MVPA_{10min}$	X	r=0.38	r=0.18	r=0.02
$\Delta TotalPA_{spor}$	r=0.38	X	r=0.23	r=0.26
Δ6MWT	r=0.18	r=0.23	X	r=-0.26
ΔFFI	r=0.02	r=0.26	r=-0.26	X

Pearson correlations are shown. MVPA, moderate to vigorous physical activity; 6MWT, 6-Minute Walk Test; FFI, functional frailty index.

Chapter 5: Discussion

Evidence to Support the Safety of PREHAB in the Frail, Older Adult Population

Previous literature has confirmed that extended wait times negatively influence mortality and HRQol amongst cardiac surgery patients.[122–124,126] Indeed, observational studies have identified that the risk of dying while on the wait-list increases by approximately 11% every month,[123] and individuals meeting CCS wait time guidelines (i.e. 6 weeks for elective procedures) are 68% less likely to experience in-hospital death when compared to individuals not meeting the guideline.[124] Based on this literature, we sought an opportunity to implement a pre-operative strategy combining exercise and educational components in an attempt to optimize risk factors prior to surgical intervention. Two previous studies have confirmed the safety and efficacy of exercise interventions prior to cardiac surgery;[26,132] however, the present study attempted to extend these results to the frail, older adult population undergoing cardiac surgery. Our novel pilot data in 26 elective cardiac surgery patients indicates that a pre-operative, interdisciplinary exercise intervention is well tolerated and does not result in increased rates of adverse events. While our results do not support our primary hypotheses that the PREHAB intervention would reduce the severity of frailty and increase MVPA accumulated in 10-minute bouts in the full PREHAB group, a sub-group completer analysis indicates that high PREHAB attenders improve FFI more than individuals that do not complete the intervention as intended. This finding is clinically relevant because current StanC does not provide patients with a strategy to reduce frailty prior to cardiac surgery, despite the literature clearly identifying an association between frailty and poor perioperative outcomes.[12]

To enroll a patient population representative of the contemporary cardiac surgery cohort, we specifically targeted the recruitment of frail individuals over the age of 60. Recent literature

indicates that over 25% of cardiac procedures are now being performed in older adults[7] and up to 50% of patients can be classified as frail.[71] Despite this, previous studies utilizing pre-operative exercise interventions have recruited considerably younger patients (i.e. 60 years) without considering frailty as an inclusion criteria.[26,132] Our study cohort is unique from previous trials in that the average age of our participants was 71.6 ± 6.4 years and all patients screened positive for frailty using the phenotype frailty model. More specifically, our cohort had an average FFI score of 0.24 ± 0.09 while expressing a mean 3.4 ± 1.4 deficits according to the phenotype model of frailty. Our study was also the first to include patients requiring valve repair/replacement surgery, as previous studies have been conducted exclusively in isolated CABG patients.[26,132] As such, this dissertation extends the results of previous studies to a representative sample of cardiac surgery patients and provides preliminary evidence that such a program is safe and feasible to implement in this population. Our data also indicates that when the PREHAB program is completed as intended, the intervention is effective in reducing frailty. It should also be noted that our study is the first to examine a pre-operative exercise intervention prior to cardiac surgery using a multi-site trial design, which enhances external validity and provides evidence that the PREHAB intervention can be implemented in a variety of geographical locations.

Developing a Novel Tool to Assess Changes in Frailty Status

Currently, there is insufficient literature to support a "gold standard" frailty assessment tool that can be universally implemented across disciplines. In fact, a recent systematic review conducted by de Vries et al. identified 20 unique instruments that have been validated to assess frailty status.[194] While each tool possesses distinct strengths and limitations, the frailty index model has been identified as one of the most suitable instrument to be implemented as an evaluative outcome measure, likely due to its continuous scoring system, clinimetric properties

and comprehensive approach to assessing frailty.[194] Intuitively, the frailty index is also advantageous to implement because it can be flexibly modified to include variables collected as part of the research process and may be more sensitive to change in response to an intervention. To explore the extent to which specific interventions influence the level of frailty, evaluative outcome measures must be developed that will be sensitive enough to reflect a change in the physiologic reserve of an individual.[195] To evaluate changes in the frailty status of our cohort, we developed a novel outcome measure (i.e. FFI) based on the original frailty index model and assessed its concurrent validity with a previously published frailty index.[71] Our results indicate that the prevalence of frailty amongst our cohort was similar to the level of frailty reported by Jung and colleagues, where 54.1% of cardiac surgery patients had a frailty index score ≥ 0.2 and 35.3% of the population had a frailty index ≥ 0.3. In comparison, 50.0% and 12.0% of our cohort had FFI scores ≥ 0.2 and ≥ 0.3, respectively. A high correlation (i.e. $r=0.80$, $p<0.05$), level of agreement (i.e. 88%) and kappa statistic (i.e. 0.75) between these two measures indicates that the FFI developed as part of the present study was a valid tool to assess frailty status amongst the cardiac surgery population. We also demonstrated a strong correlation ($r=0.84$, $p<0.05$) between the well-cited phenotype model of frailty and our FFI, supporting the conclusion that our tool was indeed a valid assessment of frailty. Our data adds to the existing literature because it is the first study to examine changes in pre-operative frailty status using a modified version of the Canadian Study of Health and Aging frailty index amongst a cohort of patients awaiting elective cardiac surgery. Our modified FFI was also unique from published literature, as previous iterations of the frailty index have failed to adequately capture functional parameters such as gait speed, grip strength and impairments in mobility.[56]

Frailty Status Improved Pre-Operatively

Frailty, defined as an increased vulnerability to physiologic stressors, has been identified as an important prognostic indicator of successful recovery following cardiac procedures.[28] Recent evidence from a systematic review of observational studies identified that frail individuals are at a nearly 5-fold (OR: 4.89 95% CI 1.64-14.60) increased risk of adverse events post-operatively[12] and the addition of frailty to traditional risk stratifying tools provides incremental model discrimination in identifying older adults at risk for major morbidity and mortality.[7,71,196] Therefore, investigating the efficacy of interventions targeting the modification of the frailty syndrome is of particular relevance to the cardiac surgery population. Our novel data demonstrates that frailty status improved from the time of surgical consent to 1-week pre-operatively in both StanC and PREHAB patients. Using the FFI score as our primary outcome, frailty decreased from 0.27 ± 0.09 to 0.22 ± 0.10 amongst patients randomized to StanC and from 0.22 ± 0.08 to 0.19 ± 0.06 in patients randomized to PREHAB. These pre-operative improvements in frailty were also confirmed using the phenotype model of frailty, which classifies individuals as frail when ≥ 3 specific criteria are present. In fact, the average number of phenotype criteria decreased from 3.6 ± 1.2 to 2.9 ± 1.4 and 3.3 ± 1.5 to 2.5 ± 1.3 in StanC and PREHAB groups, respectively. Due to a reduction in the severity of frailty, it can also be inferred that the associated surgical risk in both StanC and PREHAB groups was attenuated prior to surgical intervention. To our knowledge, our study is the first to examine changes in frailty amongst the cardiac surgery cohort and to demonstrate that frailty status can be modified during the pre-operative period. Consistent with our primary hypothesis, patients randomized to the PREHAB intervention improved their FFI score by approximately 14%. However, an

unexpected result that warrants investigation in future studies was the concurrent 18% improvement in FFI amongst the StanC group.

There are several possible mechanisms that can be speculated to underlie this observed improvement in frailty status in patients randomized to StanC, including the structure of care during the pre-operative period and the associated increase in healthcare utilization at this time. It should be noted that as part of StanC, all patients received a standard, three-hour assessment, where a nurse practitioner and anesthetist provided advice related to healthy lifestyle choices. This appointment often occurred weeks prior to the date of surgical intervention; thus, it is possible that patients enrolled in our study were receptive to this advice and improved their frailty status irrespective of group allocation. Furthermore, as a unique feature of our study, each patient participated in an intake health status assessment supervised by a cardiologist and an exercise professional, which was implemented to establish patient safety prior to randomization. This appointment consisted of a graded treadmill test and a thorough risk factor assessment, which may have been sufficient to engage patients in a process of active disease management and subsequently improve their frailty status. Another possible explanation underlying the observed improvement in frailty status amongst the StanC arm relates to a selection bias imposed by study recruitment procedures. Due to institutional guidelines for the ethical recruitment of patients in a randomized trial, research assistants were required to fully explain the details of the PREHAB intervention to all study participants. Therefore, it is likely that we specifically targeted the recruitment of individuals that were committed to improving their health status in comparison to individuals declining study participation. Collectively, we speculate that an increased number of physician contacts during the pre-operative period and a selection bias

imposed by study recruitment procedures may account for the improved frailty status amongst patients randomized to StanC.

Evidence Indicating a Dose-Response Relationship for PREHAB

Although we detected a time effect indicating that FFI score was improved in both StanC and PREHAB from baseline to pre-operatively, we also conducted a sub-analysis of patients classified as having completed the requirements of the intervention (i.e. attending a minimum of 8 sessions over 4-weeks). The decision to conduct a post hoc sub-group analysis was based on our *a priori* definition of intervention completion and previous literature indicating significant functional benefit (+174 meters, 43% improvement on 6MWT) after a minimum 4-weeks of CR attendance.[26,128,197] We determined that patients completing the intervention as intended improved their frailty status by 34.6 ± 25.4% compared to a 17.1± 20.1% improvement and 4.8 ± 26.5% decline amongst StanC and PREHAB non-completers, respectively. Several large epidemiological investigations have confirmed that a similar dose-response relationship exists between the number of CR sessions attended and long-term health outcomes.[30,198] In fact, older patients (average age 74.0) with CAD attending 36 CR sessions experience a 14% (HR: 0.86 95% CI 0.77-0.97) and 47% lower mortality risk (HR: 0.69 95% CI 0.58-0.81) compared to patients attending 24 or fewer sessions and one session, respectively.[198] A similar observational study of American Medicare beneficiaries hospitalized for coronary conditions or revascularization procedures found that patients attending a minimum of 25 CR sessions experienced a 19% reduction in the risk of mortality over 5-years, compared to patients attending 24 or fewer sessions.[30] Although the maximum number of PREHAB sessions attended by our cohort was 20, previous literature from Fiorina et al. indicates that CABG patients can improve functional ability by as much as 40% following a 15-day intensive CR program.[197] As such, the

results of our sub-analysis extend the results of previous reports and demonstrate that PREHAB reduces the severity of frailty by as much as 35% when the intervention is completed as intended. This novel data also provides preliminary evidence that a dose-response relationship exists in pre-operative programming, such that a minimum number of sessions are required to glean functional benefit from the PREHAB program.

To our knowledge, our study is the first randomized trial to examine changes in frailty using the accumulation of deficits model in any population. Previous data from the LIFE-P randomized trial reported that a 12-month progressive exercise intervention in community dwelling older adults reduced the prevalence of frailty (i.e. defined using the phenotype model) from 23% to 10% (95% CI 6.5-15.1%). Additional data from the FIT trial confirmed the results of the LIFE-P trial, finding that a 12-month interdisciplinary exercise intervention reduced the absolute prevalence of frailty relative to the control group by 14.7% (95% CI 2.4-27.0%). In contrast to these findings, our study detected a main effect of time ($p<0.05$) indicating that both PREHAB and StanC patients improved their FFI scores from baseline to pre-operatively. While PREHAB patients were enrolled in the intervention for the duration of their time on the wait list, it is possible that the length of the intervention was insufficient to result in significantly improved frailty status beyond what was observed in the StanC group. It can also be speculated that the mean number of sessions attended by our cohort was not sufficient to bring about clinically and statistically significant improvements in frailty status in the full PREHAB group. The result of our post hoc completer analysis supports this speculation, as PREHAB completers experienced significantly improved FFI scores in comparison to PREHAB non-completers. Even so, our novel data demonstrates for the first time that a frailty index (i.e. assessed by the accumulation of deficits model) can be modified over a relatively short period of time (i.e. 4 to 8 weeks). The

precise duration, dosage and model of delivery (e.g. resistance training, continuous aerobic, interval training) required to effectively modify the frailty index warrants further investigation in future studies. Indeed, previous literature using cross-sectional study designs have confirmed an association between physical activity behaviour and frailty index scores, where the most frail individuals (i.e. frailty index > 0.45) are more sedentary and less likely to meet MVPA guidelines (i.e. Frail: 9.6 hours/day, 1.1% vs. Non-Frail: 8.2 hours/day, 8.3%; $p<0.001$) when compared to non-frail individuals (i.e. frailty index ≤ 0.10).[199] These associations must be confirmed using rigorously controlled randomized trials.

Attendance at the PREHAB Intervention

An unexpected result of the study that warrants further discussion is the relatively poor attendance amongst patients randomized to the PREHAB intervention. While the inclusion criteria dictated that our cohort be older and frail by the phenotype criteria, previous investigations of a similar nature (i.e. with younger, non-frail patients) have reported more than double the number of sessions attended in comparison to our cohort. For example, study patients from Arthur et al.'s trial of pre-operative exercise programming attended an average of 14 exercise sessions over a period of 11.4 weeks.[132] Similarly, Sawatzky and Kehler et al. reported a mean 19 ± 7 exercise sessions attended across 8.2 ± 2.2 weeks.[26] In contrast, our PREHAB cohort attended just 6.7 ± 6.0 sessions over a mean 7.7 ± 5.5 weeks on the wait list. Although the average number of sessions attended by our cohort (i.e. approximately 1 session per week) is comparable to Arthur et al.'s investigation (i.e. 1.2 sessions per week), the absolute volume of sessions attended by PREHAB patients remained significantly less than Arthur et al.'s report (i.e. 6.7 in PREHAB vs. 14 in Arthur et al.).[132] These attendance figures are concerning, as our sub-group analysis demonstrated that patients completing the intervention as intended (i.e. minimum

8 sessions over 4 weeks) derived additional functional benefit compared to patients classified as non-completers. Modest rates of CR attendance and completion have been well-documented in systematic reviews and observational studies, particularly in vulnerable older adults.[200] For example, Samayoa et al. reported that just 45.0% of men and 38.5% of women enroll in CR programming following an acute cardiovascular event.[201] Amongst older (i.e. 65 years and above) American Medicare beneficiaries hospitalized for coronary conditions or revascularization procedures, only 12.2% of patients utilized CR programming.[30] This observational study of older adults also found that patients attending 25 sessions or more experienced a 19% reduced risk of mortality over 5-years, compared to patients attending 24 or fewer sessions. Taken together, these data indicate that attendance issues are not unique to the pre-operative period and consistent with our post hoc completer analysis, maximizing CR attendance is integral to ensuring full health benefits are achieved. Our data highlights the importance of maintaining consistent follow-up with local CR sites and individual patients to ensure target attendance is maintained. Other strategies such as implementing motivational rewards,[202] active referrals by a physician or health care provider[203] and reducing wait times from referral to enrollment[204] have been proposed as alternative delivery strategies to optimize CR attendance and completion. Future studies should be designed to ensure that CR sites maintain consistent contact with patients in addition to exploring alternative delivery strategies that promote attendance amongst frail, older adults.

Both PREHAB and StanC Patients Were Inactive

A secondary objective of this dissertation was to examine changes in MVPA accumulated in 10-minute bouts (i.e. $MVPA_{10min}$), from baseline to pre-operatively. While our results do not support our hypothesis speculating that $MVPA_{10min}$ would be increased in patients randomized to

the PREHAB intervention, there are several important clinical perspectives that can be drawn from our results. Firstly, our data indicates that frail cardiac surgery patients accumulate just 17 ± 60 minutes of $MVPA_{10min}$ at baseline, prior to randomization. Furthermore, just one of the 26 enrolled study patients (i.e. 4%) were actively achieving the physical activity component of the CPAG, which recommends 150 minutes of MVPA per week in bouts of at least 10 minutes.[24] This statistic is concerning, as meta-analyses demonstrate a 27% (RR: 0.73 95% CI 0.66-0.80) and 12% (RR: 0.88 95% CI 0.83-0.93) reduction in the development of CAD amongst individuals accumulating high and moderate levels of leisure time physical activity, respectively.[94] Additionally, energy expenditures of 2200 kcal per week have been associated with plaque reduction amongst patients with established CAD;[98] however, our study patients were not achieving recommended levels of activity and were unlikely to obtain significant health benefit as a result. Even more concerning is the recent evidence linking pre-operative physical activity behaviour and various health outcomes in cardiac surgery patients. Although a systematic review of observational studies in this area produced mixed findings (Table 2), several studies report physical activity during the pre-operative period as being associated with improved health outcomes.[13–16,18,19] For example, Rengo and colleagues demonstrated a significant, nonlinear association between increased levels of activity pre-operatively and post-operative survival.[13] Other studies have found significant associations between pre-operative activity and hospital LOS, where active patients have a 33% reduction in hospital LOS compared to inactive patients (HR: 0.67 95% CI 0.49-0.93).[15,16] Despite this information, our accelerometer data revealed that study patients were not engaging in sufficient levels of physical activity to derive health benefits.

Our study is unique in that previous reports of pre-operative exercise programming have failed to consistently capture changes in physical activity during the pre-operative period.[26,128] To specifically address this limitation, we implemented an interim accelerometer analysis 4-weeks following initial randomization to achieve more complete data collection. This protocol resulted in valid accelerometer data being collected in 23 of 26 (i.e. 88.5%) study patients. Based on the recommendations of a systematic review endorsing age-appropriate adjustments in accelerometer cut points,[167] we implemented an MVPA cut point (i.e. 532.5 counts per 30 seconds) to accurately determine the amount of objectively accumulated physical activity in a deconditioned cohort of older adults based on a study published by Hooker and colleagues.[163] While our results do not allow us to conclude that the PREHAB intervention increased levels of pre-operative activity performed in 10-minute bouts at any intensity, our study will provide a basis for guiding future program and research initiatives. Specifically, pre-operative CR interventions may need to be adapted to specifically target the promotion of leisure time physical activity outside of programming hours. Future trials should aim to engage patients in a process of active self-management to support physical activity beyond the confines of the structured program. This strategy would promote the maintenance of a physically active lifestyle and result in sustained behaviour change. Additionally, activities prescribed within CR programs must be of sufficient intensity to specifically target increases in MVPA accumulation, as our accelerometer data suggests that PREHAB patients were not exercising at sufficient intensities to be classified as moderately intense activity. Despite the fact that patients were classified as being safe to engage in physical activity based on our exclusion criteria, it is possible that local CR sites were concerned about pushing study participants at moderate to vigorous intensities. Although this is a

speculation on our part, concerns over patient safety and exercising at moderate intensities may explain the lack of increased $MVPA_{10min}$ in our PREHAB cohort.

Although study patients did not accumulate more physical activity in 10-minute bouts (i.e. $LightPA_{10min}$, $MVPA_{10min}$, $TotalPA_{10min}$), we detected a main group effect ($p<0.05$) for $TotalPA_{spor}$, such that PREHAB > StanC. Even so, we did not observe a significant interaction effect and thus, it is not possible to conclude that PREHAB increased $TotalPA_{spor}$ accumulation. While the CPAG do not consider activity accumulated in sporadic bouts (i.e. 30 seconds or longer), recent evidence has found significant associations between $MVPA_{spor}$, physical fitness and cardiovascular risk factors.[205,206] More specifically, Mcguire et al. investigated the health benefits associated with sporadic physical activity, and reported a strong correlation between incidental physical activity and cardiorespiratory fitness using a multivariate analysis ($r^2=0.56$, $p<0.01$).[205] Glazer et al. also provided data to support the notion that physical activity accumulated in sporadic bouts may be beneficial to health, demonstrating that for every 10 minute increase per day in $MVPA_{spor}$, there was a concurrent 0.11 mmol/L reduction in triglyderides, 0.30 cm reduction in waist circumference, a 15% decreased obesity prevalence and a 0.28% reduction in Framingham Cardiovascular Risk Score.[206] Collectively, this evidence indicates that activity accumulated in sporadic bouts may be nearly as effective as activity accumulated in 10-minute bouts. This area of literature is particularly relevant to the frail, older adult population, who spend the majority of their physically active time in light intensities and short bouts.[207] Due to the deconditioned nature of the frail, elective cardiac surgery population, we recommend monitoring activity in sporadic bouts to ensure the accurate representation of physical activity accumulation.

PREHAB Did Not Improve Functional Walking Ability

Functional walking ability, as assessed by a 6MWT, is predictive of mortality and major morbidity in patients with established cardiovascular disease. More specifically, Bittner and colleagues reported that patients walking less than 300 meters were at a 3.7-fold (OR: 3.7 95% CI 1.44-9.55) increased risk of mortality compared to those walking more than 450 meters.[182] Similarly, Beatty et al. found that for each 104 meter decrease in 6MWT distance, there was a concurrent 55% increased rate of cardiovascular events (HR: 1.55 95% CI 1.35-1.78) and a 54% higher rate of mortality (HR: 1.54 95% CI 1.32-1.80) in patients with stable CAD.[208] While patients randomized to the PREHAB intervention increased 6MWT distance by 10.3% (i.e. 332.2 ± 51.1 to 366.4 ± 57.7 meters) from baseline to pre-operatively, this result did not achieve statistical significance when compared to the 1.5% (297.7 ± 87.0 to 302.3 ± 82.7 meters) improvement amongst StanC patients. In contrast, previous data from Sawatzky and Kehler et al. demonstrated that a similar pre-operative CR intervention in elective CABG patients increased 6MWT distance from 363 ± 22 meters at baseline to 489 ± 37 meters pre-operatively, representing a 35% improvement.[26] These conflicting results are likely due to differences in the number of sessions attended by our cohort in comparison to earlier reports of pre-operative programming (i.e. 6.7 ± 6.0 vs. 19 ± 7 sessions). Additionally, we speculate that the non-significant improvement in 6MWT amongst patients randomized to PREHAB may be a result of the advanced age and frailty status of our patient population, limiting their potential for improvement. Previous data from Fiorina et al. confirmed that older cardiac surgery patients walk significantly shorter distances on the 6MWT compared to younger patients (Men < 65 years: 355 ± 80 meters; Women < 65 years: 281 ± 76 meters; Men 65-75 years: 310 ± 75 meters; Women 65-75 years: 249 ± 71 meters; Men > 75 years: 268 ± 82 meters; Women > 75 years:

206 ± 70 meters).[197] Even so, our sub-analysis of PREHAB completers reported a 28.5% improvement in 6MWT distance (i.e. from 304.8 ± 66.0 to 383.3 ± 85.9 meters) compared to a 2.7% and 4.3% improvement in StanC and PREHAB non-completers, respectively. This level of improvement in functional walking ability amongst PREHAB completers is consistent with the 35-40% improvement in 6MWT distance found in previous reports;[26,197] however, small sample sizes in our sub-group analysis limited our ability to detect a statistically significant improvement. We speculate that a higher dosage of CR programming amongst all patients randomized to the PREHAB intervention could have resulted in significant improvements in functional walking ability despite our cohort's advanced age and conditioning status. Although we did not detect a statistically significant improvement in 6MWT for the full PREHAB group, our completer analysis supports our secondary hypothesis speculating that functional walking ability (i.e. assessed by the 6MWT) would be improved by PREHAB. This data adds to the literature because it was the first trial to investigate changes in functional walking ability amongst a cohort of frail, older adults waiting for cardiac surgery.

Physical Activity was Associated with Functional Walking Ability and Frailty

Our data indicates a moderately strong correlation between $TotalPA_{spor}$ and functional walking ability, as assessed by distance walked on a 6MWT ($r=0.41$, $p=0.04$). Additionally, we reported significant associations between $TotalPA_{spor}$ and FFI score ($r=-0.41$, $p=0.04$), as well as $MVPA_{spor}$ and FFI score ($r=-0.41$, $p=0.04$). This data supports existing literature, which has found significant associations between various accelerometer physical activity parameters and 6MWT distance ($r=0.48$ to 0.61, $p<0.01$) in patients with a cardiopulmonary illness.[209] Previous literature also indicates a significant, independent association between the accumulation of MVPA and frailty index scores. Cross-sectional data from the National Health and Nutrition

Examination Survey indicates that adding 1 hour of $MVPA_{10min}$ per day decreases frailty index scores by 0.045.[199] A longitudinal study conducted by Savela et al. also reported significant associations between midlife leisure time activity and frailty in apparently healthy males, as assessed by a modified version of the phenotype frailty criteria.[210] After adjusting for age, smoking status, BMI and blood pressure, the risk of frailty was 80% lower in individuals reporting high levels of midlife physical activity compared to those reporting the lowest levels (OR: 0.20 95% CI 0.07-0.55). Our data adds to this body of literature by extending the associations between objectively accumulated physical activity, frailty and functional walking ability to a population of older adults undergoing cardiac surgery. From a clinical perspective, this information is important as it highlights the potential for alternative models of delivering pre-operative risk optimization strategies. Regardless of group assignment, $TotalPA_{spor}$ and $MVPA_{spor}$ was associated with pre-operative frailty status, indicating that it may be possible to derive benefit from increasing physical activity levels in a less structured setting. These results may be important when developing accessible programs for patients living in a rural setting or in individuals having issues with transportation to a site-specific CR program.[211–213] Since a primary reason for declining study participation in the PREHAB trial was accessibility, alternative models of delivering pre-operative CR programming should be explored in future trials.

Baseline Frailty was Associated with Changes in Frailty Status

To examine the predictive influence of baseline frailty status as a covariate on changes in select parameters, we analyzed the association between baseline FFI and $\Delta MVPA_{10min}$, $\Delta TotalPA_{spor}$, Δ6MWT and ΔFFI using Pearson correlations. Significant associations were detected between baseline FFI and ΔFFI in the entire cohort ($r=-0.48$, $p<0.05$) and in the PREHAB group ($r=-0.68$,

$p<0.05$), but not in the StanC group ($r=-0.21$, p=NS). This result suggests that baseline frailty was predictive of changes in frailty status amongst patients attending the PREHAB intervention. While we explored the option of running Analysis of Covariance to control for the effect of baseline frailty as a covariate, our sample size was significantly underpowered to detect differences between means using this statistical approach. Furthermore, the effect of other covariates, such as age and gender, in addition to frailty, would need to be included in the general linear model to robustly control for baseline characteristics. Even so, our results suggest that more frail individuals are likely to derive enhanced benefit by attending the PREHAB intervention. This result is in contrast to previous literature indicating that exercise appears to be more effective in the earlier stages of frailty (i.e. pre-frailty) in comparison to individuals in more advanced stages.[85] We speculate that in our specific cohort of frail individuals requiring cardiac surgery, a lower physiologic reserve at baseline resulted in greater potential for improvement as a result of the intervention.

Hospital Length of Stay was Unaffected by PREHAB

Previous literature from Arthur et al. demonstrated that a pre-operative CR program significantly reduced hospital LOS by one day (i.e. StanC median 6 [5-7] days; Intervention median 5 [5-6] days; p=0.001) amongst elective CABG patients.[132] In contrast, our study did not detect a significant difference in post-operative hospital LOS between StanC and PREHAB groups (i.e. StanC median 8.0 [5.3-19.5] days; PREHAB median 7.0 [6.5-8.5] days). This discrepancy in findings is likely because this thesis project was not specifically powered to detect changes in hospital LOS and recruited a significantly smaller sample size when compared to Arthur et al. (i.e. 26 in PREHAB vs. 249 in Arthur et al.'s study). Notably, the slightly longer LOS experienced by patients enrolled in our study may be due to the advanced age of our cohort

(i.e. approximately 10 years older than Arthur et al.) and the inclusion criteria necessitating all patients be classified as frail. Indeed, previous literature has confirmed that older patients tend to experience higher rates of prolonged hospital LOS, with up to 58% of octogenarians requiring a LOS exceeding 14 days after CABG.[214,215] Hospital LOS has also been demonstrated to be associated with frailty status, where frail patients are at a 2-fold (OR: 2.31 95% CI 1.15-4.65) increased risk of experiencing a prolonged stay > 7 days.[71] Collectively, these data indicate that the median LOS amongst our cohort was consistent with previous literature given the elevated level of risk imposed by advanced age and frailty status.

Hospital LOS is not only an important metric as it relates to health care expenditures, but has also been demonstrated to be predictive of short- and long-term health outcomes. In fact, reducing median hospital LOS by one day is associated with a 3% reduction in 30-day hospital readmission,[216] while each additional day spent in hospital is associated with a graded increase in 60-day mortality.[217] Although the present study did not detect a significant reduction in hospital or ICU LOS in PREHAB patients post-operatively, the outcome of prolonged hospital LOS will be specifically addressed in future reports of the PREHAB trial when a larger sample has been recruited. This outcome is clinically relevant and holds significant policy implications due to the financial burden imposed by prolonged hospital LOS following cardiac surgery.

Study Limitations

It is important to acknowledge that this study had several limitations and pitfalls. Firstly, we specifically powered our study to examine changes in FFI and $MVPA_{10min}$ from baseline to pre-operatively. Due to a slower than expected rate of recruitment, we were limited to a sample size of 26 elective cardiac surgery patients. We acknowledge that it is possible that our small sample size would not have the statistical power to provide insights about the effectiveness of the

PREHAB intervention with respect to primary and secondary outcomes. Even so, it is important to recognize that we did detect significant differences in several primary and secondary outcomes, including time effects (e.g. FFI, phenotype frailty), main group effects (e.g. $TotalPA_{spor}$) and trends towards significance (e.g. FFI $\geq$ 0.25, 6MWT). Furthermore, a post-hoc completer analysis demonstrated a significant difference in FFI percentage improvement between PREHAB completers and non-completers, suggesting a potential dose-response relationship. These data will help to inform future work and guide improvements in the delivery of pre-operative exercise and education programming in this population.

With respect to study recruitment, the inclusion and exclusion criteria utilized to identify potential study candidates may have resulted in a selection bias. While several of the exclusion criteria (e.g. severe heart failure, critical left main coronary disease, severe aortic/mitral stenosis) were implemented to ensure patient safety, these restrictions limited us to 199 eligible patients out of a possible 1192 patients (i.e. 16.7% of the total elective cardiac surgery population). We were able to recruit 44 of these patients (i.e. 22% of eligible patients), of which 26 had completed their surgical intervention at the time of data analysis. While outside the scope of this dissertation, we were unable to make a comparison between enrolled patients and patients choosing not to participate in the study, limiting our ability to generalize the observed results. Common reasons for declining study participation included lack of time, issues related to accessibility/travel or the patient had previously consented to another research study. To support patient safety, we only offered the intervention at times previously established by the local CR sites (i.e. often weekday mornings). Offering the PREHAB intervention on a more convenient schedule or utilizing alternative models of program delivery could address some of these limitations. For example, home-based CR has been demonstrated to be equally effective in

improving clinical outcomes when compared to centre-based CR in low-risk patients.[213] While this would address geographical limitations associated with our study sites, alternative models of delivery such as home-based CR or telehealth interventions would need to be adapted to ensure patient safety. It should also be noted that our study did not capture urgent, semi-urgent and very frail (i.e. CFS ≥ 7) cardiac surgery patients, as these individuals would be unable to complete the intervention as proposed. Therefore, the results of our study cannot be generalized to the entire population of patients requiring surgical intervention.

Another limitation in patient selection relates to the potential bias imposed by study recruitment procedures. Due to institutional guidelines mandating a comprehensive explanation of study details prior to enrollment, it is possible that a selection bias existed such that the patients recruited to participate in the study were more interested in improving health status in comparison to patients declining study participation. While this unavoidable selection bias is common in exercise intervention trials, we must acknowledge this as a limitation to the generalizability of our results.

Another limitation in our study relates to the use of accelerometers in the assessment of physical activity behaviour. Accelerometers are considered to be superior to self-report methods[218,219] and are the best tool for physical activity assessment across levels of frailty,[220,221] however, the devices fail to capture several common activities performed during CR programming, including stationary cycling and resistance exercise. This may have resulted in a systematic underestimation of activity accumulated by the PREHAB group. Note that we did have patients complete self-report physical activity logs; however, the logs were inconsistently completed and were not included in the final analysis.

Future Research Directions

Our novel data indicates that implementing a PREHAB program amongst frail, older adults awaiting elective cardiac surgery is well tolerated and adds to the growing body of evidence suggesting that such an approach is feasible. Furthermore, in patients completing the intervention as intended, optimizing pre-operative frailty status by as much as 35% is conceivable. Based on the results of this study, we recommend that a PREHAB intervention should be implemented as part of standard care in frail patients on the wait list for elective cardiac surgery. This recommendation is being made based on the growing body of evidence indicating that PREHAB is at least as effective when compared to StanC and, in patient's attending a sufficient number of sessions, PREHAB may be beneficial. Future research in this field should attempt to optimize the delivery of the PREHAB model in an attempt to maximize functional benefit and promote sustained behaviour change. More specifically, future studies will be required to determine the optimal dosage of PREHAB resulting in improved post-operative outcomes while maintaining implementation feasibility within the confines of a pre-specified waiting period. An unexpected finding of our study was the challenge associated with intervention attendance. Based on our attendance data, we speculate that the frail, older adult population will require additional support with respect to transportation, motivational rewards[202] or peer-mentoring[222] to promote adherence. Our intervention was specifically structured to contain intensive exercise and education programming within the first four weeks, followed by less structured programming for the remaining four weeks. We recommend that this specific cohort of patients (i.e. frail, older adults) receive structured programming and more frequent follow-up by the health care team for the duration of the intervention, as post-discharge health support has been previously demonstrated to promote CR attendance following a coronary event.[223] Other strategies such as

refresher sessions, self-management programming or cognitive behavioural therapy have been demonstrated to enhance exercise adherence in other chronic disease populations and should be explored in future research invesitgations.[224,225] Future trials must also determine whether attendance at the PREHAB intervention is associated with improved post-operative outcomes, including long-term mortality and patient-centred metrics such as HRQoL. These research questions will be specifically addressed in future reports of the multi-site, PREHAB trial.

While post-operative outcomes were not investigated as part of this dissertation, it is possible that PREHAB promotes sustained behaviour change post-operatively. For example, previous studies have reported increased attendance at post-operative CR programming amongst patients attending PREHAB[26,132] and increased physical activity levels post-operatively.[26,128] Based on this data and the CACPR quality indicator recommending the implementation of patient self-management education, future studies must ensure that effective behaviour change and maintenance techniques are incorporated to ensure sustainability of the PREHAB intervention.[226,227] Indeed, previous research has confirmed that physical activity behaviour and aerobic capacity decrease significantly in the years following completion of CR;[228,229] therefore, future studies of pre-operative programming must attempt to actively engage patients in a process of self-managed care to promote maintenance of healthy lifestyle behaviours. Strategies such as action planning, providing information about the consequences of a behaviour, prompting rewards and facilitating social comparison have been demonstrated to be the most effective behavior change techniques to improve self-efficacy and modify long-term physical activity behaviour.[230–232] The efficacy of incorporating these behaviour change techniques into standard practice for both pre- and post-operative CR programming should explored in future trials.

Based on the review of literature presented in this dissertation, we have identified that few well-conducted studies have examined the modification of frailty using interdisciplinary exercise interventions.[85,86,90,91] Furthermore, no previously published studies have examined the effect of an exercise intervention on the frailty index in the context of a randomized controlled trial, despite recent literature indicating that physically active individuals have lower frailty index scores.[199] Due to the continuous scoring system employed by the frailty index, we speculate that this tool may be more sensitive to change when compared to dichotomous scoring tools and should therefore be implemented as an outcome measure in future trials. Our results provide preliminary evidence that the frailty index can indeed be modified; however, larger trials should investigate the minimum dosage of exercise required to modify frailty and specific cohorts that may be more responsive to an exercise intervention (i.e. pre-frail, frail, most frail). Future studies should also aim to establish the ability of the FFI to predict mortality and major morbidity in a large, representative database (e.g. National Health and Nutrition Examination Survey) of older adults.

As the delivery of cardiovascular care continues to advance, interventional trials must remain at the cutting edge to ensure that the study population is representative of the target population. Based on the literature unequivocally identifying frailty status as a predictor of adverse post-operative outcomes,[12] we sought an opportunity to implement a pre-operative strategy combining exercise and educational components in an attempt to optimize frailty. However, more recent literature also indicates that frailty status is an important predictor of adverse health outcomes in patients undergoing minimally invasive procedures, such as transcatheter aortic valve replacement surgery.[74,81,82,196] As this procedure becomes more common, future trials should attempt to develop interventions that are appropriate for the high-risk population undergoing

transcatheter procedures. This population represents a cohort of patients that may derive significant functional benefit from an exercise intervention; thus, this area of research should be explored in future investigations.

To encourage researchers to enroll adequate sample sizes in future studies of pre-operative exercise and educational programming, we conducted a post-hoc power analysis using data collected as part of the present analysis. Using the observed effect size and standard deviation of the change variable in the present dissertation, to detect a statistically significant improvement in FFI, we determined that a sample size of 230 patients (i.e. 115 per group) would be required for a two-tailed alpha test of 0.05 and 80% power. We also conducted a sample size calculation to project the number of patients that would be required to detect a statistically significant improvement in $MVPA_{10min}$ in the PREHAB group when compared to the StanC arm. A sample size of 210 patients (i.e. 105 per group) were determined to be required for a two-tailed alpha test of 0.05 and 80% power for the $MVPA_{10min}$ outcome. In the future, we hope that these sample size calculations will be used by researchers to appropriately power studies of pre-operative exercise programming amongst the cardiac surgery cohort. It is important to note that this dissertation was based on preliminary evidence from the first 26 patients recruited into the PREHAB randomized controlled trial (NCT02219815). Although the larger trial was specifically powered to detect a change in the proportion of patients requiring a hospital LOS greater than 7 days, the final targeted sample size of 244 elective cardiac surgery patients will be sufficiently powered to detect changes in FFI and $MVPA_{10min}$ based on the sample size calculations above.

Conclusions

This novel study demonstrated that PREHAB is feasible to implement in a variety of geographical locations in Canada (i.e. Manitoba, New Brunswick and Nova Scotia) and may be

associated with improved pre-operative risk amongst frail, older adults awaiting elective cardiac surgery. While our results do not support our primary hypotheses speculating that PREHAB would decrease the severity of frailty and increase $MVPA_{10min}$ more than StanC, several important programming recommendations can be extracted from our data. Firstly, innovative and consistent follow-up strategies must be implemented to ensure intervention attendance is maintained throughout the duration of the PREHAB program. Our sub-group analysis indicated that frailty status improved by 17% and 35% amongst StanC and PREHAB completers, respectively; whereas, PREHAB non-completers experienced an FFI decline of 5%. As such, program completion appears to be an integral factor when attempting to maximize pre-operative reserve and physical function. Second, we reported significant associations between several objectively quantified physical activity parameters and frailty status. This data supports the recommendation that physical activity, whether engaged in through a formal intervention or during leisure time, may be associated with decreased risk prior to surgical intervention. Third, we developed a novel tool to assess changes in frailty status in a cohort of patients requiring cardiac surgery. Future studies should aim to replicate our FFI in a representative sample of older adults to examine its ability to predict mortality and improve in response to an exercise intervention. In summary, the novel data presented in this thesis suggests that the PREHAB intervention is feasible to implement and may result in improved frailty status amongst frail older adults awaiting elective cardiac surgery.

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Appendices

Appendix A: University of Manitoba Health Research Ethics Board Approval

Appendix B: St. Boniface General Hospital Research Review Committee Approval

Appendix C: Patient Information and Consent Form

Appendix D: PREHAB 30-Item Frailty Index

Appendix E: Short Physical Performance Battery

Appendix A: University of Manitoba Health Research Ethics Board Approval

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HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Full Board Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. R. Arora	UofM/Cardiac Sciences	H2014:208
HREB MEETING DATE:	**APPROVAL DATE:**	**EXPIRY DATE:**
June 23, 2014	July 10, 2014	June 23, 2015
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	The PREHAB Study - Pre-Operative Rehabilitation for Reduction of Hospitalization After Coronary Bypass and Valvular Surgery (Linked to H2010:390)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: Technology Evaluation in the Elderly (TVN)	

Submission Date(s) of Investigator Documents:	REB Receipt Date(s) of Documents:
July 4, 2014	July 9, 2014

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol:		
Clinical Study Protocol (including revisions/clarification addressed in revised submission July 4, 2014)	V. 1.1	July 4, 2014
Consent and Assent Form(s):		
Research Participant Information and Consent Form	V. 2	03/06/14
Other:		
Identification Page	V. 1.0	02/June/ 2014
Interview Package	V. 1.1	24/June/2014

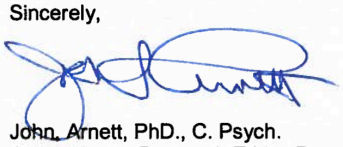
CERTIFICATION
The University of Manitoba (UM) Health Research Board (HREB) has reviewed the research study/project named on this ***Certificate of Final Approval*** at the ***full board meeting*** date noted above and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:
1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,



John Arnett, PhD., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

Appendix B: St. Boniface General Hospital Research Review Committee Approval

Hôpital St-Boniface Hospital
409 Taché Ave, Winnipeg MB Canada R2H 2A6

Research Review Committee
Approval Form

Principal Investigator: **Dr. R. Arora**

RRC Reference Number: **RRC/2014/1413**

Date: **December 9, 2014**

Protocol Title: **The PREHAB Study – Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery.**

The following is/are approved for use:

- **Protocol, Version 1.1 dated July 4, 2014**
- **Research Participant Information and Consent Form, Version 2 dated June 3, 2014**
- **Identification Page, Version 1.0 dated June 2, 2014**
- **Interview Package, Version 1.1 dated June 24, 2014**

The above was approved by Dr. B. Ramjiawan, Co-Chairperson, Research Review Committee (RRC), St. Boniface Hospital, on behalf of the Committee. As the recommendations by the Research Review Committee have been met, final approval is now granted.

Should you require assistance during any stage of your research project, please do not hesitate to contact the St. Boniface Hospital Office of Clinical Research (204-258-1044).

The Research Review Committee wishes you much success with your study.

Sincerely yours,

Dr. B. Ramjiawan
Co-Chairperson, Research Review Committee
St. Boniface Hospital

Please quote the above reference number on all correspondence.
Inquiries should be directed to the RRC Secretary
Telephone: (204) 235-3623 **Fax:** (204) 237-9860
N1004 – 409 Taché, Winnipeg, MB, Canada R2H 2A6
BR/ar

Appendix C: Patient Information and Consent Form

RAKESH C. ARORA* MD, PhD, FRCSC

Cardiac Surgeon / Intensivist
Medical Co-Director - Intensive Care Cardiac Surgery
Rudy Falk Clinician-Scientist
Assistant Professor – Department of Surgery & Physiology
*Denotes Medical Corporation

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Title of Study: The Prehab Study- Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery.

Principal Investigator: **Dr. Rakesh Arora MD PhD FRCSC FACS**
Research Director – Section of Cardiac Surgery
Research Director – Translational Research – Dept. of Surgery
St. Boniface Hospital
Ph# 204-258-1031

Co-Principal Investigator:

Dr. Todd Duhamel PhD
Associate Professor
Faculty of Kinesiology & Recreation Management
University of Manitoba

Dr. Ansar Hassan MD PhD FRCSC
Assistant Professor
Department of Cardiac Surgery
Dalhousie University

Dr. Nicholas Giacomantonio MD FRCPC
Associate Professor of Medicine
Dalhousie University

Co-Investigators:

Dr. Navdeep Tangri, Dr. Thang Ngoc Nguyen, Dr. Sarvesh Logsetty, Dr. Jitender Sareen, Dr. Colleen Metge, Dr. Hillary Grocott, Dr. Jo Anne Sawatzky, Dr. Kenneth Rockwood, Dr. Sean Bagshaw, Dr. Jonathan Afilalo, Dr. Jean-Francois Legare

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your

friends, family or (if applicable) your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information you do not clearly understand.

Purpose of the Study

This research study is being conducted to evaluate the effects of pre-operative exercise and education on the outcomes of elective cardiac surgery. The primary purpose of this study is to establish the safety of this program and evaluate the length of stay in hospital following surgery. A total of 244 patients will be recruited to participate in this study.

This study has been registered on a publicly available registry databank. ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Study Procedures

In this study, you will be randomized into one of the 2 study groups described below. Randomized means that you are put into a group by chance, like flipping a coin. You will have an equal chance of being placed in either group.

Standard Care Group Procedures:

If you are eligible for the 'current standard care' group, you will be asked to complete the following 9 appointments with the Research Assistant over a period of approximately one year:

Appointment #1/2: These appointments will take place within the next week and you will be asked to come to the St. Boniface Hospital (Winnipeg, MB). During the first appointment, you will undergo a detailed frailty assessment, a graded exercise test, and complete a 6-minute walk test. The frailty assessment will involve a variety of questions, in addition to several tests of physical function including a chair-stand test, balance tests, and grip strength. For the 6-minute walk test you will be asked to walk in a hallway, at your own pace, for a total of 6 minutes. This simple test will provide information regarding your physical fitness level; it is routinely used for clients participating in cardiac rehabilitation programs across Canada. The Research Assistant will also provide you with a Physical Activity Monitor, which is a small device that is about the size of a watch and is worn on a belt. This device measures the amount and intensity of physical activity that you complete on a daily basis. Given the small size and placement of the accelerometer at belt level, you will be able to participate in your normal daily routine without alteration. It is important to note that the monitor will only measure the amount of physical activity that you accumulate and does not store personal information. Therefore your privacy will not be adversely affected by wearing the unit. The monitor will be given to you by the research staff at each of the three meetings and you will be asked to return the unit to the St. Boniface Hospital seven days later. At the second appointment, you will be

asked to complete a series of questionnaires. Each of these appointments will take approximately 1 hour of your time.

Appointment #3: this appointment will occur approximately 4-6 weeks following initial randomization to the intervention or control group. During this appointment, the Research Assistant will provide you with a Physical Activity Monitor; you will be asked to wear this monitor for a period of 7 days. This part of the pro-operative assessment appointment will take approximately 30 minutes of your time.

Appointment #4/5: these appointments will be combined with your cardiac surgery pre-operative appointment at the St. Boniface Hospital, approximately 1 week prior to your surgery. During the fourth appointment, you will be asked to undergo a detailed frailty assessment, complete a graded exercise test, and the 6-minute walk test. The Research Assistant will also provide you with a Physical Activity Monitor; you will be asked to wear this monitor for a period of 7 days. At the fifth appointment, you will be asked to complete a series of questionnaires. Each of these appointments will take approximately 1 hour of your time.

Appointment #6/7: about 3 months after your surgery, the Research Assistant will contact you to make two appointments to come back to the St. Boniface Hospital. During the sixth appointment you will undergo a detailed frailty assessment, complete a graded exercise test, and the 6-minute walk test. The Research Assistant will also provide you with a Physical Activity Monitor; you will be asked to wear this monitor for a period of 7 days. At the seventh appointment, you will be asked to complete a series of questionnaires. Each of these appointments will take approximately 1 hour of your time.

Appointment #8/9: about 1 year after your surgery, the Research Assistant will contact you to make two appointments to come back to the St. Boniface Hospital. During the eighth appointment you will undergo a detailed frailty assessment, complete a graded exercise test, and the 6-minute walk test. The Research Assistant will also provide you with a Physical Activity Monitor; you will be asked to wear this monitor for a period of 7 days. At the ninth appointment, you will be asked to complete a series of questionnaires. Each of these appointments will take approximately 1 hour of your time.

Intervention Group Procedures:

If you are randomized to the intervention group, you will be asked to complete the same 5 appointments outlined for the standard care group above. In addition, you will be asked to participate in the "Pre-hab Program for Cardiac Surgery Patients" at your local, community-based cardiac rehabilitation facility. This unique program has been developed to meet individualized exercise and educational needs of patients waiting for cardiac surgery. Before you start the program, you will receive a baseline health and fitness assessment by the cardiac rehabilitation centre staff. This assessment includes a questionnaire, a graded exercise test, lung function test, body measurements (waist, hip and body weight) and a blood test (glucose and lipid levels). The Research Assistant will also collect these results as part of the study.

The education part of the pre-hab program will be made up of a series of 4 classes at your local, community-based cardiac rehabilitation facility. The goal of these classes is to help you to make improvements and/or changes in your lifestyle. Topics for these classes include self-management strategies for cardiac rehabilitation: risk factor reduction, medication use,

cardiovascular physiology, stress management, healthy eating and promotion of self-managed care.

The exercise part of the pre-hab program will consist of an individualized exercise program, based on your health assessment. If you choose to participate in the study and are randomized to the intervention group, we will request that you commit to attending your local cardiac rehabilitation facility for 2 supervised exercise sessions each week until you are called for your surgery or for the duration of your 8-week program. We will also ask you to keep a record of your visits to the facility.

There will be NO cost to you for participating in the exercise program, other than your time and your transportation costs.

All Study Participants: If you agree to participate in this study, we will also be obtaining information from your hospital chart. This will include information about your past medical history and details regarding your surgery/hospital stay. Participation in the study will continue for approximately 1 year after your cardiac surgery. If you are interested in receiving a summary of the study results, please designate on this form below.

Risks and Discomforts

The risks to participating in this research are considered to be minimal. However, there is a certain degree of risk involved in the initiation of any exercise program. If you are randomized to the intervention group, you will be carefully assessed by the medical fitness facility staff prior to the initiation of an exercise program. Additionally, the symptom limited, graded program of exercise would be individualized according to your personal health status. Although the exercise classes will be conducted by certified and experienced instructors, if you have reason to believe that you would be at physical risk of harm/injury by participating in the program, you are asked to decline participation in this project. The cardiac rehabilitation has trained exercise specialists on site to supervise the exercise programs offered at the facility. Additionally, trained healthcare personnel are also on site at all times. The researcher may decide to take you out of this study if your health status changes to prevent you from being able to continue to participate. For example, if your heart condition gets worse before your surgery, it may not be appropriate for you to continue participating in the study. Your participation in the study may also be discontinued upon the advice of a medical doctor.

Benefits

There may or may not be direct benefit to you from participating in this study. We intend to use the information learned from this study to benefit other individuals who are awaiting cardiac surgery in the future.

Costs

All procedures, which will be performed as part of this study, are provided at no cost to you. The cost to you will be transportation to St. Boniface Hospital for the assessment appointments.

Confidentiality

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba.

Organizations that may inspect and/or copy your research for quality assurance and data analysis include groups such as: The University of Manitoba Health Research Ethics Board or the St. Boniface Hospital Office of Clinical Research.

All study related documents will bear only your assigned study number. All data will be entered into a computer and transmitted electronic to members of the research team only. All hard copy records will be kept in a secure area and only those persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave St. Boniface Hospital. If deemed necessary by the research staff, information regarding your health status may be shared with medical staff at the St. Boniface Hospital.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. However, if you decide to stop participating in the study, we encourage you to discuss this decision with the research study staff first. There are no consequences to withdrawing from the study. Your decision not to participate or to withdraw from the study will not affect your care at this centre. If the study staff feels that it is in your best interest to withdraw you from the study, they will remove you without your consent. We will tell you about any new information that may affect your health, welfare, or willingness to remain in this study.

Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact Dr. Rakesh Arora at (204) 258-1031 or bpambrun@sbgh.mb.ca.

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389. Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read this information/consent form. I have had the opportunity to discuss this research study with Dr. Rakesh Arora and/or his staff. I have had my questions answered by them in a language I understand. This risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the

research study by any statements or implied statements. Any relationship (such as employer, supervisor, or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my records that relate to this study by The University of Manitoba Research Ethics Board and the St. Boniface Hospital Office of Clinical Research for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

I agree to be contacted for future follow-up in relation to this study – YES____ NO____

I would like to receive a summary of the study findings - YES____ NO____

If YES, please provide mailing or e-mail address:

_____

Participant signature: _____ Date: _____
(day/month/year)

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent.

Printed Name: _____ Date:_____
(day/month/year)

Signature: _____ Role in the study: _____

Appendix D: PREHAB 30-Item Functional Frailty Index

	Domain	Tool Used to Measure	Variable	Cut-Off Point	References/Justification
1	Physical	Short Physical Performance Battery	Balance (Side-by-side, semi-tandem, tandem)	Unable to complete=1 Side-by-Side = 0.67 Semi-Tandem = 0.33 Tandem = 0	Guralnik et al. (1994) Participants unable to hold side by side stance for 10 seconds (HR: 3.54 95% CI 3.04 – 4.13) and those unable to hold semi-tandem stance for 10 seconds (HR: 1.78 95% CI 1.51-2.09) more likely to die compared to those able to complete the tandem balance task.
2	Physical	Hand Dynamometer	Handgrip Strength	<u>Males</u> For BMI ≤ 24: GS ≤ 29 = 1, GS > 29 = 0 For BMI 24.1-28: GS ≤ 30 = 1, GS > 30 = 0 For BMI > 28: GS ≤ 32 = 1, GS > 32 = 0 <u>Females</u> For BMI ≤ 23: GS ≤ 17 = 1, GS > 17 =0 For BMI 23.1-26: GS ≤ 17.3 = 1, GS > 17.3 = 0 For BMI 26.1-29: GS ≤ 18 = 1, GS > 18 = 0 For BMI > 29: GS ≤ 21 = 1, GS > 21 = 0	Cut-offs as defined by Fried et al. (2001) and re-published by Searle et al. (2008) Cooper et al. (2010) The HR associated with a 1 kg increase in grip strength is 0.97 (95% CI 0.96-0.98).
3	Physical	Repeated Chair Stand Test	Chair Stand	Unable = 1 ≥16.7 seconds = 0.75 13.7 – 16.6 seconds = 0.5 11.2 – 13.6 seconds = 0.25 ≤11.1seconds = 0	Cut-offs as defined by Guralnik et al. (1994) Cooper et al. (2010) Compared to participants in the highest quartile, those in the lowest quartile (HR: 1.96 95% CI 1.56-2.46), second quartile (HR: 1.40

					95% CI 1.18-1.66) and third quartile (HR: 1.24 95% CI 1.08-1.42) at a higher risk of mortality.
4	Physical	5-metre Gait Speed Test	Gait Speed	<u>Males</u> Height > 173 cm: GS ≥ 6.56 s = 1, GS < 6.56 s = 0 Height ≤ 173 cm: GS ≥ 7.66 s = 1, GS < 7.66 s = 0 <u>Females</u> Height > 159 cm: GS ≥ 6.56 s = 1, GS < 6.56 s = 0 Height ≤ 159 cm: GS ≥ 7.66 s = 1, GS < 7.66 s = 0	Cut-offs as defined by Fried et al. (2001) Studenski et al. (2011) Gait speed associated with survival (HR per 0.1 m/sec: 0.88 95% CI 0.87-0.90).
5	Physical	6-Minute Walk Test	6-Minute Walk Test	Unable = 1 < 300m = 0.75 300-374.9m = 0.5 375-449.9m = 0.25 >450m = 0	Bittner et al. (1993) Compared to patients walking at least 450 m, patients walking less than 300 m confers a 3.7-fold increased risk of dying (OR: 3.7 95% CI 1.44-9.55); whereas, those walking from 300 to 374.9 m are at a 2.8-fold increased risk of death (OR: 2.78 95% CI 1.09-7.11). The odds of being hospitalized for chronic heart failure is increased in patients walking less than 300 m (OR: 14.02 95% CI 4.90-40.14), 300 to 374.9 m (OR: 6.21 95% CI 2.14-18.08) and a trend towards increased hospitalization in those walking 375 to 449.9 m (OR: 1.90 95% CI 0.56-6.42). In a stepwise logistic regression, distance walked remains an independent predictor of mortality (OR: 1.50 95% CI 1.11-2.03 for each 120 m decrease in distance walked) and the combined endpoint of death or hospitalization for chronic heart failure (OR: 1.77 95% CI 1.38-2.26).

					Beatty (2012) For each 104 m decrease in 6MWT distance, there is an associated 86% higher rate of heart failure (HR: 1.86 95% CI 1.51-2.31), a 47% higher rate of myocardial infarction (HR: 1.47 95% CI 1.15-1.89), a 54% higher rate of mortality (HR: 1.54 95% CI 1.32-1.80) and a 55% higher rate of any cardiovascular event (HR: 1.55 95% CI 1.35-1.78).
6	Physical	Paffenbarger Physical Activity Questionnaire	Self-Report Physical Activity	<u>Males</u> < 383 kcal/week = 1 ≥ 383 kcal/week = 0 <u>Females</u> < 270 kcal/week = 1 ≥ 270 kcal/week = 0	As recommended by Afilalo et al. (2014), questionnaires providing measures of activity in kcal/week recommended in frailty assessment using these cut-offs. Ainsworth et al. (1993) confirmed validity of the Paffenbarger Physical Activity Questionnaire in community-dwelling adults.
7	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help Eating	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
8	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help Dressing	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
9	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help Grooming	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
10	ADL	OARS Multidimensional Functional	Help Walking around house	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)

		Assessment Questionnaire			
11	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help getting in/out of bed	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
12	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help Bathing	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
13	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help Using a Telephone	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
14	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help getting to places out of walking distance	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
15	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help Shopping	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
16	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help with Meal Preparations	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
17	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help with Housework	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
18	ADL	OARS Multidimensional Functional	Help taking Medication	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)

		Assessment Questionnaire			
19	ADL	OARS Multidimensional Functional Assessment Questionnaire	Help with Finances	Yes = 1, With some help = 0.5, No = 0	Searle et al. (2008)
20	Exhaustion	Center for Epidemiologic Studies Depression Scale	Feel everything is an effort	Most of the time = 1, Moderate amount of the time = 0.67, Some time = 0.33, Rarely = 0	Searle et al. (2008)
21	Exhaustion	Center for Epidemiologic Studies Depression Scale	Have trouble getting going	Most of the time = 1, Moderate amount of the time = 0.67, Some time = 0.33, Rarely = 0	Searle et al. (2008)
22	Nutrition	Self-Report	Unintentional Weight Loss in Past 3 months	Yes = 1, No = 0	Jung et al. (2014)
23	Nutrition	Self-Report	Unintentional Weight Loss more than 10 lbs	Yes = 1, No = 0	Searle et al. (2008)
24	Nutrition	Self-Report	Decline in food intake	Yes = 1, No = 0	Jung et al. (2014)
25	Weight	Scale for Height and Weight	Body Mass Index	< 18.5 or ≥ 30 = 1 25 to < 30 = 0.5 18.5 to < 25 = 0	Flegal et al. (2007) Being underweight (BMI < 18.5) associated with significantly increased mortality from non-cancer and non-CVD causes. Overweight (BMI 25 to <30) and obesity (BMI ≥ 30) combined associated with increased mortality from diabetes and kidney disease. Obesity significantly associated with increased CVD mortality and cancers considered obesity-related.
26	Quality of Life	EuroQol 5-Dimension 5-Level	Pain/Discomfort	Extreme pain/discomfort = 1 Severe pain/discomfort = 0.75 Moderate pain/discomfort = 0.5 Slight pain/discomfort = 0.25 No pain/discomfort = 0	Janssen et al. (2008) confirmed validity of EQ-5D-5L, responses intuitively coded on 0-1 scale.
27	Quality of	EuroQol Visual	EuroQol Visual	1-(EQ-VAS Score/100)	Janssen et al. (2008) confirmed

	Life	Analogue Scale	Analogue Scale		validity of EQ-5D-5L, responses intuitively coded on 0-1 scale.
28	Depression	5-Item Geriatric Depression Scale	5-Item Geriatric Depression Scale	5 YES = 1 4 YES = 0.8 3 YES = 0.6 2 YES = 0.4 1 YES = 0.2 0 YES = 0	Hoyl et al. (1999) GDS-5 validated in frail, older adults. Responses intuitively coded based on five dichotomous responses included in questionnaire.
29	Anxiety	Generalized Anxiety Disorder-7	Generalized Anxiety Disorder-7	15-21 = 1 10-14 = 0.67 5-9 = 0.33 0-4 = 0	Spitzer et al. (2006) As per GAD-7 scoring protocol, scores of 5, 10 and 15 represent cut-offs for mild, moderate and severe anxiety, respectively.
30	Cognition	Montreal Cognitive Assessment	Montreal Cognitive Assessment	≥ 26 = 0 ≤ 25 = 1	Nasreddine et al. (2006) As per MoCA scoring protocol, a cut-off score of 26 has a sensitivity of 90% and a specificity of 87% in identifying mild cognitive impairment. This is a clinical state that often progresses to dementia.

Appendix E: Short Physical Performance Battery

Balance Test

[stand beside participant to supply support to prevent balance loss]

Side-by-side stand

"I want you to stand with your feet together side-by-side, for up to 10 seconds. Hold this position until I say stop… Ready begin."

Time: ***pre***: _____ s

Score: ***pre***: _____ pts

1 pt: ≥ 10 s
0 pts: < 10 s or unable

Semi-tandem stand [if side-by-side successful]

"I want you to stand with the side of your heel of one foot against the side of the big toe of the other foot, for up to 10 seconds. Hold this position until I say stop… Ready begin."

Time: ***pre***: _____ s

Score: ***pre***: _____ pts

1 pt: ≥ 10 s
0 pts: < 10 s or unable

Tandem stand [if semi-tandem successful]

"I want you to stand with your feet in a straight line, for up to 10 seconds. Hold this position until I say stop… Ready begin."

Time: ***pre***: _____ s

Score: ***pre***: _____ pts

2 pts: ≥ 10 s
1 pt: 3-9.99 s
0 pts: < 3 s or unable

Chair Stand Test

"Do you think you will be able to stand up from a chair without using your arms? First fold your arms across your chest and sit so that your feet are on the floor; then stand up keeping your arms folded across your chest. Please stand up as quickly as you are able five times. After standing up each time, sit down and then stand up again…Ready begin."

Able to stand up from chair five times without using armrests?

N 0 Y 1

Time: ***pre:*** _____ s

Score: ***pre:*** _____ pts

4 pts: ≤ 11.19 s, 3 pts: 11.20-13.69 s, 2 pts: 13.70-16.69 s, 1 pt: ≥16.70 s, 0 pts: > 60 s or unable

Gait Speed Test

"Now I am going to observe how you normally walk. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street. Walk all the way past the tape before you stop… Ready, begin." [Repeat task]

Trial 1:_____ s

Trial 2:_____ s

Avg: _____._____ s

SPPB: 4 pts: ≤ 6.5 s 3 pts: 6.6–8.3
2 pts: 8.4–11.6 s 1 pt: ≥ 11.7 s
0 pts: could not do

SPPB Score: _____ pts

Was the test performed with a walking aid (e.g. cane, walker, IV pole)?

N 0 Y 1