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Frailty, Cognition, and Depression in Older Subjects with Coronary Artery Disease

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Frailty, Cognition, and Depression in Older Subjects with Coronary Artery Disease

by

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A THESIS

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Abstract

Frailty is an area of increasing interest for researchers in cardiovascular health, as health providers look for ways to improve patient resiliency and outcomes. However, little is known about the behavior of frailty or frailty components, particularly cognitive and emotional vulnerability, over time and which groups are more at risk of decline in resiliency after a coronary intervention.

The Calgary Cardiac and Cognition (3C) study is a prospective, longitudinal cohort study of patients undergoing coronary angiography who subsequently received a revascularization procedure or only medical treatment. Using the 3C data, three separate but related studies were completed.

First, the independent associations of baseline potential frailty criteria with 12-month decline in activities of daily living (ADL) were compared. Those categorized as frail in the best multivariable model had 9.0 times the risk of ADL decline and 3.8 times the risk of health-related quality of life (HQRL) decline compared to those categorized as robust.

In the second study, the association over time between two frailty criteria, depression and cognition, was further investigated. Persistent depressive symptoms were more strongly associated with cognitive decline after coronary intervention than depressive symptoms measured only at baseline. Executive function scores for those with persistent depression in the first year, declined by 0.3 to 0.5 standard deviations in the subsequent 18 months.

In the third study, frailty scores on average formed a U-shaped curve with frailty declining from baseline (pre-procedure) to 6 and 12 months, and increasing again by 30 months. Women had higher scores than men, but not significantly so. Frailty trajectory by initial treatment plan

differed by age group as those aged 75 and older did not decline (improve) in frailty after the intervention for some treatment types.

A better understanding of the nature of frailty and frailty components, provided by this research, may help researchers plan and interpret future intervention studies aimed at preventing worsened frailty or better supporting frail persons in follow up to coronary intervention. It lays the groundwork for more studies designed to better anticipate and address the loss of resilience, functional decline, and quality of life in patients after coronary intervention.

Preface

For this thesis, the following three manuscripts were published, or submitted for publication. For each of the manuscripts, the first author conducted the analyses, interpreted the results and wrote the manuscripts. All three studies were completed under the guidance of the senior authors and supervisors. The manuscripts are reproduced in their entirety as chapters in this thesis, after written permission was obtained from the publishers and co-authors.

Freiheit EA, Hogan DB, Eliasziw M, Meekes MF, Ghali WA, Partlo LA, and Maxwell CJ. 2010. "Development of a frailty index for patients with coronary artery disease." J Am Geriatr Soc 58(8): 1526-1531.

Freiheit EA., Hogan DB, Eliasziw M, Patten SB, Demchuk AM, Faris P, Anderson T, Galbraith D, Parboosingh JS, Ghali WA, Knudtson M, and Maxwell CJ. 2012. "A dynamic view of depressive symptoms and neurocognitive change among patients with coronary artery disease." Arch Gen Psychiatry 69(3): 244-255.

Freiheit EA, Hogan DB, Patten SB, Wunsch H, Anderson T, Ghali WA, Knudtson M, and Maxwell CJ. 2015. "Frailty trajectories after coronary interventions in older patients with coronary artery disease." Submitted to Circulation: Cardiovascular Quality and Outcomes, July 28, 2015.

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Finally, I would like to dedicate this thesis to my husband, Theodor Freiheit. Thank you for all your patience and support.

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List of Symbols, Abbreviations, Nomenclature

Abbreviation	Definition
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
3C	Calgary Cardiac and Cognition
ADL	Activities of daily living
APOE	Apolipoprotein E
AUC	Area under the receiver operating characteristic curve
BMI	Body mass index
BVMT-R	Brief Visuospatial Memory Test-Revised
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAMDEX-R	Cambridge Mental Disorders of the Elderly Examination-Revised
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHS	Cardiovascular Health Study
CCS	Canadian Cardiovascular Society
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
EQ-5D	Standardized instrument of EuroQOL Group
FI	Frailty index
GDS	Geriatric Depression Scale
HRQL	Health-related quality of life
MMSE	Mini-Mental State Examination
MI	Myocardial infarction
MT	Medical treatment
OARS	Older Americans Resources and Services
PCI	Percutaneous coronary intervention
ROC	Receiver operating characteristic
QVSFS	Questionnaire for Verifying Stroke-Free Status
RR	Risk ratio
SE	Standard error
SD	Standard deviation
STAI	State-Trait Anxiety Inventory
TIA	Transient ischemic attack

Chapter 1: Introduction

1.1 Thesis Overview

This project examined frailty and components of frailty, specifically measures of cognitive and emotional vulnerability, in older adults with coronary artery disease (CAD) at baseline and longitudinally up to 30 months after a coronary intervention. In this document, the literature will be described, research objectives stated, three publications presented, and implications and conclusions discussed.

Section 1.2 provides background information. Knowledge gaps are discussed in Section 1.3. The data sources are described in Section 1.4. Research objectives are presented in Section 1.5, and a broad outline of the dissertation is given in Section 1.6.

Chapters 2, 3, and 4 are the main body of the dissertation including the following three papers: (1) Development of a frailty index for patients with coronary artery disease; (2) A dynamic view of depressive symptoms and neurocognitive change among patients with coronary artery disease; and (3) Frailty trajectories after coronary interventions in older patients with coronary artery disease.

The final chapter, Section 5, is a discussion of the measurement of frailty in patients with CAD in general, with reference to existing literature, and in light of the studies conducted for this dissertation. Section 5.1 provides a summary of the main study findings. In Section 5.2, study strengths, challenges and limitations are described. The implications of this work are discussed in Section 5.3, and directions for future research are explored in the Section 5.4. Section 5.5 contains a short conclusion.

1.2 Background

1.2.1 Frailty and Cardiovascular Disease

Recent publications have documented a growing number of North Americans living with coronary artery disease (CAD).[1-3] An aging population, and the increasing prevalence of some cardiovascular risk factors (e.g. obesity), combined with a reduction in mortality thanks to improved revascularization procedures, have led to the increased numbers of survivors.[2-8] To address the needs of heart disease survivors, the prediction and prevention of long-term disability and poor health-related quality of life (HRQL) has become increasingly important in the management of these patients and a research priority in both cardiovascular and geriatric medicine. [2,3,9-14]

In this area, the concept of frailty has attracted increased attention as a means of identifying patients more prone to poor outcomes after coronary care.[12,15,16] Health-care providers, who must make decisions about whether to provide risky, but potentially beneficial invasive coronary interventions, are continuously seeking ways to better differentiate those who may have difficulty recovering from a major procedure.[13,17] Traditional cardiovascular risk models use only clinical and angiographic indicators and age, typically only assess risk of mortality rather than decline in activities of daily living (ADLs) or HRQL, and were not derived from older populations.[18-20] Moreover, associations between cardiovascular risk factors and frailty,[21-23] as well as associations between CAD, depression, and cognition,[24,25] suggest that frailty may provide invaluable assistance in assessing risk of decline or poor recovery in a population with CAD.

Over 40 investigational studies were published between 2010 and 2014 addressing frailty in patients with cardiovascular disease.[15,16,26] A Pubmed search of publications using the terms

"cardiovascular" and "frailty" yielded 111 results for 2014, and 69 results from the first half of 2015 alone. Research has primarily focused on the association between baseline frailty and mortality from 30 days[27] to 12 years[28] after an event or procedure.[15,16,26] Less researched outcomes include disability,[29,30] cardiovascular events,[31,32] institutionalization,[33,34] and the association between frailty and cardiovascular risk factors.[21-23]

The prevalence of frailty in cardiovascular patients, based on systematic reviews, range from between 10% for younger and/or community dwelling populations, and up to 60% for older or hospitalized patients.[12,16,26] The investigational studies cited in these reviews estimated independent associations between frailty and mortality and morbidity risk, with relative risks or hazard ratios ranging between 1.2 to 2.2 for various outcomes. [12,15,16,26]

1.2.2 Frailty: Definition and Operationalization

During the Second International Working Meeting on Frailty and Aging (Montreal, 2006) researchers from 13 countries agreed on defining characteristics of frailty: a loss in resiliency and a "vulnerability to stressors" leading to a precipitous decline in health.[35] Frailty has a gradient whereby increased frailty indicates increased health risk. Underlying mechanisms of frailty are believed to involve impairments in multiple, inter-related systems, which may be assessed via psychosocial and cognitive measures in addition to physical measures. [36-40]

However, there has been a lack of consensus among researchers in the gerontology community as to which measurements or combination of measurements best identify and measure frailty. Many measurement approaches have been introduced, but none were developed specifically for a population with CAD. [38]. Few studies have compared different frailty definitions or components of a definition in this population.[41,42] Most studies looking at frailty in cardiovascular disease

have used physical indicators of frailty,[12,15,16] but frailty criteria which include depression, cognition, and social support as components have only rarely been used in this group.[43,44]

Of the brief frailty indices currently available, the most widely known and used for cardiovascular patients[15,16,26] is the Cardiovascular Health Study (CHS) phenotype proposed by Fried and colleagues (2001).[45] This is an index of five criteria: slow gait, weight loss, low physical activity, poor grip strength, and exhaustion developed for a cohort of community-dwelling seniors. The presence of three or more of these criteria is used to define frailty and has been found to predict worsening disability in terms of activities of daily living, falls, hospitalizations, and deaths. [45,46] The CHS operationalization has been criticized for excluding cognitive and psychosocial factors, although several of the criteria can be seen as physical manifestations of depression.[35,47-50] In fact, the measure for "exhaustion" was taken directly from two questions from the Center for Epidemiological Studies Depression (CES-D) screen.[45,51]

In brief frailty screens, the criteria employed are often disputed. The measurement of frailty is not standardized, and it is not known if the most commonly used measures are the best ones.[35] For example, the CHS operationalization, created on the basis of biological models, did not assess the predictive value of its criteria epidemiologically. In examining these criteria in subjects with CAD, both Purser, et al., (2008) and Afilalo, et al., (2010) suggest that the walk test alone has as much discrimination as the rest of the CHS criteria.[41,42] When Rothman examined the CHS index in community-dwelling seniors over age 70, after adding a cognition and depression element, two of the original CHS criteria, exhaustion and grip strength, dropped out of the model.[49] Some criteria have been found by some to be unfeasible in clinical practice. Ensrud and colleagues claimed the "walk test" was difficult to implement in clinical practice due

to space restrictions. She found that a combination of physical criteria using chair stand was as predictive as the CHS criteria using the walk test. [52]

The accumulated deficit approach proposed by Rockwood, Mitnitski and colleagues (2001)[53] counts deficits which are accumulated by a person as they age, including: disabilities, comorbidities, emotional disorders, physical characteristics, and social support indices. The frailty index (FI) does not require a pre-specified list of deficits as variables, but can be implemented using any list of potential deficits as long as the deficits fulfill the following requirements:[54] (i) the list of potential deficits must be at least 40 in number; (ii) they must be associated with health decline; (iii) they should accumulate but not saturate with increased age; and (iv) they must come from a wide range of domains (physical, cognitive, disability, comorbidity, emotional, social). Individual frailty is scored as a proportion of actual deficits divided by total possible deficits, a decimal number between 0 and 1. Although it is intended to be used as a continuous variable, the authors have associated a score of over 0.20-0.25 with the category of "frail" to relate it to other criteria, such as the CHS criteria.[54,55] The FI is easy to implement if data from various domains are already being collected, as it does not require specific prescribed data to be collected. One publication was found to have used it with cardiovascular patients. Myers, et al.,[56] calculated an FI score in 1,521 patients one week after hospitalization for acute myocardial infarction (median FI score 0.08, first quartile 0.06, third quartile 0.14) and then once again 10-13 years later (median FI score 0.19, first quartile 0.11, third quartile 0.30). Using the threshold of 0.25, 5% of the sample was categorized as "frail" at baseline, and 37% of survivors were "frail" at follow up. However, there were only 32 variables in the index, and they consisted primarily of physical disabilities and comorbidities, which may account for the low prevalence estimates at baseline.

Other frailty measurement approaches have been proposed with particular relevance to the clinical setting, but have been less commonly investigated among cardiovascular researchers.[15,16,26] Rolfson's (2000) Edmonton frail scale uses cognition, hospital admissions, self-rated health, instrumental activities of daily living, social support, polypharmacy, weight loss, mood, continence, and mobility to measure frailty.[43,57] Guralnik's (1994) short physical performance battery which includes balance, gait, and chair stands has been advocated as an alternate measurement to Fried and has been used in some heart failure studies.[26,30,58] Rockwood's (2005) Canadian Study of Health and Aging Clinical Frail Scale uses physicians' professional opinion of a patient's overall fitness (very fit, well, well with treated comorbidities, apparently vulnerable, mildly frail, moderately frail, and severely frail).[59] Finally, several researchers have advocated the use of a single physical performance criterion, "slow gait", in patients with CAD in the clinical setting.[29,32,41,42] All of the above measurement approaches have been shown to have convergent validity in measuring outcomes such as mortality, hospitalization, and decline.[41,42,60-62]

1.2.3 Depressive Symptoms and Cognitive Decline in Cardiovascular Patients

As frailty assessments in CAD patients have predominantly used the physical CHS criteria, more can be learned about the nature of potential frailty criteria that are not being utilized, but which have a large impact on increased disability and HRQL decline.[35,38] Older patients with CAD have relatively high rates of depression which is an independent risk factor for all-cause mortality and adverse cardiovascular events.[24,63-70] At the same time, these patients are at risk of developing cognitive impairment.[71-73] As both depression and cognition may be considered important components (measures) in a more comprehensive model of frailty, their combined behavior in a CAD population requires further exploration.

Only recently has the association between depressive symptoms and long term cognitive decline been explored in the CAD population.[74-76] Several prospective studies of older adult populations have found associations between depression and cognitive decline,[75,77-85] although some did not find this association.[86,87] In addition, several studies have investigated genetic risk factors such as the apolipoprotein E (*APOE)* ε4 allele which may interact synergistically with depression to worsen the risk or the magnitude of cognitive decline.[88-91] Several of the studies investigating cognitive decline after coronary intervention have incorporated depression as a potential confounder.[71] However, few studies have investigated depression as an independent risk, or the depression and *APOE* ε4 interaction as a risk on subsequent cognitive outcomes.[92-95] The few studies that exist have been limited by small sample sizes, short follow-up time, and/or few comparison groups, such as only patients undergoing coronary artery bypass graft (CABG) operations.[92-95] Prior to this investigation, no studies had explored the prognostic importance of depressive symptoms on the trajectory of cognition over time after a coronary intervention. Older patients with coronary or peripheral artery disease with new onset or with persistent depression appear to be at highest risk for subsequent mortality and cardiac events.[24,66,70,96,97] Studies of persistent depressive symptoms in older adults have estimated an increased risk of cognitive decline.[81,84] However, this had not yet been explored in patients with CAD.

1.2.4 Frailty Trajectory in Cardiovascular Patients

The trajectory of frailty over time in people with CAD is not well-known. Few studies have looked at frailty over time in cardiovascular patients,[56] and none have looked at incremental time periods before a coronary intervention through recovery, and beyond. Myers et al, (2012), already mentioned in Section 1.2.2, created a Rockwood-type FI at baseline post-acute myocardial infarction using primarily comorbidities and ADLs as criteria, and repeated the

measurement 10-13 years post-baseline.[56] Of those initially classified least frail (FI score <0.10), 66% were classified at a higher frailty group at follow-up. About 86% of those classified as frail at baseline (FI score >0.25) were still frail 10-13 years later. There was a strong association with mortality risk up to 19 years after baseline when using frailty as time-dependent covariate, independent of clinical and socio-demographic variables.[56]

In community-dwelling older populations, a few non-cardiovascular studies have been published characterizing frailty transitions,[98-100] examining potential predictors of transitions,[101-103] testing interventions to limit worsening frailty,[104] and comparing static versus dynamic frailty measures to predict functional decline.[105]

Gill and others estimated that 57.6% of community-dwelling, nondisabled seniors aged over 70 had at least one transition between CHS-defined frailty states over 54 months measured in 18-month intervals. In any one interval, up to 43% of seniors increased in frailty, and up to 23% also became less frail, but there were almost no transitions (0-1%) from frail to robust.[99] Moving from a more robust category to a frailer category was associated with diabetes, osteoarthritis, previous stroke, cognitive decline, older age, or male sex, whereas higher socioeconomic status and higher baseline vitamin D was associated with maintaining robustness or improving to a less frail category.[100-103]

Puts, et al., [105] found that both a baseline frailty measurement and a frailty decline prior to baseline were associated with functional decline in women but not in men. The authors hypothesized that perhaps the failure to find an association between dynamic frailty in men and functional decline was because frail men who declined in function dropped out of the study in greater numbers than frail men who did not decline in function. They suggested that the long

three-year intervals between time points might explain the lack of association between frailty decline and functional decline in men. Fewer than half of those who began the study completed the study, and researchers noted that completers were healthier at baseline than those who had died or dropped out.[105]

Rockwood, et al., and Armstrong, et al., [106,107] have modelled the FI as a continuous measurement in a community dwelling population as well. They showed an exponential increase in frailty with older age groups, with a limit of about 0.6 to 0.7 which seems to be the highest possible FI score. Longitudinal studies using the FI have shown this exponential rate of increase as well. [107-109]

1.3 Knowledge Gaps and Significance

Although the cardiovascular research community has embraced the topic of frailty, the research community needs to establish the best ways of identifying frailty, the trajectory frailty takes in this population, the individual frailty criteria which underlie these measurement approaches, and how they may interact to affect frailty trajectories. While some of this has been done in community-dwelling populations, this information is unknown in a clinical population with CAD. Providing these answers will give researchers a baseline for making comparisons, testing interventions, and interpreting results in future work which will inform clinical practice.

The tools that are currently being using to detect frailty, such as the CHS frailty criteria, have not been adequately examined and may not be the best way to measure frailty in this population. Some research implies that it may not have the best predictive validity or feasibility.[41] A screening tool developed particularly for a CAD population, using a wider range of domains, would give researchers a frailty measurement approach with which to test whether a disease-

specific tool can discriminate patients at risk of decline better than a generic tool. It would allow researchers to determine whether a tool incorporating cognitive and psychosocial criteria discriminates patients at risk of decline better than one with only physical components. The answers to these questions will provide a more informed approach to the identification and follow up of patients likely to decline after a coronary intervention.

Criteria used most often in frailty measurements of CAD patients often overlook psychosocial and cognitive criteria, which have not been thoroughly explored in combination or longitudinally. For example, many studies have examined baseline depression alone or as a covariate, but not the association between the trajectory of depressive symptoms and the trajectory of relevant outcomes, including cognitive decline. Investigating the combined behavior of depression and cognition may help to explain what underlies the behavior of frailty and its rate of change over time. If cognitive decline is affected by sustained depression, frailty is likely to increase accordingly. Understanding this synergy will improve people's understanding of the overall conceptualization of frailty.

Finally, very little is known about the trajectory of frailty after a coronary intervention. Does frailty change equally amongst people who are frailer and those who are less frail? Are certain subsets of patients, defined by age, sex, or particular clinical characteristics, more likely to have increased vulnerability to stressors than other subsets? Knowing the natural pattern of frailty in these groups is an important step before practical intervention studies can be designed. Interventions may involve altering the course of frailty or protecting groups that are losing their resilience. They may involve frequent frailty screening, depression screening, providing a wider range of support and surveillance during follow-up. Intervention studies would determine whether these steps are efficacious in predicting and preventing adverse outcomes such as

reduced functionality and HRQL in older patients. However, understanding the basic trajectory of frailty in different groups is important for setting goals and expectations of an intervention study. For example, keeping frailty stable or reducing the rate of increase may be a positive outcome in a group where steeply increasing frailty is the natural pattern. The long term goal for this research is to enable health care providers to prevent or slow HRQL and ADL decline in patients after coronary intervention. It is hoped that the findings presented in this thesis will contribute toward achieving that goal.

1.4 Data Source – The Calgary Cardiac and Cognition Study

A rich source of baseline and follow-up data from older patients receiving a coronary intervention was required in order to investigate the above questions. The data needed to represent a range of domains, physical performance tests, cognitive performance tests, depression screens, activities of daily living, and health-related quality of life, and needed to be collected longitudinally over the course of several years if possible. This kind of data collection project is difficult to execute due to the significant time, cost, and effort involved. It requires the collaboration of a team of cardiologists, psychiatrists, geriatricians, epidemiologists, and research nurses. The type of data collected is very rich, with a single patient visit taking one to two hours, and a large effort is required to keep data quality and patient retention high. Primary data collection solely for the purpose of this doctoral research would not have been feasible due to these constraints.

Fortunately, the Calgary Cardiac and Cognition (3C) Study had launched in 2003, and was still in the midst of data collection when the work for this project was first conceived. The 3C study is a Canadian Institutes of Health Research-funded prospective cohort investigation of the impact of neurocognitive and psychological factors on quality of life and functional recovery among

older CAD patients undergoing coronary revascularization. It is thoroughly described in Section 3.3.1-Section 3.3.6.

The 3C data were remarkably well-suited to the questions we sought to answer with this research program. A wide range of cognitive and physical performance scores, quality of life scores, health behaviors, and activities of daily living were collected at baseline (pre-procedure), and then 6, 12, and 30 months post-procedure for 374 patients undergoing coronary angiography. After the baseline assessment, 128 subjects underwent coronary artery bypass graft (CABG) surgery, and 150 underwent a percutaneous coronary intervention (PCI), with the remaining 96 patients receiving only medical treatment (MT). For 371 patients it was possible to link their 3C data to death, comorbidity, and revascularization information contained within the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry.[110] In addition, blood samples were collected and analyzed for 367 patients, and caregiver interviews were conducted for 85-93% of patients, depending on the visit. Loss to follow-up was minimal as only 40 subjects (10.7%) had withdrawn or moved by 30 months post-procedure.

This dissertation was chiefly a secondary analysis of the 3C database, for which the very similar primary objective was to describe the associations between cognition, depression and functional decline. No mention of frailty was made in the original grant proposal that funded the study. However, because the data collected represents a wide range of domains for health-related risk factors that tend to accumulate with age, 3C data were ideal for examining frailty in a population of people with CAD. Given that this type of data, particularly physical and cognitive performance scores, are not easily collected through administrative or proxy means, and given the longitudinal nature of the study, this dataset has a relatively large size for a clinical

population. In addition, having a medical treatment only group allowed comparisons between people with and without revascularization procedures.

Specific data limitations relevant to the three papers are described in Sections 3.5.3, 4.5.1, and 5.2.3.

1.5 Research Objectives and Hypotheses

1.5.1 First Objective

Develop a brief frailty screen for subjects with CAD, published 2010. [111]

a. Examine the association between individual frailty criteria and ADL decline in a sample of older patients (aged 60+) with CAD.

b. Incorporate into this frailty measure selected physical criteria, cognition, depressive symptoms, and social elements.

c. Compare the one-year risks of decline in functional ability, decline in HRQL, repeat revascularization, and death between frail, pre-frail, and robust subjects.

It was hypothesized that a frailty screen including measures of depression and cognition would best discriminate patients who worsen from baseline to month 12 in function and HRQL.

1.5.2 Second Objective

Examine the course of depressive symptoms and cognitive decline over time among a sample of older patients with CAD, published 2012. [112]

a. Compare two exposure measurements: (i) a binary measure capturing depressive symptoms (yes or no) at baseline (pre-procedure); and (ii) a dynamic measure

capturing the course of depressive symptoms between baseline and 12-months post-procedure.

b. Examine longitudinal change in separate cognitive domains: executive function, verbal and visuospatial memory, verbal fluency, and global cognitive tests which combine all cognitive domains.

c. Investigate whether the presence of the *APOE* ε4 allele is an effect modifier of any observed associations between depressive symptoms and cognitive decline.

It was hypothesized that a dynamic measurement of depressive symptoms would be more strongly associated with cognitive decline than a baseline measure; that executive function would be more sensitive to the effects of depression; and that the presence of the *APOE* ε4 allele would have a deleterious effect on cognitive decline, either overall, or in combination with a depression category.

1.5.3 Third Objective

Examine the transitions and trajectories of a frailty index (FI) based on Rockwood's[55] accumulation of deficits procedure, which contain distinct cognitive and emotional criteria, submitted July 28, 2015.

a. Create a frailty index (FI), and observe the distribution of FI scores at baseline, 6, 12, and 30 months.

b. Describe changes in the distribution of frailty scores across the four visits.

c. Explore the trajectory of the FI score over 6, 12, and 30 months, and observe if there are differences by sex, age, or treatment plan (CABG, PCI, and MT).

It was hypothesized that FI scores would be higher for women and for older people, indicating greater frailty. It was expected that revascularization procedures would lead to a temporary decrease (improvement) in frailty during the first 12 months after a revascularization procedure (CABG or PCI) compared to those who receive medical therapy only. However, it was also expected that frailty would increase in patients requiring long hospital stays, such as those undergoing CABG.

1.6 Summary

Three separate, yet related, research studies are presented in this thesis. Cumulatively, they provide a first look into the behavior of frailty and frailty components in a clinical population undergoing coronary intervention over time. Individual frailty criteria and their association with decline are examined in the first and second papers. The first and third papers demonstrate the use of different measurement approaches for CAD patients. The second and third papers track change in frailty and frailty components over time. The findings revealed by this work provide baseline associations between frailty and decline, which researchers can use while designing studies, interpreting future frailty outcomes, and determining the possible benefits of interventions. In addition, this information may be useful to health care providers wishing to assess and predict the pattern of their patients' vulnerability to additional health problems.

Chapter 2: Development of a Frailty Index for Patients with Coronary Artery Disease

2.1 Abstract

OBJECTIVES: To construct a brief frailty index for older patients with coronary artery disease (CAD) undergoing coronary angiography that includes physical, cognitive, and psychosocial criteria and accurately predicts future disability and decline in health-related quality of life (HRQL).

DESIGN: Prospective cohort.

SETTING: An urban tertiary care hospital in Alberta, Canada.

PARTICIPANTS: Three hundred seventy-four patients aged 60 and older (73% male) undergoing cardiac catheterization for CAD between October 2003 and May 2007.

MEASUREMENTS: Potential frailty criteria examined at baseline (before the procedure) included measures of balance, gait speed, cognition, self-reported health, body mass index (BMI), depressive symptoms, and living alone. The outcomes assessed over 1 year were dependency in activities of daily living (ADLs) and HRQL.

RESULTS: The five best-fitting criteria from regression analyses for ADL decline were poor balance (risk ratio (RR) = 2.4, 95% confidence interval (CI) = 1.4–4.0), abnormal BMI (RR = 1.8, 95% CI = 1.1–3.0), impaired Trail-Making Test Part B performance (RR = 2.3, 95% CI = 1.3–4.2), depressive symptoms (RR = 1.8, 95% CI = 1.1–3.1), and living alone (RR = 2.2, 95% CI = 1.3–3.8). Using the five criteria as separate variables or as a summary frailty index yielded identical areas under the receiver operating characteristic curve (0.76, 95% CI = 0.66–0.84). Patients with three or more criteria (vs none) were at statistically significant greater risk for

increased disability (RR= 10.4, 95% CI = 4.4–24.2) and decreased HRQL (RR = 4.2, 95% CI = 2.3–7.4) after 1 year.

CONCLUSION: This brief frailty index including physical, cognitive, and psychosocial criteria was predictive of increased disability and decreased HRQL at 1 year in older patients with CAD undergoing angiography. This index may have applications for clinicians and researchers but requires further validation.

Key words: frailty; disability; health-related quality of life; coronary artery disease

2.2 Introduction

Coronary artery disease (CAD) is a significant cause of death and morbidity in North America.[113] As survival rates have improved, CAD research has increasingly focused on long-term disability and health-related quality of life (HRQL) as outcomes of interest. [114]

There is no consensus as to how best to identify frail patients at greater risk for adverse outcomes. Frailty in later life is often viewed as ‘‘increased vulnerability to stressors due to impairments in multiple, interrelated systems that lead to decline in homeostatic reserve and resiliency.’’[35] Some proposed operational definitions (or indices) incorporate a parsimonious number of measures, whereas others have up to 90. Brief indices, although simple to use, lack breadth.[35] No frailty index has been designed specifically for older hospitalized patients with CAD. Indices developed for community-based populations may be neither feasible in nor relevant to such patients. The few studies that have examined frailty in older populations with CAD[12] have shown worse outcomes in those categorized as frail. One found that a single variable (slow gait) was a stronger predictor of 6-month mortality than two standard frailty indices and other simple measures.[41]

None of the proposed frailty indices have all of the following qualities: simple to use in clinical practice; based on multiple domains known to predict decline in older patients; and include criteria distinct from disability, measures of comorbidity, and healthcare utilization. Also unsettled is the choice of which measure to use to represent a particular criterion.

The purpose of the current study was to examine a range of potential frailty criteria representing diverse domains (physical, cognitive, psychosocial) in older patients with CAD undergoing coronary angiography to develop a brief, comprehensive, and feasible frailty index. Specific

objectives were to determine which components collectively best predicted greater likelihood of developing new disability in basic activities of daily living (ADLs) and assess the convergent validity of the index by examining its association with a clinically important decline in HRQL. Prior studies have shown that frailty measures can predict both outcomes.[35,114] A brief, validated, practical index of frailty in older CAD patients being considered for invasive procedures could identify a vulnerable subgroup at greater risk of adverse outcomes who could then be targeted for interventions designed to enhance recovery or spared a procedure unlikely to benefit them.

2.3 Methods

2.3.1 Study Design

This is a substudy of the Calgary Cardiac and Cognition (3C) Study, a prospective cohort investigation of the effect of neurocognitive and psychological factors on quality of life and functional recovery in older patients undergoing coronary revascularization. Three hundred seventy-four subjects aged 60 and older were enrolled between October 2003 and May 2007. All underwent coronary angiography for CAD at an urban tertiary care hospital housing centralized cardiac services for southern Alberta, Canada. Recruitment was stratified according to three initial treatments: coronary artery bypass graft surgery (CABG; n=128), percutaneous coronary intervention (PCI; n=150), and medical therapy (MT; n=96). Potential participants were excluded if they underwent an emergency catheterization, had prior revascularization, were unable to provide informed consent, or were unable to complete the assessment because of language difficulties or mental or physical impairments. Ethical approval was received from the Conjoint Health Research Ethics Board, University of Calgary.

Trained research nurses and associates administered a comprehensive standardized assessment battery including neuropsychological and physical performance tests and sociodemographic,

health behavior, self-rated health, ADL, and HRQL measures at baseline (pre-procedure) and 6 and 12 months after the procedure. Most (58%) baseline assessments were conducted in the hospital and the remainder (and all 12-month assessments) in the participant's home. The 3C database was linked with the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease,[110] a registry of all patients undergoing cardiac catheterization in the province, for baseline clinical information.

During the follow-up year, 18 participants moved or withdrew, three did not participate in the 12-month assessment, and 10 died (mortality rate 2.7%). Outcome data at 12 months were available for 343 participants (92%).

All assessment data were entered and audited against the original assessment forms. An independent psychometrician (trained by study neuropsychologist LP) reviewed and scored all cognitive testing.

2.3.2 Measures of Frailty

A pragmatic approach was taken to the development of a frailty scale. Examining the specific measures collected, it was not possible to replicate exactly any well-known frailty index.[12,41] Following review of relevant domains, existing criteria,[35] and the available measures, it was decided to examine the predictive utility of measures of self-rated health, body composition, balance, mobility, cognition, mood, and social isolation. The aim was to create an index incorporating measures widely available to practicing clinicians. Measures of healthcare use, comorbidity, and disability were deliberately excluded. Published or clinically relevant cutoff scores identifying the most-impaired proportion of patients were used to dichotomize all measures as normal versus impaired or abnormal.

Self-rated health was assessed according to the answer to the question: ‘‘In general, would you say your health is excellent, very good, good, fair, or poor?’’ Those who responded fair or poor were coded as impaired.

Balance and gait assessments were derived from the MacArthur Studies of Successful Aging physical performance tests. [115] Participants were categorized as having impaired balance if they were not able to hold a full tandem position (eyes open) for 10 seconds or longer. Participants were categorized as impaired on gait speed if they were not able to walk 2.4 m in 4 seconds or less.

Although several frailty indices include weight loss, data suggest a U-shaped relationship between body mass index (BMI) and frailty. [116] Participants were not asked about weight change, but BMI was calculated from measured height and weight. Participants were categorized as underweight [117] if their BMI was less than 21 kg/m^2 (<3% of 3C participants) and overweight if their BMI was greater than 30 kg/m^2. BMI values were dichotomized as normal (21–30 kg/m^2) or abnormal (<21 or >30 kg/m^2).

Three executive tests (letter- and animal-naming fluency tests, Trail-Making Test Part B (Trails B)) [118] and one global measure (Mini-Mental State Examination (MMSE))[119] were compared. The Trails B outperformed the other cognitive measures. It was retained and the others were excluded from further analyses. Participants were classified as impaired on the Trails B if their scores were 1.5 or more standard deviations below the mean adjusted for age, sex, and education[120] (Appendix A).

The 15-item Geriatric Depression Scale (GDS) [121] was used to determine emotional status or mood. A cutoff score of 4/5 was used to define clinically important depressive symptoms

(abnormal). [121] Two GDS subscales (one representing mood–hope and the other, withdrawal–apathy–vigor) [122] were also examined, but they were not retained because they were no more predictive than the full GDS. Living alone was used as a surrogate measure of social isolation based on preliminary analyses. (Participants who lived alone had less contact with family caregivers or were less likely to have an identified caregiver.) Living alone (especially for men) has been shown to be predictive of adverse health outcomes in patients with CAD. [123]

2.3.3 Outcome Measures

The primary outcome was an increase in ADL disability 12 months after the procedure. The secondary outcome was a clinically significant decrease in HRQL score. ADL disability was measured using the Older Americans Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire, [124] which assesses self-reported difficulties in seven personal ADLs: eating, dressing, combing hair and shaving, walking, transferring, taking a bath or shower, and using a toilet. For each, a response of ‘‘unable to perform’’ or ‘‘receiving help’’ was coded as 1 (unable to perform without help) and able to perform independently as 0. Overall scores were the sum of the seven items. Any increase in ADL scores at 12 months (difference between follow-up and baseline scores of 1) was coded as 1 (increased ADL disability). No change or improvement in ADL function was coded as 0. The EuroQOL EQ-5D, which consists of five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) each with three levels (no health problems, moderate health problems, and extreme health problems), was used to assess HRQL. [125] The U.S. scoring algorithm was used to calculate each patient’s HRQL score on a scale from 0 to 1. [125] Scores at baseline were then compared with those at 12 months. Any participant with a decline of 0.03 or more (changes of this

magnitude are felt to be clinically meaningful) [126] was categorized as having reduced HRQL. Deaths were excluded from both analyses.

2.3.4 Missing Data and Imputation

Baseline data were missing for Trails B (n=18), single ADL items (n=2), self-rated health and BMI (n=1), and balance and gait tests (n=1). The 3C clinical panel (including a neuropsychologist and geriatrician) reviewed all neurocognitive and functional data for subjects with missing Trails B data. Based on consensus, impaired scores were imputed for 13 participants, with the remaining five excluded from the analyses. The two subjects with missing self-rated health and BMI or balance and gait test data were excluded. Subjects with a single missing ADL item (including 1 subject at follow-up) were retained because it was found that the missing item did not alter their outcome determination. All EQ-5D data were complete. Seven of 374 (1.9%) participants were excluded because of missing baseline data. Of the 343 patients assessed at 12 months, 6 patients were excluded from the analyses because of missing data.

2.3.5 Model Development and Analyses

Unadjusted associations between each potential frailty measure and increased ADL disability were examined using Poisson regression with robust standard error estimates. [127] Because few events per independent variable may lead to biased covariates, [128] and there were 44 events of increased disability, a model selection approach that limited the number of independent variables to five was used. The five criteria with the largest risk ratio estimates were included in the first multivariable model. The independent variable with the lowest risk ratio was then removed and replaced, one at a time, with all other variables. The model with the highest area under the receiving operating characteristic curve (AUC) and the best representation from each of the frailty domains was selected. Correlations between independent variables were examined to

understand the role of each in the model. The process of replacing the variable with the lowest risk ratio was repeated until the model with the highest AUC and best representation of the frailty construct was found. Variables were not included in the final multivariable model either because of correlations with other variables, weaker associations with the outcome of ADL disability, or both (Tables 1 and 2 - data on correlations between variables not presented but available upon request).

A frailty index was developed with the relative magnitude of the coefficients in the final model determining the weighting of criteria. An AUC analysis of the regression model with the final criteria was compared with an AUC analysis of a model using the frailty index alone to assess its accuracy. The index was categorized based on the distribution of the data and used to predict increased ADL disability and HRQL decline. ROCKIT 0.9.1B (Kurt Rossmann Laboratories, University of Chicago, Chicago, IL) was used for the AUC analysis. SAS Version 9.1 (SAS Institute, Inc., Cary, NC) was used for all other analyses.

2.4 Results

Baseline characteristics for the 337 participants used for model development did not differ significantly from those of the total 3C cohort (n = 374) (Table 1). The distribution of patient characteristics (including frailty score) did not vary significantly according to treatment group (CABG, PCI, MT) or location of baseline assessment. The mean age and comorbid diagnoses of 3C subjects were comparable with those of all eligible patients undergoing catheterization during the recruitment period (n = 6,594), although a greater proportion of those in the study sample required less urgent care and were treated with CABG and PCI (data not shown).

The final multivariable model contained five variables: poor balance, abnormal BMI, cognitive impairment (according to Trails B), depressive symptoms (GDS score >4), and living alone (Table 2). The model of the frailty index composed of these characteristics had an AUC of 0.76 (95% confidence interval (CI) = 0.66–0.83). Gait speed alone had an AUC of 0.60.

Relative risk estimates for each of the five predictor variables were of a similar magnitude. (The ratio of the largest to smallest relative risk was 1.33/1.) Equal weights were assigned to the criteria. A frailty index score was determined by totaling the number of criteria present. Index scores were divided into four categories: 0, 1, 2, and ≥3 points (the combination of 3, 4, or 5 represented 10% of the cohort). An AUC analysis of a regression model using the categorical frailty index revealed that the index was equally as good in discrimination as the original model using the five frailty criteria separately (AUC = 0.76, 95% CI = 0.66–0.84).

There was a gradient, with increasing proportions experiencing worsening ADL function as the index score increased (Table 3). Risk ratios (RRs) were statistically significant for frailty index scores of 2 or 3 or more compared with 0 (RR = 3.03, 95% CI = 1.1–8.1 for 2 criteria and RR = 10.39, 95% CI = 4.5–24.2 for ≥3 criteria). Similarly, there was a gradient, with increasing proportions experiencing reduced HRQL as index scores increased. RRs for a decrease in HRQL were significant for scores of 1, 2, and 3 or more compared with 0 (RR = 1.77, 95% CI = 1.0–3.2; RR = 2.69, 95% CI = 1.5–4.9; and RR = 4.16, 95% CI= 2.3–7.4, respectively). Sex neither modified nor confounded the above estimates. Age showed a slight confounding effect on the associations between frailty and disability and HRQL (Table 3). The frailty index remained a significant independent predictor of ADL disability and HRQL decline after further adjustment for a comorbidity count based on diagnostic information collected at the time of catheterization (data not shown).

2.5 Discussion

The frailty index accurately predicted ADL disability and a meaningful decline in HRQL at 12 months in this study population. Participants with scores of 3 or more were 10 times as likely as those with index scores of 0 to have increased ADL disability and 4 times as likely to experience a significant decline in HRQL. The index incorporates physical, cognitive, and psychosocial domains and is derived from related yet distinct measures. Each measure has been shown to be independently associated with poor outcomes [41,117,123,129,130] in older patients and is relatively easy to obtain.

This is the first frailty index developed specifically for older hospitalized patients with CAD undergoing angiography. No claims are made at this time that this is a generic frailty index. The study population had a number of unique characteristics. It was younger and included more men and patients with less morbidity (despite their CAD) than community-based populations used to develop other frailty indices. [45,116] Few in the sample had a low BMI; many more were overweight. Similar to other investigators, [131] difficulties were encountered with gait speed because of restraining devices such as intravenous catheters. Gait speed is frequently used as a physical measure in frailty assessments. [45]

One study[41] found that gait speed alone was nearly as predictive of 6-month mortality as the frailty index developed by Fried and colleagues,[45] but gait speed did not significantly improve the predictive ability of the model developed in the current study, and alone it showed less discrimination than the overall model in relation to ADL decline. Possibly this was due to correlations with a number of other criteria, as well as difficulties in obtaining this measure in a hospital setting.

This index was designed to be practical. It was found that the required data can be obtained and scored in 10 to 15 minutes. One of the criteria, the GDS, is a valid, reliable screening tool for depression. Depression has been shown to be highly predictive of adverse outcomes in older populations, [130]including those with CAD. [132] Self-rated health and the two depression subscales examined were nearly as predictive as the GDS. Given the prevalence of depression and its association with adverse outcomes (including poor adherence) in patients with cardiac disease, [132,133] it was decided to retain the full GDS.

Definitions of frailty based purely on physical measures can be improved when a cognitive measure is added. [49,134]Measures of executive function are probably more predictive of ADL decline than global tests of cognition. [129] In the current study, all executive function tests outperformed the MMSE. Trails B was more predictive than the verbal fluency tests examined. Seventeen percent of the cohort was born in largely non-English-speaking countries, possibly limiting performance on the fluency tests. Age- and education-adjusted norms are required to interpret the results of Trails B, but they are readily available. [120,135]

Other brief frailty indices have typically not included a social domain,[35] despite evidence of significant associations between poor social integration or support and adverse health outcomes in patients with CAD. [136] Although living alone is admittedly a gross measure, it was one of the strongest criteria in the model and has been shown to predict mortality (particularly in men) in patients with CAD. [123]

When interpreting the results of the study, the following should be considered. Frailty measures were assessed only at a single time point, and these measures probably fluctuate over time, [99] although the approach replicates what would likely occur in a clinical setting. Any bias caused

by this undetected fluctuation would probably be nondifferential, leading to an underestimate of the risks. Data were not available on physical activity levels or specific comorbidities known to influence functional decline (e.g., arthritis), and the comorbidity measure was not a comprehensive or validated one. The ADL information was based on self-reports rather than performance-based evaluations. Finally, it is desirable to examine longer-term outcomes.

There is considerable uncertainty in predicting which patients with CAD will do well with invasive procedures or may require targeted long-term monitoring and rehabilitation. This frailty index, designed specifically for patients with CAD undergoing angiography, may provide relevant information on the resiliency of these older patients not currently collected. Such an index could complement the clinical data routinely collected on them, [110] although further validation of the index (including comparisons with other frailty measures) in another cohort of patients with CAD undergoing angiography is required. If validated, a clinical trial would be required to determine whether the use of this frailty index (or another one) improves patient outcomes.

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2.7 Tables and Figures

Table 2.1 Baseline Sociodemographic and Frailty Characteristics of Older Patients with Coronary Artery Disease Included in the Original Calgary Cardiac and Cognition (3C) Study Cohort and Assessed at Follow-Up.

Characteristic	3C Cohort Baseline n=374*	3C Frailty-ADL Sample† n=337
Age, mean ± SD	71.0 ± 5.9	70.8 ± 5.9
Male, n (%)	274 (73)	247 (73)
Education, years, mean ± SD	12.8 ± 3.8	12.8 ± 3.8
Poor self-rated health, n (%)	87 (23)	79 (23)
Physical frailty criteria, n (%)		
Slow gait (2.4 m in >4 seconds)	104 (28)	93 (28)
Poor balance (unable to maintain full tandem for 10 sec)	94 (25)	83 (25)
Abnormal BMI (<21 or >30 kg/m^2)	123 (33)	112 (33)
Cognitive frailty criteria, n (%)		
Mini-Mental State Examination score in lowest population decile	51 (14)	46 (14)
Letter-naming fluency test score ≥1.5 SDs below the mean	53 (14)	46 (14)
Animal-naming fluency test score ≥1.5 SDs below the mean	43 (12)	38 (11)
Trails B ≥1.5 SDs below the mean	36 (10)	27 (8)
Psychosocial frailty criteria, n (%)		
Geriatric Depression Scale score >4	78 (21)	72 (21)
Mood-hope scale score >1	99 (26)	88 (26)
Withdrawal-apathy-vigor scale score=3	68 (18)	67 (20)
Lives alone	60 (16)	53 (16)

*Because of missing values, n=373 for balance, self-rated health, and body mass index (BMI), and n=369 for Trail-Making Test Part B (Trails B).
†None of proportions in activity of daily living (ADL) sample were significantly different from baseline cohort.
SD = standard deviation.

Table 2.2 Unadjusted and Adjusted Risk Ratios for Greater Activity of Daily Living Disability at 1 Year Associated With Selected Frailty Criteria in Older Coronary Artery Disease (CAD) Patients in the Calgary Cardiac and Cognition (3C) Study†

	Univariable Model			Initial Multi-variable Model* (AUC=0.74)		Final Multivariable Model† (AUC = 0.76)	
Baseline Frailty Characteristic	**RR**	***P*-value**	**AUC**	**RR**	***P*-value**	**RR (95% Confidence Interval)**	***P*-value**
Poor self-rated health	2.59	<.001	0.62	1.85	.118		
Physical frailty criteria							
Slow gait (2.4 m in > 4 seconds)	2.08	.009	0.60				
Poor balance (unable to maintain full tandem for 10 sec)	3.21	<.001	0.65	2.99	.002	2.36 (1.37-4.04)	.002
Abnormal BMI (<21 or >30 kg/m^2)	2.10	.008	0.60			1.78 (1.07-2.95)	.026
Cognitive frailty criteria							
Mini-Mental State Examination score in lowest population decile	1.45	.311	0.53				
Letter-naming fluency test score ≥1.5 SDs below the mean	1.92	.050	0.56				
Animal-naming fluency test score ≥1.5 SDs below the mean	2.08	.032	0.56				
Trails B ≥1.5 SDs below the mean	3.04	.001	0.57	2.78	.037	2.34 (1.28-4.24)	.005
Psychosocial frailty criteria							
Geriatric Depression Scale score >4	2.41	.002	0.60	1.20	.760	1.83 (1.07-3.12)	.027
Mood-hope subscale score >1	2.46	.001	0.62	1.77	.310		
Withdrawal-apathy-vigor subscale score =3	2.13	.009	0.59				
Lives alone	2.32	.005	0.58			2.19 (1.26-3.80)	.005

* The initial model included self-rated health, balance, Trail-Making Test Part B (Trails B), Geriatric Depression Scale (GDS), and mood-hope subscale.
† The final model included balance, abnormal body mass index (BMI), Trails B Test, Geriatric Depression Scale, and living alone.
RR = risk ratio, AUC = area under the receiver operating characteristic curve.

Table 2.3 Estimated Risks, Risk Ratios (RRs), and 95% Confidence Intervals (CIs) for Greater Activity of Daily Living (ADL) Disability and Poorer Health-Related Quality of Life (HRQL) (EQ-5D Scores) at 1 Year According to Frailty Index Score

		Greater ADL Disability			Poorer HRQL (EQ-5D Scores)		
Index Score	**n (%)**	**Risk, %**	**RR (95% CI)**	**Adjusted RR (95% CI)***	**Risk, %**	**RR (95% CI)**	**Adjusted RR (95% CI)***
0	121 (36)	5	Reference	Reference	12	Reference	Reference
1	123 (36)	9	1.80 (0.7-4.7)	1.75 (0.67-4.56)	23	1.77 (1.0-3.2)	1.74 (0.99-3.07)
2	60 (18)	15	3.03 (1.1-8.1)	2.66 (1.00-7.08)	33	2.69 (1.5-4.9)	2.46 (1.35-4.50)
3+	33 (10)	52	10.39 (4.5-24.2)	9.01 (3.85-21.10)	52	4.16 (2.3-7.4)	3.79 (2.10-6.81)

*Adjusted for age. Sex was found to neither confound nor modify the association between frailty score and either outcome.

2.8 Appendix: Trail-Making Test Part B Cutoff Times

The following Trail-Making Test Part B cut points represent 1.5 standard deviations below age-, sex-, and education-adjusted norms, and were used to determine impairment on executive function. A time equal to or greater than the time cut point indicates impairment.

Table 2.4 Trail-Making Test Part B Cutoff Times (in Seconds) According to Education, Sex, and Age

	Male				Female			
Education, Years	**60-64**	**65-69**	**70-74**	**75-79**	**60-64**	**65-69**	**70-74**	**75-79**
6-8	278	278	301	301	237	278	278	301
9-11	237	237	278	278	179	237	237	278
12	179	237	237	278	179	179	237	237
13-15	179	179	237	237	131	179	179	237
16-17	131	179	179	179	131	131	179	179
≥18	111	131	131	179	111	131	131	131

Based on Heaton RK, Grant I, Matthews CG. Comprehensive norms for an expanded Halstead-Reitan battery: Demographic corrections, research findings, and clinical applications. Odessa, FA: Psychological Assessment Resources, 1991.

Chapter 3: A Dynamic View of Depressive Symptoms and Neurocognitive Change Among Patients with Coronary Artery Disease

3.1 Abstract

Context: Older patients with coronary artery disease often experience depressive symptoms and are vulnerable to developing cognitive impairment. Whether depressive symptoms increase their risk of cognitive decline is unknown.

Objectives: To examine the association between the stability of depressive symptoms and cognitive decline for 30 months among patients undergoing coronary angiography and to explore whether any observed associations were modified by the presence of the apolipoprotein E (*APOE*) ε4 allele.

Design: Cohort study.

Setting: Urban tertiary care hospital serving southern Alberta.

Participants: Three hundred fifty patients 60 years or older (73.7% male) undergoing nonemergent catheterization (October 27, 2003, through February 28, 2007) without prior revascularization. We compared a baseline measure of depressive symptoms (Geriatric Depression Scale score ≥5) with a dynamic measure capturing change from baseline to 12 months.

Main Outcome Measures: Mean change in domain (*z* scores for attention/executive function, learning/ memory, and verbal fluency) and global (raw Mini-Mental State Examination) cognitive scores from baseline to 6, 12, and 30 months and from 12 to 30 months.

Results: In adjusted models, participants with persistent depressive symptoms (at baseline and ≥1 follow-up visit) showed significantly greater declines at 30 months in attention/executive

function (mean *z* score change, −0.22), learning/memory (−0.19), verbal fluency (−0.18),and global cognition (mean Mini-Mental State Examination [MMSE] score change, −0.99) compared with participants with no or baseline-only depressive symptoms. Persistent depressive symptoms were associated with significantly greater declines in all cognitive measures from 12 to 30 months after adjusting for sociodemographic and clinical factors. For global cognition, a significantly greater decline was evident for patients with persistent depressive symptoms and the *APOE ε4* allele (mean MMSE score change, −2.93 [95% CI, −4.40 to −1.45]).

Conclusions: Depressive symptoms persist in some patients with coronary artery disease, placing them at a greater risk for cognitive decline. Whether this decline is additionally modified by the presence of *APOE ε4* requires further investigation.

3.2 Introduction

Relatively high rates of depressive symptoms have been observed among older patients with coronary artery disease (CAD), including those undergoing coronary interventions. [65,67,137] Major and minor depression are independent risk factors for all-cause mortality and adverse cardiovascular events.[65,69,70] Older patients with CAD may also be at risk for developing cognitive impairment over time.[25,138] Whether depressive symptoms exacerbate these patients' risk for long-term cognitive decline remains unexplored.

Numerous [79-84,139-142] although not all [86,87] prospective studies of older adults support an association between depressive symptoms and cognitive decline. Explanations for this association propose that depressive symptoms represent a psychological reaction to worsening cognition; early preclinical symptoms of a dementia disorder; the consequence of vascular risk factors or disease also predictive of cognitive impairment; or a true causal risk factor linked to the pathophysiological symptoms underlying cognitive decline. [143,144]

Depression may also act synergistically with other risk factors (e.g., presence of the apolipoprotein E [*APOE*] ε4 allele) to produce even greater cognitive risks. [88-90,143,144] For patients undergoing coronary interventions, attention has focused on the potential confounding effects of depression on cognitive performance test results. [71] Few studies have directly investigated the independent risk posed by depressive symptoms (or potential effect modification by the *APOE* ε4 allele) on subsequent cognitive outcomes, and findings remain inconclusive. [92,93,95,145-147] This research has largely been correlational and limited by small sample sizes, insufficient follow-up, and/or a focus on patients undergoing coronary artery bypass graft (CABG) procedures. Data are scarce for patients undergoing percutaneous coronary intervention (PCI) or medical therapy (MT) after catheterization.

No studies to date have explored the prognostic importance of the stability of depressive symptoms over time on longer-term (beyond 12 months) cognitive decline after revascularization. Emerging evidence suggests that not all depressed patients with CAD may be at risk of adverse health outcomes. Those patients with new-onset or persistent depression (possibly associated with nonresponse to treatment) appear to be at highest risk for subsequent mortality and cardiac events. [70,96,97,148] Although not yet investigated in patients with CAD, studies of persistent depressive symptoms in older adults have shown an increased risk for cognitive decline. [81,84] Persistent symptoms among patients, as opposed to transient symptoms at the time of catheterization (e.g., due to uncertainty about their diagnosis and impending procedure), may be more strongly linked with the pathophysiological mechanism(s) underlying cognitive impairment. [143,144] Prior negative findings may reflect a failure to assess for changes in depressive symptoms over time in relation to adverse health outcomes, including cognitive decline.

The primary aim of this study was to examine the effect of clinically significant depressive symptoms on longer-term (≤30 months after the procedure) changes in select cognitive domains among older patients undergoing coronary catheterization who subsequently received CABG, PCI, or MT. We compared the following 2 measures of depressive symptoms: (1) a binary measure capturing symptoms (present or absent) at baseline (before the procedure) and (2) a dynamic measure capturing the course of depressive symptoms from baseline to 12 months after the procedure. A secondary aim was to investigate whether the *APOE* ε4 allele was an effect modifier of any observed associations.

3.3 Methods

3.3.1 Study Design

The Calgary Cardiac and Cognition (3C) Study was a prospective cohort investigation of the effect of neurocognitive and psychological factors on quality of life and functional recovery among older patients with CAD undergoing coronary revascularization. A total of 374 participants 60 years or older were enrolled from October 27, 2003, through May 7, 2007. All underwent coronary angiography at an urban tertiary care hospital providing centralized cardiac services for southern Alberta. After catheterization (performed from October 27, 2003, through February 28, 2007), 128 underwent CABG procedures, 150 underwent PCI, and 96 received MT. Patients presenting for angiography underwent screening for eligibility and were approached by trained cardiovascular research nurses. Exclusion criteria included being younger than 60 years, undergoing emergency catheterization or prior revascularization, and being unable to provide informed written consent or complete the assessment owing to language difficulties or cognitive and/or physical impairments. There was purposeful oversampling of those scheduled to undergo CABG and PCI (for comparison of the study sample with all eligible patients undergoing coronary catheterization during our recruitment period, see the eTable; http://www.archgenpsychiatry.com). Ethics approval was received from the Conjoint Health Research Ethics Board of the University of Calgary.

A comprehensive standardized assessment, including neuropsychological and physical performance tests, sociodemographic items, and measures of health behavior, self-rated health, activities of daily living, and health-related quality of life, was administered at baseline (before the procedure) and at 6, 12, and 30 months after the procedure by trained research nurses/associates. Most baseline assessments (57.8%) were conducted in the hospital; the

remainder (and all follow-up assessments) were conducted in the participant's home. All data were entered and audited against the original forms. A trained psychometrician (blinded to patients' clinical characteristics) reviewed and scored all cognitive testing results. A structured interview with the patient's primary caregiver (including section H of the Cambridge Mental Disorders of the Elderly Examination–Revised [CAMDEX-R]) [149] was administered at all follow-up times, where possible. The 3C Study database was linked with the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH), [110] a comprehensive registry of all patients undergoing cardiac catheterization in the province, for baseline clinical characteristics and data on repeated revascularizations during follow-up. Three patients could not be linked because of out-of-province catheterizations (n=2) or missing hospital records (n=1).

During the 30-month study period, 31 participants withdrew, 9 participants moved or could not be located, 16 died, and 7 missed the 6- or the 12-month assessment but remained in the study (Figure 1). Loss to follow-up at 30 months was 15.0%. The number of participants with minimum outcome data at 6 or 12 months and included in our analyses was 350 (93.6%).

3.3.2 Measurement of Depressive Symptoms

The 15-item Geriatric Depression Scale [121,150]with a cut point of 5+ was used to define clinically important depressive symptoms. We examined a baseline measure (depressive symptoms [present or absent]) and a dynamic measure[81] with the following categories: (1) no clinically important depressive symptoms (at baseline and 6 and 12 months); (2) baseline-only symptoms (at baseline but not at 6 and 12 months); (3) new-onset symptoms (not at baseline but present at 6 or 12 months); and (4) persistent symptoms (at baseline and at 6 or 12 months).

3.3.3 Neurocognitive Outcomes

Based on an initial exploration of pairwise Pearson correlations and variable loadings in a factor analysis, 3 domains and 1 global cognitive measure were defined as follows:

- Learning and memory were assessed with the Brief Visuospatial Memory Test–Revised [151] and the Consortium to Establish a Registry for Alzheimer's Disease Test of Verbal Learning and Memory. [152]We calculated *z* scores on the basis of published age-, sex-, and education-specific norms for both tests. [151,152] The mean *z* score for the visuospatial test (trial 3, total and delayed recall scores) and for the verbal test (trial 3 and delayed recall tests) were then averaged together for the mean domain score.

- Verbal fluency was assessed with the Controlled Oral Word Association and Animal Naming tests. [118]

- Attention/executive function was derived from the Trail Making Test, parts A and B. [118] For both the verbal fluency and attention/executive function domains, *z* scores were calculated on the basis of published age-, sex-, and education-specific norms [118,120] and averaged together.

- Global cognition was assessed with the Mini-Mental State Examination (MMSE). [119] Raw scores were used.

3.3.4 Other Measures

The patients' sociodemographic, health, and lifestyle characteristics were assessed at baseline by study nurses. Self-reported educational level was recorded as the number of full-time completed years of education after kindergarten. Current or past smoking (including cigarettes, cigars, and

pipe) was assessed by questions on present and ever smoking patterns. Heavy drinking was indicated by self-reported drinking of at least 2 alcoholic drinks per day or by a positive response to the CAMDEX section H caregiver question, [149] "Did you ever think he/she was a heavy drinker?" Living arrangements (alone vs with a spouse and/or others) were self-reported. Self-reported health was collapsed into a dichotomous variable (fair/poor vs good/very good/ excellent). The 8-item Questionnaire for Verifying Stroke-Free Status (QVSFS) [153] was completed at each assessment. Anxiety was assessed with the State-Trait Anxiety Inventory [154] (State form only), with higher scores indicating greater anxiety.

Baseline clinical data from the APPROACH [110] database included admission diagnosis, ejection fraction, high-risk coronary anatomy (i.e., double-vessel CAD with proximal left anterior descending artery involvement, any 3-vessel disease, or left main disease), Canadian Cardiovascular Society angina class, acute coronary syndrome, and disease history (cerebrovascular, congestive heart failure, peripheral vascular, diabetes mellitus, hypertension, hyperlipidemia, pulmonary, renal, malignant neoplasm, liver, and gastrointestinal disease).

Blood samples were collected for 357 of the 374 participants (95.5%) at the time of catheterization (for patients receiving MT) or revascularization (for patients who underwent PCI and CABG). For 12 participants with missing blood work, buccal samples were collected for genotyping. We extracted DNA from blood and buccal cell samples using standard practice at the Molecular Diagnostic Laboratory of Alberta Children's Hospital and a nucleic acid purification system (Autopure LS; Gentra Systems, Inc.). The *APOE* genotype was identified using TaqMan assays as described by Koch et al [155] and reported as ε2, ε2/ ε3, ε2/ε4, ε3, ε3/ε4, or ε4. A dichotomous variable (*APOE* ε4 present vs absent) was used in the analyses.

3.3.5 Previous and Interim Cerebrovascular Events

To identify patients with stroke and/or transient ischemic attack (TIA) events before baseline and/or from baseline to their 12-month follow-up, 2 clinicians (D.B.H. and A.M.D.) reviewed the following: (1) patients' responses to individual QVSFS items at each assessment; (2) caregivers' responses at each assessment to the CAMDEX questions, "Has he/she ever had a stroke?" and "Has he/she ever passed out and then had a brief weakness or difficulty with speech, memory or vision?" If the answer to either question was yes, the time in months since the first occurrence (at baseline) or from their most recent assessment (at follow-up) was recorded; (3) all clinical notes recorded at each assessment by study nurses, including the patients' score on the National Institute of Health Stroke Scale, assessed for those scoring 1 or more on the QVSFS; and (4) all relevant diagnostic codes available from inpatient hospitalizations from fiscal years 1994-1995 through 2007-2008. Final decisions were by consensus with all uncertain cases and discrepancies verified by medical record review.

3.3.6 Missing Data and Value Assignment and Imputation

A neuropsychologist and geriatrician (D.B.H.) reviewed all neurocognitive data for participants with 1 or more missing test values. Twenty-four participants (6.4%) judged unable to complete a test owing to cognitive impairment (determined by consensus decision) were assigned a score approximately 3 SDs below the sex-/age-/education-adjusted mean because this was the low end of the distribution for those who were able to complete the test. Two participants (with dementia at follow-up) unable to answer questions about depressive symptoms were assigned Geriatric Depression Scale scores based on CAMDEX section H caregiver questions[149] about the participant's mood.

After these value assignments, 0% to 2% of participants still had missing items, depending on the test and visit. Reasons included refusal, physical impairments, and illiteracy (in 2 cases). We used multiple imputation with Markov chain Monte Carlo methods [156] to impute missing data, so that all data would have a similar sample size within each visit.

3.3.7 Statistical Analyses

Descriptive analyses were conducted to examine the distribution of the patients' sociodemographic and clinical characteristics overall and by depression status. The 2 measures of depressive symptoms (baseline present or absent and the 4-level categorical measure) were compared with regard to mean change in cognitive score (average z scores for the cognitive domains and raw scores for the MMSE) between baseline and 6, 12, and 30 months using linear mixed models with an unstructured correlation matrix (PROC MIXED procedure in SAS; SAS Institute, Inc.). For these analyses, the participant was considered to have 3 repeated measurements, with the visit modeled as a categorical variable to allow for nonlinear associations between time and cognitive change. The model included depression measure, visit, an interaction term between depressive symptoms and visit to assess the differential effect of depressive symptoms over time, and baseline cognition scores, age, sex, and educational level as covariates. The results were summarized in terms of least squares means with standard errors and P values and 95% CIs. A secondary analysis using the 4-level categorical depression measure defined as time-changing covariates was explored. Because the results led to similar conclusions, this analysis was not presented.

To examine the relevance of depressive symptom change within the first year to subsequent cognitive decline, linear regression models were used to compare the 4 depressive symptom categories in the prediction of cognitive change from months 12 to 30. We used *APOE* ε4 ×

depressive symptom interaction terms to calculate unadjusted and adjusted estimates of mean differences in cognitive domain scores (month 30 minus month 12) for those with and without the *APOE* ε4 allele in each of the 4 depressive symptom categories. Adjusted models included the following covariates (identified previously as having clinical and/or methodological significance[25,79-84,138-142]): relevant cognitive test scores (baseline and change scores to 6 months), age, sex, educational level, smoking status, anxiety, treatment group (CABG, PCI, or MT), ejection fraction of less than 50% (includes 21 not performed and 4 missing), high-risk coronary anatomy, acute coronary syndrome, history of stroke and/or TIA (before baseline), interim stroke and/or TIA (baseline to 12 months after the procedure), and comorbidity (history of congestive heart failure, peripheral vascular disease, diabetes mellitus, hypertension, and pulmonary disease). We used various modeling strategies in which covariates were added one at a time to base models (including baseline cognitive scores, depressive symptom category, age, sex, and educational level) and simultaneously with backward elimination. Because these strategies did not alter risk estimates (or standard errors of estimates) for our depressive symptom measure, we presented fully adjusted models stratified by the presence or absence of the *APOE* ε4 allele.

3.4 Results

Of the 350 patients, 74 (21.1%) had clinically significant depressive symptoms at baseline. They had lower average levels of education and were more likely to have high-risk coronary anatomy, marked/unstable angina (Canadian Cardiovascular Society class II), a history of cerebrovascular disease, diabetes, gastrointestinal tract disease, poor self-rated health, and higher anxiety levels than participants without depressive symptoms (Table 1).

During 1 year, 248 patients (70.9%) exhibited no significant depressive symptoms, 32 (9.1%) had baseline only symptoms, 28 (8.0%) had new-onset symptoms (at 6 or 12 months), and 42

(12.0%) showed persistent depressive symptoms. Few baseline sociodemographic, lifestyle, and clinical characteristics varied across the groups (Table 2). Compared with participants without significant depressive symptoms at any assessment, (1) those with new-onset symptoms were older, less educated, and more likely to be living alone and more likely to have marked/unstable angina, an acute coronary syndrome, and previous stroke, and (2) those with persistent symptoms were more likely to report poor self-rated health and higher anxiety and more likely to have a history of diabetes, marked/unstable angina, and an acute coronary syndrome. Eight participants (2.3%) experienced a stroke and 4 (1.1%) had a TIA (including 1 patient with both) during the first 12 months after the procedure (data not shown).

3.4.1 Associations between Baseline Depressive Symptoms and Neurocognitive Outcomes

Estimates of average change in cognitive domain scores from baseline to each of the follow-up visits (adjusted for baseline cognitive score, age, sex, and educational level) for patients with and without depressive symptoms at baseline are presented in Figure 2 and Table 3. Both groups showed improvement (positive change from baseline) at 6 and 12 months across all cognitive domains. For 3 domains (attention/executive function, learning/memory, and global cognition), this change was followed by decline at 30 months (overall differences among visits, $P<.001$, $P<.001$, and $P=.04$, respectively). For verbal fluency, a decline at 30 months was observed only for those with depressive symptoms. Those with depressive symptoms at baseline showed a greater decline at 30 months in verbal fluency (depression group × visit interaction, $P=.08$) and global cognition ($P=.03$) but did not differ significantly from the group without symptoms on the 2 other domains.

3.4.2 Associations between Depressive Symptom Change during Year 1 and Neurocognitive Outcomes

Estimates of average change in cognitive domain scores from baseline to each of the follow-up visits (adjusted for baseline cognitive score, age, sex, and educational level) for patients classified according to depressive symptom change are presented in Figure 3 and Table 4.

For attention/executive function, patients with new-onset or persistent symptoms showed significantly poorer performance compared with those with no or baseline-only symptoms across all visits (*P*=.006). Scores differed significantly overall by visit (*P*=.002). For learning/memory, all 4 groups showed significant improvement for the first 12 months (*P*=.005). This improvement was maintained at 30 months for patients with baseline-only symptoms. For the other 3 groups, declines in learning/memory were observed at 30 months, and this decline was most significant for those with persistent symptoms (*P*=.002). For verbal fluency, those with no or baseline-only depressive symptoms showed improvement at each follow-up, whereas those with new-onset symptoms showed initial improvement followed by decline from 6 to 12 months. Patients with persistent symptoms showed both an initial (at 6 months) and later (at 30 months) decline in verbal fluency (*P*=.04 for the overall difference between groups and *P*=.08 for the group × visit interaction). For global cognition, patients with new-onset symptoms showed a slight decline at 6 months, and those with persistent symptoms showed a significant decline from baseline at 30 months (*P*=.009). Those with no or baseline-only depressive symptoms showed little change over time in global cognition.

3.4.3 Depressive Symptom Change Over 12 Months as a Predictor of Subsequent Neurocognitive Decline

Across all cognitive domains, patients with persistent symptoms generally showed greater average declines from 12 to 30 months relative to the other 3 depression groups (Table 5). For

global cognition, there was statistical evidence of an interaction between persistent depressive symptoms and *APOE* genotype (*P*=.03), with significantly greater decline observed among those with persistent symptoms and the *APOE* ε4 allele. Although not statistically significant, a similar pattern emerged for verbal fluency. For learning/memory and attention/ executive function, the decline associated with persistent symptoms varied less by patients' *APOE* ε4 status. For learning/memory, those with no depressive symptoms showed a significant decline, whereas those with baseline-only symptoms showed improvement (in the absence of *APOE* ε4) from 12 to 30 months.

The pattern of significant declines noted for participants with persistent symptoms remained after adjusting for sociodemographic and clinical covariates, including baseline cognitive score and change in score from baseline to 6 months, age, sex, educational level, current/ past smoking, anxiety, treatment group (CABG, PCI, and MT), history of stroke and/or TIA, interim stroke and/or TIA, and all other disease and medical characteristics assessed at the time of catheterization. Treatment group was not a significant predictor of cognitive change scores for any of the domains examined.

3.5 Comment

This study is one of the first to explore the association between changes in depressive symptoms over time and long-term neurocognitive decline among older patients with CAD who are undergoing CABG, PCI, or MT. Relative to a baseline-only assessment, a dynamic measure capturing the persistence of depressive symptoms during the first year after the procedure better differentiated risk of decline across several cognitive domains during the 30-month study.

At baseline, average cognitive domain scores were consistently lower among patients who were subsequently identified as having persistent depressive symptoms relative to other symptom groups. In longitudinal models adjusted for age, sex, educational level, and baseline cognitive performance, those with persistent symptoms exhibited significantly greater decline at 30 months (relative to baseline) in attention/executive function, learning/memory, verbal fluency, and global cognition compared with those with no or baseline-only depressive symptoms. The presence of persistent symptoms within the first year was also a significant risk factor for subsequent decline (from 12 to 30 months) across all 4 cognitive measures. These associations were essentially unchanged in fully adjusted models. For global cognition (and to a lesser extent, verbal fluency), the magnitude of this decline was greater for those with the *APOE* ε4 allele.

Patients with new-onset depressive symptoms showed significant decline from baseline in attention/executive function (at multiple follow-up visits) but exhibited a less consistent pattern of decline in verbal fluency and global cognition. Participants exhibiting no or baseline-only depressive symptoms generally showed little change (or some improvement) over time in adjusted average difference scores for all cognitive domains. One exception was the significantly greater decline in learning/ memory observed from 12 to 30 months for participants without depressive symptoms, suggesting an overall vulnerability of our cohort to memory decline, possibly influenced by other factors, including the *APOE* ε4 allele. [81]

Our findings are consistent with other observational studies of older adults.[79,80,82,83,139-142] The growing literature highlights the risks posed by persistent depressive symptoms in relation to cognitive and functional decline.[81,84,157] Memory [81,84] and aspects of executive function [158,159] may be especially vulnerable to the effects of depressive symptoms, although the extent and nature of the associations remain to be elucidated. The vulnerability for executive dysfunction

may place some of these patients at further risk for functional disability [157] and poor antidepressant treatment response, early relapse, and recurrence of depression. [160]

Variation in findings across studies may reflect differences in the measures used to assess depression and neurocognitive deficits, the study design and sample characteristics, analytical approach, and length of follow-up. Our findings illustrate the potential for masking important changes in cognitive function among patients with depression when analyses are restricted to a baseline assessment of symptoms, a single cognitive domain, and/or a relatively short follow-up period. The findings observed for persistent symptoms may reflect the fact that this group captured patients with a "true" or more severe depressive disorder as opposed to those with brief or transient circumstantial symptoms. [80,157] Significant declines in the cognitive domains were generally observed only at 30 months and not within the first year after the procedure. In fact, improvement during the first year was evident for participants without depressive symptoms and with baseline-only symptoms in attention/executive function, learning/memory, and verbal fluency. This improvement (and subsequent decline) parallels findings reported in other long-term investigations of patients undergoing coronary interventions. Selnes et al. [138] showed improved cognitive function among patients undergoing CABG and those in the control groups (MT and PCI) from baseline to 12 months but a slight decline in patients' performance during the subsequent 4 years. They reported no statistically significant difference in the rate of cognitive decline or in the incidence of clinically significant impairment between treatment groups. Similarly, we found that treatment group was not a significant predictor of cognitive decline. The improvement in cognitive performance during the first year after the procedure may reflect a positive response to treatment and/or learning effects associated with repeated testing.

However, we observed initial improvement in cognitive performance even for those domains (eg, learning/ memory) for which alternative test versions were used at later examinations.

3.5.1 Possible Explanations for Observed Associations

Various explanations have been proposed for the association between depression and cognition. [143,144] The debate concerning whether depression is a cause or a consequence of cognitive decline has been clouded by inconsistent findings [86,87] and complicated by the potential for multidirectional relationships among depression, cognition, and underlying vascular disease. [139,143,144] For some of our findings (e.g., the early declines observed for patients with new-onset depressive symptoms), it is difficult to determine the direction of association given that both variables were assessed concurrently. However, the long-term decline (≤30 months) in cognitive performance associated with the new-onset (e.g., in attention/ executive function) and persistent depression groups (all domains) and the consistent finding of a strong independent association between persistent depressive symptoms (assessed during the first year) and decline from 12 to 30 months suggest that persistently elevated (and possibly new-onset) depressive symptoms among patients with CAD may have prognostic importance. Evidence from longitudinal investigations [79,81,82,84,141,161] suggests that persistent (or major) depression is likely a risk factor for cognitive decline rather than a reaction to or an early manifestation of a cognitive disorder.

Although the biological mechanisms underlying this association are likely complex and remain poorly understood, [82,143,144] several plausible pathways are being investigated. Early work emphasized the role of vascular disease and associated risk factors (e.g., hypertension and diabetes mellitus) as possible common underlying causes of depression and cognitive impairment (i.e., the vascular depression hypothesis). [162] However, in several studies, [84,139] including ours, depressive symptoms remained strongly predictive of cognitive decline after

adjustment for cardiovascular disease and vascular risk factors. Other possible pathways include (hyper)activation of the hypothalamic-pituitary-adrenal axis with subsequent glucocorticoid-related atrophy of the hippocampus, [79,141] chronic low-level activation of inflammatory mediators and processes, and an increased susceptibility to or shared causal pathways with genetic risk factors including the *APOE* ε4 genotype. [89] Although not consistently reported by others, [81,88-90] our finding of a significant interaction between the *APOE* ε4 allele and persistent depressive symptoms in relation to decline in global cognition (and possibly verbal fluency) suggests an area for future investigation. The findings presented for the *APOE* ε4 genotype should be interpreted as exploratory and hypothesis generating given the small cell sizes and multiple comparisons. Unfortunately, the lack of neuroimaging and physiological measures in the present study prevents us from speculating further about underlying mechanisms.

3.5.2 Study Strengths and Limitations

A particular strength of our study is the relatively large sample of older patients with CAD, including those undergoing CABG, PCI, and MT, followed up for a 30- month period with few participants lost to follow-up. In addition to incorporating detailed neurocognitive testing of multiple domains at baseline (before the procedure) and at several follow-up intervals, we examined an extensive list of sociodemographic and clinical covariates (including genetic factors) allowing for a greater opportunity to explore possible effect modification and confounding. Because the Geriatric Depression Scale primarily captures cognitive-affective symptoms rather than somatic ones, it offered a reliable and valid measure of depressive symptoms among our older sample. [121]

At the same time, our interpretations are limited by the observational nature of our study, absence of a clinical diagnosis of depressive disorders, and lack of information on antidepressant

use at baseline. Generally, others have not found antidepressant use to be a relevant confounding or effect-modifying variable, [83,139] although this requires further investigation. Our findings illustrate the importance of uncontrolled depressive symptoms (with or without therapy). In addition to the absence of specific diagnostic data, our ability to capture changes in depressive symptoms was limited by our assessment times and the sensitivity of the Geriatric Depression Scale. Without information on history and the date of the first episode of depressive symptoms, we are also unable to comment on the relevance of recurrent depressive episodes. The clinical significance of the lower average cognitive domain scores observed for participants with persistent depression remains unclear. The magnitude of difference in MMSE scores during the 30 months for those with persistent compared with no depressive symptoms (approximately 2-3 points) would generally be viewed as clinically meaningful. We included the MMSE because it is a commonly used measure of global cognition. However, we acknowledge that it provides a poor measure of domains likely to be vulnerable to the effects of depressive symptoms.

The generalizability of our study findings to other patient populations and possibly to the larger CAD population is limited. All our patients underwent catheterization. The eTable compares the baseline characteristics of our study sample with those of the 6,594 patients undergoing coronary catheterization at our center who fulfilled eligibility criteria (i.e., age ≥60 years and no prior PCI or CABG procedure) during the recruitment period. A higher proportion of patients undergoing CABG and PCI (compared with overall population distributions) and those with stable angina at the time of the baseline assessment were purposefully enrolled, which explains many of the differences observed.

3.5.3 Clinical and Treatment Implications

We found that older patients with CAD who had persistent depressive symptoms experienced significantly greater declines in cognitive performance during the 30 months than those with baseline-only or no symptoms during follow-up. Consequently, a 1-time assessment of depressive symptoms may be inadequate for detecting those at risk of longer-term adverse cognitive and functional outcomes. [157] These findings illustrate the need for longer term monitoring of depressive symptom severity and change by clinicians and other caregivers.

Research directed at elucidating the temporal associations among depressive symptoms, vascular risk factors, cognitive (and functional) impairment, and relevant underlying mechanisms will inform the search for possible treatment opportunities. Two recent randomized trials have shown that treating depression after CABG procedures may improve aspects of health-related quality of life, physical functioning, and mood at 8 to 9 months after the procedure. [163,164] Such findings suggest that depressive symptoms may be one of the more prevalent and potentially amenable factors involved in the pathway leading to cognitive decline and limited functional recovery of older patients with CAD who undergo coronary interventions.

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Online-Only Material: The eTable is available at http: //www.archgenpsychiatry.com.

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3.7 Tables and Figures

Table 3.1 Baseline Characteristics in the 3C Study by Presence or Absence of Depressive Symptoms Assessed at Baseline Only[a]

Characteristic	Total Sample (n=350)	Baseline Depressive Symptoms		P Value[b]
		Absent (n=276)	Present (n=74)	
Age, mean (SD), y	71.3 (5.9)	71.2 (5.9)	71.4 (5.6)	.83
Male sex	258 (73.7)	204 (73.9)	54 (73.0)	.87
Educational level, mean (SD), y	12.8 (3.8)	13.0 (3.9)	11.9 (3.6)	.02
Lives alone	55 (15.7)	40 (14.5)	15 (20.3)	.23
Current or past smoker	249 (71.1)	196 (71.0)	53 (71.6)	.92
Heavy drinker	68 (19.4)	52 (18.8)	16 (21.6)	.59
Treatment group				
CABG	121 (34.6)	90 (32.6)	31 (41.9)	
PCI	143 (40.9)	116 (42.0)	27 (36.5)	.33
MT	86 (24.6)	70 (25.4)	16 (21.6)	
Clinical characteristics[c]				
Admitted with stable angina (vs MI, unstable angina, and other)	227 (65.4)	184 (67.2)	43 (58.9)	.17
Ejection Fraction <50%	77 (22.2)	59 (21.5)	18 (24.7)	.57
High risk coronary anatomy[d]	160 (46.4)	121 (44.3)	39 (54.2)	.05
CCS angina class>II	167 (48.1)	122 (44.5)	45 (61.6)	.01
Acute coronary syndrome	89 (25.6)	64 (23.4)	25 (34.2)	.06
Medical history[c]				
Cerebrovascular disease	34 (9.8)	22 (8.0)	12 (16.4)	.03
Congestive heart failure	33 (9.5)	27 (9.9)	6 (8.2)	.67
Peripheral vascular disease[e]	31 (8.9)	22 (8.1)	9 (12.2)	.46
Type 1 or 2 diabetes mellitus	83 (23.9)	57 (20.8)	26 (35.6)	.01
Hypertension	268 (77.2)	208 (75.9)	60 (82.2)	.26
Hyperlipidemia	290 (83.6)	232 (84.7)	58 (79.5)	.28
Pulmonary disease	76 (21.9)	56 (20.4)	20 (27.4)	.20
Renal disease	10 (2.9)	6 (2.2)	4 (5.5)	.14
Malignant neoplasm	18 (5.2)	14 (5.1)	4 (5.5)	.90
Severe/debilitating liver disease	2 (0.6)	1 (0.4)	1 (1.4)	.31
Severe/debilitating gastrointestinal tract disease	26 (7.5)	16 (5.8)	10 (13.7)	.03
Additional clinical information				
APOE ε4 allele present[f]	90 (26.3)	74 (27.5)	16 (21.9)	.34
Previous stroke	20 (5.7)	13 (4.7)	7 (9.5)	.12
Previous TIA	26 (7.4)	21 (7.6)	5 (6.8)	.80
Previous stroke and/or TIA	43 (12.3)	32 (11.6)	11 (14.9)	.45
Self-rated health fair/poor[g]	80 (22.9)	41 (14.9)	39 (52.7)	<.001
Anxiety level (STAI score), mean (SD)[h]	34.4 (10.3)	32.9 (9.8)	39.6 (10.5)	<.001

Abbreviations: *APOE*, apolipoprotein E; 3C, Calgary Cardiac and Cognition; CABG, coronary artery bypass graft; CCS; Canadian Cardiovascular Society; MI, myocardial infarction; MT, medical therapy; PCI, percutaneous coronary intervention; STAI, State-Trait Anxiety Inventory; TIA, transient ischemic attack.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Calculated using the unpaired, 2-tailed *t* test with pooled variance for continuous variables and χ^2 test for categorical variables.

[c] Includes Alberta Provincial Project for Outcome Assessment in Coronary heart Disease (APPROACH) variables collected at the time of catheterization (274 patients in the group with no depressive symptoms and 73 in the group with depressive symptoms) unless otherwise noted.

[d] Includes 273 patients in the group with no depressive symptoms and 72 in the group with depressive symptoms.

[e] Includes 273 patients in the group with no depressive symptoms and 74 in the group with depressive symptoms.

[f] Includes 269 patients in the group with no depressive symptoms and 73 in the group with depressive symptoms.

[g] Includes 275 patients in the group with no depressive symptoms and 74 in the group with depressive symptoms.

[h] Includes 274 patients in the group with no depressive symptoms and 74 in the group with depressive symptoms.

Table 3.2 Baseline and Follow-up GDS Characteristics of 3C Study by Depressive Symptom Change During 1 Year[a]

Characteristic	Depressive Symptom Category				*P* Value[b]
	None (n=248)	Baseline only (n=32)	New Onset (n=28)	Persistent (n=42)	
Age, mean (SD), y	70.1 (5.8)	71.0 (6.1)	74.3 (6.5)	71.7 (5.3)	.03
Age >75 y	57 (23.0)	7 (21.9)	9 (32.1)	12 (28.6)	.11
Male sex	186 (75.0)	23 (71.9)	18 (64.3)	31 (73.8)	.67
Educational level, mean (SD), y	13.2 (3.8)	11.5 (2.7)	11.4 (4.3)	12.2 (4.2)	.01
Lives alone	31 (12.5)	8 (25.0)	9 (32.1)	7 (16.7)	.02
Current or past smoker	176 (71.0)	23 (71.9)	20 (71.4)	30 (71.4)	>.99
Heavy drinker	48 (19.4)	8 (25.0)	4 (14.3)	8 (19.0)	.77
Treatment group					
CABG	80 (32.3)	13 (40.6)	10 (35.7)	18 (42.9)	
PCI	107 (43.1)	13 (40.6)	9 (32.1)	14 (33.3)	.66
Medical Therapy	61 (24.6)	6 (18.8)	9 (32.1)	10 (23.8)	
Clinical characteristics[c]					
Admitted with stable angina (vs MI, unstable angina, and other)	168 (68.3)	19 (61.3)	16 (57.1)	24 (57.1)	.37
Ejection fraction <50%	53 (21.5)	9 (29.0)	6 (21.4)	9 (21.4)	.82
High risk coronary anatomy[d]	105 (42.7)	19 (61.3)	16 (59.3)	20 (48.8)	.17
CCS angina class>II	104 (42.3)	19 (61.3)	18 (64.3)	26 (61.9)	.01
Acute coronary syndrome	53 (21.5)	9 (29.0)	11 (39.3)	16 (38.1)	.04
Medical history[c]					
Cerebrovascular disease	20 (8.1)	4 (12.9)	2 (7.1)	8 (19.)	.14
Congestive heart failure	22 (8.9)	3 (19.7)	5 (17.9)	3 (7.1)	.45
Peripheral vascular disease[e]	21 (8.6)	2 (6.3)	1 (3.6)	7(16.7)	.57
Type 1 or 2 diabetes mellitus	52 (21.1)	11 (35.5)	4 (14.3)	15 (35.7)	.05
Hypertension	185 (75.2)	27 (87.1)	23 (82.1)	33 (78.6)	.44
Hyperlipidemia	207 (84.1)	24 (77.4)	25 (89.3)	34 (81.0)	.62
Pulmonary disease	48 (19.5)	7 (22.6)	8 (28.6)	13 (31.0)	.31
Renal disease	5 (2.)	2 (6.5)	1 (3.6)	2 (4.8)	.45
Malignancy	12 (4.9)	1 (3.2)	2 (7.1)	3(7.1)	.84
Severe/debilitating liver disease	1 (0.4)	1 (3.2)	0 (0)	0 (0)	.23
Severe/debilitating gastrointestinal tract disease	14 (5.7)	3 (19.7)	2 (7.1)	7 (16.7)	.09
Additional clinical information					
APOE ε4 allele present[f]	67 (27.6)	9 (29.0)	7 (26.9)	7 (16.7)	.51
Previous stroke	9 (3.6)	3 (9.4)	4 (14.3)	4 (9.5)	.05
Previous TIA	20 (8.1)	1 (3.1)	1 (3.6)	4 (9.5)	.60
Previous stroke and/or TIA	27 (10.9)	4 (12.5)	5 (17.9)	7 (16.7)	.57
Self-rated health fair/poor[g]	34 (13.8)	16 (50.0)	7 (25)	23 (55)	<.001
Anxiety level (STAI score): mean (SD)[h]	32.7 (9.7)	35.1 (9.2)	35.2 (10.2)	43.1 (10.2)	<.001
Baseline and follow-up GDS score					
Baseline GDS scores, mean (SD)	1.76 (1.28)	6.22 (1.64)	2.39 (1.37)	7.60 (2.67)	<.001
30-month GDS scores, mean (SD)	1.20 (1.46)	3.11 (2.25)	3.41 (2.89)	7.70 (3.70)	<.001

Abbreviations: See Table 1. GDS, Geriatric Depression Scale.
[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.
[b] Calculated using the *F* test for continuous variables and χ^2 test for categorical variables.
[c] Includes Alberta Provincial Project for Outcome Assessment in Coronary heart Disease (APPROACH) variables collected at the time of catheterization (246 patients in the group with no depressive symptoms and 31 in the group with depressive symptoms) unless otherwise noted.
[d] Includes 27 patients in the new onset group symptoms and 41 in the group with persistent depression.
[e] Includes 245 patients in the group with no depressive symptoms.
[f] Includes 243 patients in the group with no depressive symptoms, 31 in the baseline-only group, and 26 in the new-onset group.
[g] Includes 247 patients in the group with no depressive symptoms.
[h] Includes 246 patients in the group with no depressive symptoms.

Table 3.3 Least-Squares Mean Change in Cognitive Measures from Baseline at Each Follow-up Visit by the Presence or Absence of Baseline Depressive Symptoms[a]

	Baseline Score, Mean (SE)	Least-Squares Change, Mean (SE)			*P* Value		
		6 mo[b]	12 mo[c]	30 mo[d]	Between Groups	Among Visits	Group × Visit Interaction
Attention/executive function							
Depressive symptoms	-0.45 (0.10)	0.09 (0.06)	0.18 (0.06)	-0.06 (0.08)	.52	<.001	.14
No depressive symptoms	-0.30 (0.05)	0.09 (0.03)	0.16 (0.03)	0.08 (0.04)			
Learning/memory							
Depressive symptoms	-0.75 (0.11)	0.29 (0.07)	0.34 (0.07)	0.10 (0.09)	.25	<.001	.52
No depressive symptoms	-0.42 (0.05)	0.34 (0.04)	0.38 (0.04)	0.24 (0.05)			
Verbal fluency							
Depressive symptoms	-0.76 (0.09)	0.04 (0.06)	0.13 (0.07)	0.00 (0.08)	.20	.23	.08
No depressive symptoms	-0.47 (0.05)	0.09 (0.03)	0.12 (0.03)	0.20 (0.04)			
Global cognition (MMSE)							
Depressive symptoms	27.6 (0.26)	0.17 (0.17)	0.20 (0.19)	-0.38 (0.23)	.38	.04	.03
No depressive symptoms	28.3 (0.09)	0.14 (0.09)	0.15 (0.10)	0.17 (0.11)			

Abbreviation: MMSE, Mini-Mental State Examination.

[a]Data are expressed as changes in raw scores for global cognition (MMSE) and as *z* scores for all others, adjusted for baseline cognitive score, age, sex, and education level.

[b]Includes 73 patients with and 271 without depressive symptoms.

[c]Includes 74 patients with and 267 without depressive symptoms.

[d]Includes 65 patients with and 253 without depressive symptoms.

Table 3.4 Least-Squares Mean Change in Cognitive Measures from Baseline at Each Follow-up Visit by Depressive Symptom Change During 1 Year[a]

	Baseline Score, Mean(SE)	Least-Squares Change, Mean (SE)			*P* Value		
		6 mo[b]	12 mo[c]	30 mo[d]	Between Groups	Among Visits	Group × Visit Interaction
Attention/executive function							
No depressive symptoms	-0.24 (0.05)	0.12 (0.03)	0.18 (0.04)	0.12 (0.04)			
Baseline-only symptoms	-0.19 (0.11)	0.15 (0.09)	0.28 (0.10)	0.14 (0.12)	.006	.002	.31
New-onset symptoms	-0.33 (0.16)	-0.15 (0.10)	-0.06 (0.11)	-0.21 (0.12)			
Persistent symptoms	-0.70 (0.15)	0.04 (0.08)	0.09 (0.09)	-0.22 (0.10)			
Learning/memory							
No depressive symptoms	-0.34 (0.06)	0.35 (0.04)	0.38 (0.04)	0.24 (0.05)			
Baseline-only symptoms	-0.57 (0.15)	0.35 (0.11)	0.30 (0.11)	0.47 (0.13)	.19	.005	.002
New-onset symptoms	-0.76 (0.18)	0.31 (0.11)	0.42 (0.12)	0.24 (0.14)			
Persistent symptoms	-0.91 (0.16)	0.24 (0.09)	0.37 (0.10)	-0.19 (0.11)			
Verbal fluency							
No depressive symptoms	-0.47 (0.05)	0.09 (0.04)	0.13 (0.04)	0.23 (0.04)			
Baseline-only symptoms	-0.71 (0.13)	0.16 (0.10)	0.22 (0.11)	0.24 (0.12)	.04	.63	.08
New-onset symptoms	-0.33 (0.16)	0.11 (0.11)	0.04 (0.11)	0.00 (0.13)			
Persistent symptoms	-0.82 (0.12)	-0.05 (0.09)	0.06 (0.09)	-0.18 (0.11)			
Global cognition (MMSE)							
No depressive symptoms	28.5 (0.08)	0.20 (0.09)	0.18 (0.11)	0.20 (0.12)			
Baseline-only symptoms	27.8 (0.35)	0.29 (0.26)	0.27 (0.29)	0.39 (0.34)	.10	.22	.009
New-onset symptoms	27.6 (0.43)	-0.36 (0.28)	-0.13 (0.32)	-0.13 (0.35)			
Persistent symptoms	27.2 (0.40)	0.06 (0.22)	0.13 (0.26)	-0.99 (0.29)			

Abbreviation: MMSE, Mini-Mental State Examination.

[a]Data are expressed as changes in raw scores for global cognition (MMSE) and as *z* scores for all others, adjusted for baseline cognitive score, age, sex, and education level.

[b] Includes 243 patients with no depressive symptoms, 31 with baseline-only symptoms, 28 with new-onset symptoms, and 42 with persistent symptoms.

[c] Includes 240 patients with no depressive symptoms, 32 with baseline-only symptoms, 27 with new-onset symptoms, and 42 with persistent symptoms.

[d] Includes 226 patients with no depressive symptoms, 28 with baseline-only symptoms, 27 with new-onset symptoms, and 37 with persistent symptoms.

Table 3.5 Adjusted Mean Difference in Cognitive Scores (Month 30 Minus Month 12) by Depressive Symptom Change During 1 Year and *APOE* ε4 Status.

	Adjusted Mean Difference (95% CI)[b]	
Cognition Measure[a]	***APOE* ε4 Absent**	***APOE* ε4 Present**
Attention/executive function		
No depressive symptoms	-0.08 (-0.18 to 0.02)	-0.03 (-0.19 to 0.13)
Baseline only symptoms	0.04 (-0.24 to 0.32)	-0.37 (-0.83 to 0.09)
New onset symptoms	-0.11 (-0.41 to 0.18)	0.06 (-0.43 to 0.55)
Persistent symptoms	-0.29 (-0.53 to -0.05)[c]	-0.50 (-1.01 to -0.002)[c]
Learning/memory		
No depressive symptoms	-0.13 (-0.23 to -0.03)[c]	-0.20 (-0.37 to -0.04)[c]
Baseline only symptoms	0.25 (-0.05 to 0.55)[d]	0.03 (-0.45 to 0.52)
New onset symptoms	-0.06 (-0.37 to 0.25)	-0.41 (-0.92 to 0.10)
Persistent symptoms	-0.55 (-0.80 to -0.30)[c]	-0.44 (-0.96 to 0.08)[d]
Verbal fluency		
No depressive symptoms	0.07 (-0.04 to 0.18)	0.03 (-0.15 to 0.20)
Baseline only symptoms	0.10 (-0.22 to 0.42)	-0.08 (-0.61 to 0.44)
New onset symptoms	0.08 (-0.26 to 0.41)	0.06 (-0.50 to 0.62)
Persistent symptoms	-0.19 (-0.46 to 0.08)	-0.62 (-1.19 to -0.05)[c]
Global cognition (MMSE)[b]		
No depressive symptoms	-0.09 (-0.38 to 0.20)	-0.05 (-0.51 to 0.41)
Baseline only symptoms	-0.27 (-1.10 to 0.57)	0.61 (-0.75 to 1.96)
New onset symptoms	0.10 (-0.80 to 0.99)	0.27 (-1.17 to 1.71)
Persistent symptoms[e]	-0.55 (-1.25 to 0.16)	-2.93 (-4.40 to -1.45)[c]

Abbreviations: APOE, apolipoprotein E; MMSE, Mini-Mental State Examination.

[a] Data are expressed in raw scores (MMSE) and as average *z* scores for all other tests.

[b] Adjusted for baseline cognitive score (and change from baseline to 6 months), age, sex, education, smoking status, baseline anxiety, treatment plan, presence of a baseline ejection fraction of less than 50%, high risk coronary anatomy, acute coronary syndrome, peripheral vascular disease, congestive heart failure, diabetes mellitus, hypertension, cardiopulmonary disease, stroke or transient ischemic attack (TIA) before baseline, stroke or TIA from baseline to 12 months.

[c] $P < .05$.

[d] $P < .10$.

[e] For persistent depressive symptom × *APOE* ε4 interaction, $P < .05$.

Table 3.6, (eTable 1) Baseline Characteristics[a] of 3C Study Sample and Patients Undergoing Coronary Catheterization Who Fulfilled Eligibility Criteria During the Recruitment Period.

Characteristic[a]	All Eligible Catheterizations n=6,594	Calgary Cardiac & Cognition Study n=371	*P* value
Age (mean, SD)	70.7 (7.0)	71.5 (5.9)	.037
Male, %	64.9	73.1	.001
Cardiovascular disease, %			
Admitted with stable angina	33.1	65.5	<.001
Acute coronary syndrome	52.2	25.9	<.001
Congestive heart failure	15.7	10.2	.005
Canadian Cardiovascular Society angina class>II	62.6	48.0	<.001
High risk coronary anatomy[b]	35.0	46.9	<.001
Treatment after catheterization, %			
Coronary artery bypass graft	18.4	33.7	<.001[c]
Percutaneous coronary intervention	30.4	40.4	
Medical therapy	51.3	25.9	
Vascular risk factors, %			
Smoking (current)	15.7	12.4	.085
Smoking (former)	41.5	43.9	.350
Hypertension	74.9	77.6	.235
Diabetes mellitus (Type I or II)	24.4	24.0	.863
Hyperlipidemia	77.5	84.1	.003
Co-morbidities, %			
Cerebrovascular disease	9.2	10.5	.404
Peripheral vascular disease	8.4	8.9	.747
Pulmonary disease	24.8	22.4	.292
Renal disease	4.4	3.0	.199
Malignancy	7.4	5.1	.100
Liver disease	1.3	0.5	.240[d]
Gastrointestinal disease	11.8	7.0	.005

[a] All variables listed are from the APPROACH database.

[b] High risk defined as double-vessel coronary artery disease with proximal left anterior descending artery involvement, any 3-vessel disease or left main disease.

[c] Chi-square test for 3x2 contingency table comparing proportions with 3 categories: coronary bypass, percutaneous coronary intervention, and medical therapy.

[d] For liver disease, Fisher's exact test was used because of low cell counts.

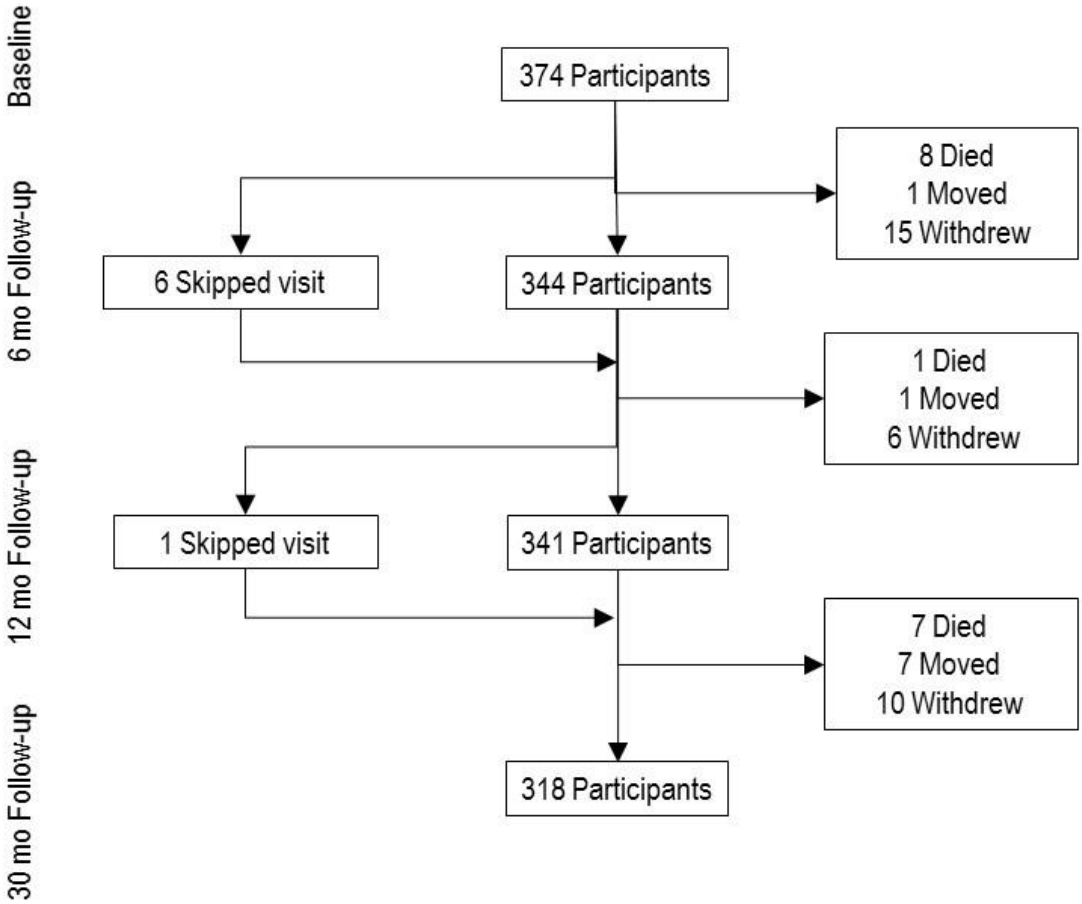

Figure 3.1 Calgary Cardiac and Cognition Study Flowchart

The 6 participants who skipped the 6-month visit returned for the 12-month visit; the 1 participant who skipped the 12- month visit returned for the 30-month visit.

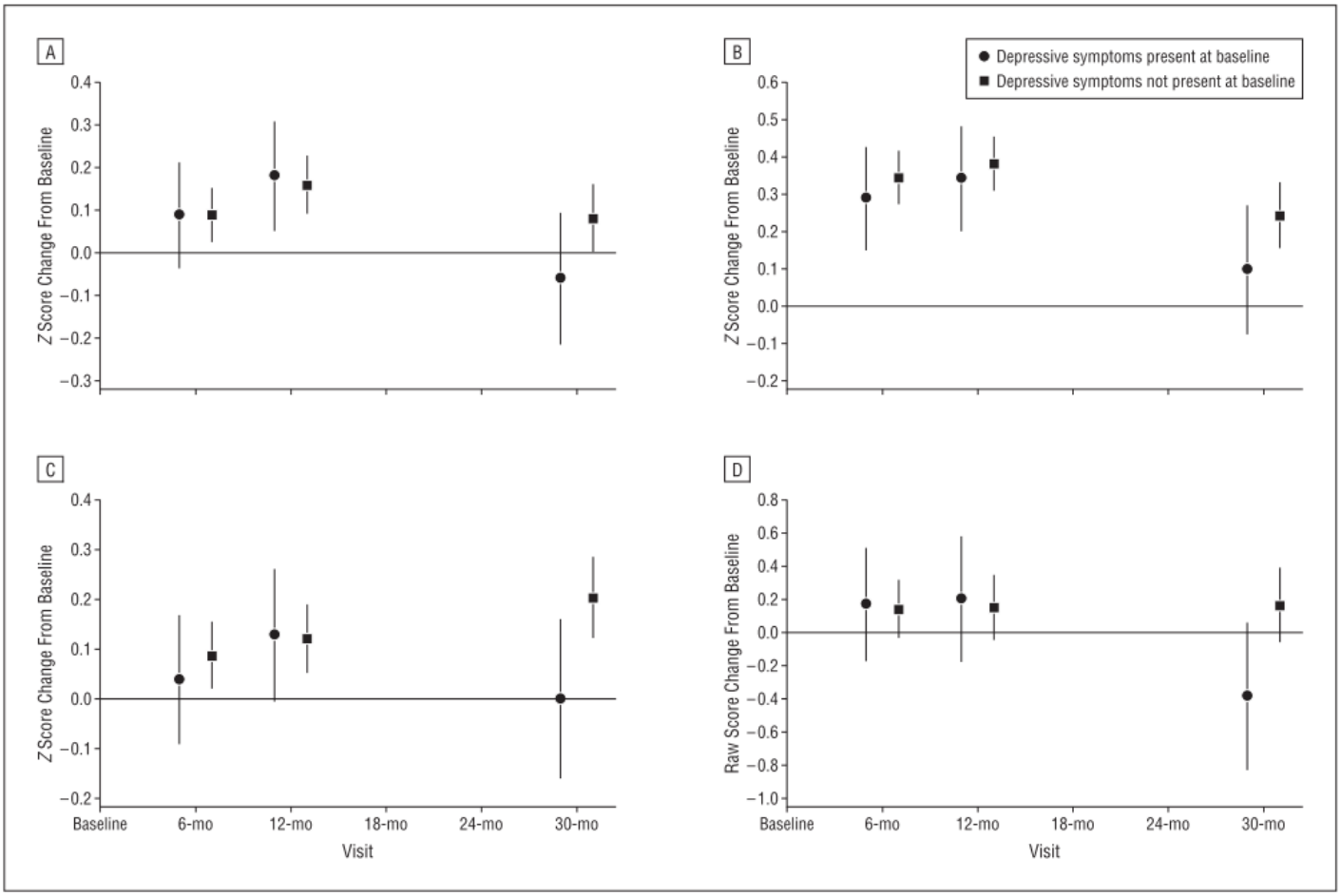

Figure 3.2. Least-squares Mean Change (95% CI) in Cognitive Measures from Baseline at Each Follow-up Visit by Presence or Absence of Baseline Depressive Symptoms.

Changes for attention/executive function (A), learning/memory (B), and verbal fluency (C) are expressed as *z* scores; for global cognition (D), changes are expressed as raw scores. Changes are adjusted for baseline cognitive score, age, sex, and educational level.

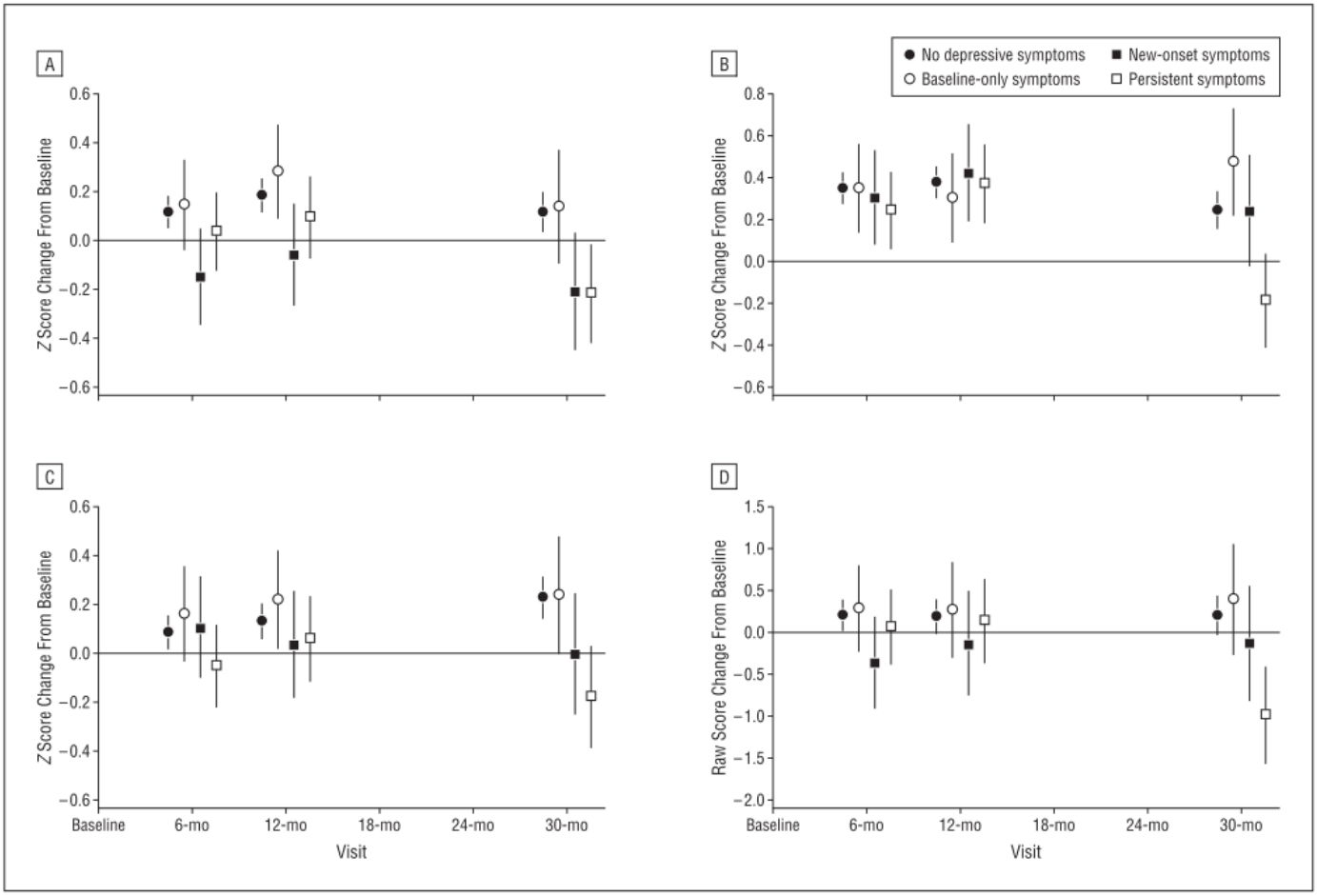

Figure 3.3 Least-squares Mean Change (95% CI) in Cognitive Measures from Baseline at Each Follow-up Visit by Changes in Depressive Symptoms During 1 Year.

Changes for attention/executive function (A), learning/memory (B), and verbal fluency (C) are expressed as *z* scores; for global cognition (D), changes are expressed as raw scores. Changes are adjusted for baseline cognitive score, age, sex, and education level.

Chapter 4: Frailty Trajectories after Coronary Interventions in Older Patients with Coronary Artery Disease

4.1 Abstract

Importance: Frailty as an independent risk factor for cardiovascular outcomes has attracted increasing research and clinical interest. However, frailty is a dynamic variable, and its trajectory after a coronary intervention is unknown.

Objective: To determine the trajectory of frailty among patients undergoing coronary angiography, overall and by sex, age, and initial treatment (i.e., coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], medical therapy only [MT]).

Design: Cohort study with 30-month follow-up after initial coronary angiogram.

Setting: Urban tertiary care hospital in Alberta, Canada.

Participants: 374 patients, 60+ years of age, 26.7% female, undergoing non-emergent cardiac catheterization (October 2003 through February 2007) without history of coronary revascularization.

Exposure: Initial frailty levels, age groups, sex, and initial treatment plans were compared.

Main Outcome(s) and Measure(s): A frailty index (FI) score based on the proportion of deficits present out of 53 potential ones was calculated at baseline (pre-procedure), 6, 12, and 30 months post-procedure. Descriptive analyses examined change over time stratified by initial

frailty level. Random effects models were used to compare FI score trajectories by sex, age, and treatment group.

Results: 128 CABG, 150 PCI, and 96 MT patients were enrolled with mean FI scores of 0.170, 0.154, and 0.154, respectively. FI scores declined (improved) 6 months after the intervention but then rose (worsened) at12 and 30 months ($p<0.001$ for differences over time). Women had non-significantly higher FI scores than men ($p=.097$), but followed the same trajectory ($p=0.352$ for differences over time). In patients aged 75+, FI scores increased throughout the period for CABG and MT, but declined in the first 6 months for PCI patients, increasing afterwards. PCI and CABG patients under 75 experienced a sustained reduction in frailty over 30 months, while MT patients under 75 had stable frailty throughout the period. P-value for differences over time by age and treatment group was 0.041.

Conclusions: After coronary intervention, frailty generally follows a U-shaped trajectory, but individual paths may differ by age and initial treatment. Further investigation is needed to more precisely identify subgroups of patients who might benefit from augmented care during the recovery period.

4.2 Introduction

Significant improvements in survival rates among patients with coronary artery disease, including those aged 75 and over, have led to a greater focus on functional and quality of life outcomes.[1,6] In this area, the concept of frailty has attracted increased attention as a means of identifying patients more prone to worse outcomes with coronary care.[26] Bergman et al. defined frailty as enhanced "vulnerability to stressors due to impairments in multiple, interrelated systems that lead to decline in homeostatic reserve and resiliency".[35] Understanding the dynamic nature of frailty may assist health care providers in providing more appropriate patient care over the entire course of management.

Recent systematic reviews note over 40 studies that address frailty in patients with cardiovascular disease published between 2010 and 2014.[15,16,26] Research has primarily focused on the association between baseline frailty and both short-term[27] and long-term[28] mortality after an event or procedure.[15,16,26] Other outcomes considered include disability,[29,30] cardiovascular events,[31,32] and institutionalization,[33,34] as well as the association between frailty and cardiovascular risk factors.[21-23] Few studies have focused on frailty as a primary outcome and described it over time in cardiovascular patients.[21,56]

Frailty scores are generally higher in women than men[165-168] and rise exponentially with increasing age.[106,108,109] Frailty trajectories may also vary by the type of coronary intervention (i.e., coronary artery bypass graft [CABG] surgery, percutaneous coronary intervention [PCI], or medical therapy only [MT]) patients receive. While a cardiac intervention might lead to an improvement in the person's frailty status by improving their clinical symptoms, a more invasive procedure might also precipitate the onset or the deterioration of their frailty status.[169-171] Using data from cardiac patients undergoing coronary angiography at a tertiary care center, we sought

to determine the patterns of frailty change post-procedure and the influence on frailty trajectories of the sex, age, and treatment group of patients.

4.3 Methods

4.3.1 Study Design and Sample

This was a substudy of the Calgary Cardiac and Cognition (3C) Study, a prospective cohort investigation of the effect of physical, neurocognitive and psychological factors on health outcomes and functional recovery in older patients undergoing coronary interventions.[112] Three hundred seventy-four subjects aged 60 and older were enrolled between October 2003 and February 2007. All underwent coronary angiography for coronary artery disease (CAD) at an urban tertiary care hospital providing centralized cardiac services for southern Alberta. Recruitment was stratified according to three initial treatments assigned after the coronary angiogram: CABG (n=128), PCI (n=150), and MT (n=96). Potential participants were excluded if they underwent an emergency catheterization, had prior revascularization, or were unable to complete the assessment because of language difficulties or mental or physical impairments. Ethical approval was received from the Conjoint Health Research Ethics Board, University of Calgary and participants provided informed consent.

Trained research nurses and associates administered a standardized assessment battery collecting neuropsychological and physical performance, sociodemographic, health behavior, activity of daily living, and health-related quality of life measurements at baseline (pre-procedure) and 6, 12, and 30 months after the procedure. The 3C database was linked with the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH),[110] a registry of all patients undergoing cardiac catheterization in the province, for baseline clinical information. Three patients could not be linked due to out-of-province catheterizations (n=2) or missing

linkage (n=1). Blood samples were collected for 357 of the 374 participants (95.5%) at the time of catheterization for patients receiving MT or at the time of revascularization for patients who underwent PCI and CABG. Figure 1 illustrates the subject flow for 3C.[112] Retention of participants was 89 percent over the course of the study. All patients were categorized according to their originally assigned treatment group.

4.3.2 Frailty Index

The outcome, frailty index (FI) score,[54,55] was calculated on all participants. An FI is the proportion of age-related health deficits an individual has accumulated. A deficit can be any disease, symptom, laboratory abnormality, or a functional or cognitive impairment associated with health decline, that accumulates but does not saturate with age. [54,55,172] The index does not require a pre-specified list of deficits as variables, but can be implemented by anyone using any list of potential deficits, provided that they are at least 40 in number and that they come from a wide range of domains (physical, cognitive, disability, comorbidity, emotional, social).[54] Individual frailty is scored as a proportion of actual deficits divided by total possible deficits, a decimal number between 0 and 1.The FI score is higher when there are more deficits.[54,55,172] A higher FI is associated with an increased risk for institutionalization, and short-term mortality.[54,55]

In 3C, 53 potential deficits were derived from the clinical assessments, APPROACH data, and blood work obtained on participants, based on the criteria described above. Our selection covers a range of systems: physical, cognitive, emotional, health-related quality of life, disability, medical condition,[54] and are described in Appendix A. The FI score was calculated as the number of deficits present in an individual divided by the number of potential deficits where data were available (i.e. less than 53 if the data were not complete).

4.3.3 Statistical Analysis

Descriptive analyses were conducted to compare baseline sociodemographic and clinical characteristics by treatment group and across visits. To compare change by initial level of frailty, categories were created, the first four of equal width (0.06 in FI score), and all scores over 0.24 for the last category. Equal-ranged categories were used, rather than sample-derived quintiles, in order to better compare the distribution and movement of data over time by comparing equal-sized ranges. For each of three transitions (baseline to 6 months, 6 to 12 months, and 12 to 30 months), proportions were estimated for FI score decrease (≥.02 decrease in FI score), stable FI score (change of <.02), FI score increase (≥.02 increase in FI score), deaths, and withdrawals.[99] A change of .02 was used as it corresponds with slightly more than a gain or loss of one deficit and its similarity to the threshold used by other researchers.[98]

To compare age, sex, and treatment group differences associated with change over time, we fitted FI scores to linear mixed models with a random intercept. Visit was modeled as a repeated categorical measure to accommodate a possible non-linear relationship between score and time. For the age comparison, age was categorized into quartiles based on the sample distribution, in order to isolate the oldest and youngest quartiles. For the age by treatment group comparison, two categories were used, 75+ and <75, as the three lower age quartiles had similar results and were combined. Models were adjusted by age, sex, and education as appropriate because all have associations with frailty criteria.[106,108,109,165,167,168,173]

Adjusted least-square means, standard errors, and accompanying p-values based on the tests of fixed effects[174] were recorded for each model. A p-value is given for change in score across visits, for mean score differences between groups overall, and for differences between groups in mean score changes across visits. Residuals were reviewed to check on assumptions of

homoscedasticity and normal distribution. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

4.4 Results

4.4.1 Baseline Characteristics

The study sample was 26.7% female with an average age of 71.4 (Table 1). The MT group had a significantly higher proportion of women (39.6%) compared with the PCI group (27.3%) and CABG group (16.4%). The CABG group had a significantly higher proportion of patients with stable angina (74.4%), high-risk coronary anatomy (90.4%) and with diabetes (38.3%) compared with the other two treatment groups. The mean baseline FI scores were not significantly different across the three treatment groups (0.170 for CABG, and 0.154 for both PCI and MT, p=.173).

4.4.2 Frailty Index

The mean FI score was 0.160 at baseline, 0.150 at 6 months, 0.151 at 12 months, and 0.162 at 30 months, (Table e1). Table 2 describes the proportions of the sample that increased, decreased or maintained their FI score (+/- 0.02) during each transition period. This is stratified by FI score category at the beginning of each transition period. Overall, a greater proportion of FI scores decreased (i.e., frailty levels improved) from baseline to 6 months post-procedure than in subsequent transition periods. Conversely, a greater proportion of FI scores increased (i.e., frailty levels worsened) in the later transition periods than in the baseline to 6-month transition period. For example, among those with an FI score between .18 and .24 at baseline, 41.5% were less frail and 18.7% were more frail 6 months post-procedure. However, among those with an FI score between .18 and .24 at month 12, 26.2% were less frail and 33.3% were frailer at 30 months post-procedure. Similar findings were observed for the less frail groups as well. Although obviously there would be little room for improvement in those with almost no deficits

(FI score 0-.06), smaller proportions worsened at 6 and 12 months (22.2%, 24.2%) than by 30 months (40.5%).

The groups with the highest and second highest frailty levels (FI scores of .24+ and .18-.24) were the most dynamic, with only one-quarter or one-third (respectively) of the group maintaining a stable FI score during any transition period. By contrast approximately two-thirds of the least frail groups maintained a stable FI score across any transition period. In the first 6 months post-procedure, there were more deaths in the highest frailty levels (>0.18) than in the less frail levels (0-0.18), but no obvious pattern was observed during subsequent time periods.

4.4.3 Frailty Trajectories by Sex, Age, and/or Treatment Groups

Figure 2 and Table 3 present the adjusted mean FI scores at baseline, 6, 12, and 30 months post-procedure for the group overall and for four subgroups (a) by sex, (b) baseline age category, (c) initial treatment group, and (d) baseline age (≥75 years) and treatment group. Overall the mean FI scores followed a U-shaped curve with scores declining after the intervention and rising thereafter ($p<0.001$ for differences over time).

As illustrated in Figure 2a and Table 3a, women showed a non-significantly higher mean FI score than men across all visits, ($p=0.097$). For both sexes, the change in the FI score over time followed a U shape with an initial decline from baseline followed by an increase post-procedure. This change over time was statistically significant ($p<0.001$). Male and female trajectories did not differ from each other ($p=0.352$).

Frailty differed by age group overall ($p<0.001$) with older age groups showing consistently higher mean FI scores than younger ones across all visits (Figure 2b, Table 3b). FI score

trajectories also differed by age group ($p<0.001$) with the oldest quartile (75+) failing to show the early improvement observed in the younger age groups.

Overall, 3C participants who underwent CABG as their initial treatment trended toward higher mean FI scores across all visits than those who underwent PCI or received MT only ($p=0.053$) (Figure 2c, Table 3c.). U-shaped curves were observed for both PCI and CABG groups. For the PCI group, the decrease in mean FI score was greater at 6 and 12 months. FI score was still slightly lower than baseline at 30 months. For the CABG group, the decrease in mean FI score was not as great at 6 and 12 months, and the score at 30 months was greater than baseline. By contrast, the mean FI score for patients assigned to MT tended to increase over time. However, the p-value for treatment differences in FI score trajectories was 0.090.

Treatment group trajectories did not vary by sex, (results not shown, $p=0.579$); however, they did vary by age (Figure 2d and Table 3d). Specifically, mean FI scores for CABG patients aged <75 years decreased in month 6 and 12, but mean FI scores for CABG patients aged 75+ increased steadily from baseline. Similarly, mean FI scores increased steadily for MT patients aged 75+, whereas mean FI scores for those aged <75 years did not. Mean FI scores declined from baseline to 6 months for all PCI patients, regardless of age. However, after month 6, mean FI scores increased for those aged 75+ receiving PCI but not for the younger PCI group. These age differences between treatment groups in change over time were statistically significant ($p=0.041$).

4.5 Discussion

This is one of the first studies to determine frailty in patients before and after a coronary intervention. Frailty took on a U-shaped trajectory for the whole sample. However, different

patterns emerged within particular age and treatment groups. Trends did not vary based on initial frailty status. However, frailty was more dynamic in frailer groups as the two frailest categories had the smallest proportion with stable FI scores across any of the three intervals.

Older participants were less likely to experience an improvement in frailty with the procedure, and tended to have steeper slopes than younger age groups. This is also consistent with literature that describes an exponential relationship between frailty and age.[106-109] The interaction between age and treatment plan has important implications for individual patient care. Despite significant improvements in survival for CAD patients undergoing coronary interventions, including older patients, these differences may impact important functional, and quality of life outcomes. For example, the negative effects of hospitalization, due to prolonged loss of mobility, may impact older age groups more than younger groups, overriding health improvements after CABG and leaving a patient with a reduced resilience.[169-171,175-177]

Consistent with the literature, women trended toward higher FI scores than men.[165,178] However, men and women followed parallel courses over the 30-month period, and treatment group differences did not vary by sex. Some researchers have asserted that in the general population, women have less risk of unfavorable outcomes than men at similar frailty levels.[55] Others have concluded that women have more risk because of higher frailty measurements.[165] Additional research is needed to determine whether greater FI scores for women with CAD place them at greater risk of poor outcomes.[179]

Numerous publications have looked at frailty longitudinally in general populations: characterizing frailty transitions,[98-100,107,109] examining potential predictors of transitions,[101-103] testing interventions to limit worsening frailty,[104] and comparing static versus dynamic frailty

measures to predict functional decline.[105] However, few have looked longitudinally at a cohort of patients with cardiovascular disease. A literature search revealed only one previous study looking at frailty at more than one-time point in patients with cardiovascular disease. Myers, et al., categorized an FI at baseline post-acute myocardial infarction and 10-13 years post-baseline using 32 variables, and found an association between the two FI measurements with mortality.[56] Our study made use of the FI as a continuous measurement, and focused on describing the trajectory of frailty as patients progressed from treatment through recovery and beyond.

4.5.1 Study Strengths and Limitations

A particular strength of our study is the large clinical sample, the detail of repeat measurements, and the 30-month length, relative to other clinical prospective studies that examined cardiovascular interventions. We compared three treatment plans including MT, and had high retention. Our FI incorporated criteria from a wide range of domains including cognitive, emotional, quality of life, as well as physical performance criteria.

One limitation of the study is that a clinically meaningful FI score change has not been established. Rockwood, et al., associated mean FI scores with other scales.[59,180] For example, 0.22 was the mean FI score for people categorized as "4-apparently vulnerable", and 0.27 was the mean FI score for people categorized as "5-mildly frail" on the Canadian Study of Health and Aging Clinical Frailty Scale. Both categories were shown to have worse survival than less frail categories. However, there was a large variance of FI scores within each category.[59] No minimum meaningful difference has yet been established for this continuous measurement to help guide interpretation of change. This represents an area for future research.

Mortality was too rare to include as an outcome in this analysis. The 3C study participants were younger and healthier than typical prospective cohorts included in frailty studies. Nevertheless, this analysis gives us important information about frailty at an early stage, when individuals may be less burdened by disabilities, but resilience is beginning to erode. Although this study is larger than many clinical prospective cohort studies of this type, it is smaller than some other community-based frailty studies.

4.5.2 Implications

We found that frailty was more dynamic in more frail patients with CAD. Female and older patients and those undergoing CABG trended toward higher frailty levels. In our sample, frailty followed a U-shaped curve after revascularization. However, relatively older patients (aged 75+ years) undergoing MT and CABG did not experience this decrease, but rather increased in frailty from baseline on. A look at frailty as a time-varying covariate with a larger sample, in a longer study, would provide additional information about the implications of differences in trajectories in terms of outcomes, and provide a more nuanced context for possible interventions.

Frailty itself is not a disease, but rather an indicator that a person has reduced resiliency. Therefore, the implications are that frailty measurements add information to the overall assessment of risk and allow for more tailored patient care in this group.[26] As of 2014, nearly 60 studies have investigated nutritional, exercise, pharmaceutical, and multi-factorial interventions in frail (non-cardiovascular) populations in hospital and home settings.[181,182] By monitoring and addressing frailty in CAD patients, not only at baseline, but throughout the recovery period, health care providers can ensure that their patients have the resiliency to reap the largest benefit from their treatments.

4.6 Acknowledgements

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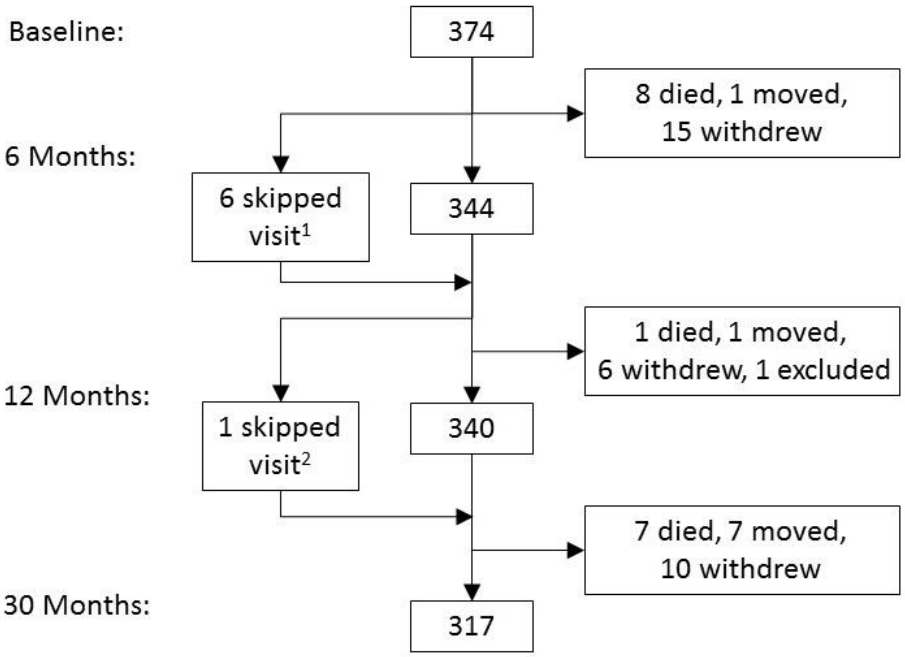
Elizabeth Freiheit was responsible for study conceptualization, data management, statistical analysis and interpretation, and drafting the manuscript. David Hogan and Scott Patten made significant contributions to the study design, obtaining funding, and data interpretation. They also provided critical review of the manuscript. Hannah Wunsch made important contributions to data interpretation and provided critical review of the manuscript. Todd Anderson, William Ghali, and Merril Knudtson made significant contributions to the study design, assisted in obtaining funding, provided clinical support, and provided critical review of the manuscript. Colleen Maxwell was responsible for the study design, obtaining funding, data acquisition, analysis and interpretation, critical revision of the manuscript, and supervision. None of the authors have any conflicts of interest relevant to this research. Elizabeth Freiheit and Colleen

Maxwell had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Elizabeth Freiheit conducted the analysis.

4.7 Tables and Figures



[1] 6 subjects skipped the 6-month visit but returned to the study for the 12-month visit.
[2] 1 subject skipped the 12-month visit but returned to the study for the 30-month visit.

Figure 4.1 3C Study Flow

Table 4.1 Baseline Characteristics of 3C Study Sample by Initial Treatment Group[a]

Characteristic	All N=374	CABG N=128	PCI N=150	MT N=96	P-value[b]
Age, mean ± SD	71.4 (5.9)	71.3 (6.5)	71.0 (5.5)	72.3 (5.5)	.193
Female sex, number (%)	100 (26.7)	21 (16.4)	41 (27.3)	38 (39.6)	<.001
Education years, mean ± SD	12.8 (3.8)	13.1 (3.8)	12.7 (3.7)	12.6 (3.8)	.506
Frailty index deficit sum, mean ± SD[c]	8.4 (4.2)	8.9 (4.2)	8.1 (3.8)	8.2 (4.9)	.239
Frailty Index score, mean ± SD[c]	0.160 (0.080)	0.170 (0.080)	0.154 (0.071)	0.154 (0.093)	.173
Cardiovascular disease, %					
Admitted with stable angina[d]	246 (65.3)	93 (74.4)	92 (61.3)	58 (60.4)	.036
Acute coronary syndrome[f]	145 (38.9)	45 (35.4)	64 (42.7)	36 (37.5)	.446
Congestive heart failure[d]	38 (10.0)	10 (8.0)	16 (10.7)	12 (12.5)	.537
Canadian Cardiovascular Society angina class>II[d]	178 (48.0)	53 (42.4)	74 (49.3)	51 (53.1)	.269
High risk coronary anatomy[de]	174 (46.9)	113 (90.4)	45 (30.0)	16 (16.7)	<.001
Ejection fraction <50%[g]	61 (18.2)	20 (18.7)	21 (14.8)	20 (22.0)	.531
Vascular risk factors, %					
Smoking (former or current)	267 (72.0)	95 (74.2)	108 (72.0)	64 (66.7)	.454
Hypertension[f]	305 (81.8)	108 (85.0)	125 (83.3)	72 (75.0)	.128
Diabetes mellitus (Type I or II)[f]	103 (27.5)	49 (38.3)	37 (24.7)	17 (17.7)	.002
Hyperlipidemia[d]	312 (84.1)	103 (82.4)	129 (86.0)	80 (83.3)	.699
Co-morbidities, %[d]					
Cerebrovascular disease	39 (10.5)	17 (13.6)	11 (7.3)	11 (11.5)	.227
Peripheral vascular disease	33 (8.9)	17 (13.6)	5 (3.3)	11 (11.5)	.012
Pulmonary disease	83 (22.4)	25 (20.0)	31 (20.7)	27 (28.1)	.289
Renal disease	11 (3.0)	4 (3.2)	4 (2.7)	3 (3.1)	.961
Malignancy	19 (5.1)	6 (4.8)	7 (4.7)	6 (6.3)	.843
Liver or gastrointestinal disease	28 (7.5)	9 (7.2)	12 (8.0)	7 (7.3)	.963

Abbreviations: CABG = coronary artery bypass graft surgery, PCI = percutaneous coronary intervention, MT= medical therapy only, SD=standard deviation

[a] Two MT patients had a subsequent PCI at 3 months and 20 months (respectively) after baseline. Three PCI patients had a subsequent CABG at 7 months, 8 months, and 12 months (respectively) after PCI procedure.

[b] Based on *F* test for continuous variables and chi-square test for categorical variables.

[c] See eAppendix A for calculation of Frailty Index Sum and Frailty Index Score.

[d] Sample size for all (n=371), CABG (n=125), PCI (n=150), MT (n=96).

[e] High risk defined as double-vessel coronary artery disease with proximal left anterior descending artery involvement, any 3-vessel disease, or left main disease.

[f] Sample combines information from APPROACH and visit questionnaires. 373 (all), 127 (CABG), 150 (PCI), 96 (MT).

[g] Sample is 336 (all), 103 (CABG), 142 (PCI), 91 (MT) due to ejection fraction not being measured in all catheterizations.

Table 4.2 Proportion of 3C Study Sample Exhibiting an Increase, Decrease, or Stable Frailty Index (FI) Scores, Stratified by FI Score at Beginning of Period[a,b,c]

	Baseline to 6 Months		6 Months to 12 Months		12 Months to 30 Months	
Transition	**Number**	**Proportion (%)**	**Number**	**Proportion (%)**	**Number**	**Proportion (%)**
FI Score: 0 - .06 (lowest frailty)		N=18		N=33		N=37
Decrease	2	11.1	0	0	0	0
Stable	11	61.1	25	75.8	18	48.7
Increase	4	22.2	8	24.2	15	40.5
Death	0	0	0	0	2	5.4
Lost to follow up	1	5.6	0	0	2	5.4
FI Score: >.06 -.12		N=109		N=124		N=119
Decrease	25	22.9	10	8.1	14	11.8
Stable	67	61.5	85	68.6	77	64.7
Increase	15	13.8	24	19.4	22	18.5
Death	0	0	1	0.8	0	0
Lost to follow up	2	1.8	4	3.2	6	5.0
FI Score: >.12-.18		N=123		N=97		N=96
Decrease	43	35.0	24	24.7	22	22.9
Stable	47	38.2	50	52.6	37	38.5
Increase	23	18.7	23	22.7	34	35.4
Death	2	1.6	0	0	2	2.1
Lost to follow up	8	6.5	0	0	1	1.1
FI Score: >.18-.24		N=65		N=44		N=42
Decrease	27	41.5	15	34.1	11	26.2
Stable	20	30.8	16	36.4	13	30.1
Increase	10	18.7	11	25.0	14	33.3
Death	4	6.2	0	0	1	2.4
Lost to follow up	4	6.2	2	4.5	3	7.1
FI Score: >.24 (highest frailty)		N=53		N=45		N=46
Decrease	23	43.4	17	37.8	11	23.9
Stable	15	28.3	12	26.7	12	26.1
Increase	12	22.6	14	31.1	16	34.8
Death	2	3.8	0	0	2	4.3
Lost to follow up	1	1.9	2	4.4	5	10.9

[a] "Decrease" and "increase" is defined as a change in more than .02 in the Frailty Index score.

[b] Note that 6 patients who skipped month 6, and 2 patients who skipped month 12 are not included in the intervals pertaining to those visits.

[c] "Stable" is defined as a change of less than 0.02 over the period.

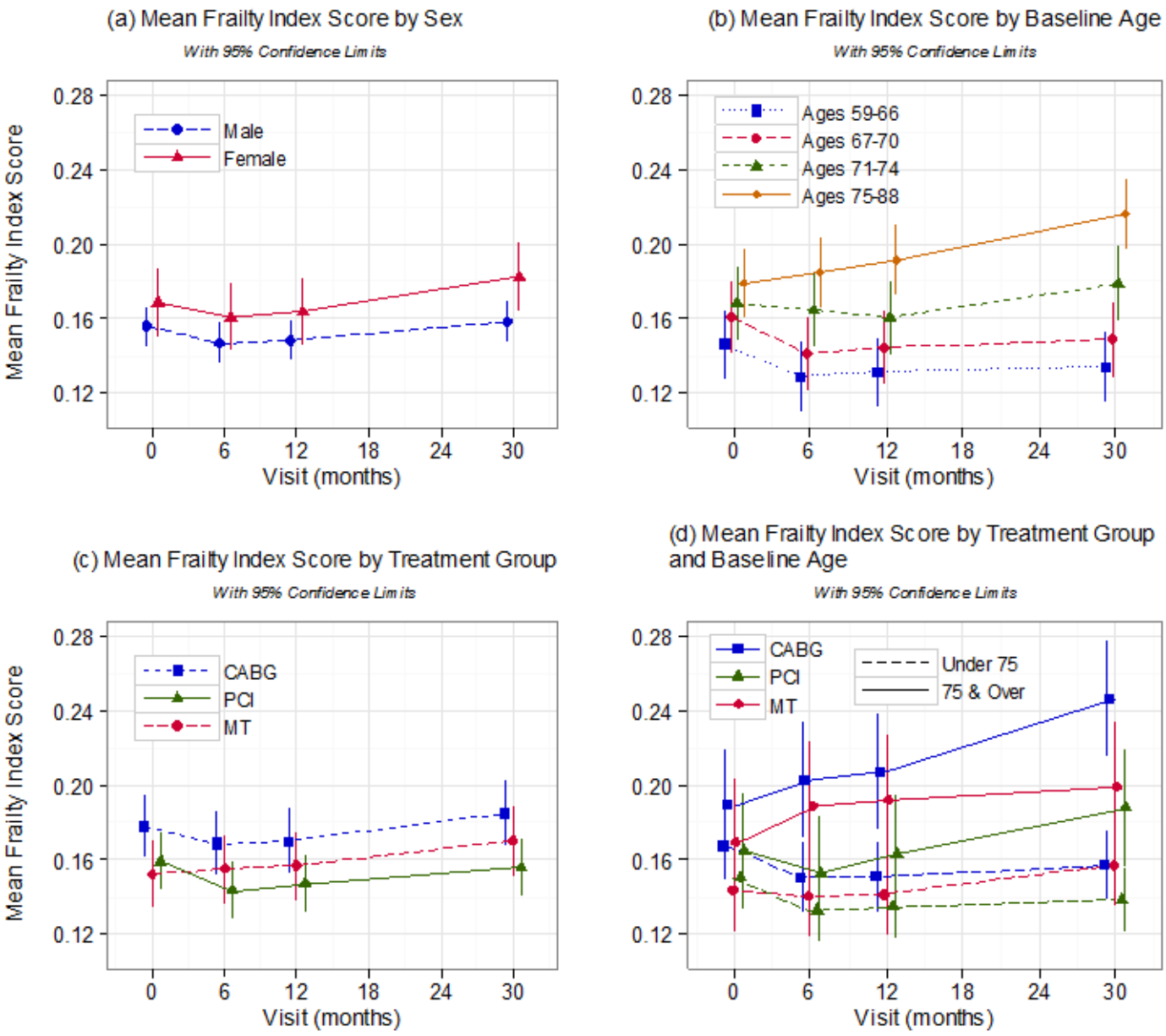


Figure 4.2 Mean Frailty Index Scores over Time by (a) Sex, (b) Baseline Age Category, (c) Treatment Group, and (d) Treatment Group by Baseline Age

Table 4.3 Mean Frailty Index Scores over Time by (a) Sex, (b) Baseline Age Category, (c) Treatment Group, and (d) Treatment Group by Baseline Age

	Sample sizes at	Least Square Means (Standard Error)[a]					
	0,6,12,30 months	Baseline	6 Months	12 Months	30 Months	P-values associated with differences	
Overall	374, 344, 340, 317	.163 (.0052)	.154 (.0052)	.156 (.0052)	.169 (.0053)	Between visits	<.001
(a)						Between sexes	.097
Female	100,91,91,83	.169 (.0191)	.161 (.0092)	.164 (.0092)	.183 (.0093)	Between visits	<.001
Male	274,253,249,234	.156 (.0054)	.147 (.0055)	.149 (.0055)	.159 (.0056)	Sexes by visits	.352
(b)							
Baseline age 59-66	100,94,95,91	.146 (.0094)	.129 (.0095)	.132 (.0095)	.134 (.0095)	Between age groups	<.001
Baseline age 67-70	91,84,81,73	.160 (.0098)	.142 (.0099)	.145 (.0099)	.149 (.0100	Between visits	<.001
Baseline age 71-74	87,81,80,73	.168 (.0101)	.164 (.0102)	.161 (.0102)	.179 (.0103)	Age groups by visits	<.001
Baseline age 75-88	96,85,84,80	.179 (.0093)	.185 (.0095)	.191 (.0095)	.216 (.0096)		
(c)							
CABG	128,120,119,111	.178 (.0085)	.169 (.0086)	.170 (.0086)	.185 (.0087)	Between treatments	.053
PCI	96,85,84,80	.159 (.0076)	.143 (.0077)	.147 (.0077)	.156 (.0078)	Between visits	<.001
Medical therapy	150,139,137,126	.152 (.009)	.155 (.0094)	.157 (.0094)	.170 (.0094)	Treatments by visits	.090
(d)							
CABG, age <75	94,90,89,82	.168 (.0094)	.151 (.0094)	.151 (.0095)	.157 (.0096)	Between treatments	.034
CABG, age 75 +	34,30,30,29	.189 (.0154)	.203 (.0158)	.208 (.0158)	.247 (.0158)	Between age <75/75+	<.001
PCI, age <75	117,108,106,96	.150 (.0083)	.133 (.0084)	.135 (.0084)	.138 (.0085)	Between visits	<.001
PCI, age 75 +	33,31,31,30	.164 (.0158)	.153 (.0159)	.163 (.0159)	.188 (.0160)	Treatments by visit	.080
Medical therapy, age <75	117,108,106,96	.144 (.0110)	.141 (.0112)	.141 (.0112)	.157 (.0112)	Age <75/75+ by Visit	<.001
Medical therapy age 75 +	29,24,23,21	.170 (.0170)	.189 (.0175)	.192 (.0176)	.199 (.0178)	Treatments by age <75/75+	.519
						Treatments by age <75/75+ by visits	.041

[a] Means are adjusted by (overall) age, sex, and education, (a) age and education, (b) sex and education, (c) age, sex, and education, (d) sex and education.
CABG=coronary artery bypass graph, PCI=percutaneous coronary intervention.

4.8 eAppendix A: Frailty Index Construction

4.8.1 Missing Data, Value Assignment

A neuropsychologist and a geriatrician reviewed all available data for persons with intermittent missing test values. A value was assigned indicating a deficit if a participant was deemed too impaired in that particular domain to complete the test. If no such deduction could be made, a single conditional mean based on a Monte-Carlo Markov Chain imputation process was used to assign a value.[112] Only 0.1% to 1.7% of any given criteria were completed based on imputation. No assignments were made for missed visits, missing APPROACH or bloodwork data.

4.8.2 Frailty Index Construction

One point was given for any of the following 53 deficits to create the FI score. Partial points were given as indicated below. Measurements were taken at all visits unless otherwise indicated. Physical characteristics (n=5) included body mass index, questions and tests from the Macarthur Studies of Successful Aging.[115,183] Health-related quality of life criteria (n=6) included a self-rated health question, and items from the EuroQOL EQ-5D questionnaire.[125,184] Cognitive criteria (n=6) were age, sex, and education-adjusted scores from the animal naming test[118], "FAS" letter naming test[118], a global cognition test[185], a trail-making executive function test[118], a verbal delayed recall test[152] and a visuospatial delayed recall test[151]. Mood criteria (n=4) include an anxiety scale[154], the 15-item Geriatric Depression Scale[121], and subscales based on the Geriatric Depression Scale.[122] Self-reported activities of daily living (n=7) and instrumental activities of daily living (n=7) provided functional criteria.[124] Baseline diseases (n=12) and medical conditions (n=5) such as ejection fraction were provided by APPROACH. Of these, diabetes, acute coronary syndrome, and hypertension were updated during caregiver interviews.[186] Self-reported strokes and TIAs were collected using a validated stroke

questionnaire.[153] Collected blood samples provided homocysteine and B12 levels. Living arrangements (n=1) were self-reported.

For the 53 criteria, data were complete for 87.2-87.8% of the study population across all visits. For between 11.0% and 11.7% of the sample, across all visits, 51 or 52 criteria were present. The denominator was between 40 and 50, due to missing data, for approximately 1% of the study sample across all visits.

Physical Characteristics and Performance[115,116,183]
1. Abnormal body mass index (< 21 or >30 kg/m^2) based on self-reported height and weight
2. Unable or didn't know if able to walk up stairs without help (self-reported)
3. Unable or didn't know if able to walk half a mile without help (self-reported)
4. Balance test: unable to hold full tandem for >10 sec
5. Gait test: unable to walk 8 feet in <4 sec

Health-Related Quality of Life [125,184]
6. Response of "fair" or "poor" to question, "In general, would you say your health is excellent, very good, good, fair, or poor?"
7. Some problems with washing/dressing (0.5); unable to wash/dress (1.0)
8. Some problems performing usual activities (work, study, housework, leisure) (0.5); unable (1.0)
9. Has moderate pain/discomfort (0.5); has extreme pain/discomfort (1.0)
10. Is moderately anxious or depressed (0.5); is extremely anxious or depressed. (1.0)
11. Self-rated health on scale of 0 to 100 (thermometer) less than or equal to 65.

Cognition[118,151,152,185]
12. Animal Naming Test 1.5 standard deviations below age and education adjusted norms
13. FAS Test 1.5 standard deviations below age and education adjusted norms
14. MMSE in the bottom 10 percentile of age, sex, education-adjusted norms
15. Trails B Test 1.5 standard deviations below age, sex, and education adjusted norms
16. CERAD Verbal Memory Delayed Recall 1.5 standard deviations below age, sex, and education adjusted norms
17. Brief Visuospatial Memory-Revised Delayed Recall Test 1.5 standard deviations below age-adjusted norms

Mood[121,122,154]
18. Current anxiety 1.5 standard deviations below sex and education-adjusted norms
19. Geriatric Depression Scale score > 4
20. Mood/hope score >1
21. Withdrawal/apathy/vigor score = 3

Functional Status[124]
22. Eats with some help = 0.5; completely unable = 1
23. Dresses with some help = 0.5; completely unable = 1
24. Cares for appearance with some help = 0.5; completely unable = 1
25. Walks with some help = 0.5; completely unable = 1

26. Transfers with some help = 0.5; completely unable = 1
27. Bathes with some help = 0.5; completely unable = 1
28. Uses toilet with some help = 0.5; completely unable = 1
29. Uses telephone with some help = 0.5; completely unable = 1
30. Travels with some help = 0.5; completely unable = 1
31. Shops with some help = 0.5; completely unable = 1
32. Prepares meals with some help = 0.5; completely unable = 1
33. Does housework with some help = 0.5; completely unable = 1
34. Takes medicine with some help = 0.5; completely unable = 1
35. Handles money with some help = 0.5; completely unable = 1

Diseases and Medical Conditions Recorded at Time of Catheterization[110]
36. Pulmonary disease at baseline
37.Cerebrovascular disease at baseline
38. Renal disease at baseline
39. Congestive heart failure at baseline
40. Diabetes Mellitus (Type I or II), self-reported updates at follow up visits
41. Dialysis at baseline
42. Hypertension, self-reported updates at follow up visits
43. Hyperlipidemia at baseline
44. Severe/debilitating liver or gi disease at baseline
45. Malignancy at baseline
46. Peripheral vascular disease
47. Acute coronary syndrome, self-reported updates at follow up visits
48. Ejection fraction at baseline <50%

Self-Reported Stroke and TIA[153]
49. Stroke prior to visit, self-reported
50. TIA prior to visit, self-reported

Bloodwork
51. High homocysteine at baseline
52. B12 deficiency at baseline

Social Support
53. Lives alone, self-reported

Table 4.4, (eTable 1) Baseline Characteristics of Study Sample by Visit

	Baseline N=374	6 Months N=344	12 Months N=340	30 Months N=317
Age at baseline, mean ± SD	71.4 ± 5.9	71.3 ± 5.9	71.3 ± 5.9	71.3 ± 6.0
Female sex, number (%)	100 (26.7)	91 (26.4)	91 (26.8)	83 (26.2)
Education years, , mean ± SD	12.8 ± 3.8	12.8 ± 3.9	12.8 ± 3.9	12.8 ± 3.8
Baseline treatment group, number (%)				
CABG	128 (34.2)	120(34.9)	119 (35.0)	111 (35.0)
PCI	150 (40.1)	139 (40.4)	137 (40.3)	126 (39.8)
MT	96 (25.7)	85 (24.7)	84 (24.7)	80 (25.2)
Frailty Index deficit sum, mean ± SD[a]	8.41 (4.22)	7.93 (4.89)	7.97 (4.96)	8.52 (5.79)
Frailty Index Score, mean ± SD[b]	.160 (0.080)	.150 (.093)	.151 (.094)	.162 (.110)

Abbreviations: SD=standard deviation, CABG =coronary artery bypass graft, PCI = percutaneous coronary intervention, MT=medical therapy.

[a] Frailty Index deficit sum is the raw sum of deficits of 53 possible criteria.

[b] Frailty Index score is the deficit sum divided by the number of nonmissing criteria, 53 if the data are complete.

Chapter 5: Discussion

5.1 Summary of Main Findings

The overall goal of this research was to expand our understanding of frailty in older people with coronary artery disease (CAD) undergoing coronary angiography and subsequently receiving a coronary intervention, specifically, coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI) or medical therapy only (MT). Results showed which baseline frailty components best predict decline individually and in combination, how they interact over time, and what pattern frailty takes in follow-up to a coronary intervention.

In paper 1, the objective was to examine a range of potential frailty criteria representing diverse domains (physical, cognitive, psychosocial) in older patients undergoing coronary angiography to develop a brief, comprehensive, and feasible frailty index. Associations between activity of daily living (ADL) decline, from baseline before procedure to 12 months after procedure, were measured against 15 potential physical, cognitive, and psychosocial variables. Variables of all categories had significant associations with decline. Interestingly, a measure of "poor balance" was more strongly associated with decline than a measure of "slow gait", a commonly used frailty component. This finding might be particular to a population that is temporarily bedridden because of the procedure they are undergoing. When assembled into a multivariable model, a model with "poor balance", "abnormal body mass index", "poor Trails B scoring", "5 or more depressive symptoms on the Geriatric Depression Scale", and "living alone" was the most strongly associated with ADL decline. As a measure of predictive validity, this model was found to be strongly associated with health-related quality of life (HRQL) decline as well as ADL decline.

In paper 2, the objective was to examine the association between two important components of frailty (and overlooked risk factors for ADL and HRQL decline), depressive symptoms and cognition, among older patients who receive a coronary procedure or medical therapy after an angiography. A dynamic measure capturing the course of depressive symptoms from baseline to 12 months after the procedure, was found to be more closely associated with cognitive change over time. In particular, those with persistent depressive symptoms, or those who developed depressive symptoms during recovery were more likely to have associated cognitive decline. This was seen particularly in the areas of executive function and global cognition, but less so in memory and verbal fluency. When depressive symptoms were measured over the first 12 months, the persistent groups experienced more cognitive decline from 12 to 30 months post-procedure. In addition, those with persistent depression had a greater decline when the apolipoprotein E (*APOE)* ε4 allele was present.

In paper 3, the goal was to implement a frequently used frailty measure, the frailty index (FI), in the group of older CAD patients undergoing a coronary intervention, and to describe the distribution of FI scores at baseline prior to intervention, the change of the distribution over time after intervention, and the differences between subgroups (sex, age group, treatment group) in FI scores overall, and over time. The general trend observed was U-shaped, as frailty tended to decline from baseline to 6 months and 12 months, and rise back to baseline-levels by 30 months. Women had slightly higher scores than men, but the difference was not statistically significant. Those aged 75 and older were frailer, and those in this age group who had had CABG or MT did not decline (improve) in frailty after the cardiac intervention, but increased (worsened) steadily over the 30-month period. The PCI group aged 75 and older had an initial reduction in frailty, but by 30 months, frailty had increased sharply. By contrast, all age groups under 75 showed a

sustained reduction of frailty after coronary procedure (CABG or PCI), and stable frailty after MT.

5.2 Study Strengths, Challenges, and Limitations

5.2.1 3C Study Strengths

The Calgary Cardiac and Cognition Study's particular strengths are a large sample size with a high retention rate, a long follow-up period consisting of four time points when data was collected, and an extensive battery of validated, standardized tests and questionnaires from a wide range of domains collected at each time point. Cognitive tests included visuospatial learning and memory, verbal learning and memory, construction, category fluency, verbal fluency, attention, executive function, and global cognition. The Geriatric Depression Scale offered a reliable, valid measure of depressive symptoms, capturing primarily cognitive depressive symptoms rather than somatic symptoms[121] which can be confounded by pain and/or health status in cardiovascular patients and older subjects.[187,188] Initial treatment for these patients included CABG, PCI, and also MT, which provided an opportunity for comparison between treatment plans, and allowed generalizations to be made to a wider population of persons with CAD. Adding to this, baseline bloodwork, genetic testing, and APPROACH linkage, the depth and breadth of 3C offered a unique opportunity to investigate frailty in a way that could not have been done with other data sources.

In the first paper, the richness of the data allowed for the comparison of variables from a wide range of domains, including cognitive and socio-emotive, which were often not included in other frailty measurement approaches developed. Within certain domains, multiple variables could be compared, for example, 3 executive function tests and one global test within the cognitive domain were compared. The second paper took advantage of the relatively large sample and long

follow-up period compared to other papers on depression and cognition in CAD. So many cognitive tests were available, that their scores could be combined into averages from multiple domains, and their trajectories compared over time. Repeated measurements from a wide variety of domains made it possible to construct a 53-criteria frailty index for the third paper and to view the trajectory of frailty in follow-up to coronary intervention. Another strength was that the frailty trajectories could be compared by revascularization procedure type (CABG and PCI) against those who had not undergone a procedure (MT). In summary, this thesis took advantage of the unique strengths of 3C to produce analyses which would not have been possible elsewhere.

5.2.2 Data Challenges

Data management procedures were instituted to use redundancies within the collected data to correct data entry and logic inconsistencies. Under the consultation of a clinical neuroscientist, more strict scoring guidelines were developed to further increase consistency in the scoring of cognitive tests, such as the Basic Visuospatial Memory Test-Revised[151] and the Animal Naming Test,[118] and then all tests were rescored by a single trained scorer. A 100% audit of the database against the paper forms was conducted for all data in all subject visits.

Once the database was clean, missing data presented a challenge. Many subjects completed a visit while leaving one or two tests or questionnaires for that visit incomplete. The quantity of this type of missing data was not large, but left unaddressed, every analysis would have had a different sample size with a slightly different set of completers.

In addition, much of the missing data could have led to bias if not corrected. Frequently, a test would be incomplete because a participant was too cognitively impaired to complete a cognitive

test, too physically impaired to complete a physical test, or even too depressed to answer the depression questionnaire. The amount of data missing this way was small, less than 1% for all but one variable, the cognitive test, Trails B, for which 3.3% was missing. However, data for these impaired people could have been influential, and not having it might have led to bias depending on the analysis and the differences between the refusal group and the completers.

Based on notes taken by the research nurses, caregiver responses, and similar questions from the visit and other visits, scores were entered for the missing responses. All data completed this way was overseen by a committee of co-investigators including a geriatrician. Any missing responses which could not be completed this way were imputed with a single conditional mean based on an average of Markov Chain Monte Carlo multiple imputation datasets. [156] This technique was appropriate as no variable had more than 1.5% of responses completed by way of single imputation.[156]

5.2.3 Study Limitations

Individual study limitations have been described in Sections 2.5, 3.5.2, and 4.5.1.

The Calgary Cardiac and Cognition (3C) data were remarkably well suited to the questions we sought to answer with this research program. However, because it was not originally designed to address frailty, there were some restrictions to what questions could be answered with the dataset. The next paragraphs describe information that was not collected which would have been useful in the analysis.

It was not possible to link the 3C data with the Alberta Inpatient Discharge Abstract Database, to model re-hospitalization as an outcome variable. This a common outcome of interest to

clinicians and those involved with frailty research.[45,189-191] Those who are frailer would be more likely to incur a hospitalization or a longer hospital stay than those who are less frail.

Of the frailty-associated outcomes that were available, it would have been advantageous to have had more long-term outcomes, such as 5- or 10-year death, ADL decline, and HRQL decline. Frailty research tends to focus on those aged 75 years and older. However, theoretically, a person's resilience may be impeded at a younger age with consequences extending over a longer term. As 3C study participants were aged 60 years and over, there were not enough deaths to use it as an outcome. In addition, there would likely be larger ADL and HRQL declines with a longer follow-up which could also be informative.

As we also looked at frailty itself as an outcome, it also would have been interesting to assess more long-term patterns with frailty, including frailty incidence in robust patients. In the first paper, nearly three-quarters of the 3C cohort were estimated to be robust at baseline. It would have been informative to investigate the rate of frailty incidence among this group, and the association between frailty incidence/prevalence and poor outcomes such as death, functional decline, and HRQL decline. Unfortunately because of time, cost, and ethical constraints, it was not possible to extend the follow-up period for the 3C study.

The 3C database did not contain medications, prescriptions, or other therapeutic information to indicate whether a person was receiving treatment for depression. This may have allowed a comparison of those who were being treated for depression with those who were untreated. However, the 3C data, with the Geriatric Depression Scale, did enable a comparison to be made between those with controlled versus those with uncontrolled symptoms regardless of treatment.

The research project also would have benefitted from a more sophisticated measurement of social support, an independent determinant of health for patients with CAD.[192-195] A systematic review by Barth, et al., (2010) reported 25 studies investigating low social support in patients with CAD, with a pooled relative risk of 1.5-1.7 toward cardiovascular or all-cause mortality.[192] In 3C, the ENRICHD (Enhancing Recovery in Coronary Heart Disease) Social Support Inventory (ESSI)[194] was collected at all visits, but due to the difficulty of conducting baseline visits in hospital, they were not collected prior to the coronary intervention. ESSI captures different aspects of social support, such as emotional support, advice, household help, and companionship. Having this information at baseline would have allowed the comparison of different aspects of social support, and the use of these separate aspects as distinct deficits in the FI.

Although the Cardiovascular Health Study (CHS) operationalization of frailty, described in Section 1.2.2, has been criticized for various reasons, it has been used frequently in frailty research with cardiovascular patients.[36] Because of this, a comparison of the CHS model, and its individual components, with the frailty screen developed in Chapter 2 would have told us whether the frailty screen which includes cognition and social criteria is an improvement over the CHS conceptual model. We could also have compared the CHS model with the FI to see if changes over time, described in Chapter 4, follow a similar pattern. Although, the 3C database did contain gait speed, weight, and a question from the Geriatric Depression Scale, "Do you feel full of energy?" which might have substituted for "feeling exhausted", there was nothing that could have approximated the grip strength test or the low physical activity components.

In the first paper, a frailty screening tool was developed. However, it has not been validated with a separate set of data, nor widely adopted. The sample size was not large enough to be able to

develop the tool using half the population, and validate it with the other half. In the course of doing the analysis for the third paper, a longitudinal analysis was also done with the frailty screen from the first paper. It also produced a U-shaped curve overall, with differences between age and treatment groups similar to the patterns that emerged with the FI. However, the decision was made not to use it in the published paper because it is not as well-known as the FI.

5.3 Clinical and Research Implications

This thesis reflects a shifting paradigm in cardiovascular research objectives. With growing numbers of survivors of CAD, including among the oldest old, there is a growing focus on ensuring that patients live fully functional, independent lives while managing the disease.[3] In older patients with CAD, this research provides the groundwork toward understanding frailty operationalization, the prognostic importance of individual criteria, the interaction and behavior of two important domains (depression and cognition), and the longitudinal trajectory of frailty in follow up to coronary intervention. These findings will help researchers plan and interpret future studies of frailty including intervention studies. It will also help health care providers better anticipate and serve the needs of their patients.

5.3.1 Frailty Operationalization

This dissertation addressed two ways to operationalize frailty in a clinical population, depending on need. The first method was a brief screen which can be implemented in less than five minutes, and results in a categorization of "frail"/"prefrail"/"robust". It is anticipated that some specialists, such as cardiologists, would prefer a brief, simple, method to a more comprehensive one.[26,196] This screen is a starting point for comparing with the CHS frailty criteria and other methods to see which brief measurement is preferred (from an ease of administration and feasibility perspective), and which is more strongly associated with poor outcomes in older persons with

CAD. The next step would be to validate it in another group of patients. It is plausible that the inclusion of social and cognitive criteria to the primarily physical conceptualization of frailty (reflected by the CHS measure) will improve the strength of the relevant associations and the ability to discern those at risk of a decline in health. Because the screen does not include disabilities and comorbidities, it allows one to view frailty as an entity that is separate but may overlap with disability and comorbidity.[35,38] This type of formulation can help establish the sequence of events between frailty, comorbidity and disability. Because it is separate, an incidence rate for frailty among those have no prior disabilities or comorbidities can be compared to an incidence rate for those are already disabled or with disease.

The second way to operationalize frailty used in this research, the frailty index (FI), is a more well-known comprehensive approach that incorporates the type of data collected from a standard geriatric assessment form, incorporating also comorbidities and disabilities. It is useful for those with easy access to a battery of information which is collected as a part of a standard process. Much of the frailty components can be derived from administrative data, supplemented with a few additional performance tests and or questionnaires if desired, and can be automated so that a frailty score is calculated after a given follow-up visit. That the FI score may be treated as a continuous variable offers interesting possibilities. Because it may be divided into any number of groupings, it may provide a finer granularity than the CHS criteria or the frailty screen which have at most three categories. There may be a clinically important change in score, which would allow a health care provider to more easily interpret FI scores and changes in FI score.[197]

In this project, both frailty measurement types were easily implemented. Both provide a baseline from which future research may address more questions, including an identification of the circumstances in which the two frailty measurement approaches are most accurate and feasible,

and a comparison of how well each method captures risk. If they work equally well, then health care providers would be able to choose the approach which is more appropriate given the time, location, and the ease of data collection for the measurement of frailty.

5.3.2 Prognostic Importance of Individual Criteria

This thesis suggested that as a component of a frailty assessment, "poor balance" may be less prone to measurement error than "slow gait" for hospitalized patients. This is important because in one study of patients with CAD,[41] "slow gait" was found to be a stronger predictor of 6-month mortality than the entire CHS frailty measure, and since then, gait speed has been promoted as being the simplest way to measure frailty.[29,41,42,49,198] However, the "balance" finding would need to be replicated as other studies have corroborated evidence that the gait test is the single most useful frailty criteria in clinical populations.[42,199]

This thesis also demonstrated that social, emotional, and cognitive measurements are associated with decline independently from physical performance in patients with CAD, and increase the discrimination of frailty assessments. Follow-up care after a coronary intervention has traditionally focused on physical rehabilitation programs and physical risk factor management.[3] In 2005 and 2008, an American Heart Association scientific statement on the core components of cardiac rehabilitation recommended specific psychosocial evaluations and interventions as core components of a rehabilitation program,[200,201] acknowledging a wider array of potential risks to health and to HRQL.[12,35,38,201] Cognitive evaluation and intervention were not included as a "core component", and the incorporation of psychosocial support into cardiac rehab programs has been slow.[202] However, a large proportion of seniors are not even participating in cardiac rehabilitation programs.[203] Low participation rates have been partially attributed to psychosocial and cognitive impairments, [204,205] so it is likely that frailer patients are not getting access to the

follow-up they need because elements of frailty have become impediments to participation. Health providers who are interested in follow-up care after a coronary intervention should be aware that social, emotional, and cognitive deficits, along with physical deficits, can combine to impede follow-up care which results in lower resiliency.

5.3.3 The Relation between Depressive Symptoms and Cognition

This dissertation also found evidence that a dynamic measure of depression is more closely associated with cognitive decline than a single measure at baseline. More frequent measurement of frailty criteria such as depression throughout the recovery period after a coronary intervention may help anticipate decline in cognition and other areas of health. Health care providers may note that cognitive decline, in association with depression as well as with CAD, will be more apparent in the area of executive function than in other areas such as memory or verbal fluency as has been noticed elsewhere.[158,206,207] This is important because executive dysfunction can more reliably predict loss of autonomy than impairments from other cognitive domains such as memory or verbal fluency, and may occur even when these other domains are not impaired.[129,208] Early detection of executive dysfunction is important for those wishing to remain independent as long as possible. [208] Those with *APOE* ε4 allele and depression may have a larger loss of cognition than those without the allele.[88,90,91] Health providers who screen regularly for depression may be better able to anticipate a subsequent decline in cognition.

This study established temporality by associating depression trajectory in the first 12 months with cognitive decline in the subsequent 18 months. However, there is no proof that this cognitive path was not already established in the first 12 months as well. It is possible that the two domains are inter-related with one manifesting itself before the other, but each promoting the other, and the trajectories taking different shapes at different times. This research did provide

evidence that repeated measurements of depressive symptoms indicate a greater likelihood of future cognitive decline, even if direct causation is not clear.

5.3.4 Frailty Trajectories after Coronary Intervention

Overall health care providers can expect that cardiovascular patients will have increased resilience after a coronary intervention which will erode over time. However, this is not necessarily the case for those aged 75 years and older. Frailty itself is not a disease, but rather a state of vulnerability. They may assist health care providers in anticipating resiliency to health setbacks during rehabilitation, follow up care, and surveillance.

The documentation of average frailty trajectories after a coronary intervention provides a useful baseline for future intervention studies aimed at changing the course of frailty, or providing additional protection to those identified as vulnerable to health insults. A successful intervention may mean a reduction in the rate of increase in frailty, if the focus is reducing frailty. If the focus is reducing poor outcomes, it is important to know how fast frailty is likely to increase over time after a coronary intervention. A baseline measurement may not be as informative as knowing the rate of increase when considering risk of poor outcomes.

5.4 Directions for Future Research

5.4.1 Long-Term Patterns of Frailty

A prospective cohort study with longer follow-up may answer many questions that remain unanswered after this research. People under 75 years old may be impacted by frailty during a short term, but outcomes such as hospitalization, length of hospitalization, disability, institutionalization and death will be observed more frequently over 5 or 10 years than over 30 months.

Determining the patterns of change in frailty would also be of interest. Change in frailty over 5 or 10 years may be gradual or marked by particular events or disease incidence. A larger sample assessed over a longer period could provide evidence as to co-morbidities or disabilities to which frail patients with CAD might be particularly susceptible compared to more robust patients. Further, it may be possible to gain additional understanding about the incidence of frailty when starting with an initially younger cohort.

5.4.2 Frailty Criteria and their Interactions

More model-building work with individual criteria would reveal whether and how certain combinations of frailty criteria add to or interact within the frailty model to increase the model's ability to discriminate people at risk for poor outcomes. There may be criteria that predict risk independently and more reliably than others within a given multivariable frailty model. A model which includes certain interactions may be better at discriminating people at risk than an additive model. For example, the above-mentioned ESSI tool has seven areas of social support. The whole tool may be important to include in a frailty model, or some criteria may be more important than others. If social support interacts with cognition or depression, a frailty model that reflects this may increase the frailty model's discrimination of risk compared to a simpler model.

5.4.3 Investigation of the Frailty Index

Because it is treated as a continuous measure, the Frailty Index (FI) score provides finer granularity in frailty levels compared to other approaches which merely employ a two or three categories, such as "robust", "prefrail", "frail". However, the appearance of greater precision resulting from this granularity may be misleading. Increments corresponding to sums of deficits may not indicate clinically or statistically important differences in risk. Very recently, publications have begun to establish clinically meaningful differences in FI scores. For example,

Hubbard, et al., estimated that a 0.1 difference in FI score was associated with twice the risk of in-patient mortality in subjects aged over seventy (not necessarily having CAD) who were admitted to hospital.[197] More can be done to estimate the risks associated with FI score differences and to identify the FI change scores over time which are clinically important, particularly in a population with CAD. Many associations can be examined, for example, a clinically significant change in risk of 5 or 10-year mortality, in 2-3 year hospitalization, in long-term care transfers, in a reduction of ADLs or HRQL.

Another topic for further research is a comparison of FI scores and their associations with poor outcomes when the FI is assembled using variables from different, possibly non-overlapping domains. Although those who use the FI are instructed to compose the index with variables from a wide set of domains,[54] some who have implemented it, such as Myers, et al., [56] used primarily disabilities and comorbidities for deficits, and estimated a low average frailty score at baseline compared with this thesis. Because these variables were the only ones used in the index, only those who were already burdened by disease and disability were identified as frail. This is a more downstream version of frailty, and would not identify as frail anyone with physical, cognitive or psychosocially impairments who had not already succumbed to disease or disability.[35,38]

Rockwood, et al., validated their FI by using randomly selected sets of variables from the same database, and determined that all FI's behaved the same as long as there were at least 40 variables included in the index as potential deficits.[172] However, an investigation should also explore what happens when the selection of variables is not random, but only includes variables from certain domains, for example, variables only available via administrative data. An FI score composed primarily of irreversible comorbidities may have different associated risks and potential interventions than an FI score based on possibly reversible physical, cognitive, and

psychosocial criteria. If a certain mix of domains is necessary, the specifications for that mix needs to be established. It is important to know how changes in the mix affect the results. For example, an FI in which social support provided seven variables may have different characteristics than an FI with no social support variables. Constructing an FI from different, non-overlapping domains may alter the prognostic value of the index, the types of risks associated with frailty, the magnitude of the risk, the modifiability of the frailty, and the people characterized as frail.

5.4.4 Investigations with Larger Samples

Research with a larger sample size would allow more demographic (e.g., sex, age), treatment group (CABG, PCI, MI), and disease (e.g., diabetes, dementia) subgroups to be examined and more patterns to be identified. Although the 3C sample was large for the amount of data collected per patient per visit, the size was not sufficient for extensive subgroup analysis. For example, only 27% of the sample (100 patients) were women. A larger sample would allow better identification of patients who would need additional monitoring, support, and possibly intervention to improve resiliency. It would also help determine whether the trends found in this research are actual and not due to random chance.

Once it is determined that frailty differs between groups, it is necessary to continue the line of questioning to determine if a higher level of frailty is clinically meaningful, and what the association is between that higher level and outcomes such as HRQL decline, increased hospital admissions, and mortality. This is a particular interest when looking at sex differences. In the third paper, women tended to have a larger average FI score than men, a difference that was small and not statistically significant at the 0.05 level, but that held steady throughout the duration of the study. A larger study could tell us if this difference is real and if this frailty

difference accounts for the worse cardiovascular outcomes in women that have been documented over the years.[179] Some have suggested,[55] however, that women are less vulnerable to negative outcomes than men at similar levels of frailty. Given the importance of sex differences as a topic in cardiovascular outcomes, this question should be pursued.

5.4.5 Primary, Secondary, and Tertiary Prevention

Finally, future research needs to focus on the possible efficacy of interventions on outcomes.[17,26,181,182,196] An ideal goal is primary prevention, i.e. helping patients avoid becoming frail. To begin this line of research there must be a clear definition of frailty, and of when incidence takes place. As frailty develops on a gradient and does not have a universally accepted standard definition,[35,38] incidence may be difficult to pinpoint. It may be brought about by a traumatic episode or life event, and/or develop gradually. Frailty prevention requires an understanding of frailty as a condition beyond a collection of disabilities and comorbidities, although most people who are frail already have chronic conditions.[35] Research using younger subjects with few comorbidities and disabilities would bring the focus more upstream, and perhaps shed some light on the component causes of frailty which would be a start to researching primary prevention of frailty.

Secondary prevention research would involve ways to reduce frailty and increase resiliency, or ways to change the trajectory of frailty from increasing to stable. Cardiac rehabilitation programs already provide opportunities for physical rehabilitation and psychosocial support, although cognition is not considered a core component.[200,201] However, referral and participation rates in cardiac rehabilitation programs among those aged 65 and over are quite low.[203] Although the referral, participation, and completion rates for patients categorized as “frail” is unknown, research has found that those who do not take up cardiac rehabilitation are older, and more likely

to have health issues and psychosocial impairments, than those that do participate.[204,205] Interventions to increase uptake are being investigated with varying success.[209] However, interventions can be improved by directly addressing the particular impediments which are preventing participation, (depression, social support, dementia), to have a greater impact on improving program uptake. [209] Once a program is underway, an investigation will need to determine if frailty can be stabilized or reduced, and if this change leads to significant long-term improvements in activities of daily living and HRQL, hospitalizations, institutionalization, and/or deaths, compared to a persons for whom frailty change is unimpeded.

Besides secondary intervention to reduce frailty, tertiary prevention can also be explored. Research can determine whether a particular intervention can support a known frail patient in surviving health threats. For example, if CABG patients aged 75 and older tend to become more frail after surgery, a study can investigate whether additional monitoring or increased hospital support meaningfully prevents or lessens the severity of incidents from which these patients might be less able to recover.

Finally, a cost-benefit analysis can help determine whether the cost of interventions, primary, secondary, or tertiary, save the health insurer money by preventing avoidable hospitalizations, or admissions to long-term care. Even if it does not result in direct savings the quality-adjusted life years may be relatively affordable and worthwhile. In the end, if the identification and treatment of frailty should prove to effectively prevent health decline and/or be a cost-effective form of preventative health, then these tasks could be incorporated into the health system and become standard clinical practice.

5.4.6 Knowledge Translation

The end goal for frailty research will be to arrive at a set of frailty tools which are practical to use in various settings, and which provide accurate assessments of risk of functional and HRQL decline, hospitalization, and institutionalization. Interventions studies will determine what actions may be taken to prevent, improve (reduce) frailty, or prevent further harm. Once this knowledge is gained, it will be essential to implement a knowledge translation strategy in order to carry over the benefits to the patients.[210,211] The most important tools and processes must be selected, and adapted to facilitate their adoption by health care providers, patients, and administrators. Frailty assessment and intervention use will need to be assessed, tailored, and monitored. Outcomes should continue to be evaluated to determine the impact of the knowledge translation, and strategies should be devised for sustained use of the frailty assessments and interventions introduced.[210,211]

5.5 Conclusion

The work conducted over the course of this dissertation has addressed several gaps in knowledge concerning the follow-up to patients undergoing a coronary intervention: the utility of "poor balance" and "poor Trails B performance" as particular frailty criteria for patients with CAD, the development a brief frailty screen developed specifically for patients with CAD incorporating cognitive and psychosocial elements, the utility of dynamic versus static measurement of depressive symptoms, the identification of persistent and new-onset depressive symptoms post coronary intervention to anticipate subsequent cognitive decline, confirmation that executive function is a key cognitive domain in patients with CAD, the identification of patterns of frailty following a coronary intervention: a U-shaped pattern overall, a steady increase for CABG and MT patients aged 75 and over, a sustained reduction for CABG and PCI patients under 75, and

stable frailty in MT patients under 75. These findings have important implications for patient care as well as for continued frailty research looking at interventions and outcomes in cardiovascular patients. It is hoped that this research will contribute toward the goal of ensuring that the growing number of people with CAD will be able to live long, healthy, satisfactory lives.

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Appendix A – Contributions of Authors

The following authors were the investigators who assisted in the conceptualization, design and implementation of the original Calgary Cardiac and Cognition (3C) study, which included the process of obtaining funding for the study: Dr. Maxwell (primary investigator), Dr. Hogan, Dr. Ghali, Dr. Faris, Dr. Anderson, Ms. Galbraith, Dr. Knudtson, Dr. Patten, Dr. Maitland, Dr. Demchuk, Dr. Parboosingh. Without their overall contributions to the 3C study, the investigations described below could not have taken place. In addition to the above contribution, their specific contributions to the individual publications are listed below:

Freiheit EA, Hogan DB, Eliasziw M, Meekes MF, Ghali WA, Partlo LA, and Maxwell CJ. 2010. "Development of a frailty index for patients with coronary artery disease." J Am Geriatr Soc 58(8): 1526-1531.

Ms. Freiheit contributed to the design of the study. She prepared the data for analysis, conducted the statistical analysis, interpreted the results, and prepared the manuscript. Dr. Maxwell contributed to the study concept, data preparation, statistical analysis, interpretation of the results, preparation of the manuscript, and overall supervision. Dr. Hogan contributed to the study concept, data preparation, interpretation of the results and critical review of the manuscript. Dr. Partlo contributed to preparation of the data, interpretation of the results, and critical review of the manuscript. Dr. Ghali contributed to the design of the study and provided critical review of the manuscript. Dr. Eliasziw contributed to the statistical analysis, interpretation of the results, and critical review of the manuscript. Ms. Meekes assisted with data acquisition and management, and critical review of the manuscript.

Freiheit EA., Hogan DB, Eliasziw M, Patten SB, Demchuk AM, Faris P, Anderson T, Galbraith D, Parboosingh JS, Ghali WA, Knudtson M, and Maxwell CJ. 2012. "A dynamic view of depressive symptoms and neurocognitive change among patients with coronary artery disease." Arch Gen Psychiatry 69(3): 244-255.

Ms Freiheit contributed to the design of the study. She prepared the data for analysis, conducted the statistical analysis, interpreted the results, and prepared the manuscript. Dr. Maxwell contributed to the study concept and design, assisted with data preparation, interpretation of the results, preparation of the manuscript, and overall supervision. Dr. Hogan contributed to the study design, interpretation of the results, and critical review of the manuscript. Dr. Eliasziw contributed to the statistical analysis and interpretation of the results. Dr. Patten contributed to the interpretation of the results and critical review of the manuscript. Dr. Demchuk assisted with review of the data and provided critical review of the manuscript. Dr. Parboosingh provided analysis of genetics data and critical review of the manuscript. Dr. Faris, Dr. Anderson, Ms. Galbraith, Dr. Ghali, and Dr. Knudtson provided critical review of the manuscript.

Freiheit EA, Hogan DB, Patten SB, Wunsch H, Anderson T, Ghali WA, Knudtson M, and Maxwell CJ. 2015. "Frailty trajectories after coronary interventions in older patients with coronary artery disease." Submitted to Circulation: Cardiovascular Quality and Outcomes, July 28, 2015.

Ms. Freiheit conceptualized the study, prepared the data for analysis, conducted the statistical analysis and interpretation, and prepared the manuscript. Dr. Maxwell contributed to the study design, analysis and interpretation, critical review of the manuscript, and overall supervision. Dr. Hogan made significant contributions to the study design, data interpretation, and critical review

of the manuscript. Dr. Patten contributed to the study design, interpretation of the data, critical review of the manuscript, and overall supervision. Dr. Wunsch made important contributions to data interpretation and provided critical review of the manuscript. Dr. Anderson, Dr. Ghali, and Dr. Knudtson provided critical review of the manuscript.

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