A multicomponent de-frailing intervention for hospitalized cardiac patients

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M.Sc. Thesis

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ENGLISH ABSTRACT

Background: The aging population presents increasing challenges for healthcare professionals to treat patients in the context of both health and function. Frailty is a reversible geriatric syndrome, which refers to the body's inability to maintain homeostasis in the face of stressors and increases risk for the development of adverse health outcomes or death. Patients with cardiovascular disease (CVD), one of the top causes of death worldwide, are disproportionately impacted by frailty. Hospitalization itself is an important stressor that may lead to the exacerbation or development of frailty due to factors such as bedrest, undernutrition, cognitive stress, and frequent tests/procedures. The purpose of this thesis is to review the literature to understand pathophysiological connections between frailty and CVD and to assess the existing interventions for de-frailing hospitalized older adults with CVD, and to present the results of a randomized clinical trial assessing a novel technique to treat frailty in CVD inpatients.

Methods: A literature review was performed on the pathophysiological connections between frailty and CVD, as well as to review existing hospital interventions to treat frailty in CVD patients. Subsequently, a randomized clinical trial (TARGET-EFT) was conducted in the acute cardiology ward at the Jewish General Hospital (Montreal, Canada) to test the effect of a targeted multicomponent de-frailing intervention in hospitalized older adults with CVD. The intervention consisted of physical exercise, cognitive stimulation, protein supplementation and anemia correction. The control group received usual clinical care. Outcomes of interest were physical frailty and functional status at discharge from the hospital and 30 days later, measured using the Short Physical Performance Battery (SPPB) and the SARC-F sarcopenia/strength questionnaire.

Results: TARGET-EFT was the first trial to study and successfully de-frail older adults hospitalized with CVD. The analysis consisted of n=135 patients (n=66 in the intervention group and n=69 in the control group), with a mean age of 79.3 ± 7.7 years and 54% females, who survived and completed the frailty assessments. The average post-randomization length of stay of patients was 11.0 ± 11.7 days, and the most common reasons for admission were evenly distributed between ischemic heart disease and heart failure, followed by arrhythmia and valvular heart disease. Patients in the intervention group showed a significant 1.52-point improvement in the SPPB at discharge and maintained these benefits in a short-term follow-up 30 days later, as evidenced by a significant 0.74-point improvement in the SARC-F questionnaire. There were no intervention-related adverse events. Subgroup analyses demonstrated that patients with low left ventricular ejection fraction had significantly attenuated benefits, and patients who underwent invasive cardiac procedures derived significantly greater benefits from the intervention.

Conclusions: Our multi-component de-frailing intervention with physical, cognitive, nutritional and anemia components was safe and feasible for hospitalized CVD patients. Furthermore, the intervention led to clinically meaningful improvements in frailty and physical function. The integration of this intervention into usual clinical care is expected to lead to subsequent improvements in the post-hospitalization quality of life of cardiac patients.

FRENCH ABSTRACT

***Contexte*:** Le vieillissement de la population pose des défis croissants aux professionnels de la santé qui doivent traiter les patients dans le contexte de la santé et de la fonction. La fragilité est un syndrome gériatrique réversible qui fait référence à l'incapacité de l'organisme à maintenir l'homéostasie face aux facteurs de stress et qui augmente le risque de développement d'effets indésirables sur la santé et de décès. Les patients atteints de maladies cardiovasculaires (MCV), l'une des principales causes de décès dans le monde, sont touchés de manière disproportionnée par la fragilité. L'hospitalisation en elle-même est un facteur de stress important qui peut conduire à l'exacerbation ou au développement de la fragilité en raison de facteurs tels que l'alitement, la dénutrition, le stress cognitif et les tests/procédures fréquents. Le premier objectif de cette mémoire était de mener une revue de la littérature sur les interventions pour réduire la fragilité au sein des personnes âgées qui sont hospitalisées avec des MCV. Le deuxième objective était de présenter les résultats de notre essai clinique aléatoire évaluant une nouvelle intervention à composants multiples pour traiter la fragilité chez les patients hospitalisés pour les MCV.

***Méthodes*:** Une revue de la littérature a été réalisée sur les liens physiopathologiques entre la fragilité et les MCV, ainsi que sur les interventions hospitalières utilisées présentement pour traiter la fragilité chez les patients atteints de MCV. Par la suite, un essai clinique aléatoire (TARGET-EFT) a été mené dans l'unité de cardiologie à l'Hôpital Général Juif (Montréal, Canada) pour évaluer l'effet de notre intervention contre la fragilité chez les personnes âgées hospitalisées souffrant de MCV. L'intervention consistait d'exercice physique, de stimulation cognitive, de supplémentation de protéines et de correction de l'anémie. Le groupe témoin a reçu les soins cliniques habituels. Le résultat d'intérêt était la fragilité physique et l'état fonctionnel à

la sortie de l'hôpital et 30 jours plus tard, mesurés utilisant le Short Physical Performance Battery (SPPB) et un questionnaire sur la sarcopénie et la force, SARC-F.

***Résultats*:** TARGET-EFT a été le premier essai à étudier et à réussir à réduire la fragilité chez les personnes âgées hospitalisées pour des MCV avec une intervention à composants multiples. L'analyse consistait de n=135 patients (n=66 dans le groupe d'intervention et n=69 dans le groupe témoin), avec un âge moyen de 79.3 ± 7.7 ans et 54% de femmes, qui ont survécu et ont effectué les évaluations de fragilité. La durée moyenne de séjour des patients après la randomisation était de 11.0 ± 11.7 jours. Les raisons d'admission les plus fréquents étaient égales entre la cardiopathie ischémique et l'insuffisance cardiaque, suivi par l'arythmie et la cardiopathie valvulaire. Les patients du groupe d'intervention ont montré une amélioration significative de 1.52 points dans le SPPB à la sortie de l'hôpital et ont maintenu ces avantages lors d'un suivi à court terme 30 jours plus tard, démontré par l'amélioration significative de 0.74 points dans le questionnaire SARC-F. Aucun événement indésirable lié à l'intervention n'a été constaté. Les analyses de sous-groupes ont montré que les patients présentant une faible fraction d'éjection ventriculaire gauche présentaient des bénéfices significativement atténués, et que les patients ayant subi des procédures cardiaques invasives ont davantage profité de l'intervention.

***Conclusions*:** Notre intervention à plusieurs composantes s'est avérée sans dangers et réalisable pour les patients hospitalisés atteints de MCV. De plus, l'intervention a entraîné des améliorations cliniquement significatives de la fragilité et de la fonction physique. L'intégration de cette intervention dans les soins cliniques habituels pourrait conduire à des améliorations dans la qualité de vie post-hospitalisation des patients de MCV.

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CONTRIBUTION OF AUTHORS

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MSc thesis candidate. Performed the literature review and wrote the literature review manuscript. Co-led the TARGET-EFT randomized clinical trial: provided insight on the Hospital Elder Life Program during trial design, performed patient recruitment, conducted frailty assessments, administered exercise and cognitive interventions, performed discharge and follow-up assessments, and completed chart reviews. Assisted in statistical analysis of trial results and wrote original manuscript on the results of the TARGET-EFT trial. Wrote five abstracts presented at both international and national conferences. Presented initial research findings to Master's Thesis Committee. Wrote entire thesis document and incorporated revisions.

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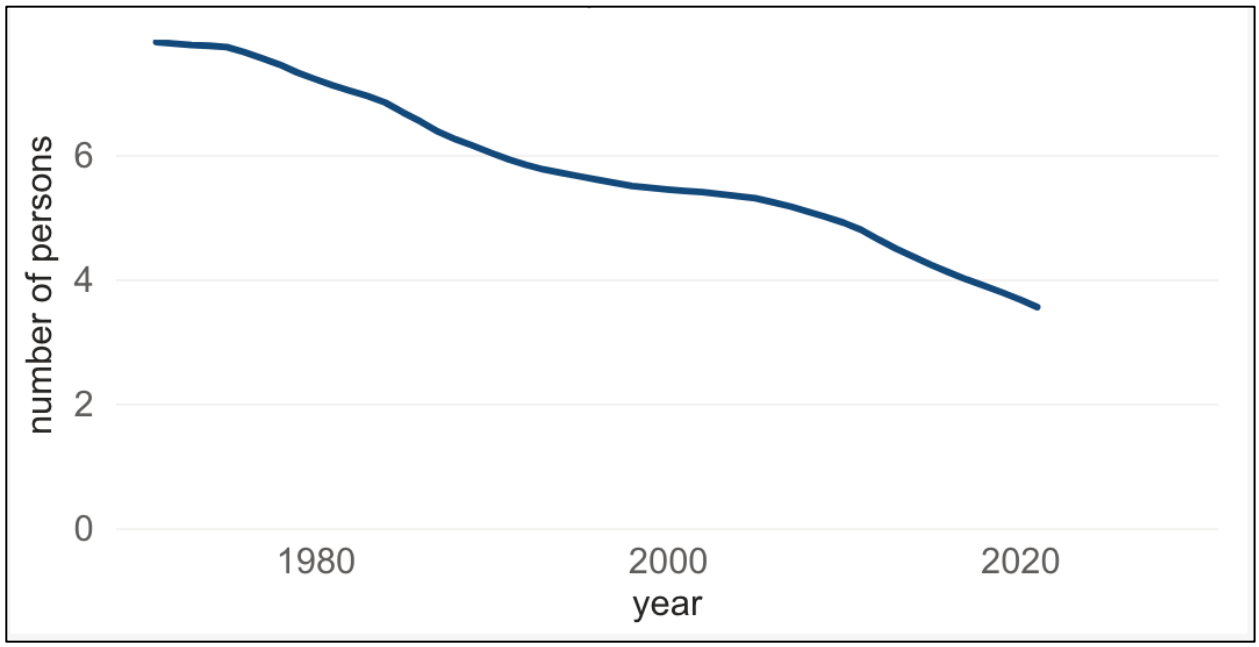
LIST OF ABBREVIATIONS

BMI	Body Mass Index
CFS	Clinical Frailty Scale
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
ECM	Extracellular Matrix
EFT	Essential Frailty Toolset
HELP	Hospital Elder Life Program
IDA	Iron Deficiency Anemia
IL	Interleukin
LVEF	Left Ventricular Ejection Fraction
MMSE	Mini Mental Status Examination
NYHA	New York Heart Association class
PONS	Preoperative Nutrition Score
RCT	Randomized Clinical Trial
SPPB	Short Physical Performance Battery
TNF-α	Tumour Necrosis Factor Alpha

CHAPTER 1: THESIS INTRODUCTION

Aging is an inevitable part of life, and societies across the world are progressively aging [1]. People who are aged 65 years and older are projected to double by the year 2030, representing a rapidly expanding population subgroup [2, 3]. Indeed, even by mid-2021, Canadians who were aged ≥65 years represented a greater proportion of the population than those who were 0-14 years old (18.5% vs 15.7%, respectively) [4, 5]. **Figure 1** highlights the declining ratio of 15-64 year old Canadians compared to ≥65 year old Canadians over the turn of the century, demonstrating the trend in increasing older adult Canadians [6].

Figure 1: Number of persons aged 15-64 per person aged 65 and older in Canada



Adapted from [6].

With increasing age comes an increasing risk for frailty, as the body's organs lose their peak functioning capacity [7]. Frailty is a reversible condition defined as a vulnerability to stressors leading to adverse health outcomes (e.g., falls, hospitalization, mortality etc.), which is

prevalent in 10% of community-dwelling older adults [8, 9]. Indeed, a study assessing frailty and mortality in ≥65 year old Canadians (n=29,302) found that those who were frail were more than three times as likely to die compared to those who were robust (25% vs 7%, respectively) [10]. Moreover, this study found that frail patients disproportionately died from CVD or respiratory diseases compared to those who were robust, highlighting a link between frailty and certain disease states [10].

Assessing frailty allows health professionals to distinguish between people of similar chronological age who are following differing trajectories of aging and thus have differing functional statuses and health states [11]. This allows healthcare professionals to make more patient-centered decisions when treating older adults. Moreover, assessment of frailty subsequently allows for its treatment, which typically includes either physical exercise, nutritional supplementation, cognitive intervention or pharmacological interventions [12]. We thus define "de-frailing" interventions as interventions that objectively lead to clinically and functionally significant improvements in frailty.

Cardiovascular disease (CVD) represents the leading cause of death worldwide, and the second leading cause of death in Canada [13, 14]. Frailty is disproportionately prevalent in CVD patients, representing up to 60% of patients [15]. Treating frailty concomitantly to CVD is thus an increasingly important challenge for healthcare professionals and public health officials in order improve or preserve patients' health, function, and quality of life. Results from a meta-analysis and exploratory regression analysis including over 31,000 patients demonstrated that both frailty and pre-frailty (a transition state between robustness and frailty) were associated with increased odds of CVD [16]. This study also assessed the longitudinal relationship between frailty and CVD and found that dedicated cohort studies demonstrated an increased risk of

developing CVD in persons with frailty or pre-frailty over a period of 4.4. years [16]. Interestingly, hospitalization itself is a stressor that CVD patients often face, which plays a role in the development and exacerbation of frailty [17]. Stressors in the hospital setting include frequent blood tests/procedures, loss of sleep, and undernutrition, amongst others [17, 18]. Mitigating hospital-setting-associated stressors can potentially prevent the loss of function patients often feel post-discharge.

With the increasingly aging population of the world, it is essential that more be done for the amelioration of health in older adults with CVD. Furthermore, given that frailty is a preventable and treatable condition, there is potential to treat people with frailty using targeted interventions to improve their functional status, quality of life and overall health status. The purpose of this thesis is to review the literature to understand pathophysiological connections between frailty and CVD and to assess the existing de-frailing interventions in hospitalized older adults with CVD, and to present the results of a randomized clinical trial (RCT) assessing a novel technique to treat frailty in CVD inpatients. **Chapter 2** will present the background and supporting literature on the topic of frailty/CVD and interventions to improve frailty in CVD patients as a literature review manuscript. **Chapter 4** will present the results our therapeutic RCT as an original research paper manuscript. Finally, **Chapter 5** will discuss our findings and highlight the strategies for implementing our de-frailing interventions in the hospital setting.

CHAPTER 2: LITERATURE REVIEW – MANUSCRIPT TO BE SUBMITTED

The following literature review manuscript, titled "Treatment of frailty in hospitalized cardiovascular disease patients – a literature review," is ready for submission.

Treatment of frailty in hospitalized cardiovascular disease patients – a literature review

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ABSTRACT

Background: The increasingly aging population of the world necessitates the treatment of both health and function in hospitalized patients. Frailty is multi-system geriatric syndrome defined by decreased homeostatic reserves leading to vulnerability to stressors that increases risk for negative health outcomes and death. The prevalence of frailty is approximately 10% in community-dwelling older adults, however in cardiovascular disease (CVD) patients, the prevalence has been estimated to be up to 60%, making this population disproportionately impacted by frailty. Though the pathogenesis of frailty includes multi-system dysregulation, CVD and frailty share a common basis in chronic low-grade inflammation, Vitamin D deficiency and increased serum cortisol. While the treatment of frailty in CVD patients has been evaluated in community-dwelling settings, there is no review on the treatment of frailty in hospitalized CVD patients. This review sought to fill this knowledge gap and identify the evidence on treating frailty concomitantly to CVD in the hospital.

Discussion: We identified six completed randomized clinical trials on the treatment of frailty in hospitalized CVD patients and one in progress using keywords such as "frailty," "intervention," "hospital," "exercise," "nutrition," "cognitive," "pharmacological," and "randomized clinical trial," on the databases of PubMed and Google Scholar. We also reviewed the bibliography of retrieved articles. Two physical interventions demonstrated a positive impact of in-hospital exercise on physical function and quality of life, however more research is required in non-surgical CVD inpatients. The nutritional intervention demonstrated a positive impact of protein supplementation, however the trial included patients admitted with conditions other than CVD. One identified pharmacological intervention demonstrated the efficacy and safety of iron replacement therapy in heart failure patients. Another pharmacological intervention trial that is

still in process is testing the effect of testosterone supplementation on frailty. Finally, a cognitive intervention led to shorter length of stay and less dependence post-hospitalization. Overall, all interventions demonstrated some benefit in frailty status and appeared to be safe, however, there is need for larger trials assessing multicomponent frailty interventions in both surgical and non-surgical CVD patients. The results of the TARGET-EFT trial are expected to shed light on this knowledge gap.

INTRODUCTION

The increasingly aging population of the world necessitates that more be done for the conservation of both health and function of older adults. Frailty is a geriatric syndrome that impacts functional status and should thus be the focus of prevention strategies for conservation of functional status and prevention of adverse health outcomes [1]. Interestingly, frailty is highly prevalent in cardiovascular disease (CVD) patients [2], which represents the number one cause of death worldwide [3]. In this review, we will be exploring the concept of frailty, CVD and their pathophysiological connections. Moreover, given the paucity of research assessing the treatment of frailty for CVD patients in the hospital setting, we will be reviewing randomized clinical trials (RCTs) assessing de-frailing interventions in this population.

FRAILTY

Frailty Definition

Frailty comes from the French word “frêle” and the Latin word “fragilis,” both of which translate to “of little resistance” and “easily broken”, respectively [4]. To date, though multiple definitions of clinical frailty have been presented in research, there is currently a lack of a gold standard definition [5]. Nonetheless, the current consensus defines frailty as an increased physiological vulnerability in response to stressors due to accumulated deficits in multiple interrelated organ systems (i.e., musculoskeletal, immune, endocrine, cardiovascular and more) that can put one at risk of adverse health outcomes (e.g., increased dependency) and/or death [1, 6, 7]. Furthermore, the current consensus characterizes frailty by diminished strength, endurance and reduced physiologic reserve [7]. Therefore, frail individuals have trouble restoring

homeostasis after an endogenous (e.g., heart attack) or exogenous (e.g., fall) stressor event due to decreased physiological reserve [1], and subsequently have increased risk of mortality, hospitalization and incident disability in activities of daily living [8]. Frailty is also described as a geriatric syndrome since both deficit accumulation and decreased physiological reserve are a part of the natural chronological aging process, however, existence of disease can also lead to the development of exacerbation of frailty [1]. Despite being described as a geriatric syndrome, given that chronological and biological age are often dyssynchronous, frailty can provide important patient-centered prognostic information in older adults of the same age with differing biological age statuses (i.e., differing health and functional statuses) [9].

Frailty Domains

The consensus defines that frailty is a multi-dimensional syndrome, primarily including the physical frailty domain, as well as nutritional, cognitive and psychosocial domains [10]. The physical frailty domain is interrelated with sarcopenia (i.e., muscle loss) and is often indistinguishable given that both present as impaired physical function [11]. Nutritional frailty consists of unintentional rapid weight loss (mainly through the loss of lean body mass) that leads to adverse health outcomes [12]. Cognitive frailty has been defined by cognitive vulnerability with at least mild impairment that can lead to vascular dementia (particularly in the presence of comorbid CVD) and other cognitive disorders [13]. The current consensus on cognitive frailty defines it by the dual presence of both physical frailty and cognitive impairment [14]. Psychological frailty is defined by vulnerability and declined mood, coping mechanisms and cognition. Finally, social frailty remains the least researched frailty domain, and is defined as being at risk for losing or having loss the required resources for social aspects of living [15].

Pathophysiology of Frailty

As previously described, frailty stems from multi-system dysregulation in the body. Frailty is said to stem from both genetic and environmental factors that lead to the accumulation of cellular and molecular level damage in various organ systems (i.e., immune, endocrine, musculoskeletal), ultimately leading to a decreased physiological reserve and homeostatic ability [2, 16]. Endocrine dysregulation, particularly through the hypothalamic-pituitary axis, causes the downstream effects of decreased testosterone, insulin resistance, and uncontrolled inflammation and increased cortisol levels due to loss of control over the glucocorticoid system [2, 16, 17]. In addition, other proposed causes of increased inflammation in frailty include lifelong antigenic exposure, angiotensin type-1 receptor activation, obesity/metabolic syndrome, insulin resistance itself, and redox imbalance [4, 18]. Increased inflammation has been assessed by circulating inflammatory markers, some of which include C-reactive protein (CRP), cytokine interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), all of which predict negative health outcomes and functional decline [18]. Increased inflammation plays a central role in muscle loss during frailty – in fact, inflammation exerts a catabolic effect on skeletal muscle, leading to the redistribution of amino acids from the muscle into other organ systems, and causing muscle mass loss [4, 19]. The combination of increased inflammation, insulin resistance, increased cortisol and low testosterone leads to a neurohormonal environment that further favours the catabolism of skeletal muscle, also causing decreased muscle mass/strength [2]. Another important player in the development of frailty is vitamin D [17]. Indeed, vitamin D deficiency plays an important role in the development of frailty through its action on genes that regulate skeletal muscle atrophy and protein synthesis [20, 21]. Thus, a combination of low testosterone, insulin

resistance, increased cortisol, increased inflammation and vitamin D deficiency leads to frailty, which is subsequently modulated by factors such as exercise, nutrition, polypharmacy, and presence of other diseases.

Operationalization of Frailty

Currently, there exist two main schools of thought on the operationalization of frailty: the frailty phenotype approach and the deficit accumulation approach [22]. The frailty phenotype defines frailty as a syndrome based on the presence of various signs/symptoms that indicate physiological vulnerability: weight loss, weakness, fatigue, slowness in walking, and low levels of physical activity [22]. Fried et al.'s frailty phenotype describes frail individuals as having three of the five aforementioned criteria [23]. In contrast, the deficit accumulation model defines frailty as a state of increased vulnerability that can be measured by the quantity of health problems that one has. Rockwood et al.'s Frailty Index is the main tool that assesses frailty based on the deficit accumulation model [24]. This tool quantifies the number of deficits (symptoms, signs, laboratory abnormalities, diseases, and disabilities) a person has over the total possible deficits possible in the model. Other than these two main schools of thought on the operationalization of frailty, many other assessment tools also exist that focus on either one domain of frailty or multiple depending on the population in which it is being used. It should be noted that given the multi-dimensional nature of frailty, the ideal frailty assessment tool can vary based on the population being studied and the setting of the assessment (i.e., hospital vs community).

Prevalence of Frailty

Due to the lack of a gold standard definition of frailty and existence of multiple frailty assessment tools, prevalence of frailty has been measured over a very wide range of estimates depending on the assessment tool used in community-dwelling older adults (4.0-59.1%) [25]. A meta-analysis done in 2012 assessed the prevalence of frailty in n=61,500 community-dwelling older adults aged ≥65 years from across the world [25]. This meta-analysis found that the weighted prevalence of physical frailty was 9.9% (approximately 1 in 10 individuals) and that the weighted prevalence for pre-frailty was 44.2%. In a subgroup analysis with studies including broader frailty definitions (including psychosocial frailty), it was found that the weighted prevalence of frailty was 13.6% and the weighted prevalence of pre-frailty was 33.5%. Prefrailty was defined as a transition stage between robustness and frailty, which also increases risk for adverse outcomes. Prevalence of frailty was also found to be increasing with age and was higher in women than in men (9.6% in women vs 5.2% in men). An increase in prevalence with age is reasonable given that frailty is a geriatric syndrome and chronic inflammation increases with age, and the increased prevalence in women can be explained by the average lower total amount of lean mass in women compared to men [25].

Financial Impact of Frailty

It is important to recognize that frailty also poses a financial burden on the healthcare system. In one study conducted in Spain, where healthcare is also a public service like in Canada, researchers found that frailty assessed by Fried's frailty phenotype was associated with increased healthcare costs (specifically, emergency room visits and hospital admissions, but not specialist consultations) [26]. In fact, the study showed that, for frail individuals, the average

total cost of health resources per year was double that of non-frail individuals. It is evident that frailty poses a serious burden on the lives of older adults and the healthcare system, and treatment of frailty would allow for better resource allocation.

CARDIOVASCULAR DISEASE

Cardiovascular Disease Defined

CVD is an umbrella term used to describe the diseases that affect the heart and its vasculature [27]. Atherosclerotic CVD is the most common subtype and encompasses four main entities [27, 28]. The first, coronary (or ischemic) heart disease, refers to decreased blood supply to the heart due to atherosclerotic plaques in the coronary arteries, and leads to angina, myocardial infarction and heart failure [27]. The second, peripheral vascular disease, is defined by arterial disease (atherosclerosis) in the limbs, and leads to claudication [27]. The third, cerebrovascular disease, consists of stroke and transient ischemic attacks in the head. Finally, the fourth, aortic atherosclerosis, is defined by atherosclerotic plaques in the biggest artery of the body (the aorta), and can lead to thoracic and abdominal aneurysms [27].

Another common type of CVD is valvular heart disease, which includes the calcification of any of the four heart valves (e.g., the aortic, mitral, tricuspid or pulmonary valves) [29]. Valvular heart disease can impact the directionality of blood flow through the heart and can lead to oxygenation issues across the rest of the body, including the heart muscle itself, which can then lead to heart failure. Finally, CVD also includes diseases of infectious and muscular nature, such as rheumatic heart disease (also impacts the valves) and cardiomyopathies (subdivided into dilated, hypertrophic, restrictive, arrhythmogenic or amyloid), respectively [30, 31].

Prevalence of Cardiovascular Disease

CVD is the leading cause of mortality worldwide and the second leading cause of death in Canada [3, 32]. Specifically, CVD led to 27% and 32% of deaths worldwide in men and women, respectively [3]. When looking at the rates in Canada alone, CVD led to 29,367 and 24,337 deaths in men and women respectively in the year of 2020, representing the second leading cause of death for both sexes [33]. Furthermore, in those living with CVD, the burden of CVD impacts their quality of life as well. One observational study done in Canada found that CVD patients live with limited health-related quality of life compared to individuals without CVD or other chronic conditions [34]. Specifically, this study found that 14% of male and 21% of female CVD patients had difficulty walking (an important aspect of frailty), compared to 2.4% of men and 3.3% of women who did not have CVD and to 0.6% of study participants (both male and female) who had no chronic conditions [34]. Not only does CVD burden patients' lives and lead to high mortality rates, but the economic burden of CVD has also been estimated to be roughly $22.2 billion per year when including physician services, hospitalizations, lost wages, and decreased productivity [35]. It is evident that CVD poses a tremendous burden on patients' lives and the healthcare system, and continued interventions (both primary and secondary) are required to alleviate this burden in a feasible manner.

Pathophysiology of Atherosclerotic Cardiovascular Disease

The primary cause of atherosclerotic CVD is the formation of atherosclerosis in the vasculature, which in turn has a basis in chronic low-grade inflammation [36, 37]. Atherosclerosis builds up within the endothelial wall (innermost layer) of the artery, develops into plaques which can cause partial or complete occlusion of the artery, which upon rupture, can

lead to life threatening events (e.g., myocardial infarction) [19]. The pathogenesis of atherosclerosis begins with high serum lipid concentrations and the accumulation of these lipids (i.e., low density lipoprotein cholesterol) within the intima of the arterial wall, particularly at sites of hemodynamic strain [19, 36]. These lipids are subsequently engulfed by macrophages (i.e., the phagocytic cells of the immune system), leading them to evolve into foam cells [19]. Accumulation of foams cells leads to growth of the lesion, which is ultimately covered by smooth muscle cells and a collagen-rich matrix, creating a fibrous cap and a narrowing of the lumen of the artery [19]. Rupturing of the atherosclerotic lesion leads to myocardial infarction and may lead to death if not intervened upon in time [19]. Research has shown that inflammation plays an important role in not only the initiation of atherogenesis, but also a central role in the oxidation of lipoproteins and plaque activation which leads to myocardial infarctions and subsequent death or negative health outcomes [4, 19].

It is important to note the role of the immune system in the development of atherosclerotic CVD. Indeed, many studies have shown increased levels of inflammatory cells to be associated with cardiovascular events, morbidity, and mortality [38]. This includes immune markers such as CRP, caused by release of the cytokine interleukin (IL)-6 from macrophages and T cells [38]. CRP is a marker of chronic low-grade inflammation and predicts cardiac events in those both with and without underlying CVD [38]. CRP has been found to be an important mediator of atherothrombotic disease and can thus shed light on subclinical CVD as well, potentially allowing for the detection of future at-risk populations [38]. In addition, the cytokine IL-6 controls vascular tone by stimulating endothelin-1 (a main vasoconstrictor of the arteries), which in turn stimulates the proliferation of smooth muscle cells and fibroblasts, both of which play important roles in development and persistence of atherosclerotic lesions [38]. While IL-6

and CRP are important markers in the development of CVD, it should be noted that these are just two of the many immune system markers that are involved in the development of CVD, demonstrating an interplay between the immune system and the pathogenesis of CVD.

Both non-modifiable genetic factors and modifiable environmental factors have been identified as risk factors for the development of CVD [39]. While genetic factors remain non-modifiable at this time (age, sex and genetics), environmental factors are important as they represent an important target for prevention strategies [36]. To note, a combination of multiple risk factors can lead to an amplification of risk which is more than just the addition of the individual risk factors [36]. Modifiable risk factors include physical inactivity, poor nutrition (high fat/sugar diet), diabetes, hyperlipidemia, tobacco use and hypertension [36].

Pathophysiology of Valvular Heart Disease

The regular makeup of a heart valve consists of a layer of endothelial cells that surrounds three layers of extracellular matrix (ECM) made of collagens, proteoglycans and elastin and interspaced by valve interstitial cells [40, 41]. Changes to the organization and localization of the ECM or disruptions to the communication between valvular endothelial and interstitial cells leads to valvular heart disease [29]. These pathophysiological disturbances can be due to congenital abnormalities that cause improper gene expression for the development of the heart valves, due to environmental factors that promote atherogenesis, or due to a combination of both [29]. The risk factors for acquired forms of valvular heart disease are the same as those that lead to the development of atherosclerotic CVD: age, sex, tobacco use, poor nutrition, hyperlipidemia, and hypertension, but with the addition of rheumatic heart disease [29]. In acquired valvular heart disease, such as calcific aortic valve stenosis, there is a progressive

hardening of the aortic valve leaflets due to calcification [29]. Inflammation has been found to play an important role in the pathogenesis of the calcification [29]. Indeed, inflammatory factors such as tumour necrosis factor, IL-1β, advanced glycosylation-end products, and oxidized low-density lipoprotein cholesterol all activate biomineralization and osteogenic signaling processes involved in valvular calcification [29, 42].

SECTION IV: COMORBID CARDIOVASCULAR DISEASE AND FRAILTY

Pathophysiological Connections

The underlying pathophysiology of both CVD and frailty share important mechanisms related to increased levels of chronic low-grade inflammation (i.e., as seen through increased levels of CRP and IL-6), vitamin D deficiency, as well as increased serum cortisol levels. Indeed, vitamin D deficiency has been found to be associated with activation of the pro-inflammatory mechanisms that promote atherogenesis and CVD events, whilst also acting on genes that regulate skeletal muscle atrophy and protein synthesis [20, 21]. It is clear that increased levels of inflammation play a dual role on the cardiovascular system and musculoskeletal system to promote both atherosclerosis/CVD and muscle loss, respectively [2]. Similarly, increased cortisol levels act to decrease muscle mass in frailty, but also predispose people to hypertension and dyslipidemia, in addition to other metabolic syndrome risk factors [43].

Prevalence of Frailty in Cardiovascular Disease Patients

Given the shared pathophysiological mechanisms for the development of CVD and frailty, it is not surprising that CVD patients are disproportionately impacted by frailty. Indeed,

the prevalence of frailty is much higher in CVD patients compared to community-dwelling older adults: while only ~10% of community-dwelling older adults have been estimated to be frail, up to 60% of CVD patients are frail, with the most increased prevalence found in the heart failure subset of patients [2].

Research has shown that CVD and frailty share a strong bi-directional association, such that frailty increases risk for development of CVD and CVD increases risk for the exacerbation of frailty [44, 45]. Results of the National Health & Aging Trends Study, that included n=4656 older adults, showed that frailty predicted the development of cardiovascular outcomes over a 6-year follow-up period, including major adverse cardiovascular events, death, acute myocardial infarction, stroke, peripheral vascular disease, or any coronary artery disease [46]. Similarly, frail CVD patients are found to suffer from more adverse health outcomes compared to non-frail CVD patients. Indeed, the hallmark FRAILTY-AVR study showed that in n=1020 patients undergoing aortic valve replacement, frail patients had increased risk of mid-term mortality, functional decline, and disability [47]. It is evident that, due to the shared mechanistic links between frailty and CVD, patients with both conditions are a high-risk subgroup who could benefit from intervention and treatment.

Frailty Assessment in Cardiovascular Disease Patients

Treatment of frailty in CVD patients must be preceded by identification of frailty via assessment. There exist a multitude of assessment tools developed for the detection of frailty in CVD patients. Ijaz et al. recently reviewed clinical frailty assessment tools for CVD patients in a state-of-the-art review and found that the most commonly cited frailty definition in the research literature was the Fried's physical frailty phenotype [45]. These researchers also commented on

tools that only assess specific domains from Fried's phenotype alone or in conjunction with other functional decline measures (e.g., the Green score which was developed for the assessment of aortic stenosis patients) [45, 48]. Furthermore, this review highlights that cognitive frailty is often assessed with a Fried+ scale, which makes use of the Fried's phenotype along a cognitive function test (i.e., Mini Mental Status Examination) and a mood assessment (i.e., short-form Geriatric Depression Scale) [45]. Ijaz et al. also discuss subjective scales such as the CSHA Clinical Frailty Scale (CFS) which relies on a physician's judgement of a patient's functional status, and the SARC-F questionnaire which allows patients to self-report on their strength levels [45]. Finally, this review concluded that the Essential Frailty Toolset (EFT) developed by Afilalo et al. is an ideal assessment tool for CVD patients since it doesn't require specialist training to administer, and is an objective and accurate tool that is not time-consuming to administer (i.e., takes <5 minutes) [47]. Indeed, the EFT was validated to predict death and functional decline in older cardiac surgery and transcatheter aortic valve replacement patients [47, 49]. Moreover, the EFT's strength is highlighted by the fact that it is better at predicting death and worsening disability compared to six other well-known frailty assessments: Fried's frailty phenotype, the Fried+ scale, the CFS, the Short Physical Performance Battery (SPPB), the Bern scale and the Columbia scale [47]. Moreover, the EFT is a multi-component frailty tool which assesses four frailty domains (**Figure 1**) allowing for a multi-domain screening of frailty.

Figure 1: Essential Frailty Toolset

Physical	5 timed chair rises • <15 seconds (1 point) • ≥15 seconds (0 point)
Cognitive	Cognitive impairment • Cognitive impairment (1 point) • No cognitive impairment (0 point)
Nutritional	Serum albumin • <35 g/L (1 point) • ≥35 g/L (0 point)
Pharmacological	Serum hemoglobin • ♂: <130 g/L or ♀: <120 g/L (1 point) • ♂: ≥130 g/L or ♀: ≥120 g/L (0 point)

Treatment Of Frailty

After assessment of a patient's frailty, treatment should be targeted towards the identified vulnerable frailty domains. Existing reviews have assessed physical exercise, nutrition, cognitive or pharmacological interventions to treat frailty [45]. While research has been done on the treatment of frailty in the community setting, it is important to review the literature on treating frailty in the hospital setting alone because hospitalization itself is a risk factor for the development and exacerbation of frailty. Indeed, not only are hospitalized patients dealing with acute CVD which upsets multiple organ systems, but the hospital setting often includes long periods of bedrest, malnutrition due to fasting before procedures and dislike of hospital food, cognitive impairment due to stressful situations, isolation and polypharmacy, delirium, as well as multiple blood tests/procedures [50, 51]. These hospitalization-associated stressors put patients at risk for iatrogenic injury and development/exacerbation of frailty, often seen as loss of function post-discharge [50, 51]. Given that heart attacks and heart failure were amongst the top three reasons for hospitalization in Canada in 2020-2021, in-hospital treatment of frailty for CVD patients is necessary to prevent future re-hospitalizations and negative health outcomes, as well

as the subsequent increased financial burden on the healthcare system [52]. Therefore, we must evaluate the existing randomized clinical trials (RCT) on the in-hospital treatment of frailty amongst older CVD patients.

INTERVENTIONS TO IMPROVE FRAILTY IN HOSPITALIZED CVD PATIENTS

Methodology

To review clinical trials aimed at improving frailty in CVD inpatients, keywords such as "frailty," "intervention," "hospital," "exercise," "nutrition," "cognitive," "pharmacological," and "randomized clinical trial," were used on the databases of PubMed and Google Scholar. The bibliographies of retrieved manuscripts were also reviewed as part of the search strategy. Research trials were excluded if they were not randomized controlled trials that had an in-hospital interventional component.

We identified seven randomized trials aimed at intervening on frailty in hospitalized CVD patients (one of which is still in progress). The trials and their brief descriptions are summarized in **Table 1**.

Table 1: Summary of Frailty Intervention Trials in CVD Inpatients

Author	Frailty Intervention	Population	Outcome(s)
Opasich et al. [53]	Physical: Personalized 1 hour physiotherapy gym sessions	• n = 224 • ≥ 70 years • Male and female post-cardiac surgery patients who are medically stable and cognitively unimpaired	• Intervention group had significantly greater improvements in independence and mobility assessed by via nursing needs, the Balance Performance Oriented Mobility Assessment, the Get-Up-and-Go test, arm curl test, and chair stand test, but not the 6-minute walk distance and EuroQol (quality of life) compared to the control group
Martínez-Velilla et al. [54]	Physical: Bi-daily individualized moderate-intensity resistance, balance, and walking exercises	• n = 370 • ≥ 75 years • Males and females admitted to an acute care unit (including CVD patients)	• Intervention group demonstrated o improved functional capacity (SPPB score) o Improved level of independence (Barthel Index of Independence) o Improved cognitive status (MMSE) o Improved quality of life (Geriatric Depression Scale and EuroQol–5)
Deutz et al. [55] & Matheson et al. [56]	Nutrition: High protein and beta-hydroxy-beta-methylbutyrate containing oral nutrition supplement 2x/day during hospitalization and continued for 90 days post-discharge	• n = 652 • ≥ 65 years • Malnourished males/females hospitalized for COPD exacerbation, congestive heart failure of acute myocardial infarction	• Intervention group had lower 90-day mortality, but not readmission • No between-group differences in length of stay or activities of daily living • Intervention group had improved odds of better nutritional status at 90 days and higher body weight at 30 days • Intervention group had higher improvement in handgrip strength at discharge
Ponikowski et al. [57]	Pharmacological: Intravenous ferric carboxymaltose for up to 4 doses at 24 weeks post-discharge (dosed to the extent of deficiency)	• n = 1108 • ≥ 18 years (mean age: 71 years) • Males/females hospitalized for acute heart failure with concomitant iron deficiency and LVEF <50%	• Intervention group demonstrated o Lower composite score of cardiovascular hospitalizations and deaths o Lower heart failure and lower cardiovascular hospitalizations o Same incident cardiovascular deaths as control group o Fewer days lost due to heart failure hospitalizations and cardiovascular death
Maggio et al. [58]	Pharmacological: 250 mg testosterone enanthate injection 2 days before surgery	• n = 200 • ≥ 70 years • Males with coronary artery disease undergoing elective on pump-CABG	• Trial is still in progress • Outcomes include: o Physical function markers: SPPB, 6MWT, grip strength o Quality of life o Blood samples: markers of inflammation and serum testosterone
Partridge et al. [59]	Cognitive: Pre-operative geriatric assessment and optimization	• n = 176 • ≥ 65 years • Males/females undergoing elective endovascular/open aortic aneurysm repair or lower-limb arterial bypass surgery	• Intervention group demonstrated o Lower hospital length of stay o Lower incidence of delirium, cardiac complications, and bladder/bowel complications o Lower likelihood to get discharged to higher level of dependency

Abbreviations: CVD, Cardiovascular Disease; CABG, Coronary Artery Bypass Grafting; LVEF, Left Ventricular Ejection Fraction; MMSE, Mini Mental Status Examination; SPPB, Short Physical Performance Battery; 6MWT, 6-Minute Walk Test.

Physical Interventions & Discussion

Two in-hospital trials using exercise interventions for treatment of frailty were identified in this review. Opasich et al. assessed the effect of a personalized physiotherapy program on the frailty status of n=224 medically stable and cognitively unimpaired post-cardiac surgery patients (aged ≥70 years) compared to usual physiotherapy (control) [53]. Patients in the intervention group were stratified by frailty status and their functional status was used to implement individualized physiotherapy. These researchers found that, though both groups showed significantly improved independence and mobility (assessed via nursing needs, the Balance Performance Oriented Mobility Assessment, the Get-Up-and-Go test, arm curl test, chair stand test, 6-minute walk test and the EuroQol), the intervention group had significantly greater increases in all measures except the 6-minute walk distance and EuroQol, when compared to the control group. Furthermore, no intervention group patient was classified as severely frail and only 9% were considered moderately frail upon discharge. These researchers concluded that post-cardiac surgery patients could safely receive individualized physiotherapy with gradual increase in intensity to improve essential components of independence: nursing needs, balance and muscle strength. Similarly, Martínez-Velilla et al. completed a randomized clinical trial in an acute care unit in a tertiary public hospital comparing functional capacity from baseline to discharge in an exercise intervention (bi-daily individualized moderate-intensity resistance, balance, and walking exercises) compared to control patients [54]. While this trial recruited geriatric patients (n=370; aged ≥75 years), the most common reason for admission was CVD for 71 of 370 patients in the trial. The researchers found that the exercise intervention led to significant improvements in functional capacity: 2.2-point improvement in the Short Physical Performance Battery (SPPB) and 6.9-point improvement in the Barthel Index of Independence.

Furthermore, the researchers found that hospitalization led to impairment in functional capacity in the control group, which the intervention was able to mitigate and improve. Additionally, the intervention also led to significant improvements in the cognitive and psychological domains of frailty, evidenced by the significant difference in the Mini Mental State Examination, Geriatric Depression Scale and the EuroQol–5 Dimension questionnaire for quality of life. This research trial demonstrated that a multicomponent individualized exercise program is safe and effective to reverse frailty, especially frailty from hospitalization-associated stressors.

Taken together, the two trials reviewed demonstrated a consistent positive effect in improvement of physical frailty and functional status with personalized in-hospital exercise. The Opasich et al. trial demonstrated the benefit of early intervention on physical frailty in post-cardiac surgery patients that have classically been seen as very fragile and in need of bedrest. Nonetheless, two of their measures that assessed physical function and health-related quality of life did not improve significantly compared to control (6-minute walk distance and EuroQoL), which brings up the questions of whether the intervention was truly better than control. In contrast, though the results of the Martínez-Velilla et al. trial are very promising and demonstrated important benefits in multiple frailty domains, it should be noted that this trial was not done in a cardiovascular population alone. Perhaps due to the pathophysiological connections between frailty and CVD, patients may necessitate greater intervention for similar improvements in a CVD-only population. Finally, both trials were performed in medically stable patients, therefore, more research is necessary to gain a more comprehensive effect of exercise intervention in acute CVD patient populations. Interestingly, Fountotos et al. have recently published the protocol of a randomized clinical trial (TARGET-EFT) assessing the impact of a targeted multicomponent frailty intervention on cardiac inpatients [60]. Results of this trial will

shed light on the benefits of not only targeting frailty interventions to the vulnerable frailty domain(s) identified but will also clarify the benefits of frailty interventions in a heterogenous cardiac population, which includes both surgical and medical cardiac inpatients.

Nutritional Interventions & Discussion

We identified one trial assessing the effect of a nutritional intervention on frailty status in the inpatient setting. Deutz et al. and Matheson et al. assessed the effect of a bi-daily high caloric and protein dense oral nutritional supplement compared to placebo on readmission, mortality, malnutrition status, activities of daily living and handgrip strength in ≥65 year old hospitalized CVD or pulmonary disease patients (total n=652) [55, 56]. These researchers included patients with a primary diagnosis of chronic obstructive pulmonary disease (COPD) exacerbation, pneumonia, congestive heart failure, or acute myocardial infarction. Though intervention group patients began taking the supplement in-hospital, they continued to do so for 90 days post-discharge, with handgrip strength assessed at baseline, discharge, 30 days, 60 days, and 90 days. This trial showed that handgrip strength was significantly higher in the supplementation group compared to placebo at all time points. This demonstrates that, even after supplementation for only the length of hospital stay, there was still a positive impact on physical frailty from the use of the supplement. Furthermore, the longer-term use of the supplement was associated with lower 90-day mortality, but no between group difference was seen in 90-day readmission. There was no between group difference in length of hospital stay or ability of perform activities of daily living, however, there were improved odds of better nutritional status at 90 days and higher body weight at 30 days.

Though the Matheson et al. trial was performed in a large sample size, the trial recruited COPD and pneumonia patients who might not respond to a nutritional intervention in the same manner as CVD patients. There has been no trial conducted in a cardiac unit of a hospital, and more research is thus required for protein supplementation in an acute cardiac care setting alone. Nonetheless, previous research has shown the benefit of oral protein supplementation in frail geriatric patients. Indeed, Niccoli et al. performed a double blinded randomized controlled trial in n=47 frail geriatric patients (not admitted for CVD specifically; aged ≥60 years) and assessed the effect of whey protein supplementation compared to control [61]. Both groups also completed a rehabilitative exercise program. The trial demonstrated that whey protein supplementation led to significantly increased average daily protein intake and significantly improved grip strength and knee extensor force compared to the control group. Furthermore, the results showed a significant difference in the amount of circulating IL-6 between the control and intervention groups. This is an important finding given that IL-6 is an inflammatory marker of frailty and impacts muscle protein synthesis. Finally, these researchers also found that there was a trend towards improvement in circulating prealbumin in the whey protein supplementation group, and this improvement was correlated to percent increase in knee extensor force. This finding confirms that the supplementation of (whey) protein was successful at physically and nutritionally de-frailing the patients in the trial, given that albumin (protein found in the blood) is a marker of nutritional frailty. While the results of this Niccoli et al. trial are positive, it is important to note the small sample size of the trial (n=47), and the fact that the trial was not performed in a CVD-only population. In CVDs such as heart failure where muscle metabolism is severely impacted (i.e., cardiac cachexia), the results of this trial would not necessarily transferrable. Overall, there is a paucity of literature evaluating protein supplementation in

hospitalized CVD patients. The results of the TARGET-EFT trial will provide insight on this research area, given that the trial will be providing protein supplementation as a part of the multi-component frailty intervention [60].

Pharmacological Interventions & Discussion

Two RCTs with pharmacological interventions were identified – one complete study and one in progress. Ponikowski et al. conducted a multi-center, double-blind RCT (AFFIRM-AHF) in n=1108 heart failure patients with concomitant iron deficiency [57]. Though the study included adults aged ≥18 years, the average age of the participants was 71 years. This trial administered intravenous ferric carboxymaltose to intervention patients at discharge from a heart failure hospitalization and continued with three more doses as needed up to 24 weeks later. Intervention group patients received an average of 1352 mg ferric carboxymaltose total, while control group patients received a placebo. Results of this trial demonstrated that intravenous iron was safe for this study population, as it led to significantly fewer heart failure hospitalizations 52 weeks later, though the rate of cardiovascular death was unaffected. Furthermore, intervention group patients incurred significant benefits from the iron supplementation, given that they had significantly greater time to first heart failure hospitalization or cardiovascular death, and significantly fewer days lost due to heart failure hospitalization and cardiovascular death. In contrast, a trial that is still in process by Maggio et al. aims to use intramuscular testosterone supplementation in older men aged ≥70 years undergoing cardiac revascularization surgery (with heart bypass machine use) to attenuate the post-surgical catabolism caused by increased inflammation, insulin resistance, acute anemia and renal dysfunction [58]. Given that testosterone levels often drop drastically post-operatively in these patients, these researchers

anticipate benefits in both clinical and functional post-operative outcomes in the intervention group. Functional status will be assessed using the SPPB, the 6-minute walk test, handgrip strength and body composition. Furthermore, these researchers will also assess serum testosterone levels, markers of inflammation, as well as mood and quality life (using various questionnaires).

The association between frailty and anemia has been established previously [62, 63]. Though the exact temporal relationship between the two has not been established, they are said to have shared mechanistic links that stem from inflammation [64, 65]. Overall, the AFFIRM-AHF presents promising results for the use of intravenous iron supplementation for de-frailing heart failure patients. However, this trial only supplements the patients at discharge when they are considered to be medically stable again – the results of this trial would therefore not shed light onto iron supplementation done throughout an index hospitalization. Moreover, this trial only focuses on heart failure patients, whereas other cardiac disease patients with iron deficiency anemia could also potentially benefit from the de-frailing benefits of iron supplementation. The multi-component de-frailing TARGET-EFT trial incorporates intravenous iron sucrose supplementation for iron deficient acute cardiac disease inpatients (dose: 300 mg for three consecutive days) [60]. The results of this trial will clarify the safety and efficacy of inpatient iron supplementation in an acutely sick and broader CVD patient population.

Cognitive Interventions & Discussion

There was only one trial identified that made use of cognitive interventions to cognitively de-frail CVD patients. Partridge et al. conducted an RCT in n=176, ≥65-year-old patients undergoing elective endovascular/open aortic aneurysm repair or lower-limb arterial bypass

surgery [59]. The patients were seen in an outpatient clinic pre-operatively, where intervention patients received Comprehensive Geriatric Intervention and optimization (e.g., medication management, discussion/management of cognitive issues, set-up of follow-up with primary care physician, etc.) and control patients received usual clinical care (to determine if they were fit for surgery/anesthesia). The results of this trial demonstrated that intervention patients had a 40% (equivalent to about 2 days) shorter length of hospital stay for the index surgery compared to control patients. Furthermore, control group patients had significantly lower post-operative delirium incidence, cardiac complications, and bladder/bowel issues. In addition, intervention group patients were less likely to be discharged to a higher level of dependency (e.g., rehabilitation or increase care needs).

This trial has important prognostic implications for elective cardiac/vascular surgery patients; however, the methodology of this intervention would be impossible to recreate for emergent or acute hospitalizations for non-surgical cardiac issues such as heart failure exacerbation. Nonetheless, the results of this trial make a strong case for the use of Comprehensive Geriatric Assessment for risk assessment and optimization for geriatric patients undergoing cardiac surgery. Future studies are needed to explore the use of cognitive intervention in non-surgical cardiac inpatients. The results of the aforementioned TARGET-EFT trial are expected to shed light on the benefits of such an intervention given that this trial will be targeting cognitive frailty through a cognitive stimulation intervention for both acute cardiac disease patients and surgical patients as well [60].

CONCLUSION

Frailty is a reversible syndrome, especially prevalent in CVD patients, given that they both share an important pathophysiological basis in inflammation, vitamin D deficiency and increased cortisol. It is evident that frailty represents an enormous burden on the lives of CVD patients, as well as financially on the healthcare system. While there is some evidence to demonstrate the benefits of treating frailty in-hospital using physical, nutritional, pharmacological and cognitive interventions, more research is required to gain a comprehensive understanding of the efficacy of each of these interventions in an inpatient cardiovascular population, given that existing trials consist of small sample sizes, include non-CVD patients, or only assess medically stable patients (excluding patients with common types of CVD).

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CHAPTER 3: COMMENTARY ON LITERATURE REVIEW

Given the multidimensional nature of frailty, our literature review firstly aimed at elucidating frailty definitions, causes, and measurement tools. It also sought to define cardiovascular disease (CVD) and its pathogenesis, as well as the pathophysiological connections between frailty and CVD, which might explain the high prevalence of frailty in this patient population. Subsequently, the literature review sought to identify randomized clinical trials aiming to de-frail CVD inpatients. The review focused on inpatient treatment of frailty, since hospitalization comes with a host of frailty risk factors itself (i.e., bedrest, undernutrition, frequent blood tests/procedures, cognitive impairment due to isolation, delirium, etc.), but also because it is an opportune time to be able to treat frailty concomitantly to patients' CVD. Indeed, hospitalization is a time when patients are focused on their health, with other obligations, such as work being put on hold. This review of de-frailing interventions revealed a paucity of trials including CVD inpatients. Nonetheless, the identified trials demonstrated a general positive impact on various measures of frailty despite brief lengths of stay compared to trials done in community-dwelling older adults that can often last months. It was clear that the trials we reviewed either included a heterogenous population including other diseases (such as respiratory diseases), only intervened on frailty using one type of intervention, or only studied a specific subset of CVD patients. Additionally, the identified trials often only included clinically stable patients, excluding post-myocardial infarction patients who could also benefit from these interventions.

Recognizing that frailty stems from and is modulated by multiple factors, a targeted multicomponent in-hospital intervention might lead to the greatest improvement in patients' frailty status. We designed the TARGET-EFT trial to test the impact of a multicomponent de-

frailing intervention that aims to tackle frailty via four targeted avenues: physical exercise, nutritional supplementation, cognitive stimulation, and anemia correction. Our trial included a diverse CVD patient population admitted to the acute cardiology unit at the Jewish General Hospital. By using interventions that targeted multiple frailty domains, we hoped to mitigate hospital-associated frailty development/exacerbation in CVD inpatients which often leads to post-discharge loss of function and quality of life.

CHAPTER 4: RANDOMIZED CLINICAL TRIAL – MANUSCRIPT ACCEPTED

The following manuscript, titled "De-Frailing Intervention for Hospitalized Cardiovascular Patients in the TARGET-EFT Randomized Clinical Trial," has been accepted at *European Heart Journal – Quality of Care & Clinical Outcomes* for publication.

De-Frailing Intervention for Hospitalized Cardiovascular Patients in the TARGET-EFT Randomized Clinical Trial

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Abstract

Aims: Frailty is disproportionately prevalent in cardiovascular disease patients and exacerbated during hospital admissions, heightening the risk for adverse events and functional decline. Using the Essential Frailty Toolset (EFT) to target physical weakness, cognitive impairment, malnourishment, and anemia, we tested a multicomponent intervention to de-frail older adults with acute cardiovascular conditions during their hospital admission.

Methods and Results: The TARGET-EFT trial was a single-center randomized clinical trial at the Jewish General Hospital, Montreal, Canada. We compared a multicomponent de-frailing intervention with usual clinical care. Intervention group patients received exercise, cognitive stimulation, protein supplementation, and iron replacement, as required. In this study, the primary outcome was frailty, as assessed by the SPPB score (Short Physical Performance Battery) at discharge, and the secondary outcome was the SARC-F score (Strength, Assistance walking, Rising from chair, Climbing, Falls) 30 days later. The analysis consisted of 135 patient (mean age of 79.3 years; 54% female) who survived and completed the frailty assessments. Compared to control patients, intervention group patients had a 1.52-point superior SPPB score and a 0.74-point superior SARC-F score. Subgroup analysis suggested that patients with low left ventricular ejection fraction may have attenuated benefits, and that patients who underwent invasive cardiac procedures had the greatest benefits from the intervention.

Conclusions: We achieved our objective of de-frailing older cardiac inpatients on a short-term basis by improving their physical performance and functioning using a pragmatic

multicomponent intervention. This could have positive impacts on their clinical outcomes and ability to maintain independent living in the future.

Keywords: randomized clinical trial, frailty, physical performance, intervention, cardiology, geriatrics

One sentence summary: The multicomponent intervention targeted to the deficits of vulnerable older adults with acute cardiovascular diseases successfully de-frailed them on a short-term basis, which can have positive implications on their post-discharge health outcomes.

Introduction

Frailty, a geriatric syndrome that interferes with the physiological mechanisms required for healthy homeostasis after a stressor, has been found to be disproportionately prevalent in cardiovascular disease (CVD) patients [1, 2]. The prevalence of frailty is estimated to be 10% in community-dwelling older adults, and up to 50% in high-risk subgroups, such as those with heart failure [3-5]. In fact, frailty and CVD have been found to have a bidirectional relationship where frailty increases risk of fatal and nonfatal CVD, CVD increases the risk of prevalent and incident frailty, and the combination increases the risk of functional decline and all-cause mortality by 2-3-fold [5-8].

The Essential Frailty Toolset (EFT) is a screening tool that focuses on four actionable domains: lower extremity weakness, cognitive impairment, malnourishment, and anemia [6, 9]. All of these are exacerbated during a hospital admission, the reasons for which are multifactorial and include: acute illness, bedrest, undernutrition, disturbed sleep patterns, and repeated blood tests [10, 11]. As a result, older patients often leave the hospital frailer than they were beforehand and have difficulty regaining their physical and mental capabilities. In turn, greater degrees of frailty using the EFT have been shown to be predictive of incident disability and mortality in clinical cardiac populations [6, 9].

Frailty is potentially modifiable, and admission to hospital presents an opportunistic timeframe and captive audience for initiating interventions aimed at de-frailing patients at the same time as their cardiac care. Research has shown positive impacts of in-hospital exercise programs, nutritional supplementation, cognitive stimulation, and anemia correction in medical patients [12-16], yet there is a paucity of evidence in acute CVD patients and using multicomponent interventions. We hypothesized that a multicomponent de-frailing intervention

would improve physical frailty in vulnerable older adults admitted to the hospital with acute cardiovascular conditions.

Methods

Trial Design & Participants

We conducted the TARGET-EFT trial (MulTicomponent Acute Intervention in FRail GEriatric PaTients with Cardiovascular Disease using the Essential Frailty Toolset) to assess the effect of a multicomponent geriatric intervention on patient-centered outcomes (ClinicalTrials.gov identifier: NCT04291690). We now report the results of a pre-planned analysis for a key secondary outcome – frailty. The methodology of the TARGET-EFT trial complied with the *Declaration of Helsinki*, was approved by the institutional review board of the Jewish General Hospital, and has previously been described in detail [17]. In brief, TARGET-EFT was a parallel-group randomized controlled trial at the Jewish General Hospital (Montreal, QC), an academic tertiary care center affiliated with McGill University. Consenting patients admitted to the cardiovascular ward who were aged ≥65 years with signs of frailty (EFT ≥1) were randomized using 1:1 block randomization stratified by sex. Detailed inclusion and exclusion criteria are listed in **Table S1**. After randomization, patients underwent further frailty assessments to confirm the frailty deficits identified through the EFT. These consisted of the Short Physical Performance Batter (SPPB) for physical weakness [18], the Mini-Mental State Examination (MMSE) for cognitive deficits [19], the Preoperative Nutrition Score (PONS) for malnutrition [20], and iron studies for anemia.

Control Group

Patients randomized to the control group received usual clinical care. This consisted of treatment of their cardiovascular condition by cardiologists, along with inpatient physiotherapy, nutritional support, treatment of anemia, and consultation with healthcare specialists at the discretion of the treating team (**Figure 1**). Physiotherapy involvement is systematic post-cardiac surgery, but otherwise it is variable depending on the elicited needs of the patient and referral of the treating clinician. Most typically on our ward, physiotherapists visit their inpatients 2-3 times per week and focus on mobility and balance. The standard cardiac diet on our ward contains three meals per day with low salt (under 2300 mg), moderate fat, and at least one protein per meal. Breakfast contains two starches; lunch and dinner contain a soup, a main meal, and a dessert (usually yogurt or some fruit).

Intervention Group

Patients randomized to the intervention group received usual clinical care, as well as the EFT-based interventions (**Figure 1**). All intervention group patients received bi-daily visits from an assigned research team member who provided orientation to time and place, encouragement to mobilize and perform chair rise exercises, encouragement to wear hearing/visual aids and dentures, encouragement to eat their regular meals, encouragement to sleep without interruptions, with help to address barriers to nutrition and sleep; if anemic, they received investigations for iron deficiency. Moreover, intervention patients received additional therapies depending on the frailty deficits identified in their individualized case.

Specifically, patients with physical weakness received bi-daily supervised, 20-minute, multicomponent exercise sessions combining strength, flexibility, balance and gait exercises for

the prevention of weakness and falls adapted from the *Vivifrail* program [21]. Patients were encouraged to continue these exercises along with a healthy diet at home post-discharge. Patients with cognitive deficits received cognitive stimulation twice daily consisting of activities, such as reading the news, doing crossword puzzles, and memory games. Those who had confirmed malnourishment received MedPass supplementation; MedPass is a 60 mL calorically- and protein-dense (2 kcal/mL) oral nutritional supplement consumed between meals 4 times per day. Finally, those with confirmed iron deficiency anemia (hemoglobin <130 g/L in men or <120 g/L in women plus ferritin <100 ug/L or <300 ug/L with iron saturation <20%) were prescribed intravenous iron sucrose at 300 mg/day for three consecutive days [22].

Outcomes

This study sought to determine whether the intervention caused changes in physical frailty as measured by the SPPB and SARC-F scales. The primary outcome for this study was the SBBP score at the time of discharge from the cardiovascular unit. SPPB includes 3 physical tests scored from 0 to 4 for a total score from 0 to 12 (0 = worst, 12 = best): time to walk 5 meters at a comfortable pace (best of two trials), time to stand 5 times from a chair without using arms, and 10-second standing balance in 3 positions (feet together, semi-tandem, and full tandem) [18]. The secondary outcome for this study was the SARC-F score ascertained by a blinded assessor at 30 days post-discharge from the cardiovascular unit. SARC-F includes 5 self-reported questions scored from 0 to 2 for a total score from 0 to 10 (0 = best, 10 = worst): difficulty with transferring, walking, carrying objects, climbing stairs and history of falls [23]. The main outcomes for the overarching trial, reported separately, were the EQ-5D-5L scale for health-

related quality of life and the OARS (Older American Resources and Services) scale for hospital-acquired disability at 30 days.

Statistical Analysis

We performed intention-to-treat analysis using multivariable linear regression to determine the effect of the intervention on the continuous physical frailty score after adjusting for the baseline score and duration of hospitalization (number of days from the date of randomization to discharge or death). We tested for effect modification for age, sex, duration of hospitalization, cardiac surgery or transcatheter valve replacement during the index hospitalization, obesity, diabetes, left ventricular ejection fraction, baseline New York Heart Association class (NYHA class), baseline Clinical Frailty Scale (CFS) score, baseline SPPB score, baseline MMSE score, and baseline PONS score. We performed randomization and data storage using REDCap electronic data capture tools hosted at the Lady Davis Institute's Centre for Clinical Epidemiology. All data analyses were performed using STATA version 17 (College Station, TX). The data underlying this article can be shared on reasonable request to the corresponding author.

Results

Out of 150 patients randomized between March 2020 and September 2021, the current study analyzed 135 patients who completed the SPPB at discharge; all but two of which also completed the SARC-F at 30 days post-discharge. The flow diagram can be found in **Figure 2**. Participant baseline characteristics by allocation group can be found in **Table 1** and **Table S2**. The mean age of participants was 79.3 ± 7.7 years and 54% of participants were females. The

most common reasons for admission were evenly distributed between ischemic heart disease and heart failure, followed by arrhythmia and valvular heart disease. The mean duration of hospitalization after randomization was 11.0 ± 11.7 days. There were no reported intervention-related adverse events and no negative effects on renal function.

Interventions

The therapies received by group can be found in **Table 2**. All intervention patients received encouragement and support for physical activity, cognitive orientation, and eating meals; in addition, depending on the frailty deficits identified, 94% received the Vivifrail exercise program (mean of 1.0 session per weekday and planned rest on weekend days), 42% received cognitive stimulation activities (mean of 1.1 session per day), 49% received oral nutritional supplements (compared to 22% of control patients), 35% received intravenous iron replacement therapy (compared 16% of control patients). There were no significant between-group differences in those who received clinical consultations with geriatric medicine specialists and allied-health professionals.

Outcomes

The mean SPPB score out of 12 (higher is stronger) was 4.5 ± 3.0 at baseline, 6.5 ± 3.3 at follow-up in the intervention group, and 5.1 ± 3.3 at follow-up in the control group. The mean SARC-F score out of 10 (lower is stronger) was 5.2 ± 2.6 at baseline, 3.6 ± 2.3 at follow-up in the intervention group, and 4.0 ± 2.4 at follow-up in the control group. The changes in SPPB and SARC-F scores from baseline to follow-up can be found in **Figure 3,** showing, on average, improved scores in intervention group patients and minimally changed scores in control group

patients. Change in frailty scores after adjusting for length of intervention and baseline score can be found in **Table 3**. Compared to the control group, the intervention led to a 1.52-point superior SPPB score (95% CI 0.75, 2.29; P<0.001; effect size 0.5) and a 0.74-point superior SARC-F score (95% CI -1.38, -0.11; P=0.02; effect size 0.3).

Subgroup Analysis

Forest plots for pre-defined subgroups can be found in **Figure 4**. Patients who had undergone cardiac surgery or transcatheter aortic valve replacement derived greater improvements in SPPB score with the intervention (interaction P=0.007). Conversely, patients who had reduced LVEF ≤40% derived lesser improvements compared to those with LVEF >40% (interaction P=0.017), although this represented a small subgroup of 36 patients. Patients who did not have diabetes mellitus trended to derive lesser improvements (interaction P=0.073) and those who were hospitalized for >7 days trended to derive greater improvements (P=0.071). There were no significant interactions by age, sex, BMI, NYHA class, cognitive function, baseline nutritional status or severity of frailty.

Discussion

In the present trial, we achieved our objective of physically de-frailing older CVD inpatients through a multicomponent targeted geriatric intervention. Our intervention was safe and led to moderate improvements in frailty, as measured by the SPPB and SARC-F scales, which were clinically apparent as gains in physical performance and functioning. While community-based frailty interventions typically span 2-3 months or longer, the current trial is unique in that it spanned an average of 11 days within the hospital. Our results also demonstrate

that patients undergoing invasive cardiac procedures have the greatest benefits from the intervention, rendering this a high-yield population for future implementation.

A paucity of randomized controlled trials have addressed de-frailing hospitalized patients, and none – to our knowledge – have been conducted on a CVD unit. Ekerstad et al. randomized 408 frail older inpatients to a comprehensive geriatric assessment-guided intervention and reported improvements in physical frailty and ability to perform activities of daily living 3 months post-discharge [24, 25]. Martínez-Velilla et al. randomized 370 frail older inpatients to a bi-daily resistance exercise intervention adapted from the *Vivifrail* program and reported improvements in the SPPB (2.2 points) at discharge [14, 26]. While they used specialized exercise equipment, we achieved similar benefits with a pragmatic bedside program. Our trial targeted patients with recently decompensated CVD, which were purposefully excluded by previous trials since they pose unique challenges such as symptomatic shortness of breath on exertion, wounds from recent cardiac interventions, and impediments from telemetry devices, oxygen tubing, and intravenous lines.

The downstream clinical impact of reducing frailty in hospitalized patients can be extrapolated from prior research. Frailty measured using the SPPB at the time of hospital discharge was associated with a 3-fold increase in subsequent mortality or readmission and a 50% incidence of functional decline and disability at 1 year [27]. Moreover, each 1-point improvement in the SPPB was associated with a 14% reduction in risk of mortality or readmission [27]. Our intervention successfully led to 1.5 points superior SPPB score, which would be expected to translate to a meaningful reduction in mortality or readmission – although this remains to be proven in a dedicated randomized controlled trial. This hypothesis is supported by epidemiology data demonstrating that adverse outcomes after a CVD hospitalization are often

non-cardiac in nature [28, 29], and driven by comorbid diseases and geriatric issues such as frailty. Furthermore, the observed 1.5 points superior SPPB score in the intervention group is greater than the previously defined threshold for minimal clinically meaningful change of 1 point [30]. Given the number of patients enrolled, *a posteriori* sample size calculations showed a power of 0.82 to detect this magnitude of effect.

The patient-centered benefits of our intervention are evidenced by the superior SARC-F score at discharge in the intervention group, which reflects the functional consequences of physical frailty and sarcopenia [31]. The observed superior SARC-F score translates to our intervention group patients feeling more capable of mobilizing, transferring, and performing physical tasks after returning to their home environment, which is critical to maintain independent living and foster rehabilitation after a CVD event. While the SARC-F has previously been used extensively to screen for frailty, including in CVD patients [32], use of the SARC-F as an outcome measure pre-post intervention is a novel aspect of this trial that appears to have empirical construct validity given the consistent effects between improving SARC-F and SPPB scales. The benefits of our intervention appeared to be less pronounced in patients with reduced LVEF, which may be driven by chance (due to the small size of this subgroup) or by the decreased volume of exercise completed during the brief 20-minute sessions (due to breathlessness and exhaustion needing frequent pauses). Successful exercise interventions in heart failure patients have entailed longer sessions, allowing for warm up and graded intervals, over a period at least 3 weeks [33].

Limitations

A number of limitations should be acknowledged. Firstly, the SPPB assessment at discharge was not blinded given that the trained personnel administering the assessment were

also involved in delivering the intervention (or control). This potential bias is minimal given that the SPPB is a series of objectively-timed physical performance tests, with little assessor influence. Moreover, SARC-F assessment was blinded and confirmed meaningful improvements in frailty. Secondly, the SARC-F questionnaire requires self-report of functional abilities that is susceptible to recall bias by the patient. This potential bias was mitigated by interviewer administration of the questionnaire and involvement of family members or caregivers whenever possible. Thirdly, though we aimed to deliver two exercise sessions per weekday for those who required this intervention, our achieved average was 1.0 sessions/weekday owing to the realities of a busy cardiovascular unit, wherein patients are often symptomatic or preoccupied with their cardiac tests and procedures. Despite this, we still achieved clinically meaningful improvements in physical frailty, further highlighting and strengthening the potential pragmatic nature of our intervention. Finally, the TARGET-EFT trial was a single center trial, the first of its kind in CVD patients; multicenter trials are required to ensure the reproducibility and generalizability of our procedures and results. This is a critical issue to account for the potential variability in "usual care" that may exist between centers, especially with respect to co-interventions such as physiotherapy and nutritional support.

Conclusions

Our multicomponent intervention targeted to the deficits of older cardiac inpatients led to clinically meaningful improvements in short-term physical frailty, which has ramifications for physical functioning and health outcomes post-discharge. These findings have important clinical implications that will enable cardiovascular clinicians to reverse physical frailty in patients with

CVD, thereby improving their physical function and health outcomes at discharge and post-discharge from the hospital.

Supplementary Data

Supplementary tables contain a complete list of inclusion/exclusion criteria, as well as additional baseline frailty metrics.

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Data Availability Statement

The e data underlying this article will be shared on reasonable request to the corresponding author.

Author Contributions

FA was responsible for conception and design, acquisition of data, project administration, analysis and interpretation of data, and writing of the original draft. RF was responsible for conception and design, acquisition of data, and project administration. NB was responsible for

acquisition of data. HM was responsible for the conception and design, and acquisition of data. JM and LGR were responsible for conception and design. MG was responsible for conception and design, and supervision. JA was responsible for the conception and design, analysis and interpretation of data, supervision, and writing. All authors critically read and reviewed the manuscript for important intellectual content and approval for publication.

Disclosures

The Authors declare that there is no conflict of interest.

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Figure Legends

Figure 1

Title: Trial Design Snapshot

Legend: The middle section depicts the timeline of frailty assessments. The left (blue) section depicts the components of usual care received by all patients. The right (green) section depicts the components of our multicomponent intervention, subdivided by systematic interventions received by all intervention group patients and deficit-targeted interventions received by only intervention group patients who had confirmed deficits in those specific domains.

Abbreviations: EFT, Essential Frailty Toolset; IV, Intravenous; MMSE, Mini Mental State Examination, PONS, Preoperative Nutrition Score; PRN, as needed per clinical indication; SPPB, Short Physical Performance Battery.

Original figure dimensions: 5980×1838

Figure 2

Title: Flow Chart

Legend: Out of 150 patients randomized, 135 patients completed the primary outcome assessment at discharge (SPPB) and 133 completed the secondary outcome assessment at 30 days (SARC-F).

Abbreviations: SPPB, Short Physical Performance Battery.

Original figure dimensions: 3101×2780

Figure 3

Title: Change in Frailty Scores from Baseline to Follow-Up

Legend: [A] The top panel depicts the change in SPPB score from baseline to discharge, which was favorable for the intervention group patients. [B] The bottom panel depicts the change in SARC-F score from baseline to 30 days post-discharge, which was favorable for the intervention group patients.

Abbreviations: SPPB, Short Physical Performance Battery.

Original figure dimensions: 2056×3061

Figure 4

Title: Effect-Modification Forest Plot

Legend: Subgroup analysis showing the adjusted beta coefficient effect for the intervention stratified by various subgroups of patients. There were 2 statistically significant interactions: patients who had invasive cardiac procedures derived greater benefits from the intervention, whereas those who had reduced left ventricular ejection fraction derived lesser benefits. There were 2 other trending interactions: patients who had longer length of stay and thus received a greater volume of intervention visits appeared to derive greater benefits, whereas nondiabetic patients appeared to derive lesser benefits.

Abbreviations: BMI, Body Mass Index; CFS, Clinical Frailty Score; MMSE, Mini Mental State Examination; NYHA class, New York Heart Association functional classification; PONS, Preoperative Nutrition Score; SPPB, Short Physical Performance Batter.

Original figure dimensions: 3857×5335

Text Tables

Table 1: Mean Baseline Characteristics of Participants by Group

	Intervention N=66	Control N=69
Clinical Characteristics		
Age (years)	78.2 ± 8.0	80.2 ± 7.3
Female Sex	35 (53.0%)	38 (55.1%)
BMI (kg/m^2)	28.3 ± 7.0	28.5 ± 6.3
LVEF (%)	51.7 ± 17.9	55.6 ± 15.6
NYHA Class	2.6 ± 1.0	2.4 ± 1.0
Heart Failure	22 (33.3%)	19 (27.5%)
Diabetes	29 (43.9%)	42 (60.9%)
Percutaneous Coronary Intervention *	8 (12.1%)	88 (11.6%)
Cardiac Surgery / Transcatheter Valve Procedure *	15 (22.7%)	15 (21.7%)
Hospital Days Post-Randomization	11.5 ± 12.7	10.5 ± 10.7
Reason for Admission: Ischemic Heart Disease Arrhythmia Valvular Heart Disease Congestive Heart Failure Other	 21 (31.8%) 13 (19.7%) 6 (9.1%) 16 (24.2%) 10 (15.2%)	 19 (27.5%) 5 (7.2%) 8 (11.6%) 23 (33.3%) 14 (20.3%)
Frailty Markers		
EFT (out of 5)	2.7 ± 1.1	2.8 ± 1.0
SPPB (out of 12)	4.4 ± 3.1	4.6 ± 2.9
SARC-F (out of 10)	5.4 ± 2.6	4.9 ± 2.6
CFS (out of 9)	4.4 ± 1.5	4.6 ± 1.4

MMSE (out of 30)	25.4 ± 3.6	25.6 ± 3.3
PONS (out of 3)	0.8 ± 0.8	0.6 ± 0.7
Albumin (g/dL)	34.0 ± 4.5	34.8 ± 4.4
Hemoglobin (g/dL)	105.1 ± 20.0	107.4 ± 19.4
IDA	28 (42.4%)	23 (33.3%)

* During the index hospital admission. Abbreviations: BMI, Body Mass Index; CFS, Clinical Frailty Scale; EFT, Essential Frailty Toolset; IDA, Iron Deficiency Anemia; LVEF, Left Ventricular Ejection Fraction; MMSE, Mini Mental State Examination; NYHA Class, New York Heart Association Functional Classification; PONS, Preoperative Nutrition Score; SPPB, Short Physical Performance Battery.

Table 2: Therapies Received by Group

	Intervention N=66	Control N=69
Trial interventions		
Vivifrail exercise	93.9% (1.0/day)	-
Cognitive stimulation	42.4% (1.1/day)	-
Nutritional supplementation	48.5%	21.7%
Intravenous iron replacement	34.8%	15.9%
Non-trial intervention		
Physiotherapy consult	56.1%	55.1%
Occupational therapy consult	33.3%	21.7%
Nutritionist consult	33.3%	37.7%
Geriatrics consult	6.1%	2.9%
Psychiatry consult	10.6%	2.9%

Table 3: Multivariable Linear Regression for Frailty Outcome Measures

	SPPB at discharge Beta (95% CI); P-value	SARC-F at 30 days Beta (95% CI); P-value
Intervention	1.52 (0.75, 2.28); P<0.001	-0.74 (1.38, -0.11); P=0.02
Baseline frailty score	0.75 (0.62, 0.89); P<0.001	0.36 (0.23, 0.49); P<0.001
Hospitalization days	-0.04 (-0.07, -0.004); P=0.03	0.07 (0.04, 0.10); P<0.001

* A positive beta denotes stronger SPPB, whereas a negative beta denotes stronger SARC-F.
Abbreviations: CI, Confidence Interval; SPPB, Short Physical Performance Battery.

Figures

Figure 1: Trial Design Snapshot

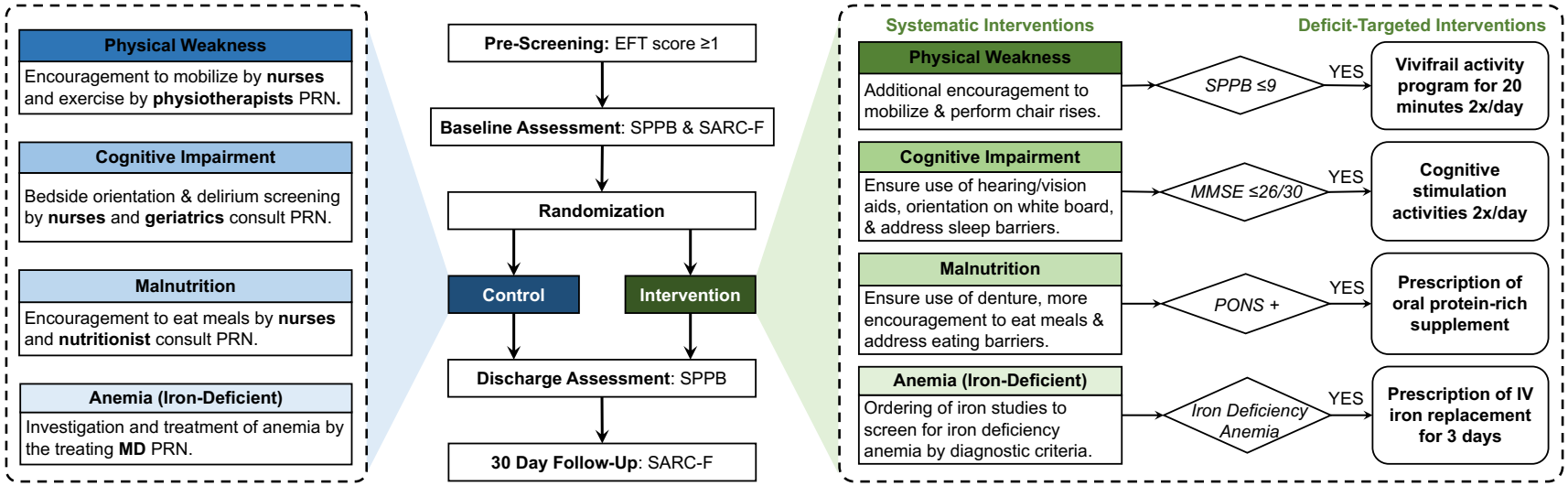


Figure 2: Flow Chart

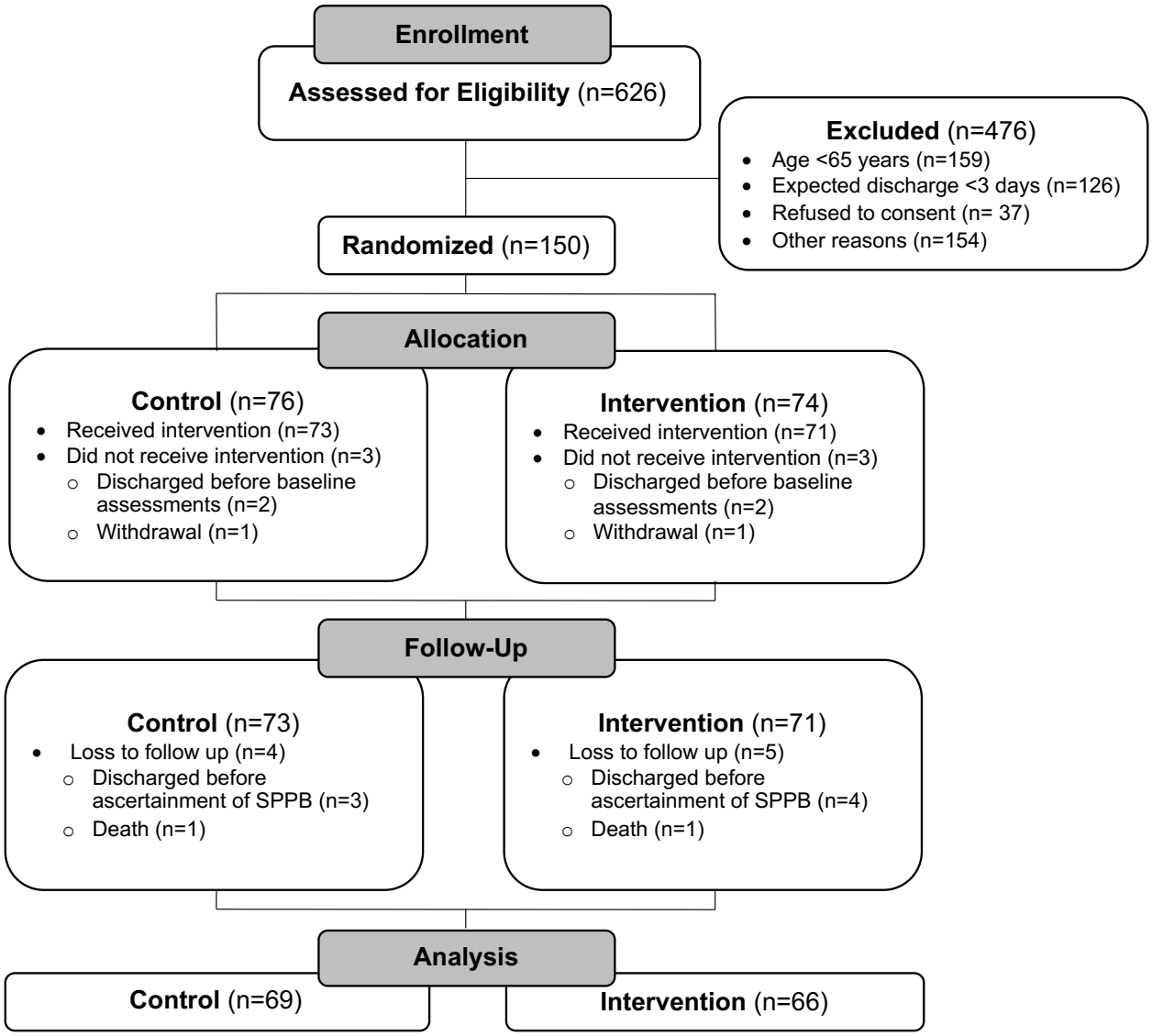
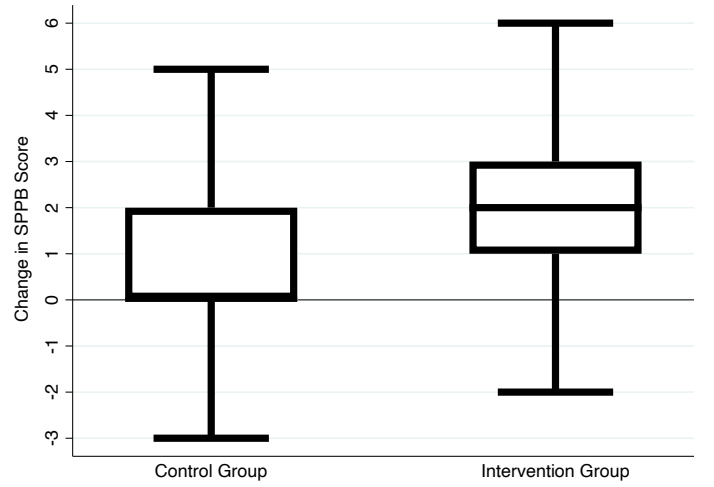


Figure 3: Change in Frailty Scores from Baseline to Follow-Up

[A]



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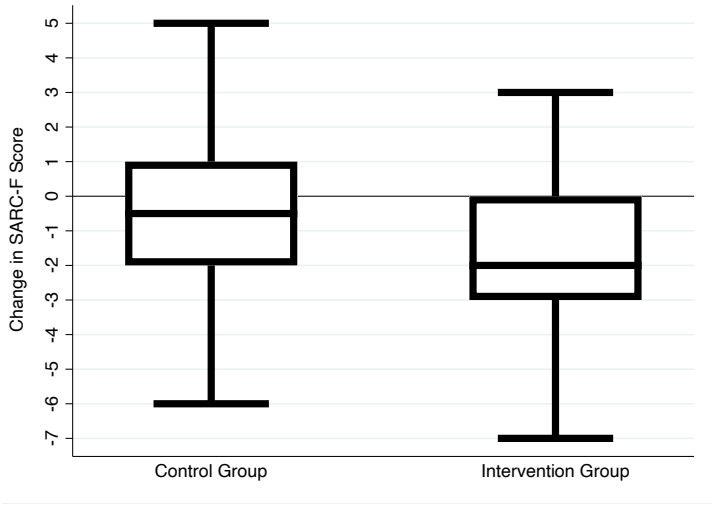
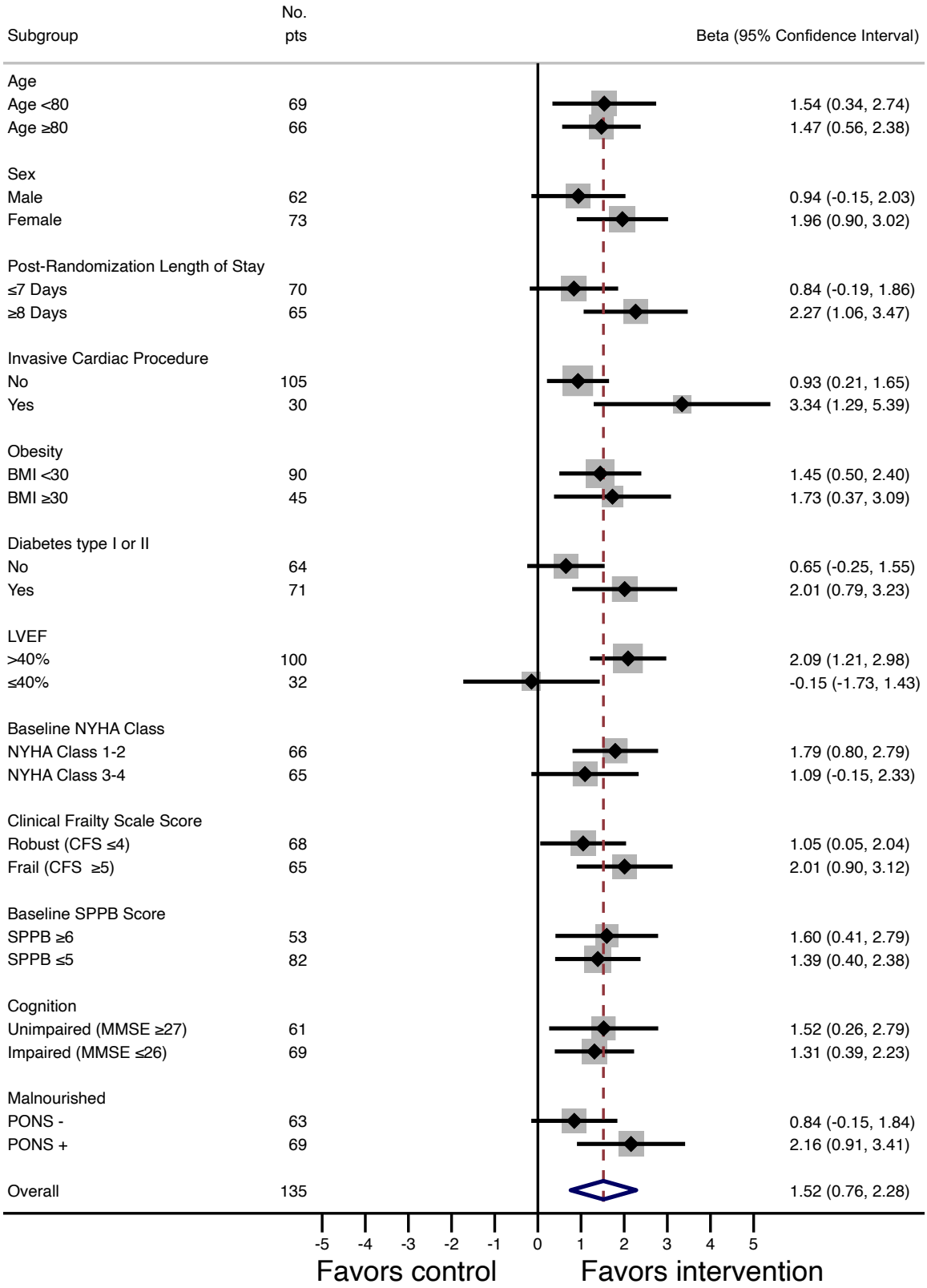


Figure 4: Effect-Modification Forest Plot



Supplementary Files

Table S1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Age ≥ 65 years	1. Expected discharge within <3 days
2. Frail or pre-frail (EFT score ≥1)	2. Cardiac surgery within <3 days
3. Admission to the Cardiovascular Unit	3. Clinically unstable *
4. Signed informed Consent	4. Severe dementia (MMSE ≤10/30)
	5. Delirium (CAM+)
	6. Psychiatric condition precluding coop.
	7. Not English or French speaking
	8. Parkinson's Disease
	9. Recent stroke <7 days
	10. Bed-bound or paraplegic
	11. End-of-life care plan
	12. Positive or rule-out for SARS-COV-19

* Clinically unstable: unstable vital signs, low-threshold coronary ischemia, uncontrolled heart failure, uncontrolled arrhythmia.

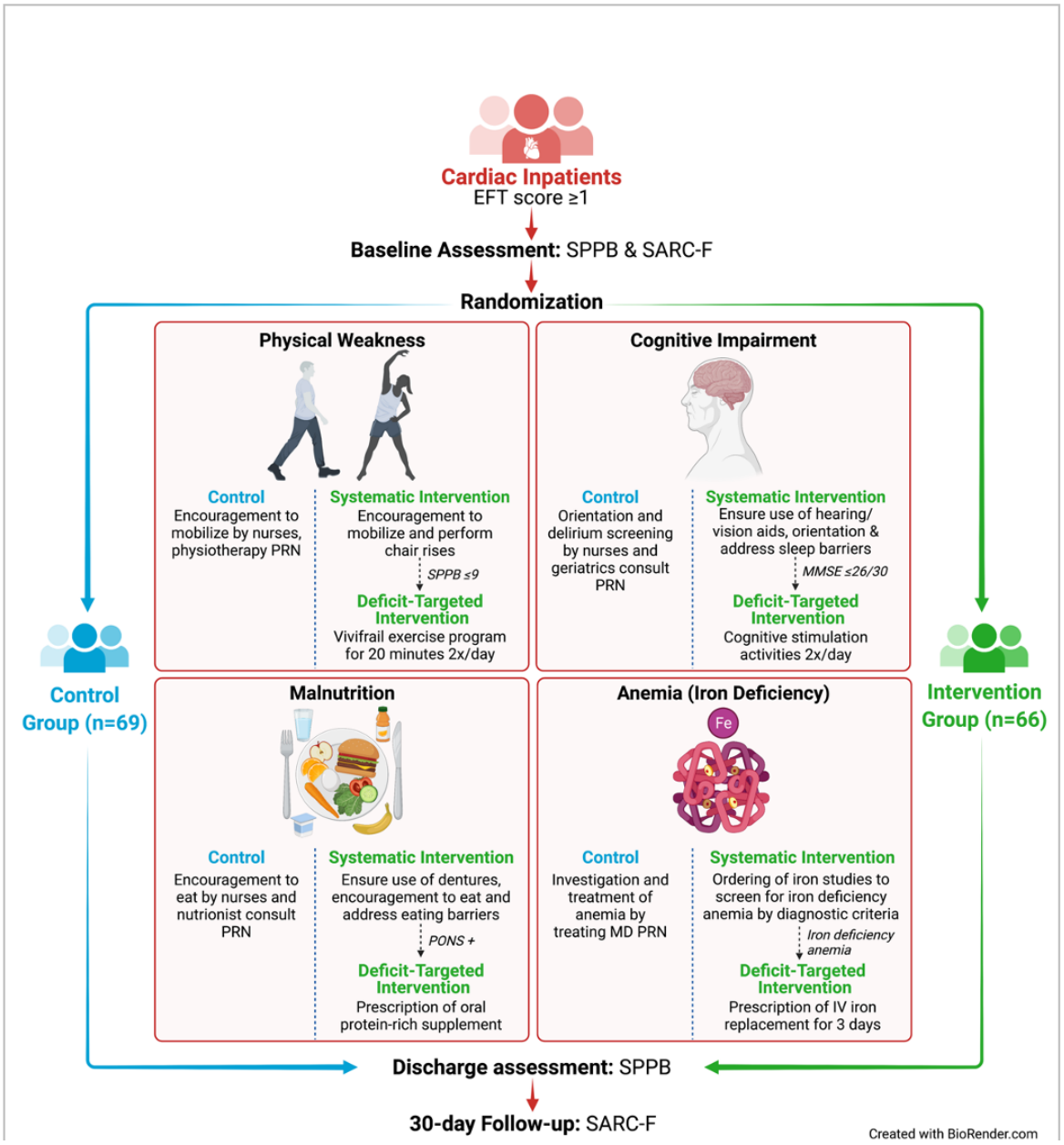
Table S2: Additional Frailty Metrics

	Intervention N (%)	Control N (%)	P-value
EFT Scores			0.75
1	9 (13.6)	7 (10.1)	
2	21 (31.8)	20 (29.0)	
3	16 (24.4)	24 (34.8)	
4	18 (27.3)	16 (23.2)	
5	2 (3.0)	2 (2.9)	
EFT Subdomains			>0.10
Physical weakness	59 (89.4)	61 (88.4)	
Cognitive deficit	2 (3.0)	6 (8.7)	
Anemia	58 (87.9)	62 (89.9)	
Hypoalbuminemia	34 (51.5)	33 (47.8)	
Living Where			0.43
Facility with assistance	7 (10.6)	9 (13.0)	
Home with assistance	9 (13.6)	11 (15.9)	
Home independently	50 (75.8)	49 (71.0)	
Living With			0.30
Caretaker	1 (1.5)	0 (0)	
Family member	33 (50)	42 (60.9)	
Alone	32 (48.5)	27 (39.1)	

Abbreviations: EFT; Essential Frailty Toolset.

Structured Graphical Abstract

Key question(s)	Key finding(s)	Take-home message
Can a multicomponent de-frailing intervention (physical exercise, cognitive stimulation, nutritional supplementation, and anemia correction) improve physical frailty in vulnerable older adults admitted to the hospital with acute cardiovascular conditions?	Compared to usual care, patients randomized to the intervention group demonstrated improvements in Short Physical Performance Battery Score and SARC-F score at discharge from the hospital and 30-days later, respectively.	Our multicomponent de-frailing intervention led to clinically meaningful improvements in short-term physical frailty, which has positive ramifications on post-discharge physical functioning and health outcomes in patients admitted to the hospital with cardiovascular diseases.



CHAPTER 6: THESIS DISCUSSION

The results of our randomized clinical trial (RCT) have filled an important gap in the literature that we identified in our literature review, with regards to the in-hospital multi-component treatment of frailty in hospitalized cardiovascular disease (CVD) patients. Through our RCT, we have not only demonstrated that a multi-component de-frailing intervention is safe for patients, but we have also demonstrated that a short intervention lasting only the length of stay of hospitalized CVD patients can physically de-frail them on a short-term basis, such that they can still feel the effects on their functional status one month later as well (evidenced by significantly improved SPPB and SARC-F scores at and post-discharge from the hospital). Moreover, we have identified cardiac surgery patients to be a subpopulation which derive the greatest benefit from such an intervention and have further identified that those with low left ventricular ejection fraction may not derive as much benefit from such an intervention.

After the successful completion of our trial, the next step is undoubtedly to translate and implement our findings into usual clinical care so that future hospitalized CVD patients may benefit from this intervention on a regular basis. The implementation of this four-part multi-component intervention would require four application strategies to ensure successful adoption. **Table 1** at the end of this chapter highlights the barriers to the implementation of each type of intervention, and our proposed mitigation strategies.

Implementation of Exercise Therapy

Historically, mobilization and exercise for hospitalized CVD patients, specifically those with ischemic heart disease, has been viewed as unsafe, with bedrest often being promoted in

this population [17]. However, research has shown the benefits of early mobilization and exercise therapy for hospitalized patients [18]. Indeed, Semsar-Kazerooni et al. conducted a study comparing early mobilization in the cardiovascular intensive care unit to usual care at the same hospital where we completed our trial, and they found that the intervention group was more likely to be discharged back home (less dependency) and less likely to die in-hospital [18]. In order to implement an exercise intervention for frail CVD inpatients, we will need to move away from the idea that exercise is a high-risk activity for CVD patients and overcome hospital-setting associated barriers. Barriers that have previously been identified for early mobilization of patients include lack of staff and time, risk of self-injury, as well as increasing the work burden of physiotherapy staff [19, 20].

We believe that the introduction of certified kinesiologists or exercise physiologists into the hospital-setting will help overcome a large proportion of barriers to exercise for hospitalized CVD patients. Kinesiologists receive specialized training in exercise training and are amenable to integration into a clinical setting to provide specialized care to CVD patients. Moreover, kinesiologists serve as not only trainers but also as educators in physical activity for patients they work with, using specialized techniques to keep patients motivated to exercise (e.g., motivational interviewing). This will allow patients to not only exercise while in-hospital, but also learn about exercise and how to stay active post-discharge as well. By allowing kinesiologists to work on an everyday basis with frail CVD patients, we will be able to alleviate an overburdening on physiotherapists, who can continue on with their roles/responsibilities in parallel. Nonetheless, we recognize that there needs to be a formal division of labour between physiotherapists and kinesiologists that will allow them to work together more seamlessly. With regards to risk of self-injury with exercise, we believe that the supervisory and educational role of a kinesiologist

can largely mitigate such an issue: a kinesiologist can help patients deal with wirings from urinary catheters, intravenous lines, and oxygen nasal prongs, whilst also monitoring vital signs such as heart rate, oxygen saturation, electrocardiogram, rate of fatigue, and other symptomology (i.e., breathlessness, dizziness, etc.). Overall, kinesiologists are clearly well-educated in the field of exercise therapy and can help in the implementation of exercise for frail CVD patients. Indeed, in our RCT, two kinesiologists led the interventions by assessing baseline frailty status, providing exercise therapy and cognitive stimulation activities, as well as acting as mediators that raise concern to nutritionists for patients who were malnourished and to doctors for patients who had iron-deficiency anemia.

Implementation of Cognitive Stimulation

The implementation of cognitive stimulation activities is rather simple, as it only requires providing patients with crossword puzzles, word-searches, reading material and other mentally stimulating activities. This is something that is often already done by nursing staff on the cardiology unit where we completed our RCT, but it can also be done by a kinesiologist who routinely visits patients (as was done in our trial) or hospital volunteers. The barrier to the implementation of this intervention does not lie in the physical implementation of it, but rather in educating hospital staff on the identification of patients who can benefit from such an intervention. In our trial, we provided this intervention to patients with relatively mild-to-moderate cognitive impairment (defined as a Mini Mental Status Examination (MMSE) score of ≤26/30), but we excluded those with severe impairment (defined as MMSE score of ≤10/30) or who were delirious. The cognitive intervention in our trial was based on the Hospital Elder Life Program which serves to protect hospitalized older adults from delirium, and subsequent

negative health outcomes (i.e., increased length of stay, incident delirium, cognitive impairment and decreased functional status) [21]. By focusing on patients without severe impairment we targeted a population which is more likely to appropriately complete and subsequently respond to the intervention. The identification of patients in this MMSE range can be time consuming given that just the administration of the test alone can take up to ten minutes (without including the rating of the test afterwards) [22]. To circumvent this time constraint and screen more patients, we utilized a short three-part cognitive screening test which included a three-word recall, as well as identification of the date and the patient's current location. This shorter test can be administered daily by nurses, kinesiologists, volunteers, or physicians to help screen those that need more thorough testing using the MMSE or need a geriatrics consultation for cognitive impairment. Furthermore, healthcare professionals can benefit from workshops on how to administer these cognitive tests and when to refer patients for geriatric consultation vs simply intervene through stimulation activities.

Implementation of Iron Supplementation

In our trial, we assessed patients for iron-deficiency anemia (IDA), and, if diagnostic criteria were met, we recommended to the treating cardiologist to prescribe 300 mg of intravenous iron sucrose for three consecutive days. This required systematic screening, firstly, of hemoglobin levels, and subsequently, of iron studies (e.g., ferritin, saturation) for confirmation of IDA. The implementation of in-hospital intravenous treatment of IDA in CVD patients will require more systematic screening. Though in our trial, the hemoglobin screening was performed by kinesiologists, who then asked a cardiologist to order iron studies and prescribe intravenous iron sucrose as needed, we believe this process can be even less hospital staff-dependent in the

future. This can be achieved through a program within the electronic medical record system (i.e., *Oacis* used at the Jewish General Hospital and in the McGill University Health Center Hospitals) that can automatically screen for lab results (i.e., hemoglobin levels being outside of pre-defined cut-offs) and alert the treating physician for further testing. Indeed, a program that assesses frailty status automatically based on laboratory test results is currently being developed in our laboratory.

A secondary barrier to the use of intravenous iron-replacement therapy for hospitalized CVD patients consists of the notion that it might put patients at risk for infection. While it is true that certain bacteria depend on iron for their growth (e.g., Escherichia coli, Klebsiella, Pseudomonas, Salmonella, Yersinia, Listeria, Staphylococcus species, and Haemophilus influenzae) [23, 24], it is important to recognize that the overshadowing benefits of iron replacement therapy in CVD patients, specifically heart failure patients [25, 26]. Indeed, the AFFIRM-HF trial with intravenous iron supplementation for heart failure patients found a decreased risk of heart failure hospitalizations with similar rates of infection in both the intervention and control groups [26]. Furthermore, the adverse effects of intravenous iron replacement have been observed in those receiving higher intravenous doses compared to lower doses [27], and those who received supplementation for longer periods of time (i.e., 5-6 months) [23]. Our intervention takes place over the course of 3 days and, and though we recommend a dose of 300 mg for 3 days consecutively as per Canadian Cardiovascular Society Guidelines for Heart Failure, it is on the discretion of the treating physician to prescribe what they deeme is safe and feasible based on the patient's individual case. A workshop for physicians that allows them to review the current research on the usage of intravenous iron replacement therapy in CVD

patients and steps to mitigate infection/sepsis with its usage would be recommended to make this intervention safe and common practice.

Implementation of Nutritional Supplementation

The implementation of nutritional supplementation for malnourished CVD patients in our trial relied heavily on an open line of communication between the nutritionist, the treating physician who signs off on the prescription, and nursing staff who deliver the supplement. The kinesiologists in our trial assessed for malnourishment using the Preoperative Nutrition Score, a score that uses the lab results of serum albumin (a part of routine hospital blood tests), BMI, weight loss, and food consumption. They then alerted the nutritionist of any findings who went ahead with recommending the prescription of a calorically dense protein supplement prescribed between meals four times a day to the treating physician. Clearly, this is a multi-step process that requires confirmation by two parties before nursing staff can begin the supplementation process. One way to mitigate such a problem is again by using a program in the electronic medical record system that alerts nutritionists of low albumin levels. By flagging these patients to nutritionists right upon admission, the nutritionist can immediately perform the PONS scoring (which should take <5 minutes) and promptly contact the treating physicians for a prescription of the protein supplement.

A second barrier to the adoption of this intervention is issues relating to diabetes and control of blood sugar, as well as lactose intolerance. The supplement we provided in our trial (MedPass) does contain sugars which might increase blood glucose, especially in those with uncontrolled diabetes. Nonetheless, we suggest that in cases like this, an alternate

supplementation would be *Glucerna,* which contains carbohydrates that are less likely to cause blood glucose spikes. Similarly, for those who are lactose intolerant, we suggest the use of *Ensure* as this supplement is labelled as lactose free.

Table 1: Barriers and mitigation strategies for frailty interventions

Intervention	Barriers	Mitigation Strategies
Exercise Therapy	• Traditional view of exercise as risky for CVD patients • Increased burden on physiotherapy staff or lack of hospital staff • Lack of time • Risk of self-injury (patient)	• Increased education on the benefits of exercise for CVD inpatients • Integration of kinesiologists into the hospital setting for more frequent, safe and systematic exercise sessions with patients
Cognitive Stimulation	• Identification of patients who can benefit from this intervention is time consuming	• Use of shorter time-efficient screening tool to detect patients who need more thorough assessment
Iron Supplementation	• Detection of iron deficiency anemia is not systematically performed on cardiology wards • Risk for bacterial infection	• Use of automatic screening and flagging of patients with blood test results indicative of iron deficiency anemia within the electronic medical record system • Improved education on the benefits of intravenous iron supplementation in CVD patients • Increased education on the safe use of intravenous iron supplementation to reduce risk of infection
Nutritional Supplementation	• Prescription of nutritional supplement is preceded by multiple complex steps (screening for malnutrition, nutritionist recommendation, and physician sign-off) • Diabetic patients can lose control of blood glucose • Lactose intolerant patients can suffer from gastrointestinal symptoms	• Use of automatic screening and flagging of patients with blood test results indicative of malnutrition within the electronic medical record system • Use of alternative supplements such as Glucerna for diabetic patients (that don't cause spike in blood sugar) • Use of Ensure for lactose intolerant patients, as it is lactose free

Abbreviations: CVD, Cardiovascular Disease.

Future Directions

After having reviewed the results of this trial and discussing potential ways to overcome the barriers to its implementation, the next step is performing a knowledge translation study that includes implementing the multicomponent interventions in various hospitals and surveying the hospital staff (i.e., cardiologists, nutritionists, physiotherapists, kinesiologists, and nurses) about their experiences with the four interventions. Subsequently, this information can be used to improve the intervention strategy and increase both its efficacy and efficiency within the hospital setting. Finally, this newer model can be adopted as usual clinical care and continue to grow as more research evidence emerges in the field.

Other future directions for our trial include long-term follow-ups on patients to assess whether the intervention has any effect on mid-term frailty status or readmission/mortality. Furthermore, future trials can also assess the impact of longer intervention lengths that continue at home post-discharge from the hospital. Indeed, our laboratory is currently in the process of completing the PERFORM-TAVR trial, which seeks to identify the benefit of an exercise and nutrition home-based intervention in older transcatheter aortic valve replacement patients who are frail [28].

CHAPTER 6: THESIS CONCLUSION

As a part of our objectives, we had set out to review the concepts of frailty, CVD, their pathophysiological connections, and the existing RCTs on in-hospital de-frailing interventions for CVD patients. We were able to successfully define frailty, CVD and identify the potential mechanisms that lead to their co-existence in older patients: chronic inflammation, vitamin D deficiency and chronic increased cortisol levels due to dysregulation in the hypothalamic-pituitary axis. We also identified six completed RCTs and one ongoing trial that tested various types of de-frailing interventions in the hospital setting: exercise, protein supplementation, intravenous iron replacement, geriatric assessment and optimization, and testosterone supplementation. All the completed RCTs identified demonstrated positive effects, though some trials included mixed disease populations, with patients admitted for other diseases then CVD, and some only included clinically stable patients. There was also a lack of trials including multicomponent de-frailing interventions for broad CVD inpatients (not specialized to a specific subtype of CVD). We then conducted the TARGET-EFT randomized clinical trial to assess the effect of a targeted multicomponent (exercise, protein supplementation, iron replenishment, cognitive stimulation) de-frailing intervention for CVD patients hospitalized in the cardiology ward of the Jewish General Hospital. Our results demonstrated that such an intervention is safe and can mitigate the functional decline that is seen post-discharge from a cardiac hospitalization. We also identified subpopulations that can attain greatest benefit from this intervention (i.e., patients undergoing invasive cardiac procedures such as cardiac surgery), as well as patients who appeared to not procure as much benefit (i.e., patients with low LVEF). The findings of our RCT have the potential to transform in-hospital care for older patients admitted with CVD through its simultaneous treatment of both frailty and CVD. We have identified barriers to the

implementation of this de-frailing intervention and have developed mitigation strategies which would allow for a smoother adoption of the intervention. We hope that this intervention will allow older CVD patients to have improved functional status and quality of life post-discharge, at least on a short-term basis, something which is important given the numerous frailty risk factors that exist in the hospital setting and the rapidly aging population. Future studies can focus on knowledge translation of our intervention to ensure proper implementation to other hospitals and focus on interventions that continue post-discharge from the hospital, as well.

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* These references pertain to the entire thesis document, excluding Chapters 2 and 4, for which the references are at the end of the respective chapters.