Frailty and bleeding risk prediction in older adults

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May 2018

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master's of Science in Experimental Medicine

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English Abstract

BACKGROUND: Frail patients are more vulnerable to physiological stressors, and are therefore more susceptible to adverse events and medical complications. The risk of bleeding complications, which are strongly associated with mortality and adverse effects, is heightened in older adults.

OBJECTIVES: The objectives of this thesis are to: 1) further understand the relationship between frailty and bleeding, and 2) explore the role of frailty in predicting bleeding complications, in both a) the postoperative setting following cardiac transcatheter and surgical procedures, and b) in the clinical setting regarding anticoagulation for atrial fibrillation.

METHODS: After performing a literature review of frailty and bleeding, two studies were performed. The first study is a retrospective analysis of the FRAILTY-AVR database to examine the predictive value of frailty scales to predict in-hospital major bleeding following transcatheter or surgical aortic valve replacement (TAVR or SAVR). The second study is a prospective investigation the effect of muscle mass and sarcopenia on direct oral anticoagulant (DOAC) pharmacokinetics in older adults.

RESULTS: The FRAILTY-AVR cohort consisted of 1,195 patients of which 358 (30%) patients had a major bleeding event (137/747 [18.3%] in the TAVR group and 221/448 [49.3%] in the SAVR group). The Essential Frailty Toolset was identified as independent predictor of major bleeding complications in both TAVR (OR 1.66, 95% CI 1.39 to 1.99) and SAVR (OR 1.67, 95% CI 1.34 to 2.07), and outperformed other frailty models in predicting bleeding

complications. Major bleeding complications were strongly associated with 1-year mortality in both patient groups. The prospective study consisted of 62 patients receiving rivaroxaban or apixaban for atrial fibrillation recruited at the Jewish General Hospital. Fifteen (25%) patients had a higher DOAC peak activity, while 10 (16.4%) patients had a high DOAC trough activity level. Appendicular lean mass was identified as the independent predictor of high DOAC levels, at both trough (OR 0.78, 95% CI 0.62 to 0.98) and peak (OR 0.84, 95% CI 0.73 to 0.99) time points, and had superior predictive ability in trough (C-statistic 0.88, 95% CI 0.80 to 0.96, AIC=49.32) and peak (C-statistic 0.76, 95% CI 0.63 to 0.90, AIC=61.17) than the basic model composed of the current considered factors of age, weight and renal function.

CONCLUSION: Frailty is associated with a higher risk of bleeding events, and is shown in this thesis to predict both postoperative bleeding complications and higher levels of anticoagulation. Incorporating frailty into clinical decision-making could help refine bleeding complication risk predictions for older adults and allow clinicians to tailor therapy accordingly.

French Abstract

INTRODUCTION: Les personnes de constitution frêle sont plus vulnérables quant aux facteurs de stress physiologiques et sont donc plus sensibles aux effets indésirables et aux complications médicales. Les cas de saignement sont des complications graves associée à la mortalité et aux effets indésirables dont les risques sont accrus chez les personnes âgées.

OBJECTIFS: Les objectifs de cette thèse sont: 1) de mieux comprendre la relation entre fragilité et les complications de saignement, et 2) d'explorer la valeur pronostique de la fragilité afin que l'on puisse prévoir les complications hémorragiques a) post-opératoires et b) les incidents hémorragiques causer par l'anticoagulation pour la fibrillation auriculaire.

MÉTHODES: Après avoir effectué une revue de la littérature par rapport à la fragilité et les complications de saignement, deux études ont été retenues. La première présente une analyse rétrospective de la base de données FRAILTY-AVR afin d'évaluer la valeur pronostique de la fragilité physique sur les saignements majeurs en hôpitaux suite à une procédure de remplacement valvulaire aortique par voie transcathéter (RVAT) ou chirurgicale. La seconde étude est une enquête prospective qui avait pour objectif d'évaluer l'effet de la masse musculaire et la sarcopénie sur la pharmacocinétique des anticoagulants oraux directs (AOD) chez les personnes âgées.

RÉSULTATS: L'étude FRAILTY-AVR portait sur 1 195 patients, dont 358 (30%) ont vécus un évènement hémorragique majeur (137/747 [18.3%] du groupe RVAT et 221/448 [49.3%] du groupe chirurgicale). L'outil de fragilité essentielle a été identifié en tant que facteurs prédictifs

indépendants des complications hémorragiques majeures dans le groupe RVAT (OR 1,66, IC 95% 1.39 à 1.99) et chirugicale (OR 1,67, IC 95% 1.34 à 2.07), et a et surpassé d'autres modèles de fragilité pour prédire les complications hémorragiques. Les complications hémorragiques majeures étaient fortement associées à la mortalité à 1 an dans les deux groupes de patients. L'étude prospective comprenait 62 patients recrutés à l'Hôpital Général Juif recevant du rivaroxaban ou de l'apixaban pour la fibrillation auriculaire. Quinze patients (25%) avez un niveau de AOD élevé au temps pic et dix (16,4%) patients avez un niveau de AOD élevé au temps creux. La masse maigre appendiculaire a été identifiée comme indicateur indépendant de niveaux AOD élevés, tant au creux (OR 0,78, IC 95% 0,62 à 0,98) qu'au pic (OR 0,84, IC à 95% 0,73 à 0,99), et avait une capacité prédictive supérieure creux (C-statistique 0,88, IC à 95% 0,80 à 0,96, CIA = 49,32) et pic (C-statistique 0,76, IC à 95% 0,63 à 0,90, CIA = 61,17) que le modèle de base composé des facteurs d'âge, poids total et fonction rénale.

CONCLUSIONS: La fragilité est associée aux risques élevés de complication hémorragique. L'intégration de la fragilité dans la prise de décision clinique pourrait aider à améliorer les prédictions de risque de complications hémorragiques chez les personnes âgées et permettent aux praticiens d'adapter la thérapie en conséquence.

Acknowledgements

I would like to sincerely thank my supervisor Dr. Jonathan Afilalo for the opportunity to complete this master's program. Working with Dr. Afilalo has been an invaluable experience and his mentorship has led me to become a more independent and self-assured researcher and person. This thesis and the included manuscripts would not have been possible without his constant support and guidance throughout this entire process. I would like to thank my collaborators for their participation, expertise and insight, especially in the development of the prospective study. I would also like to acknowledge the contributions of the research coordinators and assistants of the FRAILTY-AVR study. Thank you to the Frailty Research Group for their encouragement and enthusiasm, especially to Amanda Trnkus, research coordinator, for her helpful advice and her friendship. Finally, I would like to thank my family for their constant support.

Contribution of Authors

Melissa Bendayan is the thesis candidate and primary author of this thesis under the supervision and guidance of Dr. Jonathan Afilalo. Two co-authored papers were included in this manuscript-based thesis. The first manuscript, "Patient-Level Predictors of Bleeding Complications in Older Adults Undergoing Aortic Valve Replacement: Insights from the FRAILTY-AVR study", is an analysis of the FRAILTY-AVR database, a multi-center cohort study coordinated by Dr. Jonathan Afilalo. Melissa assisted in patient recruitment and data collection for the FRAILTY-AVR study at the Jewish General Hospital site and designed the analysis for the study. Dr. Nathan Messas contributed in co-authoring the manuscript. For the second manuscript, "Association of Muscle Mass With Direct Oral Anticoagulant Activity in Older Adults", Melissa Bendayan designed the study, developed the protocol, questionnaire and consent forms, prepared and submitted documentation for ethics approval, screened and recruited patients, obtained informed consent, administered questionnaires and coordinated hospital visits. For all articles, Melissa Bendayan is the first author, and was primarily responsible for generating the design of the study, conducting analyses, interpreting the study results, and drafting the manuscripts. All co-authors critically revised and contributed to their respective manuscripts. Dr. Jonathan Afilalo reviewed and provided critical revision on all aspects of this thesis.

List of Tables and Figures

Tables

Figures

Abbreviations

ACS – acute coronary syndrome

AF – atrial fibrillation

ALM – appendicular lean mass

AUC – area under the curve

BC – bleeding complication

BMI – body mass index

BSA – body surface area

CABG – coronary artery bypass graph

CAD – coronary artery disease

CFS – clinical frailty scale

CT – computed tomography

CYP - cytochromes P450

DDI – drug-drug interactions

DOAC – direct oral anticoagulants

DXA – dual-energy X-ray absorptiometry

EFT – essential frailty toolset

EWGSOP - European Working Group on Sarcopenia in Older People

GFR – glomerular filtration rate

MMSE – mini mental status exam

MRI – magnetic resonance imaging

OR – odds ratio

P-gp – P-glycoprotein 1

PCI – percutaneous coronary intervention

PRBC – packed red blood cells

SAVR – surgical aortic valve replacement

SPPB – short physical performance battery

TAVR – transcatheter aortic valve replacement

VARC-2 - Valve Academic Research Consortium-2

V_D – volume of distribution

Chapter 1: Thesis Introduction

Frailty is a multi-faceted geriatric syndrome defined by a diminished capability to recover from pathological or iatrogenic stressors due to aging-related impairments.[1] Frail patients are more vulnerable to physiological stressors, and are therefore more susceptible to adverse events and medical complications. Bleeding events are an important complication that is strongly associated with mortality and adverse effects.[2,3] The risk of bleeding is heightened in older adults, and is even higher in frail older patients.[4]

Current established surgical risk scores are designed to predict mortality in the general demographic, but underperform in the elderly patient cohort.[5] Incorporating frailty assessment has been advocated to improve risk prediction for older adults. Bleeding risk prediction is vital in surgical settings, as bleeding is one of the most important postoperative complications. Assessing bleeding risk is imperative since learning about a patient's increased risk preoperatively can facilitate the implementation of strategies that could prevent postoperative bleeding complications.

Another domain where bleeding risk is important to consider is for patients with atrial fibrillation (AF). When deciding on anticoagulation, clinicians must optimize the patient's stroke and bleeding risk, in order to choose an appropriate therapy and dose. Accurately predicting bleeding risk in older adults is a significant issue, given that the incidence of AF rises with age.[6] Since coming into the market in the last decade, the direct oral anticoagulants (DOAC) have replaced warfarin as the anticoagulant of choice for AF.[7,8] However, there is uncertainty in the medical community regarding their efficacy and safety in older adults. For patients of advanced age or

with low body weight that appear frail, clinicians may prescribe reduced doses of DOACs as an "off-label" practice, which can lead to reduced drug activity and consequently an increased risk of ischemic events and mortality.[9] Having a proper dosing strategy that takes into account frailty and increased bleeding risk in this population is especially important for the DOACs, as there is no specific antidote for reversal at the present time.

Incorporating frailty when assessing bleeding risk could increase the utility of risk assessment in older population, and consequently lead to reduction in adverse events and bleeding complications. Thus, the objectives of this thesis are to: 1) further understand the relationship between frailty and bleeding, and 2) explore the role of frailty in predicting bleeding complications, in both a) the postoperative setting following cardiac transcatheter and surgical procedures, and b) in the clinical setting regarding anticoagulation for atrial fibrillation. In Chapter 2 of this thesis, definitions of frailty are reviewed and the relationship between bleeding and frailty are explained. The knowledge gaps regarding this issue are also described. Chapter 3 contains the first manuscript, entitled **"Patient-Level Predictors of Bleeding Complications in Older Adults Undergoing Transcatheter and Surgical Aortic Valve Replacement: Insights from the FRAILTY-AVR Study."** This study analyses the FRAILTY-AVR database to examine the predictive value of frailty scales to predict in-hospital major bleeding following a transcatheter or surgical aortic valve replacement, and determines the impact of bleeding events on long-term mortality in this population. Chapter 4 is a transitioning chapter, commenting on the preceding manuscript and explaining the protocol for the prospective study in the following chapter. Chapter 5 consists of the second manuscript, entitled **"Association of Muscle Mass With Direct Oral Anticoagulant Activity in Older Adults"** which investigates the effect of

muscle mass and sarcopenia on anticoagulant pharmacokinetics in older adults. Chapter 6 summarizes the main findings this thesis, their clinical significance and highlights further research pathways. Finally, Appendices A, B, C, D, E, F and G delineate the frailty measures discussed in this thesis in greater detail, and Appendix H lists established bleeding risk prediction scores.

Chapter 2: Literature Review

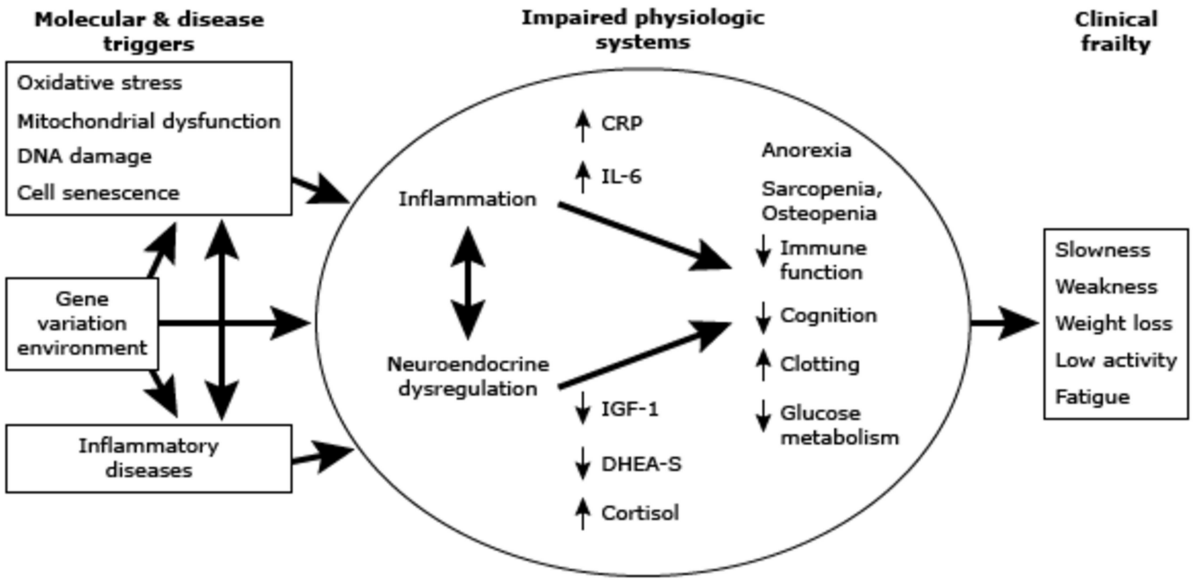
1. Frailty

1.A. Geriatric syndrome of frailty

Frailty is a geriatric syndrome that increases an individual's vulnerability to physiological stressors, such as acute or chronic disease and iatrogenic stressors.[10] This syndrome arises from an imbalance in multiple physiological systems that lead to the decline in homeostasis, and represents the difference between chronological age and biological age.[11] The Frailty phenotype is characterized by low physical activity, weakness, exhaustion, slowness, and weight loss.[12] Frailty can also be characterized as an accumulation of health deficits, such as comorbidities and disabilities.[13]

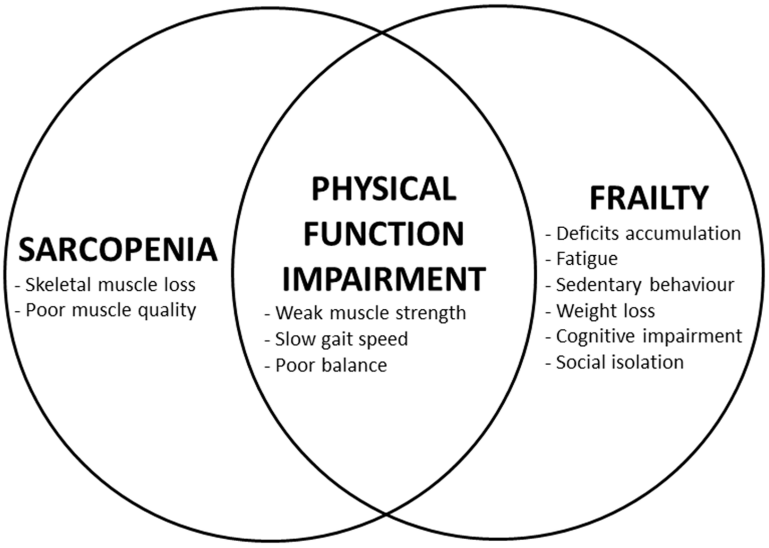
The pathophysiology of frailty involves the deregulation of the immune, hormone, and endocrine systems, notably upregulation of inflammatory cytokines such as interleukin-6 and C-reactive protein, decreased testosterone levels, and insulin resistance.[14,15]

Figure 1 – Conceptual diagram of the pathophysiology of frailty[16]



This age associated activation of inflammatory cells and decreased androgen levels upsets the balance between anabolic and catabolic stimuli, causing muscle breakdown and exacerbating the effect of aging on protein metabolism.[14,17,18] This progressive decline in muscle mass and strength is known as sarcopenia.[19] Sarcopenia represents an aspect of physical frailty, which is a component of the greater frailty syndrome.[20]

Figure 2 – Relationship among sarcopenia, frailty, and physical function impairment[21]



1.B. Sarcopenia as a core component of frailty

Sarcopenia plays an important role in the development of frailty.[20] It is regarded as the "biological substrate of frailty" since muscle is crucial for physical functioning and for mobilization of amino acids in times of stress response and healing.[20,22-24] Sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as a progressive and generalized loss of skeletal muscle and muscle strength.[25] Diagnosis of sarcopenia requires

documentation of low muscle mass and either low muscle strength or low physical performance (see Table 1).

Figure 3: Mechanisms of sarcopenia[25]

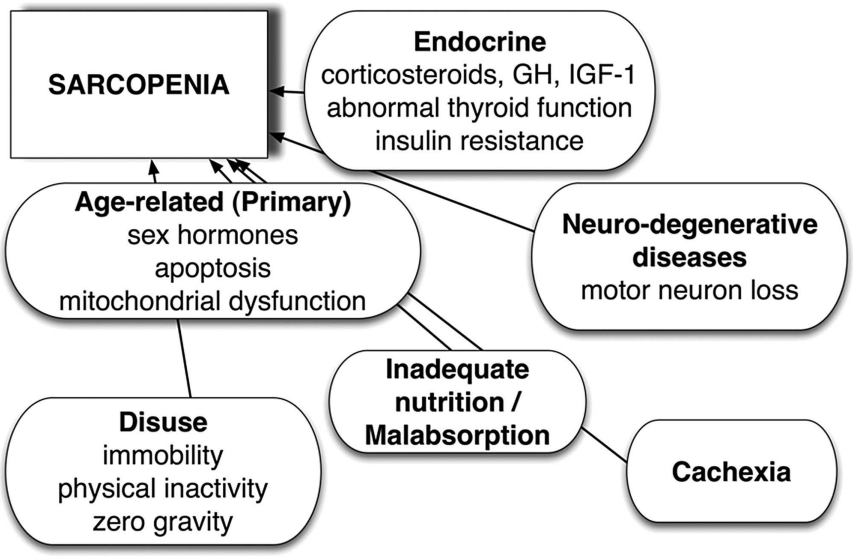


Table 1: EWGSOP definition of sarcopenia[25]

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)
1. Low muscle mass
2. Low muscle strength
3. Low physical performance

Existing frailty tools focus on muscle strength and performance, but lack a direct measure of muscle mass. Muscle strength can be easily measured with handgrip strength test, using a dynamometer to measure grip strength.[26] This simple test correlates with leg strength, is easily measured and influenced by age, gender and body mass index (BMI). Physical performance can

be ascertained with the Short Physical Performance Battery (SPPB) test, consisting of a gait speed test, time it takes to rise and sit from a seated position five times without using arms (chair rise test), and ability to balance standing for 10 seconds in a tandem or semi-tandem position, each scored out of 4 for a total score out of 12.[27]

The gold standards for measuring muscle mass are magnetic resonance imaging (MRI) and computed tomography (CT) scan.[25,28] However, high cost and limited access precludes their routine clinical use. Therefore, the preferred method to measure muscle mass for clinical and research use is by a dual-energy X-ray absorptiometry (DXA) scan. DXA is a whole-body x-ray scan used to measure body composition aspects such as bone density, body fat, and muscle mass.[29] One of the emerging ways muscle mass can be measured is with bioimpedance.[25,28] The bioimpedance scale uses undetectable micro-currents to measure weight, body fat and muscle mass. It can be located at the point of care, and newer technology has vastly improved accuracy.

Weight loss is often used to indirectly represent the muscle mass state. However, this measure is flawed because excess adiposity can mask low muscle mass.[30] "Sarcopenic obesity," defined as loss of muscle mass and increase in fat mass, is especially prevalent in the elderly. In a study of elderly cancer patients, while only 7.5% of patients were found to be underweight, 46.8% were sarcopenic when evaluated by a CT scan.[28] Muscle mass is an attractive measure of frailty because it is quantitative and independent of patient compliance, acuity, and symptom status, all which can vary day-to-day in elderly cardiovascular disease patients.

1.C. Negative impact of frailty and sarcopenia on outcomes in cardiovascular patients

Frail patients with cardiovascular disease have a worse prognosis than non-frail patients, as frailty confers a two-fold increase in mortality and major morbidity.[18,31,32] Frailty is strongly associated with increased postoperative risk following cardiac surgery, general surgery and transcatheter procedures.[33] In a study of patients aged 65 years and older undergoing a percutaneous coronary intervention (PCI), the 3-year mortality was 28% in frail patients compared to 6% in non-frail patients.[34] Frailty status can also independently predict emergency room visits and increase hospitalization.[35] Furthermore, sarcopenia is associated with increased adverse outcomes, including falls, functional decline, low quality of life, and increased mortality.[36] A 2012 study showed that sarcopenia was associated with a significant increased risk of all-cause-death in older nursing home residents.[37]

The presence of frailty can indicate the patient's resilience to withstand a stressor. Frail patients are thus more vulnerable to adverse events and important medical complications, such as bleeding.

2. Bleeding

2.A. Higher risk of bleeding complications in elderly

Bleeding is a common postoperative complication, and can be defined as fatal blood loss, major hemorrhage, intracranial or gastrointestinal bleeding, and blood loss resulting in hemoglobin drop or requiring blood transfusion. The incidence of major bleeding complications has been reported to vary between 0.7–8.9% after PCI,[38] 15-20% after TAVR,[39] and 22-44% after SAVR.[40-42] The risk of bleeding complications is heightened in older adults.[43,44] In patients undergoing PCI, one of the strongest predictors for major bleeding was advanced age: compared

to a cohort age <50, age 80 years and above is associated with an odds ratio (OR) of 1.9 (compared with age <50 years, p = 0.001).[2] Similarly, bleeding during long-term follow-up was also doubled in patients aged 80 to 89 years when compared with those aged 70 to 79 years.[44] A study of patients aged 65 and older taking warfarin with AF found that patients greater than 80 years old experienced higher rates of major bleeding compared with the younger patients (13.08 versus 4.75 per 100 person-years).[43]

2.B. Higher risk of bleeding complications in frail cardiovascular patients

The increased risk of bleeding complications in older adults is even higher in frail patients: frailty markers have been associated with increased bleeding.[45] In a study of patients undergoing TAVR, a frailty score of >5 out of 12 was associated with in-hospital life-threatening or major bleeding event at 30 days post operation.[46] In hospitalized patients with acute coronary syndrome (ACS), frailty was an independent predictor of major bleeding, conferring an adjusted hazard ratio (HR) of 2.7 (95% CI 1.2 to 5.7, p=0.012).[47] Frailty was also associated with bleeding in catheterized patients following a myocardial infarction (MI).[48] There is a fragile balance between bleeding and thrombosis in stenting procedures, which can be easily disrupted in a frail patients who are more vulnerable to stressors and have decreased homeostatic reserve.[49]

2.C. Bleeding is strongly associated with mortality

Bleeding complications are strongly associated with mortality and adverse effects.[2,50] Bleeding is an independent marker of adverse outcomes, and has an increased prognostic impact in older patients.[47] Patients undergoing PCI with major bleeds had a higher in-hospital and one-year mortality rate compared to patients with minor and no bleeds.[2] ACS patients receiving

anticoagulant and antiplatelet therapy that experienced a major bleeding event post-surgery had a five-fold higher incidence of death in the first 30 days compared to patients without bleeding events (12.8% vs. 2.5%), and a 1.5-fold higher incidence of death between 30 days-6 months (4.6% vs. 2.9%).[51] Importantly, the risk of death increased with the rising severity of bleeding. Following a transcatheter procedure, patients with bleeding complications had increased readmission and a three times greater risk of mortality three years post-procedure.[50,52] Major bleeding is also likely to lead to the discontinuation of antithrombic medications following a procedure, increasing the risk of MI or stroke and thus strengthening the link of death with major bleeding complications.[51]

3. Bleeding and frailty

3.A. The importance of frailty in calculating postoperative bleeding risk

The presence of the frailty syndrome plays an important role in guiding clinical decisions for older adults, as predicting risk is more complex given their highly variable status. Clinicians are able to use the frailty assessment to better predict the risk of adverse events in this population and to choose an appropriate therapy for their patients. For instance, preoperative presence of frailty can indicate the patient's ability to withstand the stressor of surgery, and their postoperative risk of mortality and complications.

Although several frailty scales used for this purpose are prominent in the literature, the lack of consensus around which scale to use and the definition of frailty has limited its integration into routine clinical practice and pre-surgical assessment. These scales include the previously mentioned SPPB, the Fried scale, and the Rockwood Clinical Frailty Scale (CFS). The SPPB

scale is out of 12, with a score of 5/12 or below to diagnose frailty. The Fried scale consists of 5 items, with a score of 3/5 required to diagnose frailty: 5-meter gait speed, handgrip strength, unintentional weight loss, low physical activity, and exhaustion. The Rockwood Clinical Frailty Scale allows for the global assessment of the patient's symptoms, physical activity, energy, mobility, and disability for basic and instrumental activities of daily living, assigned a score ranging from 1 (least) to 9 (most) frail, among others. These scales are used to assess pre-operative risk on both cardiac and non-cardiac surgeries.[5,18]

The recent prospective multi-center cohort FRAILTY-AVR study, conducted by our research group, compared the predictive value of these frailty scales in older adults undergoing TAVR or SAVR procedures.[4] The Essential Frailty Toolset (EFT) was found to be the strongest predictor of mortality and disability at one year from all the scales compared. The EFT consists of 4 items, the chair rise test (1 point if <15s, 2 points if unable to complete), cognition (1 point if Mini-Mental State Examination score <24), hemoglobin (1 point if <13 g/dl in men or <12 g/dl in women), and serum albumin (1 point if <3.5 g/dl, or if serum albumin was not measured then Mini-Nutritional Assessment score <8), for a composite score out of 5. However, these scales have not yet been used to assess bleeding, despite the increased bleeding rate for frail older adults.

3.B. Bleeding assessment in anticoagulation

Bleeding risk assessment plays an important role when deciding on anticoagulation. AF is the most common clinically significant cardiac arrhythmia, and 10 million North Americans are estimated to be affected.[53,54] The prevalence of AF is growing globally, with the rates

increasing from 569.5 per 100,000 in males and 359.9 per 100,000 in females in 1990, to 596.2 per 100,000 in males and 373.1 per 100,000 in females in 2010.[55] AF increases the risk for stroke by five-fold and is associated with increased morbidity and mortality.[56] Both the incidence and prevalence of AF increases with advancing age.[55] The incidence of AF doubles each decade after age 55.[53] While the prevalence of AF is 0.5-3% in the general population, it is 5-6% in adults above the age of 65, and up to 15% in those above age 80.[57] Furthermore, 70% of those with AF are 65 years or older.[6]

Treatment for AF includes anticoagulation to prevent thromboembolic complications and address the increased risk of stroke. Warfarin, a vitamin K antagonist, was the standard treatment for AF and the most commonly prescribed anticoagulant. However, warfarin prescription rates have decreased since the approval of DOACs.[58] Since 2010, four DOACs have been approved by the United States Food and Drug Administration: dabigatran (2010), rivaroxaban (2011), apixaban (2012), and edoxaban (2015). The new generation of anticoagulants are advantageous and have been preferred over warfarin due to their predictable anticoagulant effect, shorter half-life, and can be prescribed in fixed doses without routine coagulation monitoring.[59] The literature has shown that the DOACs are superior or equivalent to warfarin in preventing stroke or systemic embolism, with lower rates of hemorrhage.[7,8,60]

Clinicians have to consider both the stroke risk and bleeding risk when deciding on anticoagulation therapy. One tool that is commonly used is the CHA_2DS_2-VASc score, which assesses the stroke risk of a patient with AF.[61] Estimating the risk of stroke is based on the following factors: congestive heart failure, hypertension, diabetes mellitus, and sex (1 point

each), age ≥75 years old and stroke/transient ischemic attack/thromboembolism (2 points each), history of vascular disease, age 65 to 74 years old, and female sex (1 point each), for a total of 9 points. A higher score corresponds to a greater stroke risk. Having a score of 2 or greater points is an indication for anticoagulation. (Table 2)

Table 2: CHA_2DS_2-VASC Score for Stroke Risk Prediction

CHA_2DS_2-VASc Risk Criteria	**Score**
Congestive heart failure	1 point
Hypertension	1 point
Age ≥75 years	2 points
Diabetes mellitus	1 point
Stroke/Transient Ischemic Attack/Thromboembolic event	2 points
Vascular disease (prior MI, PAD, or aortic plaque)	1 point
Age 65 to 74 years	1 point
Female sex	1 point

Advanced age is a major risk factor for DOAC-related bleeding adverse events.[62] The bleeding risk for older adults receiving DOACs is estimated to be 1.5% per year for major bleeding and 3.5% per year for non-major bleeding.[43,63] Oral anticoagulants are the most common cause of drug-related hospital visits in older adults, accounting for 18% of such visits.[64,65] The risk of bleeding is especially concerning for DOACs since antidotes are only now being developed and are not widely available for reversal in patients presenting with life-threatening bleeds.

Due to the known increase in bleeding in frail older adults, some clinicians are reticent to prescribing these medications. Physicians are uncertain about balancing the risk of stroke and the risk of bleeding in the elderly, leading to underuse of anticoagulation.[66] In a study of family

medicine residents, regardless of training level, the residents preferred warfarin to DOACs due to a fear of adverse bleeding events, highlighting the knowledge gap in this area.[67] Moreover, dose reductions are often prescribed "off-label" for frail older patients due to the perceived risk of bleeding complications. In the Unites States, almost 1 in 8 patients received the wrong DOAC dose, with those who received an off-label dose more likely to be older.[68] A recent Canadian registry found that 1 in 5 patients received an inappropriate DOAC dose.[69] The patients who were dose inappropriately were more likely to be older and of lower weight. Maes *et al*. found that half of the population above age 75 did not receive any anticoagulation, despite there being a clear indication warranting such therapy.[70] Furthermore, frail patients are even less likely to receive anticoagulation.[71] Nursing home residents classified as frail was associated with low frequency of DOAC use despite high stroke risk, with fewer than 50% of residents receiving DOACs.[72] Nguyen *et al*. found that frailty significantly decreased the likelihood of anticoagulant prescription upon hospital discharge, with prescription rates from 62.6% in the non-frail cohort to 49.3% among frail patients (p=0.02).[57] Lefebvre *et al*. found that non-frail patients were 3.5 times more likely to receive anticoagulation therapy compared to patients who were severely frail, independent of age and bleeding risk.[73] Despite the increased bleeding risk, older adults have a higher stroke risks than the general population and would benefit the most from stroke risk reduction.[74,75]

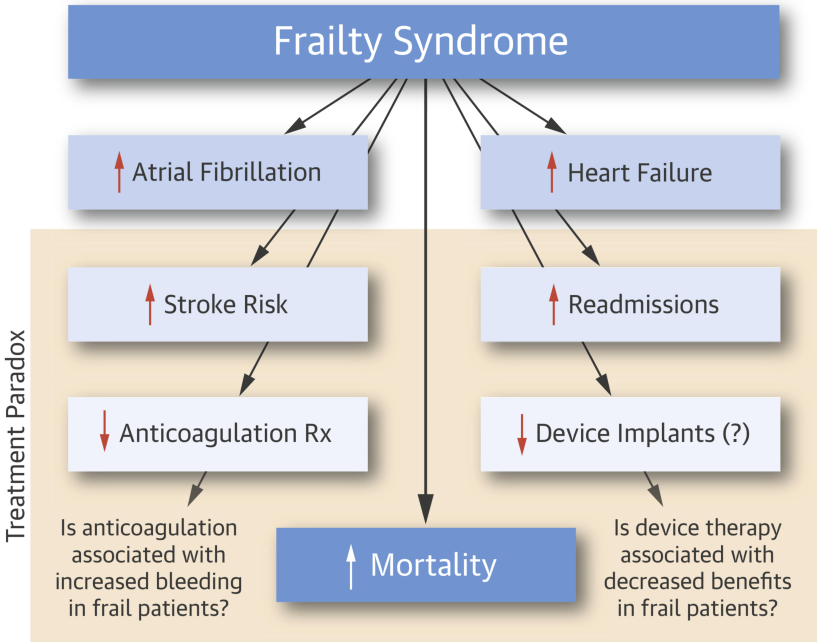
There are no specified geriatric dosing adjustments for older adults. To limit the risk of bleeding associated with DOACs, dose reduction is recommended for apixaban-treated patients with two of the following three criteria: ≥80 years of age, low body weight (<60 kg), or high serum creatinine (≥133 mmol/L; ≥1.5 mg/dL).[76] Dose reduction is recommended for rivaroxaban-

treated patients with a creatinine clearance of 30-50 ml/min, while age and body weight are not specifically considered.[77] Furthermore, there are no specific dosing recommendations for frail patients.[78] In practice, DOACs are frequently prescribed at a lower-than-recommended dose, such that 15% of low dose DOAC prescriptions do not meet the approved criteria for dose reduction.[74] Off-label dosing is associated with worse clinical outcomes, including a higher rate of cardiovascular hospitalization, systemic embolism, major bleeding, and death.[75]

Despite the prevalence of AF in older adults, less than 25% of the participants in the landmark DOAC trials were above age 80.[79] Many studies conducted on DOACs since their approval has included older participants, including a comprehensive meta-analysis of over 25,000 patients age 75 and above from Sardar *et al*. which confirmed the non-inferiority of DOACs compared to warfarin in this population.[80] However, the authors of this meta-analysis cautioned that this did not truly reflect the "real word" elderly population, since elderly trial patients had fewer comorbidities, superior cognitive and physical functioning, and lower frailty. The absence of frailty is important, as using chronological age is not sufficient surrogate measure marker for biological age. Relying on clinician judgment alone has been shown to often overestimate bleeding risk and underestimate thromboembolic risk, especially older adults.[81] A reason for this may be that physicians are more concerned by the prospect of a harm, causing a hemorrhage from prescribing an anticoagulant, that the opportunity for benefit, of preventing more strokes. [82] There is a need for a frailty assessment in this context to better assess risk for older adults and help frame clinical decision making in an objective manner.

The gap in knowledge regarding DOAC dosing in older adults has been well articulated in the literature.[79,83-86] A recent review of frailty in AF highlighted a treatment paradox in which higher risk frail patients were less likely to receive treatment for AF.[87] The authors found that while frail patients had an increased prevalence of AF compared to age-matched non-frail patients, frail AF patients had lower use of oral anticoagulation, despite having a higher risk of fatal and nonfatal stroke and systemic embolism.

Figure 4: Effect of Frailty on Prevalence, Prognosis, and Therapy for Atrial Fibrillation[87]



Current tools available to assess the benefit-risk ratio in elderly population are suboptimal. Many decision-making aids and scales have been developed, but utility in frail older adults have not yet been established. This uncertainty could explain why there is such a high percentage of off-label DOAC dosing, as physicians may be tailoring the doses of these medications to the individual patient's underlying risk based on their judgement as opposed to dosing guidelines.

3.C. Current Bleeding Risk Prediction Scores

At present, there exist many prediction scores that aim to calculate bleeding risk. Identifying those most at risk for bleeding complications is important in order to implement preventative strategies prior to the procedure to reduce bleeding risk. There are a large number of therapies available to physicians to decrease blood loss when the risk is known, such as activated factor VII or aprotinin.[88] Other strategies include ameliorating the underlying factors that contribute to the increased bleeding risk. Similarly, detecting patients at higher risk for a bleeding complication can guide clinicians when deciding on an anticoagulant and identify patients that need closer follow-up.

Despite the importance and utility of such a prediction tool, there is no unified score. Therefore, further studies are needed to improve management perioperative bleeding. Furthermore, there is a need for such scales to be verified in elderly. A list of common bleeding risk prediction scores can be found in Appendix H. Table 1 highlights scores developed for use in cardiac surgery and percutaneous interventions, while Table 2 lists scores used for atrial fibrillation. In short, there is a need to improve bleeding management and to identify those with elevated bleeding risk.[89]

While the association between frailty status and increased bleeding is clear, the underlying mechanisms require further investigation. Given what is known about the relationship between frailty and bleeding, the objective of this thesis was to explore the role of frailty in predicting bleeding complications, in both the post operative setting by retrospectively analyzing the

FRAILTY-AVR database (see chapter 3), and by prospectively exploring the relationship between muscle mass and anticoagulant activity in atrial fibrillation (see chapter 5).

Chapter 3: Retrospective cohort study

Manuscript to be submitted: "Patient-Level Predictors of Bleeding in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement: Insights from the FRAILTY-AVR study"

This study was presented at the 2016 Canadian Cardiovascular Congress, Montreal, QC, October 24th, 2016.

Frailty and Patient-Level Predictors of Bleeding Complications in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement: Insights from the FRAILTY-AVR Study

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ABSTRACT

BACKGROUND: Bleeding complications are harbingers of mortality and major morbidity in patients undergoing transcatheter (TAVR) or surgical (SAVR) aortic valve replacement. Despite the high prevalence of frailty in this population, little is known about the effect of frailty on bleeding risk. In this study, we sought to examine the predictive value of frailty to predict in-hospital major bleeding following TAVR and SAVR, and to determine the impact of major bleeding on mid-term mortality.

METHODS: Post hoc analysis of the FRAILTY-AVR cohort study that prospectively enrolled older adults aged 70 years or older undergoing TAVR or SAVR at 14 institutions in Canada, the United States, and France between 2012 and 2017. Before the procedure, trained researchers administered a frailty questionnaire and physical performance battery, and ascertained comorbid conditions and laboratory data from the electronic health record. For the purposes of this analysis, the primary endpoint was major or life-threatening bleeding during the index hospitalization defined according to the Valve Academic Research Consortium (VARC)-2 criteria, and the secondary endpoint was units of packed red blood cells transfused.

RESULTS: The cohort consisted of 1,195 patients with a mean age of 81.3 ± 6.0 years. The incidence of life threatening bleeding, major bleeding with a clinically apparent source, and major bleeding without a clinically apparent source was 3%, 6%, 9% in the TAVR group, and 8%, 10%, 31% in the SAVR group, respectively. Multivariable regression identified frailty, as measured by the Essential Frailty Toolset (EFT), as an independent predictor of composite major bleeding events and packed red blood cell transfusions for both groups. Major bleeding events

were associated with 1-year mortality following TAVR (OR 3.40, 95% CI 2.22 to 5.21) and SAVR (OR 2.79, 95% CI 1.25 to 6.21).

CONCLUSIONS: Frailty defined according to the EFT is predictive of major bleeding complications among older adults undergoing TAVR or SAVR. Major bleeding complications are associated with a threefold increase in mid-term mortality, underscoring the need for preventative strategies to reduce the risk of bleeding in vulnerable patients.

INTRODUCTION

Patients undergoing transcatheter or surgical aortic valve replacement (TAVR or SAVR) are exposed to a non-negligible risk of post-procedural bleeding and transfusions.[39,40,90] The incidence of major bleeding complications (BC) has been reported to vary between 15-20%[39] after TAVR and 22-44%[40-42] after SAVR, and has been consistently shown to be associated with early and late mortality.[40,52,91] Given the prognostic impact of bleeding after these procedures, patient factors that increase the risk of bleeding should be considered by clinicians to improve risk stratification and allow for preventative strategies. Although numerous predictors of BC and packed red blood cell (PRBC) transfusions have been identified,[40,92-98] little is known about the effect of frailty markers on BC.

Frailty, a geriatric syndrome defined by a diminished capability to recover from pathological or iatrogenic stressors due to aging-related impairments, has been established as a major risk factor for death and disability following TAVR and SAVR.[4] However, it remains unknown whether different frailty markers are useful for prediction of BC in older patients undergoing these procedures. The Essential Frailty Toolset (EFT) is a pragmatic frailty scale that encompasses physical weakness, cognitive impairment, anemia, and hypoalbuminemia; all of which have plausible mechanistic ties to bleeding. Thus, we sought to examine the incremental value of frailty to predict major BC in the multicenter FRAILTY-AVR study, and subsequently, to determine the impact of BC on mid-term mortality.

METHODS

Study design

The FRAILTY-AVR cohort study consisted of older adults undergoing TAVR or SAVR prospectively enrolled at 14 institutions in Canada, the United States, and France. The study protocol has been previously described;[4] in brief, consecutive patients were approached and invited to complete a pre-procedural geriatric assessment consisting of physical performance tests and frailty questionnaires. Major and minor BC were ascertained according to Valve Academic Research Consortia (VARC-2) criteria by trained researchers from medical records. Vital status was ascertained up to 1 year. This study was registered on ClinicalTrials.gov (Identifier NCT01845207) and approved by the ethical review boards at the participating hospitals. All patients signed an informed consent form prior to participating.

Study population

Patients with symptomatic aortic stenosis were screened in aortic valve clinics and inpatient wards. Patients were included if they were aged 70 years or older, scheduled to undergo TAVR or SAVR with or without concomitant revascularization, and consented to participate between January 2012 and December 2017. Patients were excluded if there was a need for emergency surgery, concomitant replacement of another heart valve or aorta, clinical instability (unstable vital signs, refractory ischemia, acute decompensated heart failure), severe neuropsychiatric impairment, or if there was a prohibitive language barrier.

Frailty scales

A number of frailty scales were examined for the purposes of this study. The EFT is scored 0-5 and consists of: timed chair rises, cognitive assessment, hemoglobin, and serum albumin. The Fried scale is scored 0-5 and consists of 5 items: gait speed, grip strength, weight loss,

exhaustion, and physical activity. The Rockwood Clinical Frailty Scale (CFS) is scored 1-9 and reflects of a global assessment of the patient's frailty and disability. The Short Physical Performance Battery (SPPB) is scored 0-12, where a higher score is less frail, and consists of: gait speed, timed chair rises, and standing balance. The Columbia scale is scored 0-12 and consists of gait speed, grip strength, serum albumin, and disability for activities of daily living.

Covariates

Patient-level covariates were defined *a priori* to capture risk factors and effect-modifiers known to be associated with BC. Patient interviews and medical records were used to extract cardiac and non-cardiac comorbidities, procedural data, laboratory data (including pre- and post-procedural hemoglobin levels), imaging data, and information on disposition and repeat hospitalizations. Time-dependent medication prescriptions were not collected, although current atrial fibrillation and recent myocardial infarction were considered as proxy covariates for anticoagulation therapy and dual-antiplatelet therapy, respectively. Researchers were trained at the beginning of the study, with adjudication of uncertain cases by site investigators, and central review of all data for quality and integrity.

Study outcomes and definitions

The primary endpoint was the occurrence of major or life-threatening BC during the index hospitalization, termed "major BC" and defined according to the VARC-2 criteria as fatal bleeding, bleeding in a critical organ, bleeding causing hypovolemic shock, or bleeding leading to one of the following: ≥3 g/dl hemoglobin drop, ≥2 units of PRBC transfusions, or causing hospitalization, permanent injury, or reoperation.[99] Sensitivity analysis was performed restricting

this endpoint to major BC for which a bleeding source was clinically apparent (excluding cases solely defined by a hemoglobin drop or PRBC transfusions). The secondary endpoint was the number of PRBC units transfused. One-year mortality was defined as death from any cause occurring during the first year following TAVR or SAVR.

Statistical analysis

Continuous variables were expressed as means±standard deviations, and categorical variables were expressed as frequencies and percentages. After stratifying the cohort by TAVR or SAVR, summary statistics were generated and compared between patients with and without major BC using the student t-test for continuous variables and chi-square test for dichotomous variables. Multivariable models were constructed to determine the association between frailty and the endpoints of interest after adjusting for patient-level covariates, using logistic regression for major BC and linear regression for number of PRBC transfusions. To investigate the relation between in-hospital major BC and mid-term mortality, survival analysis was performed using the Kaplan-Meier estimates and log-rank test. The incremental value of frailty compared to no frailty measure was evaluated using the c-statistic and the Akaike information criterion (AIC). All analyses were performed with the STATA 14 software package (College Station, Texas).

RESULTS

The FRAILTY-AVR cohort consisted of 1,195 patients, of which 747 underwent TAVR and 448 underwent SAVR; 238 with and 210 without concomitant coronary artery bypass grafting. The mean age was 83.4±5.6 years (45% female) with a Society of Thoracic Surgeons predicted risk

of mortality of 6.1±4.2 % in the TAVR group, as compared to 77.6±4.6 years (36% female) with a Society of Thoracic Surgeons predicted risk of mortality of 3.4±2.1 % in the SAVR group.

Incidence of bleeding and univariate predictors

In the TAVR group, 26 (3%) had a life-threatening bleed, 42 (6%) had a major bleed with a clinically apparent source, 69 (9%) had a major bleed without a clinically apparent source, and the mean number of PRBC transfusions was 0.9±2.8 units. In the SAVR group, 38 (8%) had a life-threatening bleed, 43 (10%) had a major bleed with a clinically apparent source, 140 (31%) had a major bleed without a clinically apparent source, and the mean number of PRBC transfusions was 2.7±2.8 units. Correlates of BC are summarized in Table 1.

Multivariable predictors of bleeding and PRBC transfusions

In the TAVR group, frailty defined according to the EFT was independently predictive of major BC (OR 1.66 per EFT point, 95% CI 1.39 to 1.99, p<0.000) and of PRBC transfusions (Beta 0.46 per EFT point, 95% CI 0.28 to 0.64, p<0.001). The other predictors of major BC were pre-procedural platelet count (OR 1.03 per $10x10^9$/L, 95% CI 1.01 to 1.06) and non-femoral access site (OR 2.32, 95% CI 1.44 to 3.75). In the SAVR group, the EFT was independently predictive of major BC (OR 1.67 per EFT point, 95% CI 1.34 to 2.07) and PRBC transfusions (ß 0.69 per EFT point, 95% CI 0.39 to 0.98). The other predictors of major BC were weight (OR 0.97 per kg, 95% CI 0.96 to 0.99), recent myocardial infarction (OR 4.84, 95% CI 1.29 to 18.15), and concomitant CABG (OR 1.94, 95% CI 1.34 to 2.07) (Table 2 and 3).

Comparison of frailty scales

The EFT was more predictive of incident BC as compared to the Fried, SPPB, CFS and Columbia frailty scales in the TAVR and SAVR groups (Table 4). Addition of EFT to the clinical risk model improved the C-statistic from 0.71 to 0.74 in the TAVR group, and from 0.72 to 0.76 in the SAVR group.

Impact of bleeding on outcomes

In the TAVR group, patients with a major BC had higher rates of mortality at 30 days (3% vs. 13%, OR 4.24, 95% 2.19 to 8.21, P<0.001) and 1 year (14% vs. 36%, OR 3.40, 95% 2.22 to 5.21, P<0.001). In the SAVR group, patients with a major BC had higher rates of mortality at 30 days (0% vs. 6%, OR 14.13, 95% 1.83 to 108.92, P=0.01) and 1 year (4% vs. 11%, OR 2.79, 95% 1.25 to 6.21, P=0.01). Kaplan-Meier curves are shown in Figure 3 and 4. Major BC were associated with 1-year mortality following TAVR (OR 3.40, 95% CI 2.22 to 5.21) and SAVR (OR 2.79, 95% CI 1.25 to 6.21) groups. Patients with a major BC had higher risk of serious postoperative complications, prolonged length of stay, and need for discharge to specialized healthcare facilities (Table 5).

Sensitivity analysis

When restricting the primary endpoint to life-threatening bleeding or major bleeding with a clinically apparent source (i.e. excluding events characterized by a hemoglobin decline or a PRBC transfusion), the multivariable logistic regression model yielded similar results (Table 6). Frailty defined according to the EFT was independently predictive of clinically apparent major BC (OR 1.30 per EFT point, 95% CI 1.10 to 1.53, p=0.002). The other predictors of clinically apparent major BC were recent myocardial infarction (OR 2.22, 95% CI 1.05 to 4.69, p=0.04)

cirrhosis (OR 6.06, 95% CI 1.84 to 19.94, p=0.003), and combined SAVR/CABG procedures (OR 3.97, 95% CI 2.39 to 6.61, p<0.001).

DISCUSSION

FRAILTY-AVR is the largest prospective study to date specifically designed to investigate the impact of frailty on a variety of adverse health outcomes in older adults undergoing TAVR and SAVR. The aim of the current study was to ascertain the ability of frailty scales to predict in-hospital major bleeding events and identify the main predictors of this complication. Our results can be summarized as follows: (1) A substantive number of high-risk older patients suffer major BC after a TAVR or SAVR procedure. (2) Frailty as measured by the EFT was an independent predictor of major BC and PRBC transfusions. (3) Finally, major BC were associated with a downstream risk of prolonged length of stay, serious postoperative morbidity, and mid-term mortality.

Predictors of BC and PRBC transfusions after aortic valve replacement have been examined in several registries and clinical trial databases, although most of these did not afford access to prospectively collected measures of frailty. Predictors of BC have included: female sex, low BMI,[94,95] anemia, atrial fibrillation,[95,100] peripheral arterial disease,[98] chronic kidney disease,[95-97] diabetes,[97,101] and dual anti-platelet therapy.[96] Green at al. measured frailty using the Columbia scale and reported a trend towards more BC in frail patients undergoing TAVR, although the sample size of 159 patients was underpowered to prove a definitive effect.[46] Our study adds to this body of evidence, having validated clinical predictors of BC and establishing frailty as an additive predictor in a large cohort of older patients. The four components of the EFT (physical

weakness, cognitive impairment, anemia, and hypoalbuminemia) have plausible empirical and mechanistic connections to bleeding.

Sarcopenia is the co-occurrence of low muscle mass and weakness,[102] which can be assessed with the chair rise test. The chair rise test records the time taken to rise and sit from a seated position five times,[27] and has been shown to predict poor outcomes and disability.[103,104] This simple test reflects the underlying state of the muscle, tissue quality, and body composition. In particular, sarcopenic patients have a smaller volume of distribution for hydrophilic drugs, including anticoagulant heparin-based drugs commonly used in high-dosages during cardiopulmonary bypass for SAVR. This pharmacokinetic alteration results in less drug distribution in muscle and more drug distribution in plasma, and therefore supra-therapeutic anticoagulation effect and risk of bleeding. Anticoagulant drugs are also more likely to cause bleeding in the presence of cognitive impairment. The MMSE, as used in this study, was shown to be predictive of BC in older adults with atrial fibrillation – a common complication after cardiac surgery.[105] The MMSE was also predictive of postoperative delirium,[106-108] which is associated with postoperative morbidity,[109] and specifically with BC in the setting of abdominal surgery[110], elective non-cardiac surgery,[111] vascular surgery[112], and cardiac surgery.[113]

Serum albumin levels are inversely correlated with the risk of major complications, including BC, following cardiac surgery[114,115] and TAVR.[46,116,117 117,118] Serum albumin is a crude indicator of health status and systemic inflammation, and hypoalbuminemia is well known to be associated with morbidity and mortality in various settings.[119-121 122,123] The impact of hypoalbuminemia has been repeatedly demonstrated in critically ill patients,[122,124] prompting the incorporation of serum

albumin levels into the Acute Physiology and Chronic Health Evaluation (APACHE) III score to classify the disease severity in the intensive care unit.[125] Although the mechanistic link between hypoalbuminemia and BC has yet to be elucidated, one possible explanation is that hypoalbuminemia is acting as an marker of disease severity, acuity, and consequent risk of morbidity.[126 127] Another possible explanation is that hypoalbuminemia is causing a shift to the equilibrium of protein-bound drugs, such as anticoagulant drugs that are often prescribed in this patient population.[128,129] When there are reduced plasma proteins, there is a reduction in drug-protein binding, causing an increase in the amount of unbound active drug; in the case of anticoagulant drugs, an increase in drug level could directly increase the bleeding risk.

Serum hemoglobin levels are inversely correlated with the risk of BC following cardiac surgery[130] and TAVR.[92-94,100] Stepinska *et al*. showed that nearly half of patients had anemia before TAVR and that this was an independent predictor of in-hospital major BC and long-term mortality.[93] Rannuci *et al*. showed that preoperative anemia was associated with a 35% relative increase in operative mortality risk after adjustment for other confounders.[130] Furthermore, serum hemoglobin levels are inversely correlated with the need for PRBC transfusions, which has been associated with subsequent morbidity and mortality in cardiac surgery. By starting from a lower serum hemoglobin, anemic patients are naturally more likely to cross a transfusion threshold and receive PRBCs; however, our data suggests that anemic patients are also more likely to develop clinically overt BC (not simply low serum hemoglobin values triggering reflexive transfusions). A possible mechanistic explanation may be related to the sheer stress caused by anemia-induced high-output hyperdynamic state on circulating blood vessels and tissues, which heightens their propensity to bleed.[131,132]

In the current report, in-hospital major BC adversely affected the mid-term survival of TAVR and SAVR patients. This is consistent with previous reports that have highlighted the deleterious effects of BC on mortality and major morbidity.[97,98,100,133] Tamburino *et al.* compared the one-year outcomes of patients undergoing TAVR or SAVR and found life-threatening BC to be among the strongest predictors of all-cause mortality.[91] Similarly, in a post-hoc analysis of the PARTNER I trial, major BC occurring within 30 days were strongly and independently associated with one-year mortality after SAVR, although less so after TAVR (presumably because of the lower average severity of bleeding events in the latter).[40] The CoreValve Italian Registry found that BC were highly predictive of mortality at 30 days and at 3 years.[52] Furthermore, PRBC transfusions are known to have their own deleterious effects on patient outcomes, with increased PRBC transfusions being associated with acute kidney injury and volume overload.[134] Thus, preventing BC would dually benefit patients by obviating the need for post-procedural PRBC transfusions.

The risk factors identified in this study may be targeted to potentially reduce the risk of BC. Anemia could be investigated and optimized pre-procedure, in particular seeking to correct iron deficiency if present, or to prescribe erythropoietin supplementation in qualifying patients with chronic kidney disease.[135,136] Hypoalbuminemia could trigger a consultation with a clinical dietician to evaluate and optimize nutritional status. While serum albumin is a recommended parameter in the evaluation of malnutrition,[137,138] it is multifactorial and may reflect non-nutrition factors.[121,139] Another potential strategy to increase serum albumin levels may be administering an intravenous infusion of albumin While some studies have shown promise in

critically ill patients,[140] more evidence is needed to confirm the benefits of albumin infusion in cardiac patients.[141] Muscle mass and weakness can be increased through prehabilitation, which can also benefit cognitive functioning. Moreover, the procedural approach can be tailored on the basis of frailty to mitigate the heightened risk of BC, either by opting for the least invasive type of procedure, or by instituting blood conservation techniques and pharmacotherapies that may be beneficial and cost-efficient if selectively applied in this high-risk patient subset.

Limitations

There are a number of limitations to this study. Although standardized criteria were used to define bleeding events, these were ascertained by chart review and were not centrally adjudicated, leading to a source of non-differential misclassification bias. Different thresholds may be considered clinically meaningful for hemoglobin decline and PRBC transfusions following TAVR or SAVR; nevertheless, a common definition was used and ultimately proved to have a similar association with downstream mortality regardless of the type of procedure. Less clinically meaningful major bleeds without an apparent source were included, but the predictors were remarkably consistent when these were excluded from the primary composite endpoint. Since this was a post hoc analysis of the FRAILTY-AVR study, certain bleeding-related covariates were not available for adjustment, leading to a potential source of confounding bias. Medications are one such source, in particular, antiplatelet and anticoagulant drugs. Adjustment for these drugs would have had to be undertaken in a time-dependent manner, since they are typically held during and shortly after an invasive procedure. Given that the use of heparin anticoagulation is routine during SAVR and dual-antiplatelet therapy is routine after TAVR, the inter-patient variability in these drugs is largely a function of co-morbid atrial fibrillation or

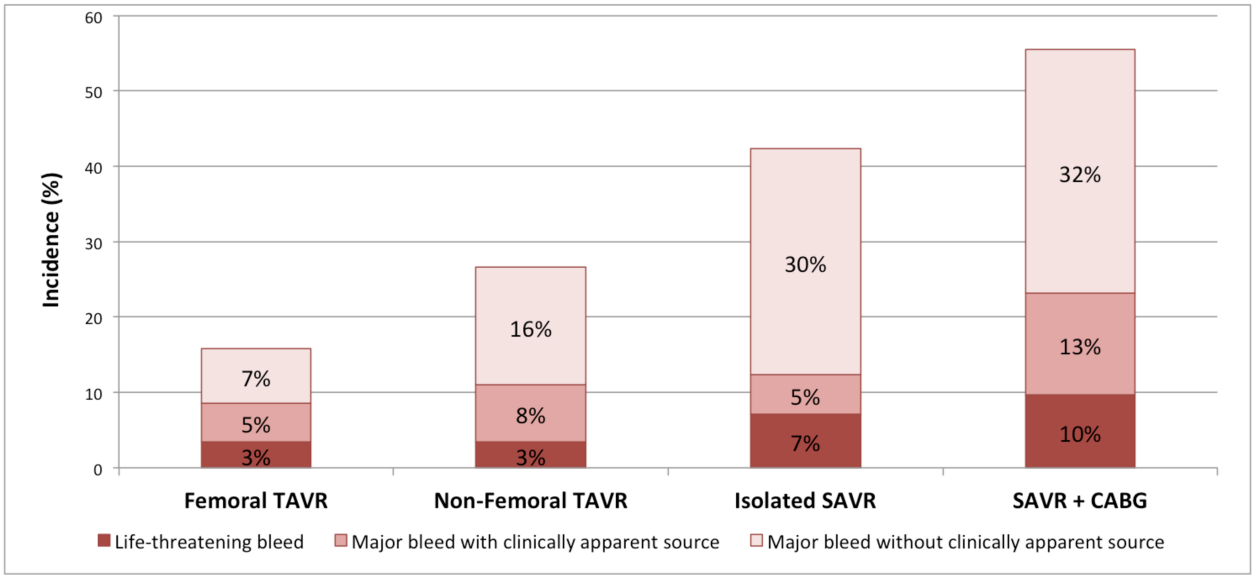
recent myocardial infarction – both of which were adjusted for in our multivariable models.

CONCLUSIONS

Major bleeding is a common and potentially devastating complication following TAVR and SAVR that is associated with a threefold increase in mid-term mortality. Frailty, when defined by the EFT, is an incremental yet under-recognized risk factor to help predict BC and PRBC transfusions. Within the EFT, a number of actionable biomarkers can be targeted to potentially mitigate the risk of major BC; correction of preexisting anemia, nutritional intervention, and prehabilitation appear promising in this regard. While technical procedural factors remain the most direct determinants of bleeding, the aforementioned patient-level factors should be carefully considered for their prognostic and therapeutic implications.

FIGURE LEGENDS

Figure 1: Incidence of Bleeding Complications by Procedure Type



Abbreviations: CABG, coronary artery bypass graft; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Table 1: Baseline Characteristics

	TAVR			SAVR		
	No Major Bleed N=610	*Major Bleed N=137*	*P-value*	*No Major Bleed N=227*	*Major Bleed N=221*	*P-value*
Age, years	83.2±5.6	84.5±5.3	0.02	76.9±4.7	78.4±4.9	<0.001
Female	260 (43%)	77 (56%)	0.004	66 (29%)	93 (42%)	0.004
BMI, kg/m^2	26.9±5.4	26.4±5.7	0.35	29.5±5.1	28.1±5.7	0.005
COMORBIDITIES						
Hypertension	466 (76%)	108 (79%)	0.54	175 (77%)	168 (76%)	0.79
Dyslipidemia	408 (67%)	86 (63%)	0.36	159 (70%)	146 (66%)	0.37
Diabetes	155 (25%)	42 (31%)	0.21	65 (29%)	75 (34%)	0.23
CAD	360 (59%)	79 (58%)	0.77	141 (62%)	147 (67%)	0.33
Recent MI	20 (3%)	2 (1%)	0.26	4 (2%)	22 (10%)	<0.001
PAD	103 (17%)	26 (19%)	0.56	18 (8%)	24 (11%)	0.29
Cirrhosis	6 (1%)	3 (2%)	0.24	1 (0%)	4 (2%)	0.17
GI disease	105 (17%)	36 (26%)	0.01	35 (15%)	53 (24%)	0.02
Tumor	99 (16%)	27 (20%)	0.33	26 (11%)	29 (13%)	0.59
Chronic lung disease	122 (20%)	26 (19%)	0.79	27 (12%)	24 (11%)	0.73
Prior stroke	46 (8%)	19 (14%)	0.02	8 (4%)	15 (7%)	0.12
Atrial fibrillation	225 (37%)	57 (42%)	0.30	52 (23%)	48 (22%)	0.76
LVEF, %	55.4±12.6	55.5±12.6	0.91	57.2±12.6	57.9±11.9	0.57
LAB VALUES						
GFR, $mL/min/1.73m^2$	55.1±16.7	50.7±17.4	0.006	63.9±14.5	60.4±16	0.02
Hemoglobin, g/L	121.5±15.8	112.3±18.1	<0.001	134.5±15	120.9±16.6	<0.001
Anemia	346 (57%)	101 (74%)	<0.001	52 (23%)	124 (56%)	<0.001
Albumin, g/L	38.8±4.5	36.8±5.3	<0.001	40.4±4.3	38.4±6	<0.001
Platelets, $x10^9/L$	197.4±65.1	220.3±90.5	<0.001	196.5±60.8	212.6±69.7	0.010
FRAILTY						
EFT, out of 5	1.9 ± 1.1	2.6 ± 1.2	<0.001	1.1 ± 1	1.7 ± 1.1	<0.001
SPPB, out of 12	6.5±3.2	4.9±3.3	<0.001	8.2±2.8	7.2±2.9	<0.001
Fried, out of 5	2.1±1.4	2.7±1.3	<0.001	1.5±1.3	1.7±1.3	0.13
CFS, out of 9	3.9±1.3	4.6±1.2	<0.001	3.1±1.2	3.6±1.3	0.004
Gait speed, m/s	0.7±0.3	0.6±0.3	<0.001	1±0.3	0.9±0.3	<0.001
Chair rise time, s	29.8 ± 19.8	40 ± 20.9	<0.001	21.7 ± 15.1	26.9 ± 18.3	0.001
MMSE, out of 30	26.5±3.2	25.5±3.7	<0.001	27.3±2.7	27.2±2.7	0.70
Cognitively impaired	109 (18%)	44 (32%)	<0.001	21 (9%)	21 (10%)	0.93
Malnourished	55 (9%)	22 (16%)	0.01	11 (5%)	14 (6%)	0.49
Falls	122 (20%)	33 (24%)	0.29	32 (14%)	36 (16%)	0.52

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CFS, Clinical Frailty Scale; EFT, Essential Frailty Toolset; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MMSE, Mini-Mental Status Examination; PAD, peripheral arterial disease; SAVR, surgical aortic valve replacement; TSPPB, Short Physical Performance Battery; AVR, transcatheter aortic valve replacement.

Table 2: Multivariable Logistic Regression Models for Major Bleeding

	TAVR *Odds Ratio (95% CI)*	**SAVR** *Odds Ratio (95% CI)*
Age, per year	1.03 (0.99, 1.08)	1.02 (0.97, 1.07)
Female	1.02 (0.56, 1.84)	1.05 (0.56, 1.95)
Weight, per kg	1.00 (0.98, 1.01)	0.97 (0.96, 0.99)
Height, per cm	0.97 (0.94, 1.00)	0.99 (0.96, 1.01)
Recent MI	0.38 (0.08, 1.79)	4.84 (1.29, 18.15)
Atrial fibrillation	1.25 (0.82, 1.92)	0.90 (0.53, 1.53)
LVEF, per %	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)
PAD	1.06 (0.61, 1.83)	1.51 (0.73, 3.16)
Cirrhosis	3.05 (0.61, 15.38)	9.52 (0.95, 95.34)
GI disease	0.90 (0.41, 1.97)	3.15 (0.83, 12.02)
GFR, per 10 mL/min/1.73m^2	0.96 (0.85, 1.08)	0.93 (0.80, 1.08)
Platelets, per 10x10^9/L	1.03 (1.01, 1.06)	1.03 (1.00, 1.07)
Procedure type*	2.32 (1.44, 3.75)	1.94 (1.23, 3.05)
EFT, per point	1.66 (1.39, 1.99)	1.67 (1.34, 2.07)

* Procedure type refers to non-femoral procedures in the TAVR group and combined SAVR/CABG procedures in the SAVR group.

Abbreviations: EFT, Essential Frailty Toolset; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Table 3: Multivariable Linear Regression Models for PRBC Transfusions

	TAVR *Beta (95% CI)*	**SAVR** *Beta (95% CI)*
Age, per year	0.00 (-0.04, 0.04)	0.09 (0.02, 0.16)
Female	0.00 (-0.61, 0.61)	-0.42 (-1.24, 0.41)
Weight, per kg	0.01 (0.00, 0.03)	-0.03 (-0.05, -0.01)
Height, per cm	-0.02 (-0.05, 0.02)	-0.03 (-0.06, 0.00)
Recent MI	-0.75 (-1.95, 0.45)	2.74 (1.33, 4.15)
Atrial fibrillation	0.24 (-0.19, 0.68)	0.07 (-0.69, 0.82)
LVEF, per %	0.00 (-0.02, 0.01)	0.00 (-0.03, 0.03)
PAD	-0.13 (-0.69, 0.44)	-0.32 (-1.39, 0.75)
Cirrhosis	0.49 (-1.41, 2.39)	3.30 (0.41, 6.20)
GI disease	0.61 (-0.21, 1.43)	0.20 (-1.50, 1.89)
GFR, per 10 $mL/min/1.73m^2$	-0.07 (-0.20, 0.06)	-0.06 (-0.27, 0.15)
Platelets, per $10x10^9/L$	0.02 (-0.01, 0.05)	0.01 (-0.04, 0.06)
Procedure type*	0.91 (0.40, 1.43)	1.12 (0.48, 1.76)
EFT, per point	0.46 (0.28, 0.64)	0.69 (0.39, 0.98)

* Procedure type refers to non-femoral procedures in the TAVR group and combined SAVR/CABG procedures in the SAVR group.

Abbreviations: EFT, Essential Frailty Toolset; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Table 4: Comparison of Frailty Scales to Predict Major Bleeding Complications

	TAVR		SAVR	
	OR (95% CI)	*C-statistic*	*OR (95% CI)*	*C-statistic*
No frailty scale	-	0.69	-	0.72
Fried scale	1.10 (0.93, 1.31)	0.71	1.34 (1.14, 1.57)	0.73
SPPB scale	0.90 (0.83, 0.97)	0.71	0.88 (0.82, 0.94)	0.73
CF scale	1.12 (1.03, 1.22)	0.70	1.14 (1.06, 1.23)	0.73
Columbia scale	1.22 (0.99, 1.50)	0.72	1.47 (1.24, 1.76)	0.72
EFT scale	1.67 (1.34, 2.07)	0.74	1.66 (1.39, 1.99)	0.76

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CFS, Clinical Frailty Scale; EFT, Essential Frailty Toolset; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MMSE, Mini-Mental Status Examination; PAD, peripheral arterial disease; SAVR, surgical aortic valve replacement; SPPB, Short Physical Performance Battery; TAVR, transcatheter aortic valve replacement.

Table 5: Clinical Outcomes

	TAVR			SAVR		
	No Major Bleed N=610	*Major Bleed N=137*	*P-value*	*No Major Bleed N=227*	*Major Bleed N=221*	*P-value*
Death at 30 days	21 (3%)	18 (13%)	<0.001	1 (0%)	13 (6%)	<0.001
Death at 6 months	54 (9%)	36 (27%)	<0.001	5 (2%)	19 (9%)	0.002
Death at 1 year	82 (14%)	47 (36%)	<0.001	9 (4%)	22 (11%)	0.009
Reintervention	31 (5%)	43 (31%)	<0.001	1 (0%)	40 (18%)	<0.001
Stroke	4 (1%)	12 (9%)	<0.001	4 (2%)	7 (3%)	0.34
Sepsis	3 (0%)	7 (5%)	<0.001	1 (0%)	11 (5%)	0.003
Prolonged intubation	6 (1%)	24 (18%)	<0.001	5 (2%)	27 (12%)	<0.001
Acute kidney injury	38 (6%)	27 (20%)	<0.001	8 (4%)	25 (11%)	0.002
Major vascular event	8 (1%)	36 (26%)	<0.001	1 (0%)	6 (3%)	0.05
Post-op atrial fib.	25 (6%)	13 (16%)	0.004	66 (38%)	71 (41%)	0.53
Delirium	180 (30%)	45 (34%)	0.40	182 (81%)	170 (79%)	0.57
Discharge to facility	143 (23%)	84 (61%)	<0.001	62 (27%)	93 (42%)	0.001
Length of stay, days	6±6.2	14±14.2	<0.001	8.4±9.6	14.6±15.4	<0.001
PRBCs, units	0.1±0.3	4.6±5.2	<0.001	0.3±0.5	5.1±4.2	<0.001

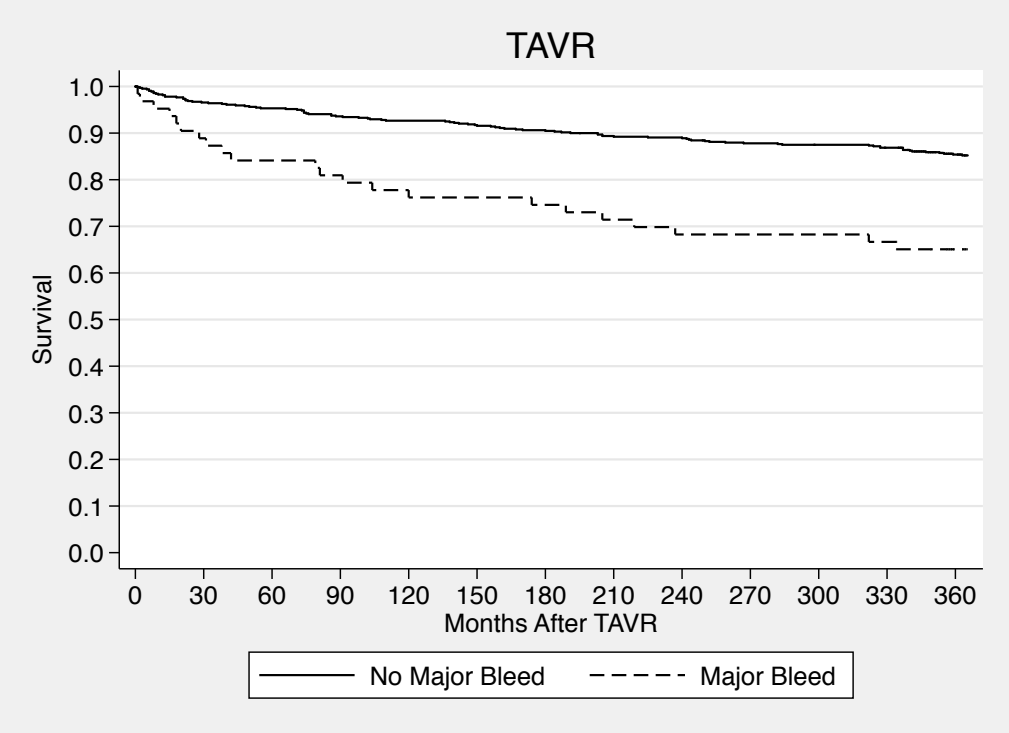
Abbreviations: PRBC, packed red blood cells; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement. Complications defined according the VARC-2 classification.

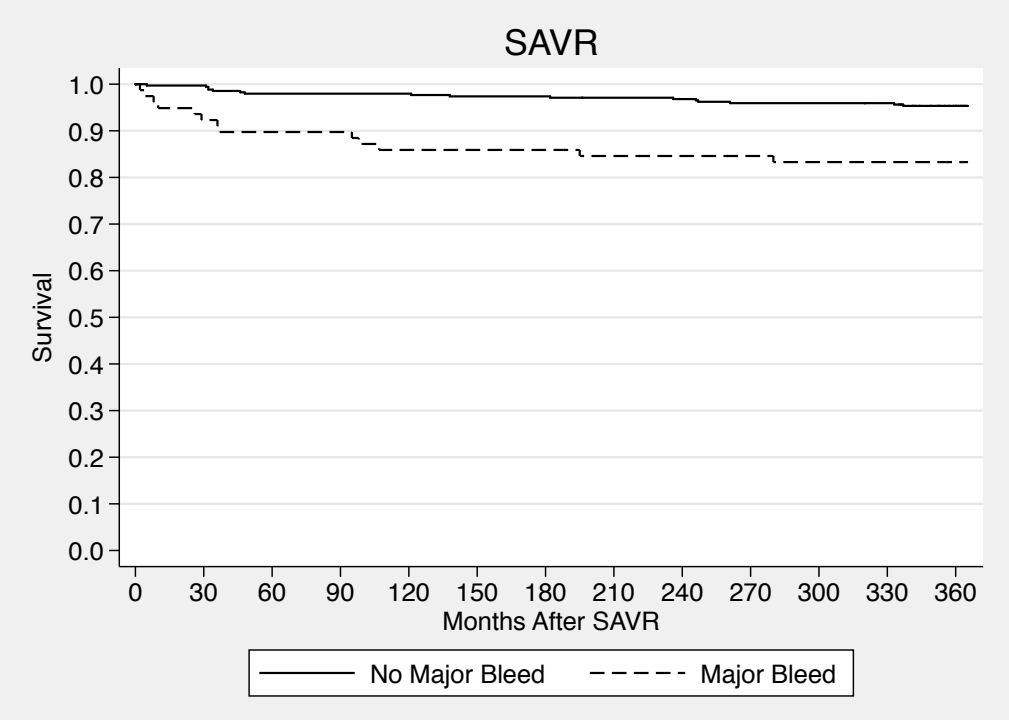
Table 6: Multivariable Logistic Regression Model for Major Bleeding with Clinically Apparent Source

	TAVR & SAVR *Odds Ratio (95% CI)*
Age, per year	1.02 (0.98, 1.06)
Female	1.32 (0.80, 2.18)
Weight, per kg	1.00 (0.99, 1.01)
Height, per cm	1.00 (0.98, 1.03)
Recent MI	2.22 (1.05, 4.69)
Atrial fibrillation	0.97 (0.64, 1.46)
LVEF, per %	1.01 (0.99, 1.03)
PAD	0.95 (0.54, 1.66)
Cirrhosis	6.06 (1.84, 19.94)
GI disease	0.96 (0.42, 2.15)
GFR, per 10 $mL/min/1.73m^2$	1.08 (0.95, 1.21)
Platelets, per $10x10^9/L$	1.02 (0.99, 1.04)
Procedure type	1 (Referent) 1.32 (0.71, 2.44) 1.75 (0.97, 3.14) 3.97 (2.39, 6.61)
EFT, per point	1.30 (1.10, 1.53)

Abbreviations: EFT, Essential Frailty Toolset; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Figure 2: Kaplan-Meier Survival Analysis





Chapter 4: Transition from retrospective to prospective study

We showed in our retrospective analysis of the FRAILTY-AVR study that frailty is predictive of increased bleeding complications, and that bleeding complications were strongly associated with long-term mortality and serious postoperative complications. The predictive power of frailty denotes an underlying physiological change in frail older adults that lead to a higher risk of bleeding. This increased bleeding risk can be mitigated by incorporating assessment of frailty prior to the procedure, and addressing the underlying issues through, for example, protein administration to improve nutritional status, physical activity to improve physical function and underlying muscle conditioning, and addressing sources of anemia.

Aside from preoperatively, another domain where bleeding risk is assessed is in anticoagulant decision-making. For patients with AF, clinicians must decide whether to choose anticoagulation based on their assessment of the patients bleeding and stroke risk, and balancing the two. However, since the emergence of the DOACs, the decision-making has been difficult for clinicians with older patients. The study populations of the landmark studies were not reflective of the real world population, underrepresenting older adults, leading to uncertainty in how to apply the results to real world practice. Furthermore, other DOAC studies focused on the elderly population included participants who were healthier and more robust than the general population, and lacked a true measure of frailty. The ambiguity regarding DOAC dosing has important clinical consequences, with 15% of patients receiving a reduced DOAC dose without a clear indication to warrant a dose reduction.[69,142] Furthermore, in contrast to warfarin, laboratory monitoring is not currently recommended for DOACs to measure if coagulation level is within the therapeutic range.

Conventional dosing strategies for DOACs do not provide specific or comprehensive recommendations for patients with conditions that increase the risk of bleeding complications. The dosing recommendations for rivaroxaban do not include any dose modifications based on body composition or age.[77] A population PK/PD model developed to compare once-daily or twice-daily rivaroxaban showed that the volume of distribution (V_D) is influence by body weight, as expressed as body surface area (BSA).[143] The model showed that V_D decreases or increases by 6.4% per 0.1 m^2 below or above the median body surface area of 1.84m^2. While the authors determine that the average influence of this factor and the others studied are modest within the studied population, others have concluded that low body weight will increase rivaroxaban exposure and thus potentially increase the risk of bleeding complications with a standard dose.[144] Low body weight also affects apixaban concentrations. Patients with body weights <50 kg have 30% greater exposure than those with body weights of 60-85 kg, who had a 30% greater exposure than patients with body weights >120 kg.[76] This increase in exposure can be compounded by age; patients over 65 years of age had 32% greater area under the curve (AUC).[76,145] For apixaban, the increased exposure from low body weight is considered modest, but caution is warranted in the presence of additional factors that contribute to increased apixaban exposure.[146] A dose reduction from 5 mg of apixaban to 2.5 mg is only recommended for apixaban in patients who present with two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromole/L (1.5 mg/dL).

Therefore, for patients with low body weight or advanced age, clinicians may prescribe reduced DOAC doses as an “off-label” practice; however, this is not supported by randomized clinical

trials. Off-label dose reduction can lead to reduced anti-Xa activity and consequently an increased risk of ischemic events and mortality.[9] Having a proper dosing strategy that takes into account various factors that affect drug kinetics to prevent overdosing is especially important for the DOACs, as there is no specific antidote for reversal at the present time.

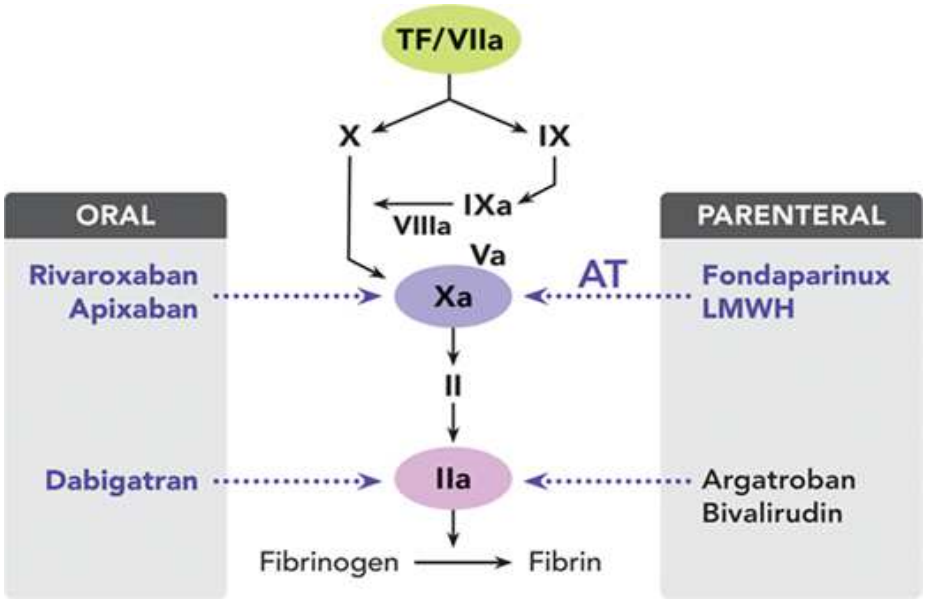
Low muscle mass, by affecting the volume of distribution of the hydrophilic anticoagulants, could possibly explain the increased bleeding risk, and represent the underlying physiological change in frail older adults. The distribution of a drug in the body after administration is of great importance to optimize therapeutic effects and prevent undesirable side effects. The volume of distribution (V_D), equal to the administered dose of a drug (mg) divided by its resulting plasma concentration (mg/L), represents the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma.[147] The V_D reflects the drug distribution between the plasma and the rest of the body after dosing.

Interpatient variability can affect the volume of distribution: modifications of body composition, such as changes in fat mass to total mass ratio can impact where a drug is distributed in the body. For patients with low muscle mass, hydrophilic drugs are less distributed in muscle and results in a higher plasma concentration and a lower V_D. This unbalanced distribution results in a higher plasma concentration and a lower V_D. The increase in drug exposure and plasma levels due to low muscle mass have been shown to increased risk of bleeding complications. For instance, high peak anti-Xa level is an independent predictor for bleeding events.[148] The aging process can have a significant effect on how a drug is distributed in the body. Aging is associated with a

decrease in muscle mass and relative increase in body fat, with older adults having approximately a 20% decrease in fat-free mass compared with individuals below the age of 70.[145,149] As a consequence of decreased relative lean body mass and increased adipose tissue, elderly adults are more sensitive to both main and side effects of drug treatment.[150] The aging process is also associated with a decrease of total body water that further affects the V_D of water-soluble drugs. [27,145] The V_D is critical for determining the dose necessary to achieve the adequate concentration of the drug in the desired location where the drug can exert its primary effect.

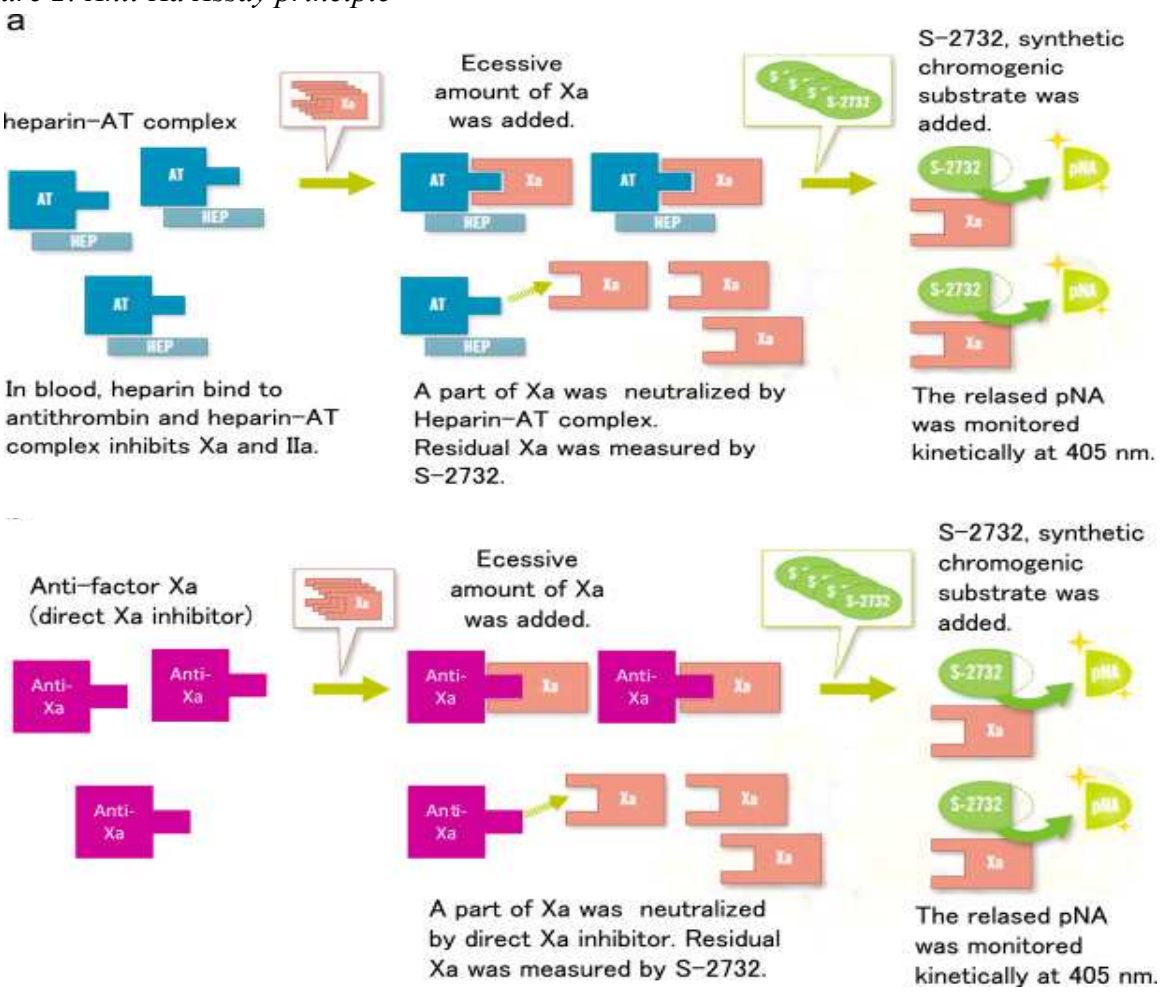
DOACs impede coagulation by inhibiting factor Xa, which is part of the coagulation cascade. Rivaroxaban and apixaban are direct anti-Xa inhibitors that suppress coagulation by directly inhibiting factor Xa.[151]

Figure 1: Mechanism of Action of Xa inhibitors Rivaroxaban and Apixaban[152]



Although DOACs have stable and relatively predictable drug activity when administered in standard dosages to typical adult patients, there are certain clinical scenarios where it may be useful to monitor drug concentration and/or activity and adjust dosage accordingly, such as to determine the anticoagulation effect of DOACs in the elderly.[153] According to the recent literature, the best method for monitoring DOAC activity is with an anti-Xa assay.[154,155]

Figure 2: Anti-Xa Assay principle [156]



The most commonly used methodology for the anti-Xa assay is the chromogenic assay. This assay incorporates the addition of known amounts of chromophore-linked Xa and antithrombin

to the sample. Upon cleavage of the Xa substrate by factor Xa, a colored compound is released. The anticoagulant forms an inhibitory complex with antithrombin and inactivates Xa, reducing its capacity to inactivate the chromophore-linked substrate. The excess amount of Xa remaining in the sample is inversely proportional to the anticoagulant. The lower chromogenic intensity in the sample, the lesser amount of Xa remaining in the sample, thus the higher the level of the anticoagulant will be present in the sample.

Clinical features, such as body weight, have been shown in the literature to affect the drug exposure of DOACs. In the ENGAGE AF-TIMI 48 trial, higher- and lower-doses of edoxaban, another DOAC, were compared with warfarin in patients with AF.[157] Each dosing regimen of edoxaban in the trial incorporated a dose reduction of 50% if the patients presented with a clinical feature known to increase drug exposure: body weight below 60 kg, creatinine clearance of 30-50 ml/min, or concomitant drugs that significantly increased drug exposure based on pharmacokinetic modelling.[158] Patients who qualified for dose reduction had increased bleeding and ischemic events in both the 60 mg and 30 mg dose regimens. Moreover, patients who qualified for dose reduction in the 60 mg group (and had their dose reduced to 30 mg) had more increased bleeding and ischemic events than patients randomly assigned to the 30 mg group. Furthermore, a recent study similarly investigated the efficacy DOACs in underweight patients with atrial fibrillation, classifying weight according to BMI.[159] Their results demonstrated that the major bleeding rate and all-cause death was higher in the underweight group compared to the group with normal weight or who were overweight. These results were shown even in age-matched groups.

The results of these studies validate a strategy of tailoring the DOAC doses based on patient clinical factors and body composition to prevent excess drug concentrations and optimize ischemic and bleeding risks. To confirm these findings, we developed a research protocol that would study the effect of muscle mass on DOAC drug activity, by measuring DOAC activity with the anti-Xa assay 4 hours after dose and 1 hour before drug dose, representing respectively the peak and trough activity levels. The patient's muscle mass was measured by bioimpedance and a DXA scan. Patients with a pacemaker or an internal defibrillator did not have their muscle mass measured with bioimpedance since bioimpedance use is contraindicated in these patients. Instead, their muscle mass was measured solely with a DXA scan. Muscle strength was measured by the handgrip strength test and chair rise test.

Other factors that can affect pharmacokinetics in elderly patients were considered and controlled for in our protocol. Kidney function is an important factor that influences the effect of a drug, particularly when there are active drug moieties that are renally cleared. When renal clearance decreases, so does the clearance of the drug. Reduced drug clearance results in higher drug concentration and exposure and therefore causes greater drug effect.[160] Higher drug concentrations can result in increased adverse effects: for example, patients taking enoxaparin with renal insufficiency have a much greater incidence of bleeding (51%) compared to patients with normal renal function (21%.)[161] Older age is strongly associated with a greater prevalence of moderately or severely decreased kidney function; the Third National Health and Nutrition Examination Survey (NHANES) found that 7.6% of the individuals aged 60–69 years and 25.9% of those aged >70 years had a glomerular filtration rate (GFR) of 15–60 ml/min/1.73 m^2, compared to 1.8% of those aged 40–59 years and 0.2% of those aged <40 years.[162] The dosing

recommendations for DOACs include dosing readjustments for cases of reduced renal clearance, as calculated by creatinine clearance. However, creatinine clearance can be misleading in older adults, since apparent normal concentrations of serum creatinine can mask significant renal impairment in patients with low lean body mass.[163] Serum cystatin C is an alternative biomarker used to estimate the glomerular filtration rate instead of creatinine clearance. Cystatin C is less sensitive to muscle mass compared to creatinine clearance, which makes it more useful in subpopulations, like patients with low muscle mass. This biomarker is especially important in the elderly, because reduced GFR is often seen in this patient group.[164]

Plasma proteins are another critical factor influencing the effect of drug levels. Patients that are classified as frail often also have less plasma proteins, such as albumin, circulating in their blood.[165] This decrease in plasma protein levels could affect the plasma concentration of drugs that are protein bound.[128] Drugs are active when they are in their unbound state, and inactive when they are bound to the plasma proteins. In cases of reduced plasma proteins, there is a reduction in drug-protein binding, causing a shift to the bound:unbound equilibrium and an increase in the amount of unbound active drug. Both rivaroxaban and apixaban are highly protein-bound (92-95% and 87%, respectively),[76,77] therefore changes in plasma protein levels could substantially impact the serum concentration level of these drugs.

Drug-drug interactions (DDIs) can also alter peak and trough activity levels of drugs. Drugs can affect the activity of other drugs when they are taken together, either synergistically or antagonistically. These consequences of DDIs are especially important to consider in elderly adults, as they are likely to have other comorbidities requiring other drugs and polypharmacy is

common.[166] Drug that affect the activity of Permeability Glycoprotein (P-gp) is an example DDIs that can occur with DOACs. P-gp is a transporter that mediates the transport of rivaroxaban and apixaban across the kidneys, lungs and small intestines. Drugs that increase or decrease the P-gp activity level can change the level of drug absorption and excretion. An increase in P-gp activity can potentially lead to increased plasma concentrations, which in the case of DOAC, increased bleeding risk. Conversely, drugs that reduce P-gp activity can lead to reduced drug concentrations and reduced efficacy in preventing thromboembolism or stroke.[166] Drugs that affect Cytochrome P450 enzyme (CYP) is another example of DDIs that can affect DOACs. The CYP3A4 enzyme found in the liver is involved in oxidation of many drugs. Both DOACs are metabolized by CYP enzymes, and drugs that increase or decrease the CYP enzyme would affect DOAC levels.

We decided to further study the relationship between frailty and bleeding complications, in the anticoagulated population and in a prospective fashion, by investigating the effect of low muscle mass on anticoagulant activity in older adults with atrial fibrillation. Our hypothesis was that older adults with low muscle mass who are receiving a DOAC will have increased serum concentration and activity of these drugs, which in turn predisposes them to a higher risk of bleeding complications.

Chapter 5: Prospective cohort study

Manuscript to be submitted: "Association of Muscle Mass With Direct Oral Anticoagulant Activity in Older Adults"

Association of Muscle Mass With Direct Oral Anticoagulant Activity in Older Adults

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ABSTRACT

BACKGROUND: Direct oral anticoagulants (DOACs) are increasingly used to treat older adults with atrial fibrillation (AF). While current dosing recommendations are based on total body weight, the plasma levels of these hydrophilic drugs are actually determined by lean mass. In the presence of low lean mass, DOACs are distributed less in lean tissues and more in plasma. Thus, frail patients with low muscle mass may be at risk for supratherapuetic DOAC plasma levels and bleeding complications.

METHODS: A prospective cohort study was conducted to determine the association between appendicular lean mass (ALM) and DOAC plasma levels in patients 65 years and above receiving rivaroxaban or apixaban for AF at the Jewish General Hospital (Montreal, Canada) between January and December 2017. ALM was measured at the point of care using a portable multi-frequency bioimpedance device, and secondarily, using a dual x-ray absorptiometry scan. DOAC levels were measured using a standardized anti-Xa assay 4 hours after (peak) and 1 hour before (trough) ingestion.

RESULTS: The cohort consisted of 62 patients, of which 47% were female, with a mean age of 77.7 ± 6.1 years. The prescribed DOAC was apixaban 2.5 mg in 21%, apixaban 5 mg in 53%, and rivaroxaban 20 mg in 25%. Overall, 25% and 16% of patients had supratherapeutic DOAC levels at peak and trough, respectively. Lower ALM was found to be an independent predictor of supratherapuetic DOAC levels at trough (OR 0.78, 95% CI 0.62 to 0.98) and peak (OR 0.84, 95% CI 0.73 to 0.99). Addition of ALM to a logistic regression model consisting of age, total body weight, and renal function resulted in improved discrimination for supratherapuetic DOAC

levels at trough (C-statistic 0.88) and peak (C-statistic 0.76). When used in place of ALM, the SARC-F questionnaire for sarcopenia was similarly found to be an independent predictor of supratherapuetic DOAC levels.

CONCLUSION: Our proof-of-concept study has identified an association between sarcopenia and DOAC levels in older adults with AF. Further research is needed to determine the impact of ALM on bleeding complications and the potential role of ALM-guided dosing for frail patients.

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent type of cardiac arrhythmia, affecting an estimated 10 million North Americans.[167] The incidence of AF increases with advancing age, doubling each decade to reach a peak prevalence of 30% at 85 years of age.[55,167] Oral anticoagulants are indicated in patients at risk for embolic events, with a growing number of patients receiving one of the direct oral anticoagulants (DOACs) rivaroxaban and apixaban. While literature has shown that the DOACs are superior or equivalent to warfarin in preventing stroke or systemic embolism, with lower rates of hemorrhage,[60,8,7] there remains uncertainty about balancing the risk of stroke and the non-trivial risk of bleeding in older adults.[66] Oral anticoagulants are the most common cause of adverse drug events related hospital visits in older adults, accounting for 18% of such visits.[64,65]

To limit the risk of bleeding associated with DOACs, dose reduction is recommended for apixaban-treated patients with two of the following criteria: ≥80 years of age, low body weight (<60 kg) or high serum creatinine (≥133 mmol/L; ≥1.5 mg/dL).[76] Dose reduction is recommended for rivaroxaban-treated patients with a creatinine clearance of 30-50 ml/min, while age and body weight are not specifically considered.[77] Moreover, dose reductions are often prescribed "off label" for frail older patients due to the perceived risk of bleeding complications, such that 15% of low dose DOAC prescriptions do not meet the approved criteria for dose reduction.[142] Off-label dosing is associated with worse clinical outcomes, including a higher rate of cardiovascular hospitalization, systemic embolism, major bleeding, and death.[68]

Frailty is a multi-faceted geriatric syndrome, characterized in part by an age-related decline in skeletal muscle mass and strength known as sarcopenia. Since DOACs are hydrophilic drugs, their volume of distribution and plasma concentration are influenced by changes in body composition, notably by water-containing lean tissues such as skeletal muscle mass. As muscle mass decline, the relative distribution of hydrophilic DOAC drugs becomes lower in muscle and higher in plasma. Therefore, we hypothesized that frail older adults with low muscle mass would have supra-therapeutic DOAC plasma levels. The potential significance of this was shown in recent studies, which found that high DOAC levels were strongly predictive of future major and non-major bleeding complications.[148,157,168]

It remains unknown whether frailty and low muscle mass affect DOAC pharmacokinetics, and whether low muscle mass is independently associated with higher DOAC levels after adjusting for potential confounders that alter pharmacokinetics such as renal failure. Thus, we sought to prospectively examine the association between low muscle mass and plasma activity of rivaroxaban and apixaban in older adults with AF.

METHODS

Study design

A prospective observational cohort study was conducted by enrolling patients who were receiving rivaroxaban or apixaban for AF. Patients were screened daily for inclusion in the study by reviewing pharmacy prescriptions and electronic medical records. After administering a baseline questionnaire, patient's muscle mass and muscle strength were measured by dual x-ray absorptiometry (DXA) and bioimpedance. Blood samples were drawn one hour prior to DOAC

administration, and 4 hours after administration to measure the patient's trough and peak drug activity levels, respectively. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[169] and was approved by the CIUSS West-Central Montreal Research Review Office. All patients signed an informed consent form prior to participating.

Setting and Participants

The study was conducted at the Jewish General Hospital in Montreal, Canada. Patients were recruited from the cardiology ward and the outpatient cardiology clinics. Data was managed and analyzed at the Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital. Inclusion criteria were: (1) age ≥ 65 years, (2) actively receiving a DOAC for AF, and (3) ability to provide informed consent. Exclusion criteria are: (1) clinical instability, (2) decompensated heart failure due to the effect of acute fluid shifts on bioimpedance measurement accuracy, (3) not English or French speaking, (4) moderate or severe cognitive impairment, or (5) recently initiated DOAC <7 days. No patients had cirrhosis or dialysis-dependent kidney disease. Two patients receiving rivaroxaban 15 mg per day were enrolled but subsequently excluded due to the lack of a validated anti-Xa reference range for this dosage.

Measurement of Muscle Mass and Strength

The primary predictor variable was appendicular lean mass (ALM; continuous variable in kg) measured using a multi-frequency segmental bioimpedance device (InBody S10, Seoul, Korea). ALM is the fat-free mass of the upper and lower extremities, which is predominantly composed of skeletal muscle. ALM was also measured using a DXA scanner (GE Lunar, Milwaukee, WI,

USA). Both bioimpedance and DXA are guideline-endorsed modalities to assess sarcopenia in older adults.[25] Since bioimpedance currents may theoretically interfere with cardiac implanted electronic devices, patients with these devices underwent DXA only. Muscle strength was measured using a handgrip dynamometer and sit-to-stand test (time required to stand up from a seated position five times without the use of arms).

Measurement of DOAC Levels

DOAC plasma activity was measured using a chromogenic plasma anti-Xa assay with HemosIL® Liquid Anti-Xa (Instrumentation Laboratory, Bedford, MA, USA) at peak and trough time points. To ensure steady state, blood was drawn after at least 7 days of uninterrupted treatment with the DOAC.[28] Patients were not asked to fast.[170] Blood was drawn in a light blue 3.2% sodium citrate tube, and centrifuged for 15 minutes at 3000g within 60 minutes of collection. Plasma samples were aliquoted and immediately stored at -80°C until the time of analysis. While laboratory monitoring of DOACs is not routinely required, the current consensus is that the anti-Xa assay is the preferred method for monitoring DOAC activity when indicated.[154] Anti-Xa activity was converted to estimated plasma concentration using the BIOPHEN® Calibrator and Control kit (HYPHEN, BioMed, Neuilly-sur Oise, France) which has been determined to be a comparable substitute for LC-MS/MS.[171] Supra-therapeutic concentration was defined according to observed reference ranges reported in the literature (Table 1).[76,143,172]

Covariates

DOACs are partially renally excreted and heavily protein-bound, therefore their activity may be influenced by kidney function and plasma protein levels. Kidney function was assessed by measuring serum creatinine and cystatin C, and plasma protein levels were assessed by measuring serum albumin and total protein. These were measured from blood samples drawn concurrently with the anti-Xa test. Physical frailty was evaluated using the SARC-F questionnaire, encompassing strength, assistance with walking, rising from a chair, climbing stairs, and falls, with each scored 0-2 points for a composite score of 0-10 points.[173] Comorbidities and medications were extracted from the patient's medical record, in particular, medications with the potential for DOAC drug interactions (dilitazem, naproxen, clarithromycin, fluconazole, rifampin, carbamazepine, phenobarbital, St. John's wort, aspirin, clopidogrel, prasugrel, ticagrelor, warfarin and grapefruit).[153]

Statistical Analysis

Characteristics of patients with therapeutic and supra-therapeutic anti-Xa levels were compared using the student t-test for continuous variables and chi-square test for dichotomous variables. Multivariable logistic regression models were employed to determine the association between ALM and supra-therapeutic peak and trough anti-Xa levels after adjusting for age, body weight, and glomerular filtration rate (GFR), the three parameters currently recommended to guide DOAC dosing. The incremental value of ALM to these three parameters was evaluated using the c-statistic and the Akaike information criterion (AIC). Secondary analyses were performed to determine the incremental predictive value of sex, albumin level, co-administration of a potentially interacting drug, handgrip strength, chair rise time, and the SARC-F score. All analyses were performed with STATA 14 (College Station, Texas).

RESULTS

Patient Characteristics

Our cohort consisted of 62 patients with a mean age of 77.7 ± 6.1 years, of which 46 (45% females) received apixaban and 16 (50% females) received rivaroxaban. A reduced dose was prescribed in 13/46 apixaban patients and 0/16 rivaroxaban patients. Patients were recruited from the outpatient clinics (79%) and the cardiology ward (21%). The mean CHA_2DS_2VASC score was 3.4 ± 1.4. Patient characteristics stratified by supra vs. therapeutic levels are shown in Table 2. Patient characteristics stratified by low vs. normal ALM are shown in Supplemental Table 1. A subset of 16 (26%) patients with cardiac implanted electronic devices had ALM measure by DXA only (without bioimpedance).

DOAC Levels

Distributions of peak and trough DOAC levels were found to be right-skewed and are accordingly reported as medians with their interquartile ranges IQR). The median trough apixaban level was 99.1 ng/ml (IQR 55.8, 175.0), while the median peak level was 210.4 ng/ml (IQR 149.8, 253.8). The median trough rivaroxaban level was 60.7 ng/ml (IQR 45.3, 72.6), while the median peak level was 279.3 ng/ml (IQR 200.2, 368.4). Fifteen (25%) patients had a supra-therapeutic peak level, of which 10 (22%) were receiving apixaban and 5 (31%) were receiving rivaroxaban. Ten (16%) patients had a supra-therapeutic trough level, of which 8 (22%) were receiving apixaban and 2 (13%) were receiving rivaroxaban. Seven (12%) patients had both supra-therapeutic peak and trough levels.

Univariate Correlates of DOAC Levels

Correlates of supra-therapeutic peak and trough levels are summarized in Table 2. Patients with supra-therapeutic trough levels had lower ALM than those with normal levels (17.0 ± 2.4 kg vs. 23.4 ± 5.6 kg, p=0.0009), and they were more likely to be female, with low body weight, short stature, self-reported weight loss, low handgrip strength, high SARC-F score, and high CHA_2DS_2VASC score, Patients with supra-therapeutic peak levels were more likely to have short stature, low handgrip strength, and low GFR.

Multivariable Modeling of Supra-Therapeutic DOAC Levels

ALM was independently associated with supra-therapeutic DOAC levels at both trough (OR 0.78, 95% CI 0.62 to 0.98) and peak (OR 0.84, 95% CI 0.73 to 0.99) as shown in Table 3. Addition of ALM yielded incremental predictive value (C-statistic 0.88, 95% CI 0.80 to 0.96, AIC 49.32) when compared to the baseline model consisting of age, weight, and GFR (C-statistic 0.84, 95% CI 0.73 to 0.95, AIC 53.13) for the trough measurement as shown in Table 4. Similarly for the peak DOAC level, ALM yielded incremental predictive value (C-statistic 0.76, 95% CI 0.63 to 0.90, AIC 61.17) when compared to the baseline model (C-statistic 0.71, 95% CI 0.55 to 0.86, AIC 70.01).

Sensitivity Analyses

Receiver operating characteristic curves revealed an optimal cut-point for ALM of <20.0 kg to predict a supra-therapeutic trough DOAC level (sensitivity 75%, specificity 90%). The association between ALM and DOAC levels remained similar after further adjustment for sex, serum albumin, cystatin C, and interacting drugs. When used in place of ALM, the SARC-F

score (reflecting a questionnaire-based estimation of ALM) was independently associated with supra-therapeutic DOAC levels at both trough (OR 0.78, 95% CI 0.62 to 0.98) and peak (OR 0.84, 95% CI 0.73 to 0.99) and yielded incremental predictive value as shown in Table 5.

DISCUSSION

To the best of our knowledge, this study is the first to examine the association between sarcopenia and DOAC pharmacokinetics in older adults. Sarcopenia was assessed at the point of care and yielded novel insights to identify older adults at risk for supra-therapeutic DOAC levels. Our results can be summarized as follows:

(1) Up to 25% of older adults receiving apixaban or rivaroxaban for AF had supra-therapeutic anti-Xa levels; this is in spite of the observed tendency to prescribe "off label" low dose apixaban for elderly patients not otherwise meeting criteria for dose reduction.

(2) Low ALM – a marker of sarcopenia – was found to be an incremental predictor of supra-therapeutic anti-Xa levels beyond traditional risk factors such as advanced age, low total body weight, and renal impairment.

(3) A brief questionnaire assessment of sarcopenia, notably with the SARC-F score, was similarly found to be associated with supra-therapeutic anti-Xa levels and may be a practical alternative when the equipment to directly measure ALM is not readily available.

Our findings highlight the important yet under-recognized relationship between ALM and DOAC pharmacokinetics in the body. For sarcopenic patients with low ALM, hydrophilic drugs are less distributed in lean muscle tissues and therefore more relatively distributed in plasma. This unbalanced distribution results in a higher plasma concentration and a lower volume of

distribution. In the case of DOACs, increased plasma concentration leads to increased anticoagulation activity, which in turn, has been shown to be a powerful predictor of subsequent major and non-major bleeding complications. In the ENGAGE AF-TIMI 48 trial, higher trough edoxaban levels were associated with a graded increase in risk of major bleeding over 3 years.[157] A recent of the ENGAGE-AF TIMI 48 trial also found that higher trough edoxaban levels were predicitive of major gastrointestinal bleeding.[168] In a smaller study by Sakaguchi et al., supra-therapeutic peak apixaban levels were associated with a twofold higher risk of major and minor bleeding.[148]

Previous studies have examined DOAC pharmacokinetics in relation to crude measures of body composition, namely total body weight and BMI. The ENGAGE AF-TIMI 48 trial[157] compared high and low doses of edoxaban vs. warfarin; each dosing regimen of edoxaban incorporating a 50% dose reduction for patients with body weight <60 kg, creatinine clearance 30-50 ml/min, or concomitant drug interactions.[158] Despite this dose reduction, patients with low body weight still had higher rates of bleeding. Park *et al.*[159] investigated DOACs and found that, after matching for age, low BMI was associated with a 4-6-fold higher risk of major bleeding and all-cause death as compared to normal or overweight BMI. Thus, underweight older patients face a higher risk of bleeding with DOACs. Our results build on these findings and put forth that ALM, rather than total body weight or BMI, is a more precise measure of body composition to identify sarcopenic older adults at risk for supra-therapeutic DOAC levels.

The pharmacokinetic profile of DOACs is dependent on lean mass, not total body mass, since the hydrophilic drug molecules are more distributed in water-containing lean tissues as compared to

water-poor adipose tissues. Lean mass and total body mass are closely correlated in most individuals, such that total body mass, which is easier to measure, can often be used as a surrogate. However, there are two important groups of patients in whom lean and total body mass are very poorly correlated: (1) obese patients with relatively low lean:fat mass due to excess adiposity,[174] and (2) sarcopenic patients with low lean:fat mass due to progressive loss of skeletal muscle mass. The sarcopenic obese patients, an increasingly recognized subset, are particularly difficult to discern because their total body weight and BMI may actually be increased and mask a profound reduction in underlying muscle mass.[175] Prior research in the field of thrombosis has examined the pharmacokinetic of low molecular weight heparins, similarly hydrophilic anticoagulants, in morbidly obese patients, and found that dosing based on total body weight resulted in supra-therapeutic anti-Xa levels.[176,177] The authors suggested that dosing be based on lean body weight or that these drugs be avoided in morbidly obese patients. However, prior research had not systematically examined the pharmacokinetics of hydrophilic anticoagulant drugs in sarcopenic patients.

The reasons for the lack of prior studies are likely multifactorial. DOACs, only recently introduced in the past decade,[7,8] were touted for their stable pharmacokinetics such that dosing of DOACs obviated the need for routine laboratory monitoring, which has been the major challenge of vitamin K dependent oral anticoagulants. Measurement of lean body mass required specialized equipment (DXA, MRI, CT) that was not directly accessible at the point of care; and older-generation single-frequency bioimpedance devices were not sufficiently accurate to be relied upon for decision making in individual patients. Technological advances leading to the advent of multi-frequency bioimpedance devices have provided a more accurate and practical

solution to assess lean mass in the clinical setting.[28] Given the widespread prescription of DOACs in frail octogenarians and nonagenarians with AF, recent data have evoked a rising incidence of bleeding complications that warrants closer reappraisal of our dosing strategies in vulnerable patients.[74,79,178,179]

Off-label dosing of DOACs continues to be a topical issue. In this study, of 46 patients receiving apixaban, 21% received a reduced dose of 2.5 mg twice daily. However, only 5 of these 13 patients met the manufacturer-approved criteria for dose reduction, and 8 of these 13 were prescribed off-label dose reduction. Furthermore, one patient received a full dose of apixaban when dose reduction was indicated, and another patient received a full dose of rivaroxaban when dose reduction was indicated. Overall, 16% received a non-approved DOAC dose, confirming the results from previous studies reporting on the rate of non-approved dosing between 12.5% and 20%.[68,69] These results re-emphasize the need to both understand the motivations behind off-label dosing and develop better tools to prevent inappropriate dosing of DOACs. An exploratory analysis of our data suggested that low ALM may (justly or unjustly) be one of the factors associated with off-label prescription of low-dose DOACs.

ALM was found to be more predictive of trough than peak anti-Xa levels in our multivariable models (C-statistic 0.88 vs. 0.76). One possible explanation may be the greater reliability of trough levels, with a lower likelihood of being influenced by absorption and distribution issues. Peak levels represent the time point when drug concentration reaches its maximal value, which is between 3-5 hours after administration of apixaban and 2-4 hours after administration of rivaroxaban. Inter-patient variability in absorption can significantly delay the time at which peak

plasma concentrations are attained. Conversely, trough levels better represent the underlying coagulation state and risk of bleeding,[180] such that most large-scale studies have tended to preferentially reported trough levels when studying DOAC activity.[157]

A number of limitations should be acknowledged. First, this proof-of-concept study had a modest sample size that requires validation in a larger multi-center study before being implemented in clinical practice. Second, given the sample size and relatively low incidence of bleeding complications, this study was not powered to detect differences in bleeding events. Third, the therapeutic range for anti-Xa levels with DOACs has yet to be firmly established; however, reference ranges were retrieved from drug monographs and published pharmacokinetic studies. Fourth, despite our best efforts to adjust for relevant covariates, potential unmeasured confounders may still be present, although did not appear to be prominent in our sensitivity analyses. Finally, bioimpedance could not performed in all patients due to the manufacturer warning for potential interference with cardiac pacemakers. Although this concern has largely been dispelled in recent reports,[181-183] we opted to use an alternative modality (DXA) for these patients. In patients that had both modalities, the correlation between DXA and bioimpedance measurements of ALM was 0.94 ($P<0.001$).

CONCLUSIONS

Despite the favourable pharmacokinetic profile of DOACs, which has obviated the need for routine laboratory monitoring, a subset of older patients experience supra-therapeutic anticoagulant activity and may potentially be exposed to a higher risk of bleeding complications. The decision to prescribe a reduced dose of DOAC is currently based on age, total body weight,

renal function, and the physician's judgment; our data suggest that ALM may be incrementally useful to guide decision-making for DOAC dosing in selected frail older adults who have evidence of sarcopenia that may predispose them to a higher risk of bleeding. Accordingly, this study reinforces the pharmacokinetic rationale linking sarcopenia with higher activity of hydrophilic drugs such as DOACs. Further research is needed to validate these findings and to investigate the effect of low muscle mass on DOAC-related bleeding complications.

ACKNOWLEDGEMENTS

We would like to sincerely thank the team of nurses that performed blood draws for this study, in particular Rose Abi Rached from the Department of Emergency Medicine, Jessica Pinto and Lyda Lesenko from the Division of Cardiology.

DISCLOSURES

Bendayan, M: None. Mardigyan, V: None. Williamson, D: None. Chen-Tournoux, A: Consultant fees for Roche Diagnostics. Eintracht, S: None. Rudski, L: Minor stock holding outside of a managed portfolio in General Electric. McNamara, E: None. Blostein, M: Advisory board for Pfizer and Bayer; received grant from Bayer and Boehringer. Afilalo, M: None. Afilalo, J: None.

FUNDING SOURCES

Melissa Bendayan was supported by the McGill University Division of Experimental Medicine Recruitment Award. Dr. Jonathan Afilalo is supported by the Canadian Institutes of Health Research and Fond de Recherché du Québec en Santé.

Table 1: Reference Ranges for DOAC Concentrations Using the Anti-Xa Assay

	Peak Concentration	Trough Concentration
Apixaban 2.5 mg	69-221 ng/ml	34-162 ng/ml
Apixaban 5 mg	91-321 ng/ml	41-230 ng/ml
Rivaroxaban 15 mg	*Not reported*	*Not reported*
Rivaroxaban 20 mg	160 – 360 ng/ml	4 – 96 ng/ml

Table 2: Patient Characteristics by DOAC Levels

(A) Trough

	Therapeutic N=51	Supratherapeutic N=10	P-value
Age	77.1 ± 6.3	81.2 ± 3.9	0.05
Female	20 (39.2)	8 (80)	0.018
Weight, kg	84.6 ± 20.1	68.7 ± 13.4	0.0198
Height, m	1.67 ± 0.1	1.57 ± 0.1	0.018
BMI, kg/m^2	30.8 ± 9.2	27.9 ± 5.8	0.34
BSA, m^2	1.97 ± 0.26	1.73 ± 0.17	0.0061
Obesity (BMI >30 m^2)	21 (41.2)	3 (30)	0.51
Underweight (BMI <18.5 m^2)	2 (3.9)	0 (0)	0.52
Apixaban prescription	38 (74.5)	8 (80)	0.71
Drug interactions	11 (21.6)	2 (20)	0.91
Myocardial infarction	6 (11.7)	1 (10)	0.87
LVEF, %	57.9 ± 12.3	55 ± 15.5	0.52
Pacemaker/ICD	13 (25.5)	3 (30)	0.77
Prior stroke	4 (7.8)	2 (20)	0.24
Diabetes	16 (31.3)	5 (50)	0.26
GI disease	12 (23.5)	2 (20)	0.81
COPD	9 (17.6)	3 (30)	0.37
Weight loss, kg	1.2 ± 2.9	3.7 ± 5.6	0.0349
Grip strength, kg	25.5 ± 10.0	15.1 ± 4.6	0.0023
Chair rise, s	13.2 ± 9.2	12.5 ± 9.15	0.82
CHA_2DS_2VASC score	3.2 ± 1.4	4.6 ± 1.2	0.0061
SARC-F score	6.6 ± 2.3	9.2 ± 2.4	0.0022
Falls	13 (25.5)	4 (40)	0.35
Creatinine, μmol/L	84.7 ± 20.9	98.9 ± 27.3	0.07
GFR, mL/kg/1.83 m^2	82.1 ± 24.1	70.7 ± 31.7	0.20
Cystatin C, mg/L	1.39 ± 0.6	1.73 ± 0.4	0.09
Hemoglobin, g/L	132.4 ± 21.6	128.4 ± 18.8	0.59
Albumin, g/L	39.9 ± 5.4	37.2 ± 5.5	0.16
Total Protein, g/L	64.2 ± 7.8	63.4 ± 8.2	0.75
Appendicular lean mass, kg	23.4 ± 5.6	17.0 ± 2.4	0.0009
Fat free mass, kg	54.6 ± 11.9	46.0 ± 16.4	0.05
Fat mass, kg	30.9 ± 14.3	23.5 ± 12.6	0.13

Abbreviations: BMI, body mass index; BSA, body surface area; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; GI disease, gastrointestinal disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate.

(B) Peak

	Therapeutic N=45	Supratherapeutic N=15	P-value
Age	77.0 ± 6.48	79.7 ± 4.71	0.14
Female	18 (40)	9 (60)	0.18
Weight, kg	82.6 ± 19.5	81.9 ± 20.5	0.90
Height, m	1.67 ± 0.11	1.58 ± 0.11	0.01
BMI, kg/m^2	29.5 ± 6.3	33.4 ± 13.2	0.13
BSA, m^2	1.9 ± 0.3	1.9 ± 0.2	0.40
Obesity (BMI >30 m^2)	16 (35.6)	8 (53.3)	0.22
Underweight (BMI <18.5 m^2)	2 (4.4)	0 (0)	0.40
Apixaban prescription	35 (77.8)	10 (66.7)	0.39
Drug interactions	8 (17.8)	3 (20)	0.85
Myocardial infarction	5 (0.1)	2 (13.3)	0.82
LVEF, %	56.3 ± 14.5	59.5 ± 5.8	0.42
Pacemaker/ICD	12 (26.7)	3 (20)	0.61
Prior stroke	5 (11.1)	1 (6.7)	0.62
Diabetes	15 (33.3)	5 (33.3)	1.00
GI disease	11 (24.4)	3 (20)	0.72
COPD	9 (20)	2 (13.3)	0.56
Weight loss, kg	1.3 ± 3.3	2.3 ± 4.4	0.33
Grip strength, kg	25.4 ± 10.6	19.5 ± 6.8	0.048
Chair rise, s	12.67 ± 8.0	15.2 ± 12.8	0.36
CHA_2DS_2VASC score	3.3 ± 1.5	3.7 ±1.3	0.34
SARC-F score	6.78 ± 2.42	8.0 ± 2.48	0.10
Falls	13 (28.9)	5 (33.3)	0.75
Creatinine. µmol/L	82.53 ± 21.8	95.4 ± 21.1	0.05
GFR, mL/kg/1.83 m^2	85.3 ± 26.5	70.0 ± 19.0	0.0435
Cystatin C, mg/L	1.37 ± 0.63	1.61 ± 0.37	0.16
Hemoglobin, g/L	133.7 ± 20.7	123.8 ± 24.1	0.13
Albumin, g/L	39.9 ± 5.3	37.1 ± 5.9	0.09
Total Protein, g/L	64.1 ± 8.1	63.1 ± 2.9	0.69
Appendicular lean mass, kg	23.3 ± 5.8	20.4 ± 4.7	0.09
Fat free mass, kg	54.4 ± 12.3	47.5 ± 10.3	0.06
Fat mass, kg	29.2 ± 13.2	34.9 ± 15.1	0.16

Abbreviations: BMI, body mass index; BSA, body surface area; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; GI disease, gastrointestinal disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate.

Table 3: Multivariable Logistic Regression Model for Supratherapeutic Anti-Xa Activity

(A) Trough

	OR (95% CI)	P-value
Age	1.04 (0.91, 1.20)	0.560
Weight	0.98 (0.93. 1.04)	0.509
GFR	0.99 (0.96, 1.02)	0.433
ALM	0.78 (0.62, 0.98)	0.035

(B) Peak

	OR (95% CI)	P-value
Age	1.02 (0.91, 1.15)	0.723
Weight	1.03 (0.97, 1.08)	0.171
GFR	0.97 (0.94, 1.00)	0.064
ALM	0.84 (0.73, 0.99)	0.039

Abbreviations: GFR, glomerular filtration rate; ALM, appendicular lean mass.

Table 4: Incremental Predictive Value of ALM for Supratherapeutic Anti-Xa Activity

(A) Trough

Model	C-statistic (95% CI)	AIC
Age, Weight, GFR	0.84 (0.73, 0.95)	53.13
+ ALM	0.88 (0.80, 0.96)	49.32
+ sex	0.87 (0.78, 0.96)	51.81
+ drug interaction	0.84 (0.73, 0.95)	55.12
+ albumin	0.85 (0.73, 0.96)	53.65

(B) Peak

Model	C-statistic (95% CI)	AIC
Age, Weight, GFR	0.71 (0.55, 0.86)	70.01
+ ALM	0.76 (0.63, 0.90)	67.17
+ sex	0.75 (0.60, 0.89)	69.03
+ drug interaction	0.70 (0.55, 0.86)	72.01
+ albumin	0.77 (0.64, 0.91)	67.45

Abbreviations: GFR, glomerular filtration rate; ALM, appendicular lean mass.

Table 5: Multivariable Models for Supratherapeutic Anti-Xa Activity with SARC-F (Instead of ALM)

(A) Trough

	OR (95% CI)	P-value
Age	1.00 (0.85, 1.16)	0.958
Weight	0.95 (0.90. 1.00)	0.047
GFR	0.98 (0.96, 1.00)	0.124
SARC-F	1.62 (1.09, 2.40)	0.017

* C-statistic 0.89 (0.80, 0.98), AIC 47.65

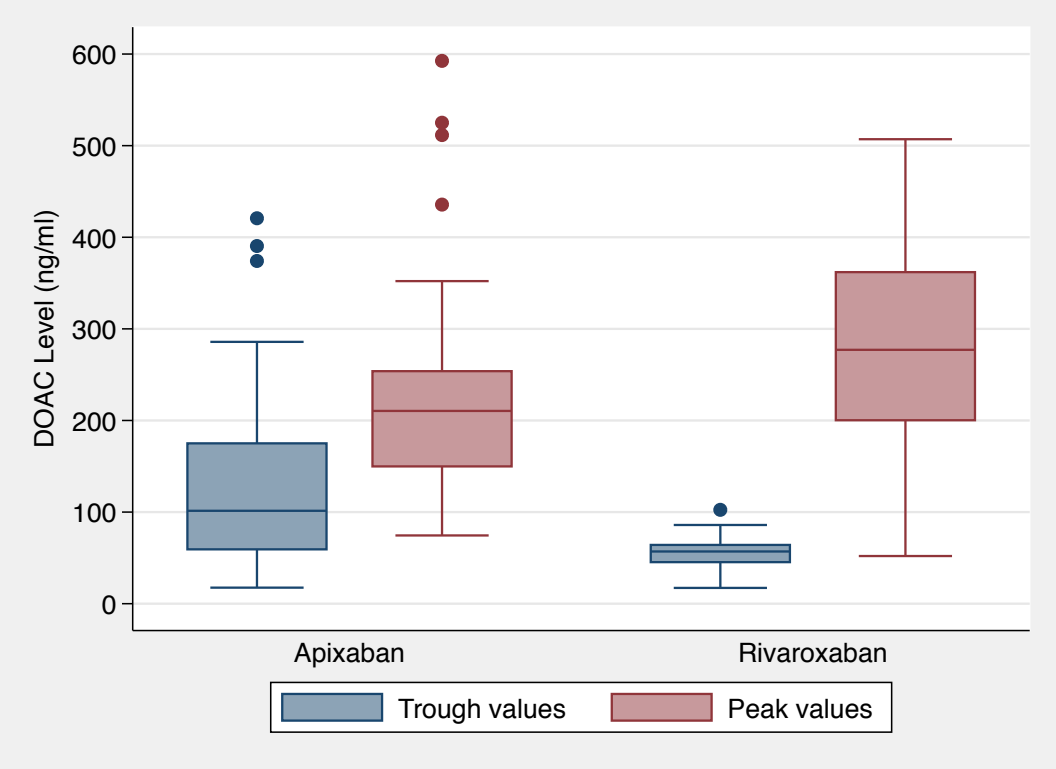
(B) Peak

	OR (95% CI)	P-value
Age	1.02 (0.91, 1.15)	0.716
Weight	1.00 (0.97, 1.04)	0.856
GFR	0.97 (0.94, 1.00)	0.072
SARC-F	1.24 (0.94, 1.64)	0.133

* C-statistic 0.72 (0.56, 0.88), AIC 69.70

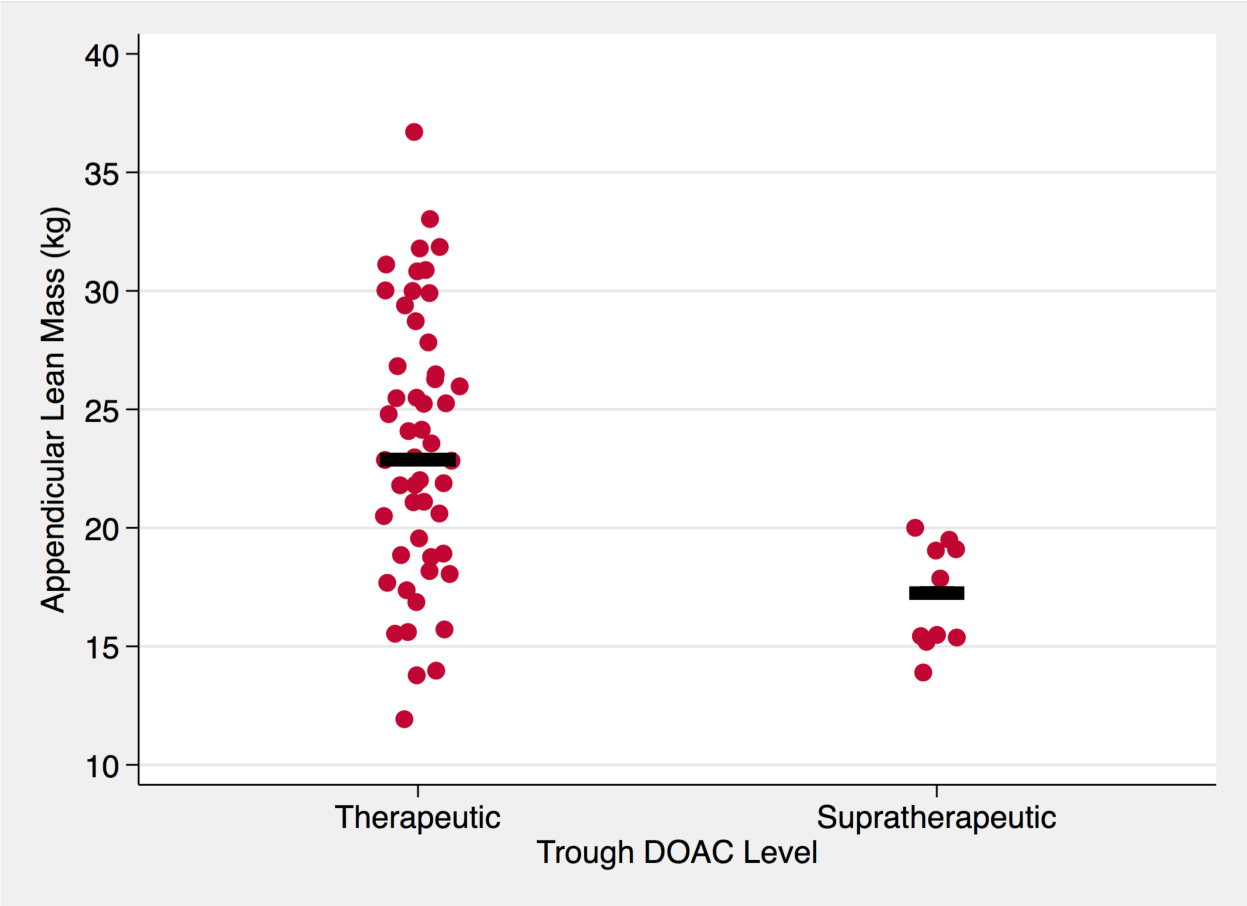
Abbreviations: GFR, glomerular filtration rate; ALM, appendicular lean mass.

Figure 1: Trough and Peak DOAC Levels



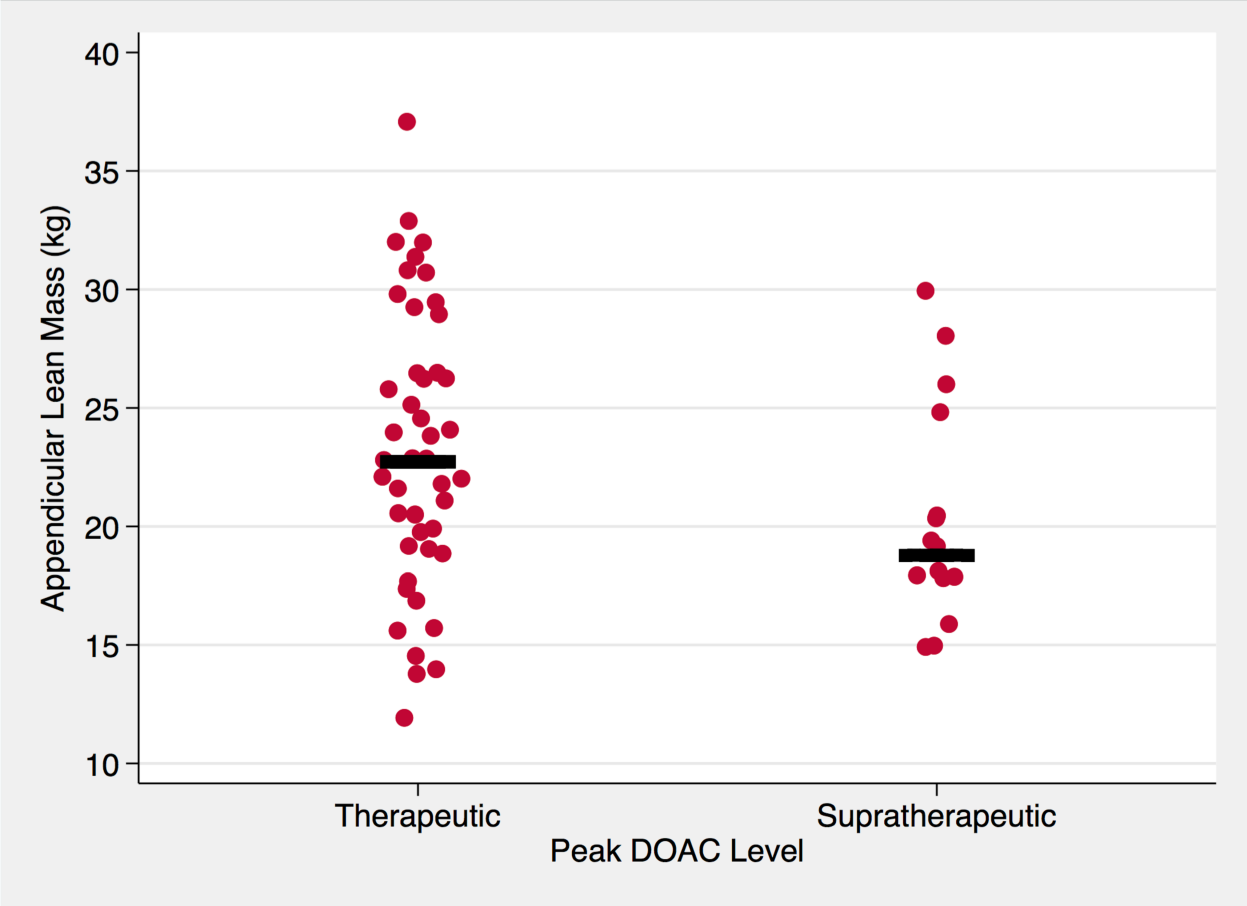
In our cohort, 46 patients (74%) received apixaban and 16 patients (26%) received rivaroxaban. The median trough apixaban level was 99.1 ng/ml (IQR 55.8, 175.0), while the median peak level was 210.4 ng/ml (IQR 149.8, 253.8). The median trough rivaroxaban level was 60.7 ng/ml (IQR 45.3, 72.6), while the median peak level was 279.3 ng/ml (IQR 200.2, 368.4).

Figure 2: Appendicular Lean Mass vs. Trough DOAC Level



When stratified by trough DOAC level, patients with levels within the therapeutic range had a higher appendicular lean mass (median 21.86 kg) than those in the supratherapeutic range (median 15.88 kg).

Figure 3: Appendicular Lean Mass vs. Peak DOAC Level



When stratified by peak DOAC level, patients with levels within the therapeutic range had a higher appendicular lean mass (median 21.82 kg) than those in the supratherapeutic range (median 18.10 kg).

Supplementary Table 1: Patient Characteristics by ALM

	ALM > median N=31	ALM < median N=31	P-value
Age	76.3 ± 5.5	79.2 ± 6.4	0.06
Female	3 (9.7)	26 (83.9)	< 0.0
Weight, kg	91.8 ± 18.7	72.3 ± 15.8	< 0.0
Height, m	1.73 ± 0.1	1.57 ± 0.1	< 0.0
BMI, kg/m^2	31.0 ± 6.9	29.8 ± 10.3	0.60
BSA, m^2	2.09 ± 0.2	1.77 ± 0.2	< 0.0
Obesity (BMI >30 m^2)	14 (45.3)	11 (35.5)	0.44
Underweight (BMI <18.5 m^2)	1 (3.2)	1 (3.2)	1.0
Apixaban prescription	25 (80.7)	21 (67.7)	0.25
Drug interactions	5 (16.1)	8 (25.8)	0.35
Myocardial infarction	4 (12.9)	3 (9.7)	0.69
LVEF, %	57.95 ± 10.1	57.07 ± 15.1	0.79
Pacemaker/ICD	8 (25.8)	8 (25.8)	1.00
Prior stroke	2 (6.5)	4 (12.9)	0.39
Diabetes	9 (29.0)	12 (38.7)	0.42
GI disease	7 (22.5)	7 (22.5)	1.00
COPD	5 (16.1)	7 (22.6)	0.52
Weight loss, kg	0.68 ± 2.3	2.44 ± 4.3	0.048
Grip strength, kg	30.41 ± 8.0	17.10 ± 6.8	< 0.0
Chair rise, s	12.69 ± 7.6	14.04 ± 10.7	0.57
CHA_2DS_2VASC score	2.84 ± 1.4	4.03 ± 1.3	< 0.0
SARC-F score	1.32 ± 1.7	3.0 ± 2.5	0.0033
Falls	8 (25.8)	10 (32.3)	0.58
Creatinine, µmol/L	87.3 ± 17.4	85.9 ± 27.1	0.82
GFR, mL/kg/1.83 m^2	77.7 ± 20.2	83.8 ± 30.1	0.35
Cystatin C, mg/L	1.33 ± 0.5	1.56 ± 0.7	0.11
Hemoglobin, g/L	133.0 ± 25.5	129.1 ± 16.7	0.49
Albumin, g/L	39.9 ± 4.8	38.7 ± 6.2	0.40
Total Protein, g/L	63.6 ± 6.9	64.2 ± 9.0	0.78

Values are given as mean ± SD or n (%). Abbreviations: BMI, body mass index; BSA, body surface area; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; GI disease, gastrointestinal disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate.

Chapter 6: Conclusion

The connection between frailty and bleeding complications has been explored in depth in this thesis. The literature review pointed out the association between frailty and bleeding complications, identified the gaps of knowledge surrounding this issue and demonstrated the lack of consensus bleeding risk prediction score that has been validated in older adults. This thesis brings forth new tools that can be used to predict bleeding complications in frail patients.

The first manuscript, entitled "Patient-Level Predictors of Bleeding in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement: Insights from the FRAILTY-AVR study" explores the value of frailty markers to predict major bleeding complications following a transcatheter or surgical aortic valve replacement. A third of patients suffered a major bleeding complication during the index hospitalization. Frailty markers of low albumin, low serum hemoglobin, cognitive impairment and low chair rise time, composing the EFT scale, were independently predictive of major bleeding outcomes and blood transfusions. Other frailty scales were not as predictive in identifying those are at higher risk of bleeding complications. This study has shown that frail older adults undergoing TAVR or SAVR who have major bleeding complications have worse postoperative outcomes and greater mortality. Furthermore, patient factors have been identified that can be considered to improve risk stratification and allow for preventative strategies to be implemented preoperatively. The EFT is a rapid assessment that can be easily integrated into clinical practice. As more older adults who are frail undergo these procedures, having bleeding complication predictors for frail patients will enable clinicians to target those who are at greatest risk for bleeding complications for therapeutic optimization.

The second manuscript, entitled "Association of Muscle Mass With Direct Oral Anticoagulant Activity in Older Adults" examines the association between low muscle mass and sarcopenia with DOAC plasma activity in older adults with atrial fibrillation. This is the first study to have investigated and discovered as association between muscle mass and DOAC pharmacokinetics in older adults with AF. Our results showed that low appendicular lean mass as measured with bioimpedance was an incremental predictor of supra-therapeutic DOAC levels beyond the traditional risk factors from the pharmaceutical dosing guidelines. Furthermore, sarcopenia, when briefly assessed with a SARC-F score, was similarly associated with supra-therapeutic DOAC levels. Given the growing burden of AF in the aging population, this study has timely implications to understand the impact of frailty on DOAC activity and bleeding complications. This proof-of-concept study will be instrumental to catalyze future research on tailored dosing strategies for frail older adults suffering from atrial fibrillation. If clinical markers of sarcopenia prove to be predictive of DOAC activity and subsequent bleeding complications, then this could facilitate the clinicians' task to tailor therapy to their patients. The "one size fits all" concept of dosing is gradually being replaced by strategies aimed at delivering "personalized medicine", especially to the heterogeneous group of frail older patients. The shift to individualized dosing has the potential to improve drug efficacy, minimize adverse events, and optimize outcomes for vulnerable patients. While a larger multi-center study is required before being implemented in clinical practice, bioimpedance technology has evolved such that these devices are now integrated at the point of care.

The knowledge gained with this thesis suggests that frailty can be used to better assess bleeding risk in older adults, both preoperatively and for anticoagulation. Incorporating frailty into clinical

decision-making could help refine bleeding complication risk predictions for older adults. Knowing of a patient's bleeding risk will allow clinicians to have a more comprehensive assessment of their patient and tailor therapy accordingly. Future efforts should be directed towards validation of the results presented in this thesis.

Chapter 7: Appendices

Appendix A: Fried Frailty Scale[12]

Frailty Domain	Method of Measurement	Cutoffs for Measurement
1 Slowness	5-meter gait speed *Patient is asked to walk at a comfortable pace from a 0-meter start line to past a 5-meter finish line, the cue to start and stop the stopwatch is the first footfall after the start line and first footfall after the finish line, this is repeated 3 times and the average time is recorded*	Sex- and height-based cutoff Male: ≤173 cm: **≤0.65 m/s** >173 cm: **≤0.76 m/s** Female: ≤159 cm: **≤0.65 m/s** >159 cm: **≤0.76 m/s** Simplified cutoff (preferred) Male/Female: **≤0.83 m/s**
2 Weakness	Handgrip strength *Patient is asked to squeeze a handgrip dynamometer as hard as possible, this is repeated 3 times (with each hand and then with the strongest hand) and the maximum value is recorded*	Sex- and BSA-based cutoff Male: ≤24 kg/m^2: **≤29 kg** 24.1-28 kg/m^2: **≤30 kg** >28 kg/m^2: **≤32 kg** Female: ≤26 kg/m^2: **≤17 kg** 26.1-29 kg/m^2: **≤18 kg** >29 kg/m^2: **≤21 kg** Simplified cutoff (preferred) Male: **≤30 kg** Female: **≤20 kg**
3 Low physical activity	Paffenbarger Physical Activity Questionnaire[184]	Male: **<383 kcal/week** Female: **<270 kcal/week**
4 Weight loss	Self-reported	**>10 lbs or >5% in past year**
5 Exhaustion	2 questions: How often do you feel like- 1) "Everything I did was an effort" 2) "I could not get going"	If answered either question- **Most of the time or** **Moderate amount of the time**

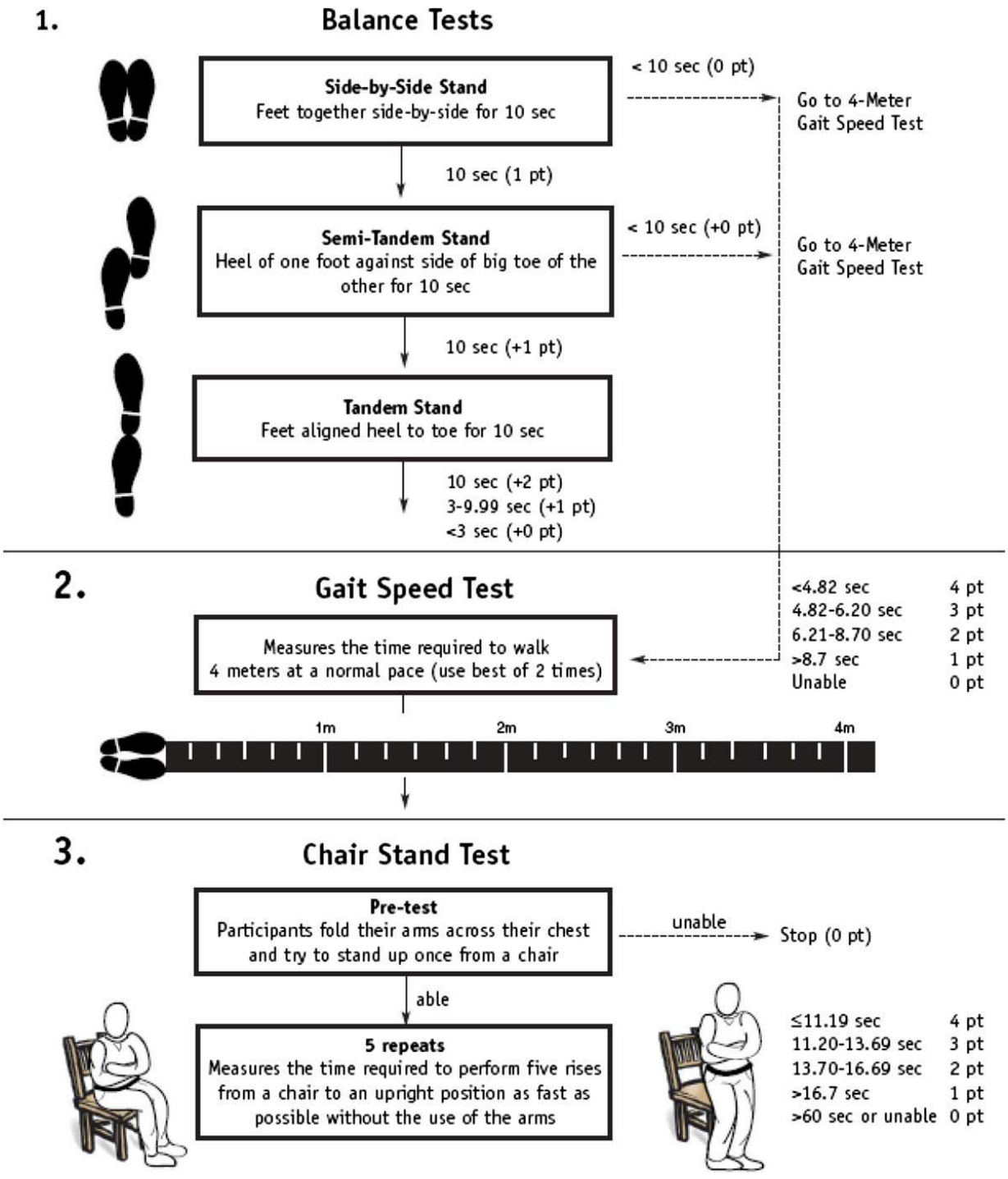
≥3 Criteria Required for a Diagnosis of Frailty

Appendix B: Modified Fried Frailty Scale

Frailty Domain	Method of Measurement	Cutoffs for Measurement
1 Slowness	5-meter gait speed *Patient is asked to walk at a comfortable pace from a 0-meter start line to past a 5-meter finish line, the cue to start and stop the stopwatch is the first footfall after the start line and first footfall after the finish line, this is repeated 3 times and the average time is recorded*	Sex- and height-based cutoff Male: ≤173 cm: **≤0.65 m/s** >173 cm: **≤0.76 m/s** Female: ≤159 cm: **≤0.65 m/s** >159 cm: **≤0.76 m/s** Simplified cutoff (preferred) Male/Female: **≤0.83 m/s**
2 Weakness	Handgrip strength *Patient is asked to squeeze a handgrip dynamometer as hard as possible, this is repeated 3 times (with each hand and then with the strongest hand) and the maximum value is recorded*	Sex- and BSA-based cutoff Male: ≤24 kg/m^2: **≤29 kg** 24.1-28 kg/m^2: **≤30 kg** >28 kg/m^2: **≤32 kg** Female: ≤26 kg/m^2: **≤17 kg** 26.1-29 kg/m^2: **≤18 kg** >29 kg/m^2: **≤21 kg** Simplified cutoff (preferred) Male: **≤30 kg** Female: **≤20 kg**
3 Low physical activity	Paffenbarger Physical Activity Questionnaire[184]	Male: **<383 kcal/week** Female: **<270 kcal/week**
4 Weight loss	Self-reported	**>10 lbs or >5% in past year**
5 Exhaustion	2 questions: How often do you feel like- 1) "Everything I did was an effort" 2) "I could not get going"	If answered either question- **Most of the time or** **Moderate amount of the time**
6 Cognitive impairment	Mini-mental status examination	Score **<27/30**
7 Depressed mood	Geriatric depression scale (5-items)	Score **≥2/5**

≥3 Criteria Required for a Diagnosis of Frailty

Appendix C: Short Physical Performance Battery[185]



≤5 Criteria Required for a Diagnosis of Frailty

Appendix D: Rockwood Clinical Frailty Scale[186]

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

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

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

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

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

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

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

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

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

Scoring frailty in people with dementia

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

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

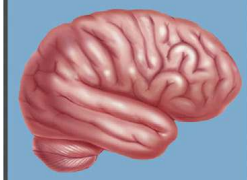
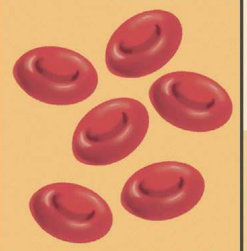
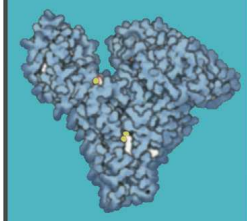
In **severe dementia**, they cannot do personal care without help.

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

Appendix E: Columbia Frailty Scale[187]

Frailty Marker	Method of Measurement	Score
Slowness	Gait speed	0-3
Strength	Grip strength	0-3
Nutrition	Serum albumin	0-3
Disability	Katz activity of daily living survey	0-3
	Total Score	**0-12**

Appendix F: Essential Frailty Toolset[4]

	Five chair rises <15 seconds		0 Points
	Five chair rises ≥15 seconds		1 Point
	Unable to complete		2 Points
	No cognitive impairment		0 Points
	Cognitive impairment		1 Point
	Hemoglobin	≥13.0 g/dL ♂ ≥12.0 g/dL ♀	0 Points
	Hemoglobin	<13.0 g/dL ♂ <12.0 g/dL ♀	1 Point
	Serum albumin	≥3.5 g/dL	0 Points
	Serum albumin	<3.5 g/dL	1 Point

Appendix G: SARC-F Sarcopenia Scale[173]

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, uses aids or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1-3 falls = 1 4 or more falls = 2

≥4 Criteria Predictive of sarcopenia and poor outcomes

Appendix H: Bleeding Risk Prediction Scores

Table 1: Cardiac Surgery or PCI

First Author	Journal Year	Model name	Included in model			Age/frailty?
Alghamdi *et al.*[188]	Transfusion - 2006	TRUST - Transfusion Risk Understanding Scoring Tool	**Risk Factor**		**Point Value**	Age >65 yrs
			Hemoglobin <135 g/L		+1	
			Weight <77 kg		+1	
			Female sex		+1	
			Age >65 years		+1	
			Non-elective surgery		+1	
			Serum creatinine level >120 μmol/L		+1	
			Previous cardiac surgery		+1	
			Non-isolated surgery		+1	
Subherwal *et al.*[189]	Circulation - 2009	CRUSADE – Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines	**Risk Factor**		**Point Value**	No
			Baseline hematocrit, %	<31	+9	
				31-33.9	+7	
				34-36.9	+3	
				37-39.9	+2	
			Creatinine clearance, mL/min	≤15	+39	
				>15-30	+35	
				>30-60	+28	
				>60-90	+17	
				>90-120	+7	
			Heart rate, bpm	71-80	+1	
				81-90	+3	
				91-100	+6	
				101-110	+8	
				111-120	+10	
				≥120	+11	
			Female sex		+8	
			Signs of CHF at presentation		+7	
			Prior vascular disease		+6	
			Diabetes mellitus		+6	
			Systolic blood pressure, mm Hg	≤90	+10	
				91-100	+8	

<table>
<tr><td></td><td></td><td></td><td><table><tr><td>101-120</td><td>+5</td></tr><tr><td>121-180</td><td>+1</td></tr><tr><td>181-200</td><td>+3</td></tr><tr><td>≥201</td><td>+5</td></tr></table></td><td></td></tr>
<tr><td>Ranucci et al.[88]</td><td>Vox Sanguinis
-
2009</td><td>TRACK - Transfusion Risk and Clinical Knowledge score</td><td><table><tr><th>Risk Factor</th><th>Point Value</th></tr><tr><td>Age >67 years</td><td>+6</td></tr><tr><td>Weight M: <85 kg / F: <60 kg</td><td>+2</td></tr><tr><td>Female sex</td><td>+4</td></tr><tr><td>Complex surgery</td><td>+7</td></tr><tr><td>Hematocrit (cont.)</td><td>+1/each value (%)</td></tr></table></td><td>Age >67 yrs</td></tr>
<tr><td>Mehta et al.[190]</td><td>Circulation: Cardiovascular Intervention
-
2009</td><td>-</td><td><table><tr><th>Risk Factor</th><th>Point Value</th></tr><tr><td>STEMI</td><td>+10</td></tr><tr><td>NSTEMI</td><td>+3</td></tr><tr><td>Cardiogenic shock</td><td>+8</td></tr><tr><td>Female sex</td><td>+6</td></tr><tr><td>Previous CHF</td><td>+5</td></tr><tr><td>No previous PCI</td><td>+4</td></tr><tr><td>NYHA class IV CHF</td><td>+4</td></tr><tr><td>PAD</td><td>+2</td></tr><tr><td>Age 66-75 years</td><td>+2</td></tr><tr><td>Age 76-85 years</td><td>+5</td></tr><tr><td>Age >85 years</td><td>+8</td></tr><tr><td>eGFR</td><td>+1 /10 unit ↓ if <90</td></tr></table></td><td>Age 66-75 yrs
Age 76-85 yrs
Age >85 yrs</td></tr>
<tr><td>Mehran et al.[191]</td><td>Journal of the American College of Cardiology
-
2010</td><td>ACUITY-HORIZONS - The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction</td><td><table><tr><th colspan="2">Risk Factor</th><th>Point Value</th></tr><tr><td colspan="2">Female sex</td><td>+8</td></tr><tr><td rowspan="5">Age, years</td><td><50</td><td>+0</td></tr><tr><td>50-59</td><td>+3</td></tr><tr><td>60-69</td><td>+6</td></tr><tr><td>70-79</td><td>+9</td></tr><tr><td>≥80</td><td>+12</td></tr><tr><td rowspan="5">Serum creatinine, mg/dL</td><td>>1.0</td><td>+2</td></tr><tr><td>>1.2</td><td>+3</td></tr><tr><td>>1.4</td><td>+5</td></tr><tr><td>>1.6</td><td>+6</td></tr><tr><td>>1.8</td><td>+8</td></tr><tr><td rowspan="4">White blood cell count (giga/L)</td><td>≥2.0</td><td>+10</td></tr><tr><td>>10</td><td>+2</td></tr><tr><td>>12</td><td>+3</td></tr><tr><td>>14</td><td>+5</td></tr><tr><td>>16</td><td>+6</td></tr></table></td><td>Age 50-59 yrs
Age 60-69 yrs
Age 70-79 yrs
Age >80 yrs</td></tr>
</table>

				>18	+8	
				≥20	+10	
			Anemia		+6	
			STEMI		+6	
			NSTEMI (w/↑ biomarkers)		+2	
			Bibalirudin therapy		-5	
Vuylsteke *et al.*[192]	European Journal of Cardiothoracic Surgery - 2011	BRiSc – Papworth Bleeding Risk Score	**Risk Factor**		**Point value**	Age >75 yrs
			Urgent/emergency surgery		+1	
			Surgery not CABG or single valve surgery		+1	
			Aortic valve disease		+1	
			BMI <25		+1	
			Age >75 years		+1	
Matthews *et al.*[193]	The American Journal of Cardiology - 2011	ACTION Registry-GWTG - The Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guideline In-hospital Major Bleeding Risk Score	**Risk Factor**		**Point value**	Age 51-60 yrs Age 61-70 yrs Age 71-80 yrs Age 81-90 yrs Age ≥91 yrs
			Age	41-50	+1	
				51-60	+2	
				61-70	+3	
				71-80	+4	
				81-90	+5	
				≥91	+6	
			Baseline Serum Creatinine, mg/dL	0.8-1.59	+1	
				1.6-1.99	+2	
				2.0-2.99	+4	
				3.0-3.99	+6	
				4.0-4.99	+8	
				5.0-5.99	+10	
				≥6	+11	
			On dialysis		+11	
			Baseline hemoglobin, g/dL	<5	+17	
				5-7.9	+15	
				8-9.9	+13	
				10-10.9	+12	
				11-13.9	+9	
				14-15.9	+6	
				≥16	+2	
			Heart rate on admission, bpm	41-60	+2	
				61-70	+3	
				71-80	+5	
				81-100	+6	
				101-110	+8	
				111-120	+9	
				121-130	+11	

				131-150	+12
				≥151	+14
			Weight, kg	≤50	+5
				51-70	+4
				71-100	+3
				101-120	+2
				121-140	+1
			Female sex		+4
			Home warfarin use		+2
			Diabetes mellitus		+3
			Heart failure		+3
			Heart failure with shock		+15
			ST-segment depression		+3
			ST-segment elevation		+7
			Previous PAD		+3
Biancari *et al.*[194]	Thrombosis and Haemostasis - 2017	WILL-BLEED	**Risk Factor**		**Point Value**
			LMWH/Heparin		+1
			Antiplatelet pause >5 days		+2
			Female sex		+2
			ACS		+2
			Anemia+3		+3
			eGFR <45 ml/min/1.73m^2		+3
			Critical postoperative state		+5
					No

Table 2: Atrial Fibrillation

First Author	Journal Year	Model name	Included in model		Age/frailty?
Gage *et al.*[195]	American Heart Journal - 2006	$HEMORR_2HAGES$	**Risk Factor**	**Point Value**	Age > 75 yrs
			Hepatic or renal disease	+1	
			Ethanol abuse	+1	
			Malignancy	+1	
			Age > 75 years	+1	
			↓ platelet count or function	+1	
			Rebleeding (Prior Bleed)	+2	
			Hypertension	+1	
			Anemia	+1	
			Genetic factors (CYP 2C9 single-nucleotide polymorphisms)	+1	
			Excessive fall risk	+1	
			Stroke	+1	
Pisters *et al.*[196]	Chest - 2010	HAS-BLED	**Risk Factor**	**Point Value**	Age >65 yrs
			Hypertension	+1	
			Renal disease (dialysis, transplant, Cr >2.26 mg/dL or 200 μmol/L)	+1	
			Liver disease (cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal)	+1	
			Stroke history	+1	
			Prior major bleeding or predisposition to bleeding	+1	
			Labile INR (unstable/high INRs, time in therapeutic range < 60%)	+1	
			Age >65 years	+1	
			Medication usage predisposing to bleeding	+1	
			Alcohol usage (≥ 8 drinks/week)	+1	
Fang *et al.*[197]	Journal of the American College of Cardiology - 2011	ATRIA	**Risk Factor**	**Point Value**	Age ≥ 75 yrs
			Anemia	+3	
			Severe Renal Disease/Dialysis	+3	
			Age ≥ 75 years	+2	
			Stroke History	+1	
			Prior Hemorrhage	+1	
			Hypertension	+1	

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