ORIGINAL RESEARCH

# Retrospective Cross-sectional Analysis of Older Adults Living with Frailty and Anticoagulant Use for Atrial Fibrillation

Jennifer Bolt, PharmD[1,2], Arden R. Barry, PharmD[1,3,4], Jamie Yuen, BSc, Pharm[1], Kenneth Madden, MD[4,5], Manrubby Dhillon, PharmD[1], Colleen Inglis, PharmD[1,6]

*[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver; [2]Pharmacy Services, Interior Health Authority, Kelowna; [3]Pharmacy Services, Fraser Health Authority, Surrey; [4]Faculty of Medicine, University of British Columbia, Vancouver; [5]Geriatric Medicine, Vancouver General Hospital, Vancouver; [6]Island Health Authority, Courtenay, BC, Canada*

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## ABSTRACT

### Background

Oral anticoagulation (OAC) is recommended for most individuals with atrial fibrillation (AF), including those who are frail. Based on previous literature, those who are frail may be less likely to be prescribed OAC, and up to one-third may receive an inappropriate dose if prescribed a direct oral anticoagulant (DOAC). The objectives of this study were to determine the proportion of frail ambulatory older adults with AF who are prescribed OAC, compare the rates of OAC use across the frailty spectrum, assess the appropriateness of DOAC dosing, and identify if frailty and geriatric syndromes impact OAC prescribing patterns.

### Methods

Retrospective cross-sectional review of individuals with AF referred to an ambulatory clinic for older adults living with frailty and/or geriatric syndromes. Rockwood clinical frailty score of ≥4 was used to define frailty and DOAC appropriateness was assessed based on the Canadian Cardiovascular Society AF guidelines.

### Results

Two hundred and ten participants were included. The mean age was 84 years, 49% were female and the median frailty score was 5. Of the 185 participants who were frail, 82% were prescribed an OAC (83% with frailty score of 4, 85% with a frailty score of 5, and 78% with a frailty score of 6). Of those prescribed a DOAC, 70% received a guideline-approved dose.

### Conclusions

Over 80% of ambulatory older adults with frailty and AF were prescribed an OAC. However, of those prescribed a DOAC, 30% received an unapproved dose, suggesting more emphasis should be placed on initial and ongoing dosage selection.

**Key words:** frailty, frail elderly, anticoagulants, atrial fibrillation, aged

## INTRODUCTION

Frailty is defined as a reduced functional reserve and an increased vulnerability to physical, social or psychological stressors. It does not exclusively occur in older adults, but its prevalence increases with age.[1] Older adults living with frailty are more susceptible to stressors and deterioration of health status compared to those without frailty.[1,2]

Atrial fibrillation (AF) is a common comorbidity both in older adults and in those who are frail. The prevalence of AF in frail individuals ranges from 48.2% to 75.4%, while the prevalence of frailty in those with AF ranges from 4.4% to 75.4%, with higher rates as age increases.[3] Individuals living with concomitant AF and frailty are at an increased risk of all-cause mortality, stroke, worsening symptom severity, and longer hospital stay, compared to those with AF alone.[4,5] Oral anticoagulant (OAC) therapy is generally recommended for all patients with AF over the age of 65.[6,7,8] As contemporary evidence supports that direct oral anticoagulants (DOACs) are at least non-inferior to vitamin K antagonists for efficacy with superior safety, guidelines now recommend the use of DOACs over warfarin.[6,7,8] The Canadian Cardiovascular Society and European Society of Cardiology also specifically recommend initiating OAC therapy in most frail older adults with AF as the benefits outweigh the risks.[6,7]

Despite guideline recommendations, previous literature has found frail older adults to be less likely to receive OAC

therapy compared to those who are not frail.[4,5,9,10,11] The majority of this data is from hospitalized cohorts, making it difficult to extrapolate to community dwelling populations. More recently, data from the SAGE-AF registry found neither frailty nor geriatric syndromes to be associated with under-utilization of OAC therapy.[12,13] However, of all older adults in the SAGE-AF cohort who were prescribed a DOAC, only 77% received a dose consistent with the product monograph. Within the subset of frail older adults in SAGE-AF, only 69% received an approved dosing regimen.[14] Beyond the SAGE-AF findings, little is known about OAC utilization in community dwelling older adults living with AF, frailty, and geriatric syndromes.

The purpose of this study was to describe the use of OAC therapy in a population of ambulatory older adults living with frailty, geriatric syndromes and AF. The primary objective of this study was to determine the proportion of ambulatory older adults living with frailty and AF who were prescribed an oral anticoagulant for stroke prevention. Secondary objectives were to compare of rates of OAC utilization for older adults with AF across the frailty spectrum, identify if frailty or geriatric syndromes impact OAC use in ambulatory older adults with AF, and assess the appropriateness of DOAC therapy when used for AF in frail older adults. We hypothesized that the rate of OAC use and appropriateness of DOAC dosing would be similar to the 85% and 69%, respectively, as seen in the SAGE-AF study.[12,13,14]

# METHODS

## Design and Setting

This study utilized a retrospective cross-sectional review of electronic medical records (EMRs) of older adults referred to an ambulatory clinic within an urban centre in British Columbia, Canada. The clinic consists of a multidisciplinary team of geriatricians, general practitioners, pharmacists, nurses, and other allied health-care professionals and provides educational experiences to health-care professional trainees. The clinic provides short-term (3–6 month) assessment and management of individuals living independently or in assisted living facilities, but does not provide care to residents of long-term care or institutional facilities.

## Participant Selection

Individuals who were seen at the clinic between October 4, 2017 and September 30, 2021, and who had a documented diagnosis of AF or atrial flutter and medication history recorded in the EMR were eligible for study inclusion. Exclusion criteria were documented alternate indications for OAC (mechanical heart valve, left ventricular thrombus, venous thromboembolism within the last six months, recurrent venous thromboembolism, conditions associated with thrombophilia), end-stage renal dysfunction receiving hemodialysis, and those without a documented frailty score. For individuals referred to the clinic more than once during the study period, only their first referral with documented atrial fibrillation was eligible for inclusion.

## Data Collection

Data were extracted from the two clinic-based EMRs, Profile (Intrahealth Canada Ltd, North Vancouver, British Columbia) and Meditech (Medical Information Technology Inc, Westwood, MA), by two researchers (MD and JB) and collated in REDCap (Research Electronic Data Capture, REDCap Consortium, Nashville, TN) electronic data capture tool hosted by the University of British Columbia. Data were extracted in duplicate for the first 10 participants, followed by every fifth participant. Discrepancies were recorded and resolved by consensus.

Information collected from the EMRs included: demographics, Rockwood clinical frailty score, medical comorbidities, geriatric syndromes (cognitive impairment, insomnia, depression, falls, urinary incontinence, polypharmacy), diagnostics (laboratory values and echocardiogram), medication history, and self-reported alcohol use. Information was collected from the initial intake assessments; subsequently documented information and interventions completed through the course of care at the clinic were not collected. Medication histories documented in the EMR had been obtained by clinical pharmacists through interviews with patients/caregiver and verified against at least one additional source of information, including PharmaNet, the provincial database of dispensed medications. Rockwood clinical frailty was collected from the intake clinician's assessment record. Geriatric syndromes were identified from the participants' initial clinic intake assessment form. A fall was defined as at least one event in the past year wherein the participant inadvertently came to rest upon the floor, ground or other lower level.[15] Cognitive impairment was defined as a referral to the clinic for cognitive concerns, pre-existing diagnosis of dementia or mild cognitive impairment, previous Mini-Mental Status Examination (MMSE) score <24 or Montreal Cognitive Assessment (MoCA) score <26. Depression was defined as presence of a clinical diagnosis or self-reported depression. Insomnia was defined as diagnosis of insomnia, self-reported poor quality of sleep or regular use of a medication only indicated for insomnia (e.g., zopiclone). Urinary incontinence was defined as presence of a clinical diagnosis, regular use of a medication only indicated for incontinence (e.g., mirabegron, oxybutynin) or self-reported symptoms of incontinence. Polypharmacy was defined as five or more scheduled prescription medications.[16] Potentially interacting medications were screened according to the European Heart Rhythm Association guidance document on DOACs in AF.[17] Bleeding was defined as a documented previous bleeding episode (e.g., gastrointestinal bleed) or any bleeding requiring hospitalization, resulting in a drop in hemoglobin of 20 g/L or more, or requiring a transfusion. Frailty was defined as a Rockwood clinical frailty score of 4 (very mildly frail) to 9 (terminally ill).[18] The CHADS2, CHA2DS2-VASc, HAS-BLED scores, and creatinine clearance using Cockcroft-Gault equation (standardized to 72 kg) were calculated from collected data.

Appropriateness of OAC therapy was determined by evaluating indication, drug interactions, and dose. An indication for anticoagulation was determined using the Canadian Cardiovascular Society CHADS-65 algorithm wherein age over 65 years or any of the CHADS2 risk factors provide an indication for OAC.[6] DOAC's were classified as inappropriate in participants concomitantly receiving a medication identified as an absolute contraindication in the European Heart Rhythm Association guidance document[17] DOAC dosing was assessed for appropriateness based on criteria outlined in the Canadian Cardiovascular Society guidelines.[6] Apixaban dose of 5 mg twice daily was considered appropriate, unless the participant possessed two or more of the following: age ≥80 years, serum creatinine ≥133 μmol/L or body weight ≤60 kg, in which cases a dose of 2.5 mg twice daily was considered appropriate. Rivaroxaban 20 mg daily was considered appropriate if the creatinine clearance was greater than 50 mL/min, and 15 mg daily was considered appropriate if the creatinine clearance was 15–50 mL/min. Dabigatran 110 mg twice daily was considered appropriate for all participants and 150 mg twice daily was considered appropriate only if the participant was less than 80 years of age.[6] In addition, any non-standard dose was considered inappropriate.

### Sample Size

Investigators assumed and used a prevalence rate of 85% based on existing literature.[12] A sample size of at least 196 participants was determined to be required to achieve a precision of 0.05.[19]

### Statistical Analysis

Categorical data were reported as percentages, continuous data were reported through means, and standard deviations and ordinal data were reported as medians with interquartile ranges. A stepwise multivariate logistic regression was used to assess the impact of age, sex, presence of frailty, and geriatric syndromes on OAC use. Cohen's kappa was used to assess the inter-reliability. IBM SPSS Statistics (version 28, IBM Corporation, Armonk, NY) was used for statistical analysis.

This study was approved by the clinical research ethics board at the Interior Health Authority (2021-22-060-H).

## RESULTS

A total of 2,738 charts were screened for study eligibility and 265 met the inclusion criteria. Fifty-five potential participants met an exclusion criterion, leaving 210 participants in the analysis (Figure 1). Cohen's kappa was 0.954, indicating a high level of inter-rater reliability.

Forty-nine per cent of participants were female, mean age was 83.8 years (SD 5.8) and median clinical frailty score was 5 (IQR 4, 5) (Table 1). One hundred eighty-five participants were frail (clinical frailty score of 4 or greater), of whom 152 (82%) were prescribed an OAC for AF (Table 2). Rates of OAC utilization ranged from 75% (frailty score of 6) to 100% (frailty score of 2). Following regression analysis, polypharmacy was associated with a higher use of OAC (odds ratio [OR] 2.47, 95% confidence interval [CI] 1.10-5.57, $p$=.029), while insomnia (OR 0.36, 95% CI 0.16-0.80, $p$=.012) and age (OR 0.93, 95% CI 0.87-0.998, $p$=.044) were associated with lower OAC use.

All frail participants had an indication for OAC therapy based on the Canadian Cardiovascular Society CHADS-65 algorithm. There were no clinically meaningful pharmacokinetic drug interactions in those receiving a DOAC that would result in an absolute contraindication. DOAC dosing

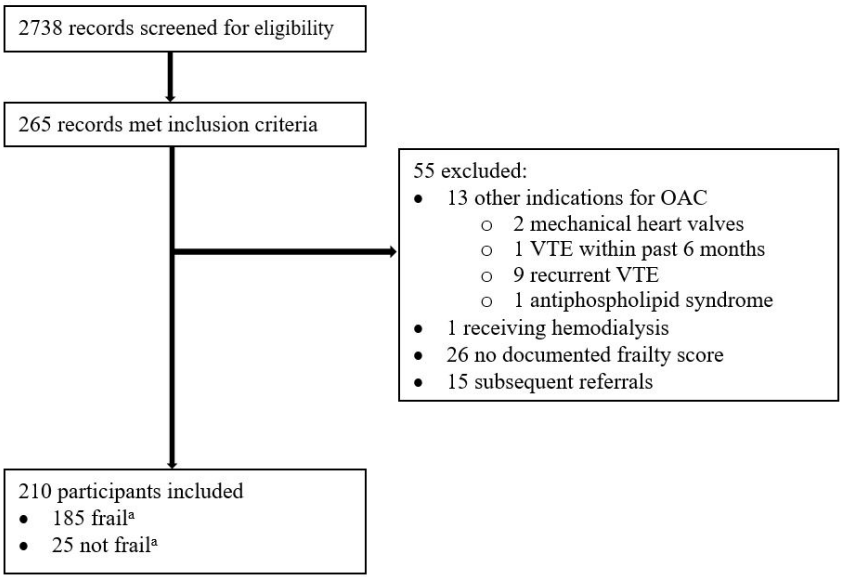


FIGURE 1. Study recruitment flow chart
[a]Frail = Rockwood clinical frailty score of 4 or higher.
OAC = oral anticoagulant, VTE = venous thromboembolism.

TABLE 1.
Participant characteristics

| *Parameter* | *N=210* |
|---|---|
| Female, n (%) | 103 (49.0) |
| Mean age, years (SD) | 83.8 (5.8) |
| Mean weight, kg (SD)[a] | 75.5 (16.2) |
| Median Rockwood clinical frailty score (IQR) | 5 (4, 5) |
| *Comorbidities* | |
| Dementia, n (%) | 36 (17.1) |
| Stroke, n (%) | 82 (39.0) |
| Transient ischemic attack, n (%) | 44 (21.0) |
| Heart failure, n (%) | 64 (30.5) |
| HFrEF | 26/64 (40.6) |
| HFmrEF | 6/64 (9.4) |
| HFpEF | 30/64 (46.9) |
| EF unknown | 2/64 (3.1) |
| Coronary artery disease, n (%) | 66 (31.4) |
| Hypertension, n (%) | 152 (72.4) |
| Diabetes mellitus, n (%) | 41 (19.5) |
| Chronic kidney disease, n (%) | 61 (29.0) |
| Previous bleeding event, n (%) | 28 (13.3) |
| Gastrointestinal bleed | 22 (10.5) |
| Intracranial hemorrhage | 1 (0.5) |
| *Geriatric Syndromes* | |
| Cognitive impairment, n (%) | 138 (65.7) |
| Insomnia, n (%) | 65 (31.0) |
| Depression, n (%) | 79 (37.6) |
| Falls, n (%) | 120 (57.1) |
| Urinary incontinence, n (%) | 103 (49.0) |
| Polypharmacy, n (%) | 156 (74.3) |
| *Scores* | |
| Median $CHADS_2$ score (IQR) | 3 (2, 4) |
| Median $CHA_2DS_2$-Vasc score (IQR) | 5 (4, 6) |
| Median HAS-BLED score (IQR) | 2 (1, 2) |
| Mean number of medications (SD) | 6.6 (3.0) |
| Mean CrCl (ml/min/72 kg) (SD)[b] | 56.3 (23.6) |
| *Stroke Prophylaxis* | |
| Prescribed OAC, n (%) | 175 (82.9) |
| Apixaban | 71 (33.8) |
| Dabigatran | 13 (6.2) |
| Rivaroxaban | 54 (25.7) |
| Warfarin | 37 (17.6) |
| Antiplatelet agent, n (%) | 18 (8.6) |
| No stroke prophylaxis, n (%) | 18 (8.6) |

[a]Weight was missing for 2 participants.
[b]Unable to calculate CrCl for 7 participants (2 participants missing weight, 5 participants missing serum creatinine).
CrCl = creatinine clearance, EF = ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, OAC = oral anticoagulant.

was appropriate in 83/118 (70%) of frail participants, while 20 (17%) received an inappropriately low dose and 15 (13%) received an inappropriately high dose (Table 3). Out of 16 frail participants taking warfarin who had International Normalized Ratio (INR) data available, eight had a time-in-therapeutic range of ≥60%.

## DISCUSSION

This study evaluated the use of OAC in older adults living with AF, frailty, and geriatric syndromes in an ambulatory care setting. The results show that 83% of all participants and 88% of frail participants were prescribed an OAC, which is consistent with the SAGE-AF study that found an OAC utilization rate of 85.5% within the total study cohort of older adults with AF and 86.6% within the subgroup of participants who were frail.[13] Also, in alignment with the SAGE-AF study, this study did not find an association between frailty and OAC usage; however, there was a trend towards lower OAC usage in those with a frailty score of 6.[13]

The SAGE-AF investigators found similar rates of OAC utilization as the present study.[13] However, there are notable differences when comparing the two studies. In the SAGE-AF cohort, the mean age was 76 years and median CHADS2-VASc score was 4, compared to this study's population with a mean age of 83.3 years and median CHADS2-VASc score of 5.[12,13] In addition, a greater proportion of participants in the present study had a history of falls, cognitive impairment, and frailty. Unlike the SAGE-AF study, we did not exclude those with an absolute contraindication to OAC.[12,13] It is worth noting that the SAGE-AF investigators assessed cognitive impairment and frailty using the MoCA and Cardiovascular Health Survey frailty scale, respectively, and falls having occurred in the past six months.[12,13] Within our study, cognitive impairment was documented through the participant's medical diagnoses, reason for referral to the clinic or previous MoCA or MMSE scores, frailty was assessed using the Rockwood clinical frailty score, and falls were collected if they occurred within the last year. Despite these differences in definitions, our results were consistent with respect to the

TABLE 2.
Summary of clinical frailty scores and rates of oral anticoagulant utilization

| *Frailty Score*[a] | *Number of Participants* | *OAC Utilization* |
|---|---|---|
| Frailty score 2 | 2 | 2/2 (100%) |
| Frailty score 3 | 23 | 20/23 (87.0%) |
| Frailty score 4 | 54 | 45/54 (83.3%) |
| Frailty score 5 | 91 | 77/91 (84.6%) |
| Frailty score 6 | 40 | 31/40 (77.5%) |
| Frailty score 4–6 | 185 | 152/185 (82.2%) |

[a]There were no participants with frailty score of 1,7, 8 or 9.

Table 3.

Appropriateness of direct oral anticoagulant dosing in frail older adults[a]

| *DOAC* | *Appropriateness* | *Inappropriately Low Dose*[b] | *Inappropriately High Dose*[c] |
|---|---|---|---|
| Apixaban, n/N (%) | 45/64 (70.3) | 14/64 (21.9) | 5/64 (7.8) |
| Rivaroxaban, n/N (%) | 27/43 (62.8) | 6/43 (14.0) | 10/43 (23.3) |
| Dabigatran, n/N (%) | 11/11 (100) | 0/11 (0) | 0/11 (0) |
| Total DOAC appropriateness based on age, frailty and renal function, n/N (%) | 83/118 (70.3) | 20/118 (16.9) | 15/118 (12.7) |

[a]Three participants unable to be assessed due to missing weight or serum creatinine data.
[b]Inappropriately low dose: Apixaban 2.5 mg twice daily with one or less of the following: age ≥80 years, serum creatinine ≥133 μmol/L or body weight ≤60 kg; Rivaroxaban 15 mg daily with creatinine clearance greater than 50 mL/min.
[c]Inappropriately high dose: Apixaban 5 mg twice daily with two or more of the following: age ≥80 years, serum creatinine ≥133 μmol/L or body weight ≤60 kg; Rivaroxaban 20 mg daily with creatinine clearance of 15–50 mL/min; Dabigatran 150 mg twice daily with age 80 or greater.
DOAC = direct oral anticoagulant.

overall prevalence of OAC prescribing in this population and the lack of impact of these geriatric syndromes on OAC utilization. Both studies found a rate of OAC utilization rate exceeding that found in the general adult AF population (approximately 60%).[20]

Frailty and geriatric syndromes such as cognitive impairment, depression, falls, and urinary incontinence did not appear to impact the rate of OAC utilization in this study. In a systematic review and meta-analysis of older adults with frailty and AF, Wilkinson and colleagues found that those with frailty were less likely to receive an OAC prescription compared to those without frailty, although the majority of included studies involved hospitalized cohorts.[4] They also showed that OAC prescribing was lower as age increased, which is consistent with the findings of this study.[4] Conversely, the TILDA study found an association between frailty and increased OAC use, but no association with polypharmacy, as was found in the present study.[21] In SAGE-AF, geriatric syndromes (cognitive function, frailty, social isolation, sensory impairment, and depression) did not impact prescribing of an OAC.[13] One of the unique findings from this study regarding the impact of frailty on OAC prescribing is the trend toward underutilization of OAC in those with moderate frailty (Rockwood clinical frailty score of 6). The present study was not designed to assess for the significance of this finding, and this finding has not been confirmed by other studies. Previous studies reporting on an association or lack thereof between frailty and OAC have looked only at frailty as a discrete category, as opposed to varying degrees of severity.[4,5,12,13,21] This finding suggests the need to thoroughly assess the indication for OAC therapy in populations with a higher frailty scores, but these findings require further investigation.

Approximately 70% of the frail patients with AF in this study were on an appropriate dose of DOAC therapy, while 17% received a dose that was too low and 13% received a dose that was too high. This is higher than a recent retrospective study of those aged of 80 and older with AF that found a 61% dose appropriateness rate, with 34% of participants being underdosed and 5% being overdosed.[22] Our study is more closely aligned with the SAGE-AF, which found 77% of the participants received a dose consistent with the product monograph, 18% were underdosed, and 5% were overdosed. Additionally, within the subset of frail older adults in SAGE-AF, 69% received an approved DOAC dosing regimen.[14] As creatinine clearance is the ideal parameter to guide renal dosage adjustments for DOACs, we selected a creatinine clearance threshold of 50 mL/min in the assessment of rivaroxaban renal dose adjustments, using the most recent creatinine clearance measurement available. Similarly, a serum creatinine threshold of 133 μmol/L was used in the assessment of apixaban dosage adjustments, using the most recent serum creatinine measurement available, along with age and body weight. While this may not be consistent with the approach used in clinical practice, it was important to apply a standard threshold to maintain consistency across participants. Higher than recommended dosing of DOACs has not been found to lower the risk of stroke and has been associated with higher rate of bleeding complications, hospitalizations, and death.[23,24] Similarly, underdosing of DOACs has not been found to lower the risk of bleeding, but has been associated with higher rates of thromboembolism, hospitalization, and mortality.[23,24] It is currently unknown whether inappropriate DOAC dosing contributes other negative health outcomes in older adults living with frailty, such as falls or cognitive impairment. Only drug–drug interactions resulting in an absolute contraindication were considered inappropriate, as interactions resulting in a "use with caution" recommendation do not accurately capture the nuances in the decision-making process. As only half of the participants taking warfarin had an INR time-in-therapeutic range of at least 60%, this highlights the opportunity to discuss the appropriateness of switching to DOAC therapy in candidates who are not able to achieve adequate time-in-therapeutic range.[6,7,8]

This study has several strengths. It provides an assessment of one of the largest cohorts of frail ambulatory older adults living with atrial fibrillation—it included 185 frail

participants, as compared to 172 frail older adults in SAGE-AF and even fewer in the TILDA cohort (an unstated proportion of 118 participants with documented evidence of AF).[13,21] Further, it is the first to outline the rates of OAC across increasing levels of frailty.

There are several limitations to consider when interpreting the results of this study. First, the study was conducted in a single urban Canadian site and thus the findings may not be generalizable to other sites, including rural and remote areas or other clinical settings. We also did not look at the impact of the clinic on OAC utilization, as we performed a cross-sectional study looking only at clinic admission. This study relied on the accuracy of the documented data in the EMR. Some data, such as socioeconomic status, were not documented in the EMR and therefore could not be assessed for influence on OAC utilization. The threshold for renal dosing was assessed using the most recent creatinine clearance or serum creatinine measurement and did not assess any previous trends in renal function. Finally, a significant portion of participants taking warfarin did not have INR data available in the clinic EMR, limiting the ability to assess time-in-therapeutic range. Future studies should evaluate the rates of OAC across the frailty spectrum with AF population across multiple sites and further assess the impact of geriatric syndromes on OAC usage and the impact of DOAC dosing on geriatric syndromes.

## CONCLUSIONS

This cross-sectional study found that OAC was prescribed to over 80% of community-dwelling older adults with frailty, geriatric syndromes, and AF. While there was no statistically significant association between frailty and OAC prescription, there was lower OAC use in the frailest patients. As well, approximately one-third of frail older adults received an incorrect dose. Given the higher risk of morbidities and mortality in frail older patients with AF, this study suggests a need to focus on ensuring appropriateness of DOAC dosing in this population.

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Not applicable.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood the *Canadian Geriatrics Journal*'s policy on disclosing conflicts of interest and declare the following interest: KM is the Editor-in-Chief of the *Canadian Geriatrics Journal*. JY received the Canadian Foundation of Pharmacy Innovation Fund Grant in 2021. JB, AB, MD, and CI have no conflicts of interest to declare.

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**Correspondence to:** Jennifer Bolt, PharmD, Interior Health Authority
Kelowna Community Health Centre, 505 Doyle Ave, Kelowna, BC V1Y 6V8
**Email:** Jennifer.bolt@ubc.ca