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REVIEW ARTICLE

Frailty and oral anticoagulant prescription in adults with atrial fibrillation: A systematic review

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Abstract

Objectives: The objectives of this study were to determine the prevalence of frailty in the context of atrial fibrillation (AF); to identify the most commonly used frailty instruments in AF; and to describe the effect of frailty on non-vitamin K oral anticoagulant (NOAC) prescription for stroke prevention in adults with AF.

Methods: A systematic search of databases, including Medline, Embase, Web of Science, Cochrane Library, Scopus, and CINAHL, was conducted using search terms including "atrial fibrillation," "frailty," and "anticoagulation." A narrative synthesis was undertaken.

Results: A total of 92 articles were screened, and 12 articles were included. The mean age of the participants (n = 212,111) was 82 years (range = 77–85 years) with 56% of participants identified as frail and 44% identified non-frail. A total of five different frailty instruments were identified: the Frailty Phenotype (FP; n = 5, 42%), the Clinical Frailty Scale (CFS; n = 4, 33%), Cumulative Deficit Model of Frailty (CDM; n = 1, 8%), Edmonton Frail Scale (n = 1, 8%) and the Resident Assessment Instrument – Minimum Data Set (RAI-MDS 2.0; n = 1, 8%). Frailty was identified as an important barrier to anticoagulant therapy with 52% of the frail population anticoagulated vs 67% non-frail.

Conclusion: Frailty is an important consideration in anticoagulation decision making for stroke prevention in patients with AF. There is scope to improve frailty screening and treatment. Frailty status is an important risk marker and should be considered when evaluating stroke risk alongside congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (CHA_2DS_2-VASc) and Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile, Elderly, and Drugs (HAS-BLED) scores.

KEYWORD
anticoagulation, atrial fibrillation, frailty

1 | INTRODUCTION

Atrial fibrillation (AF) is the most diagnosed cardiac arrhythmia in clinical practice, with increasing incidence and prevalence among older people.[1,2] Aging is a major risk factor, with 70% of patients with AF between the ages of 65 and 85 years old.[3-6] Particularly with the aging population, the risk of AF continues to rise. The global burden of AF is expected to double from 125 million to 434 million over the next two generations, it is an increasingly important public health issue.[7] This has pertinent implications on the future of health

care planning as AF is an important risk factor for stroke.[8] Stroke can significantly decrease quality of life.[9] The burden of AF, however, extends beyond the individual, with significant socio-economic burden. Despite this, frail older adults remain under-represented in clinical research and under-diagnosed in clinical practice.[10,11] This presents significant challenges in the appropriate identification, treatment, and ongoing management of AF in frail older adults.

Frailty is an age-associated syndrome characterized by a decline in biological reserves and failure of homeostatic mechanisms.[12,13] It is hypothesized frailty and AF could share common pathophysiological underpinnings; however, the precise biology is not well understood and requires further investigation.[14-17] Frailty among the aging AF population is associated with adverse health outcomes, and increased risk of ischemic stroke and thromboembolism.[18] Current clinical practice guidelines recommend non-vitamin K oral anticoagulants (NOACs) for treatment of non-valvular AF as they overcome the main limitations of vitamin K antagonists (VKAs).[19] These limitations include drug–drug and drug-food interactions,[20] frequent international normalized ratio (INR) monitoring, and dose adjustment.[11,21] Recent trials have found NOACs to have equal or greater efficacy than standard therapy (warfarin and aspirin) and no excess intracranial hemorrhage. This is an important advancement in stroke prevention.

However, due to the complex clinical consequences of frailty and AF on multiple systems, optimizing anticoagulant therapy for this population is clinically challenging.[22] Discerning whether to initiate or withhold NOAC treatment is a growing challenge for prescribers.[23] Barriers to anticoagulation, such as complex multimorbidity and high-risk bleeding are significant in the frail AF population. Within literature, the rate of prescription of NOACs in this population is suboptimal (<50%).[18,24,25] In the absence of these barriers, NOACs provide many benefits that are safe and effective for the prevention of stroke.[26] Overall, balancing stroke risk and bleeding risk is recommended. Stroke and bleeding risk stratification tools, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (CHA_2DS_2-VAS_C) and Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly, and Drugs (HAS-BLED) can be helpful to inform decision making in practice.

Frailty assessment is a useful tool that can be utilized in the clinical management of older adults to mitigate the challenges that surround appropriate and guideline-adherent anticoagulant prescription in older adults with AF.[27,28] There are numerous frailty assessment instruments available, including the Fried Frailty Phenotype,[29] Cumulative Deficit Model of Frailty (CDM),[30] Survey of Health, Aging, and Retirement in Europe Frailty Index (SHARE-FI),[31] and the Clinical Frailty Scale (Rockwood).[32] Clinician estimated frailty (e.g., the end-of-the-bed, "eye-ball" test) has been shown to be inaccurate when compared against the use of frailty assessment instruments.[33,34] Therefore, the use of a validated instrument may assist in decision making for anticoagulation for stroke prevention. Despite increasing interest in the assessment of frailty in the context of AF, the impact of frailty on the appropriate use of NOACs for stroke prevention remains unclear.

1.1 | Aims and Objectives

The objectives of this review were to:

1. to determine the prevalence of frailty in the context of AF;
2. to identify the most commonly used frailty instruments in AF;
3. to describe the effect of frailty on NOAC use for stroke prevention in adults with AF.

2 | DESIGN AND METHODS

A systematic review with narrative synthesis was conducted by three reviewers in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol guidelines. In December 2021, a systematic search of key electronic bibliographic databases, including Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, Web of Science, Cochrane Library, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL) was undertaken. Search terms combined "atrial fibrillation," "frailty," and "anticoagulation" and their alternative terms using Boolean Operators. Refer to Appendix A for detailed search strategy. The search strategy was designed to provide high sensitivity for finding relevant studies and was restricted to primary original research studies. Peer reviewed literature, including randomized controlled trials, cohort studies, case–control studies, and cross-sectional studies, that were published in the English language were included.

2.1 | Inclusion and exclusion criteria

The dates searched ranged from January 2005 to May 2021. Dabigatran was the first of three NOACs released in the Australian pharmaceutical market. The Dabigatran trial data was released in 2008/2009. The criterion begins from 2005 to include any preliminary data that may have been released prior to 2008. Therefore, the date criterion was limited to 2005–2021 to ensure all data are relevant to contemporary issues surrounding frailty and AF. Studies were included if they addressed frailty and NOAC prescription for patients with AF. This review focuses on the impact of frailty on NOAC prescriptions, the cohort of participants receiving NOACs had to be over 15% to ensure study relevancy. Studies were excluded if less than 15% of the frail AF population received NOACs. Secondary articles, such as editorials, scientific conference abstracts, correspondence, letters, and review papers, were excluded. Case reports, clinical trial registrations, and protocols were also excluded. Articles that adhered to these inclusion/exclusion criteria were then assessed through a full text review. The authors' personal libraries were searched. All studies that were not full length and did not meet defined criteria were excluded for relevancy and validity purposes.

3 | RESULTS

The search retrieved a total of 92 articles, of which 12 studies were included in this review. Of these studies, six were retrospective observational studies conducted in Canada, Italy, Japan, and the United States, four studies were prospective observational studies conducted in Sweden, Spain, Greece, and the United States, and one was a cross-sectional study conducted in Quebec. There was only one experimental study, which was a randomized controlled clinical trial that was conducted in the United States. Refer to Figure 1 for a detailed PRISMA flow diagram, with results of the screening of included and excluded studies.

Based on the descriptive characteristic data extracted for the 12 studies, the number of participants per study ranged from 104 to 150,487 participants with a median of 649 participants (interquartile range = 10,655). The mean age of the participants was 82 years (range from 77–85 years.). Eleven articles reported the number of female and male participants, and the median was 54.3% (n = 334) female participants.

We examined the use of frailty assessment instruments. A total of five different frailty instruments were identified. However, the most used were modified frailty instruments that were based on the Frailty Phenotype (n = 5/12, 42%) and the Clinical Frailty Scale (CFS; n = 4/12, 33%). Other frailty instruments that were identified were the CDM (n = 1, 8%), the Edmonton Frail Scale (n = 1/12, 8%), and the Resident Assessment Instrument – Minimum Data Set (RAI-MDS 2.0; n = 1/12, 8%). Frailty was measured at hospital admission in half of the articles (n = 6/12), at discharge in 8% of the articles (n = 1/12), and was operationalized retrospectively through chart reviews or databases in 58% of the articles (n = 7/12). Of the included participants, 56% of participants (n = 118,788) were identified as frail and 44% identified non-frail (n = 93,334). The prevalence of frailty in the included studies ranged from 14% to 100%. The characteristics of each study including risk factors for stroke are described in Table 1.

Of the included studies, 10 found that frailty is significantly associated with poor rates of prescription for NOACs (Figure 2). Overall, a negative correlation was found between frailty and anticoagulant prescription (52% frail vs 67% non-frail). Of the 12 included studies, seven included a breakdown of anticoagulant use. Across these seven studies, the most commonly prescribed anticoagulant was VKAs (32%), followed by apixaban (19%), edoxaban (11%), rivaroxaban (11%), and dabigatran (10%; Figure 3). The mean CHA_2DS_2-VAS_C score was 4.52, with results ranging from 2.83 to 5.62 in the included studies.

4 | DISCUSSION

We found that about half of those with AF were frail (56%), but this varied with the frailty instrument. Frailly was associated with less anticoagulant therapy use. The prevalence of frailty among the AF population found in this review was higher than the 40.2% in a previous prospective study of 500 participants in the Chinese Atrial Fibrillation Registry.[27] Furthermore, a 2012 systematic review of participants in a community-based setting found the prevalence of frailty was 15.7%[35] and the Framingham Heart Study reported a frailty prevalence of 6%.[17] Conversely, a 2020 cross-sectional study of 536,955 patients in the GARFIELD AF Registry reported that

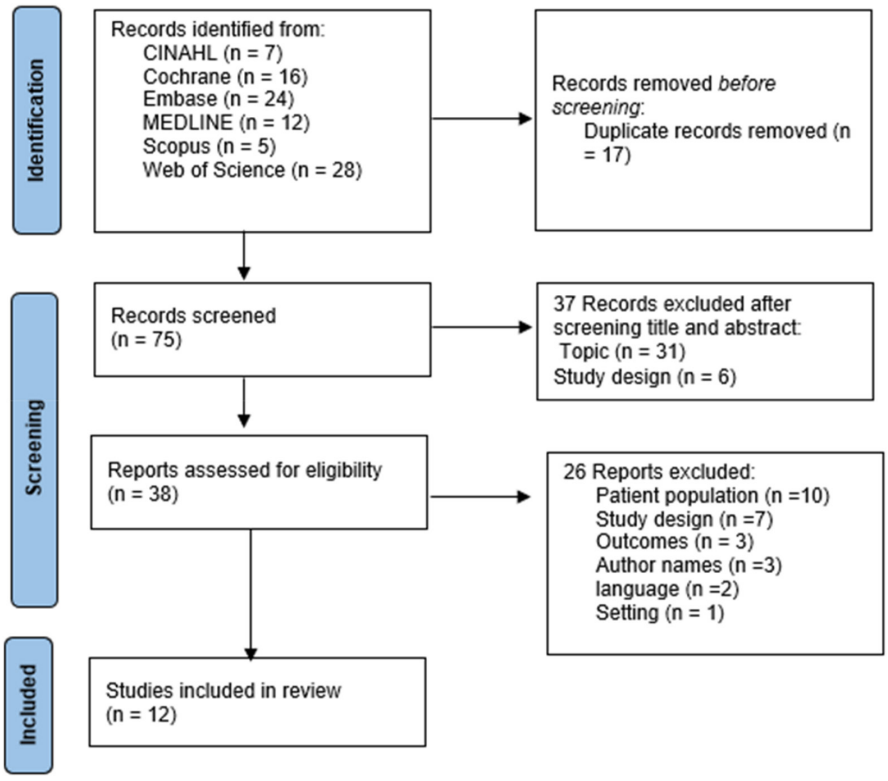

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

TABLE 1 Characteristics of included studies

Author (year)	Study design	Age ± SD (years)	Frail *n* (%)	Frailty instrument	Anticoagulated with NOACS (%)	Stroke risk			CHA_2DS_2-VASc score (mean)	Findings
						Stroke/SE *n* (%)	Hypertension *n* (%)	CHF *n* (%)		
Campitelli et al. (2021)	Retrospective cohort	85.2 ± 8.40	17,778 (48.8)	RAI-MDS 2.0 (modified)	25.8	9482 (26.0)	25,614 (70.2)	10,181 (27.9)	4.83	**Receiving anticoagulants (*n* = 181,514; 50.8%) (DOACs ± Warfarin)** Frail (*n* = 8767, 47.4%) Pre-frail (*n* = 6690, 36.1%) Non-frail (*n* = 3057, 16.5%) **Not receiving anticoagulants (*n* = 17,952; 49.2%)** Frail (*n* = 9011, 50.2%) Pre-frail (*n* = 6295, 35.1%) Non-frail (*n* = 2646, 14.7%) *Frailty shows little to no significant association with NOAC use*
De Simone et al. (2020)	Retrospective cohort	85.0 ± 4.10	300 (41.1)	REFS (modified)	100.0	523 (71.6)	682 (93.3)	178 (24.3)	4.80	**Receiving DOACS (*n* = 731; 100%)** Frailty (*n* = 300, 41.1%) Mode CHA_2DS_2-VASc score = 4 Mean CHF = 24.3% Mean hypertension = 93.3% Stroke/transient ischemic attack = 71.6% *DOACs were associated with lower rates of stroke and systemic embolism compared to patients receiving VKAs.* **Hazard ratio covariates for therapy interruption** Frailty = 2.91 (95% CI) Full dose = 0.53 (95% CI) *Frailty status shows significant association with NOAC prescription and therapy discontinuation.*
Ekerstad et al. (2018)	Prospective observational	84.7 ± 4.80	408 (97.4)	FP (modified)	16.0	N/A	98 (82.4)	67 (56.3)	4.90	**With anticoagulation (*n* = 119; 63%)** Mean age = 84.7 ± 4.8 Frailty score = 3.4 ± 0.88 CHA_2DS_2-VASc = 4.9 ± 1.5 CHF (*n* = 67, 56.3%) Hypertension (*n* = 98, 82.4%) *Frailty status shows significant association with anticoagulant prescription.*

TABLE 1 (Continued)

Author (year)	Study design	Age ± SD (years)	Frail *n* (%)	Frailty instrument	Anticoagulated with NOACS (%)	Stroke risk				Findings
						Stroke/SE *n* (%)	Hypertension *n* (%)	CHF *n* (%)	CHA_2DS_2-VASc score (mean)	
Gullón et al. (2018)	Prospective observational	84.6 ± 5.03	297 (48.3)	FP (modified)	15.4	105 (17.1)	543 (88.3)	413 (67.2)	5.62	**Prescription of antithrombotic treatment (frail patients on admission, *n* = 263; 48.1%)** VKA (*n* = 141, 53.6%) DOACs (*n* = 26, 9.9%) LMWH (*n* = 11, 4.2%) **Prescription of antithrombotic treatment (frail patients on discharge, *n* = 260; 46.7%)** Mean age = 84.58 ± 5.03 Frailty (*n* = 173, 44.5%) VKA (*n* = 111, 42.7%) DOACs (*n* = 40, 15.4%) LMWH (*n* = 22, 8.4%) CHA_2DS_2-VASc = 5.35 ± 1.39 *Frailty is associated with increased comorbidity, higher thrombotic risk, and institutionalization.* *Frailty status shows nonsignificant association with receiving NOACs.*
D. Lefebvre et al. (2016)	Cross-sectional	85.3 ± 3.94	170 (24.9)	CFS	15.0	168 (35.4)	422 (88.8)	150 (31.6)	N/A	**Receiving anticoagulants (*n* = 474; 69.5%)** Mean age = 85.3 ± 3.94 *A high risk of stroke ($CHADS_2 \geq 3$) and the absence of severe frailty (CFS < 7) were independently associated with anticoagulant prescription*
Lip et al. (2021)	Retrospective observational	77.2 ± 4.20	150, 487 (100)	FP (modified)	58.0	1328 (15.2)	N/A	N/A	N/A	**Receiving DOACS (*n* = 87,332; 58%)** Apixaban (*n* = 35,780, 23.8%) Rivaroxaban (*n* = 42,228, 28.1%) Dabigatran (*n* = 9324, 6.2%) No. of events stroke/SE (incidence/100 person/year) Ischemic; apixaban (*n* = 310, 1.77) Rivaroxaban (*n* = 608, 2.50) Dabigatran (*n* = 150, 2.60) Hemorrhagic; apixaban (*n* = 59, 0.34) Rivaroxaban (*n* = 130, 0.53) Dabigatran (*n* = 16, 0.28) SE; apixaban (*n* = 13, 0.07) Rivaroxaban (*n* = 32, 0.13) Dabigatran (*n* = <11, 0.12) *Compared to non-frail, frail patients with AF have higher incidence of stroke and death but not major bleeding.*

(Continues)

TABLE 1 (Continued)

Author (year)	Study design	Age ± SD (years)	Frail *n* (%)	Frailty instrument	Anticoagulated with NOACS (%)	Stroke risk				Findings
						Stroke/SE *n* (%)	Hypertension *n* (%)	CHF *n* (%)	CHA_2DS_2-VASc score (mean)	
Ohta et al. (2021)	Retrospective cohort	77.7 ± 9.50	34 (28.3)	CHS	59.2	29 (24.2)	73 (60.8)	113 (95)	3.10	**Major bleeding event (518 days follow-up) (*n* = 17; 14.6%)** CHS frailty index Non-frail (*n* = 2.5, 0.9%) Pre-frail (*n* = 11, 64.7%) Frail (*n* = 6, 35.3%) Underdosing of OAC administration Warfarin (*n* = 2, 11.8%) DOAC (*n* = 2, 11.8%) **No major bleeding event (518 days follow-up) (*n* = 103; 85.8%)** CHS frailty index Non-frail (*n* = 14, 13.6%) Pre-frail (*n* = 61, 59.2%) Frail (*n* = 28, 27.2%) Underdosing of OAC administration Warfarin (*n* = 13, 12.6%) DOAC (*n* = 15, 14.6%) *Frailty is associated with increased bleeding events related to anticoagulant therapy. Frailty status also shows small association with underdosing of anticoagulants*
Papakonstantinou et al. (2018)	Prospective observational	84.9 ± 5.00	104 (100)	CFS	37.4	N/A	54 (51.9)	68 (65.38)	4.23	**Anticoagulation therapy (on admission) (*n* = 104; 100%)** **Anticoagulation therapy (on discharge) (*n* = 99; 95%)** **Death rates (*n* = 57; 54.8%)** VKA (*n* = 10, 17.5%) NOAC (*n* = 16, 28%) No anticoagulant (*n* = 20, 35.1%) *Frailty is associated with increased mortality and lower probability of receiving anticoagulants.*

TABLE 1 (Continued)

Author (year)	Study design	Age ± SD (years)	Frail *n* (%)	Frailty instrument	Anticoagulated with NOACS (%)	Stroke risk			CHA_2DS_2-VASc score (mean)	Findings
						Stroke/SE *n* (%)	Hypertension *n* (%)	CHF *n* (%)		
Shinohara et al. (2019)	Retrospective cohort	83.8 ± 3.60	354 (100)	CFS	77.1	71 (20.0)	273 (77.1)	117 (33.1)	5.30	**Receiving DOACs (*n* = 273; 77.1%)** Dabigatran (*n* = 64, 23.4%) Rivaroxaban (*n* = 8, 29.7%) Apixaban (*n* = 100, 36.6%) Edoxaban (*n* = 28, 10.2%) **Inappropriately low doses (*n* = 42, 15.4%)** **Inappropriately high doses (*n* = 21, 7.7%)** 1/100 persons-year had bleeding events 1.5/100 persons-year had thromboembolic events *Frailty is associated with significant undertreatment of NOACs*
Wang et al. (2019)	Prospective observational	76.5 ± 7.00	145 (14)	CHS	42.9	107 (10.3)	941 (90.7)	402 (38.8)	4.60	**High anticoagulation burden (*n* = 254; 23.6%)** Mean age = 74 ± 7 CHA_2DS_2-VASc = 4.6 ± 1.6 **Frail patients with AF (*n* = 145; 14%)** Frailty (univariate analysis) = 2.0 (1.3–3.1) ***odd ratio in relation to high anticoagulation burden* *Frailty was significantly associated with high anticoagulation burden.*
Wilkinson et al. (2020)	Randomized controlled clinical trial	78.0 ± 8.40	3982 (19.5)	CDM	66.6	1576 (7.6)	3853 (18.5)	2899 (13.9)	2.83	**Receiving anticoagulants (*n* = 20,867; 100%)** Pre-frailty (*n* = 12,326, 59.1%) Mild–moderate frailty (*n* = 3722, 17.8%%) Severe frailty (*n* = 260, 1.7%) **$CHADS_2$ score by frail category** $CHADS_2$ score (pre-frail) = 2.80 $CHADS_2$ score (mild–moderate) = 3.37 $CHADS_2$ score (severe) = 4.03 *After 1 year follow-up period, risk of stroke/SE increased by 37% + major bleeding by 42% for each 0.1 increase in the frailty index.*

(Continues)

TABLE 1 (Continued)

Author (year)	Study design	Age ± SD (years)	Frail *n* (%)	Frailty instrument	Anticoagulated with NOACS (%)	Stroke risk				Findings
						Stroke/SE *n* (%)	Hypertension *n* (%)	CHF *n* (%)	CHA_2DS_2-VASc score (mean)	
Yamamoto et al. (2019)	Retrospective observational	81.2 ± 7.8	120 (50)	CFS	100	70 (58.3)	78 (65.0)	53 (44.2)	5.00	**Frail (*n* = 120; 50%)** Mean age = 81.2 ± 7.8 HF (*n* = 53, 44.2%) Hypertension (*n* = 78, 65%) Stroke/TIA (*n* = 70, 58.3%) DOAC under-dosed (*n* = 8, 6.7%) DOAC over-dosed (*n* = 5, 4.2%) **Indicators of stroke/SE/bleeding/mortality (univariate analysis)** Frail = 5.72 *Frailty status shows association with underdosing of NOAC prescription.*

Abbreviations: CDM, Cumulative Deficit Model of Frailty; CFS, Clinical Frailty Scale; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CHS, XXX; CI, confidence interval; DOAC, direct oral anticoagulant; FP, Frailty Phenotype; HF, heart failure; LMWH, low-molecular-weight heparin; N/A, not applicable; NOAC, novel oral anticoagulants; OAC, oral anticoagulant; RAI-MDS, Resident Assessment Instrument – Minimum Data Set; SE, systemic embolism; VKA, vitamin K antagonist.

89.5% of patient population were frail.[36] In this study, participants aged 18 years or older with diagnosis of non-valvular AF (according to standard local procedures) within the past 6 weeks and at least one additional risk factor for stroke were eligible to participate.[37] The requirement for an additional risk factor causes selection bias as eligible participants are already at an increased risk of stroke. Frail patients are already more inclined to comorbidity and stroke risk factors; therefore, a higher population of frail patients can be expected in the selection pool.

The observed heterogeneity of frailty prevalence may also be explained by the wide array of frailty instruments used in the studies. In the same patient cohort and under similar setting conditions, a study found that frailty prevalence can vary between 17.9 and 66.4% based on the type of frailty instrument used.[38] A recent European review presented a similar trend among the AF population, with the prevalence of frailty in AF patients ranging from 4.4–75.4%.[39] Wide variance of frailty prevalence due to the use of multiple frailty instruments is a prominent theme across many clinical conditions highlighting the need for a consistent frailty assessment approach.[40] The results of this review further emphasize the importance of formulating a universally accepted, clinically relevant, and standardized frailty instrument specified to the AF subgroup. Although the congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (CHA_2DS_2-VASc) tool has been well-validated for stroke risk prediction, the lack of frailty measurement in this score may now be a disadvantage.[41,42] In anticoagulant assessment, the adoption of future scores for stroke risk should include a frailty measure in order to conceptualize individual patient needs, and thus, achieve the best safety and adherence.[2] Overall, the variabilities in frailty prevalence highlight the complex nature of frailty and the importance of future studies to address frailty, the underlying pathophysiology, similarities to AF, and implications on stroke prediction and prevention.

A negative correlation was found between the presence of frailty in the AF population and the prescription of anticoagulants. The large underuse rate (~50%) of anticoagulants is concordant with a previous retrospective study[11] indicating the high anticoagulation burden for frail patients with AF. Furthermore, a large retrospective cohort study found the hazard ratio covariates for therapy interruption and discontinuation were 2.95 (95% confidence interval) for frailty status, highlighting the significant association between frailty and anticoagulant underuse. The frail patients are a high-risk population – multimorbidity and high-risk of bleeding events (intracranial hemorrhage and gastrointestinal bleeding)[23,43,44] are reported reasons for non-prescription of NOACs. This may be due to the increased multimorbidity associated with frailty and AF, such as cognitive dysfunction, sarcopenia, and chronic heart failure.[45] Further, the presence and severity of frailty is associated with cardiovascular mortality and major cardiovascular events, independent of underlying cardiovascular disease.[16] The risk of bleeding (particularly fatal bleeding) remains

the most feared consequence of anticoagulation from the perspective of the provider.[23,46]

Currently, there are limited data assessing the risk-to-benefit ratio of anticoagulants for those with frailty. The Clinical Excellence Commission NOAC guidelines advise treatment should be individualized after careful assessment of the treatment benefit against the risk for bleeding.[47] NOACs have been shown to reduce the risk of stroke and systemic embolism compared to patients receiving VKA's deeming them safe and effective in stroke prevention.[26,48,49] In the ENGAGE-AF TIMI 48 study, edoxaban presented a lower annualized stroke or systemic embolism incidence rate compared to warfarin (1.18% vs 1.50%). The study also highlighted a lower annualized hemorrhagic stroke incidence rate in favor of edoxaban (0.26% vs 0.47%).[49] Furthermore, in the AVERROES study, apixaban was superior to aspirin in reducing the risk of stroke or systemic embolism without significant increase in major bleeding.[48] Despite these benefits, there is inconsistent evidence to support the withholding of NOACs due to their risks,[27] making the prescribing of NOACS increasingly challenging for physicians. In addition, there is a lack of data concerning the outcomes associated with anticoagulation use for frail patients with AF.[44]

The underuse of anticoagulants found in this study cohort reflects the extensive uncertainty surrounding the risk–benefit ratio of NOACs, for the frail AF population. It is evident that anticoagulation therapy is complex and requires an individualized assessment and management to promote patient safety and outcomes. In clinical practice, patients with AF have significantly better outcomes in nurse-led clinics where shared decision making is valued and at the forefront of anticoagulation therapy.[50,51] Furthermore, the use of an integrated care approach whereby patients are provided comprehensive and coordinated care has been associated with reduced cardiovascular hospitalizations and all-cause mortality.[52] Frailty assessment is recommended and should be integrated into these care decisions to mitigate the challenges surrounding anticoagulant treatment.

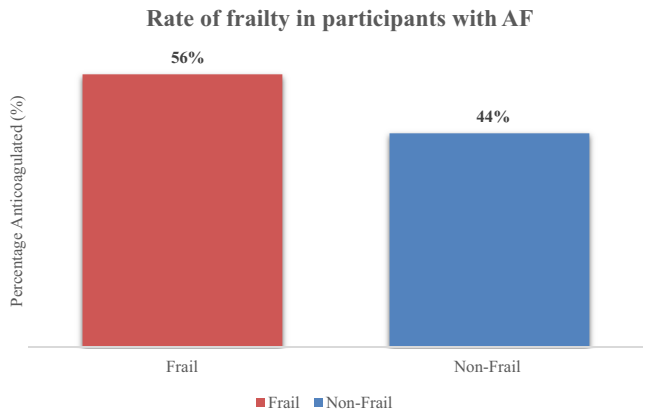

FIGURE 2 Rates of frailty vs proportion prescribed anticoagulant amongst participants with atrial fibrillation (AF)

5 | STRENGTHS AND LIMITATIONS

It is important to note that this study was a scoping review in nature, allowing us to present a broad range of information about frailty and NOAC prescription. Due to the strictly defined inclusion criteria, a large pool of studies that analyzed the issue of frailty and anticoagulants were excluded. Thus, establishing the criterion to investigate frailty and NOAC prescription specifically, limited the ability to establish epidemiological issues. More specifically, the epidemiological significance of frailty in the AF population in general. Furthermore, this study is limited by the fact it is not systematic and, thus, does not examine the quality of evidence of each article. Despite this, we were able to mitigate bias by adhering to the clearly defined selection criterion and following a methodological approach in the research accumulation and screening process.

6 | CONCLUSION

Frailty is an important clinical factor in anticoagulant prescription in patients with AF. The CFS was the most used frailty instrument across included studies. Overall, this review found a negative correlation between frailty and anticoagulant use. We suggest that frailty

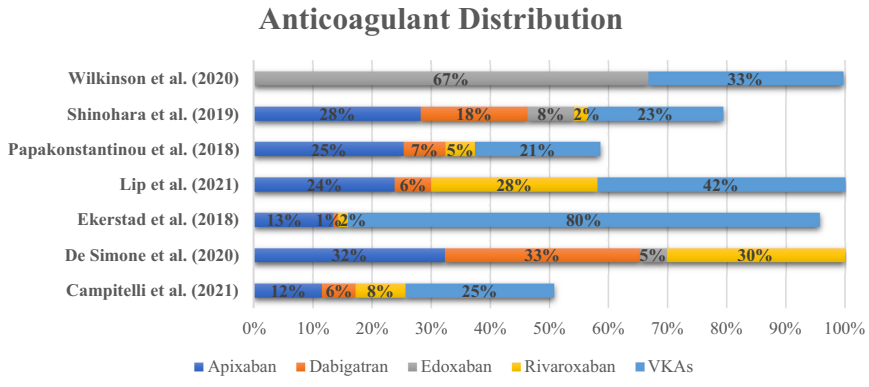

FIGURE 3 Anticoagulant distribution. VKA, vitamin K antagonist. *Excludes the following studies: Gullón et al. (2018), D. Lefebvre et al. (2016), Ohta et al. (2021), Wang et al. (2019), and Yamamoto et al. (2019)

*Excludes the following studies: *Gullón et al. (2018), D. Lefebvre et al. (2016), Ohta et al. (2021), Wang et al. (2019), Yamamoto et al. (2019)*

assessment should become mutually inclusive with routine clinical assessment of people with AF, particularly in future registries or trials.

AUTHOR CONTRIBUTIONS

C.F. and M.B. conceived the study. C.F., F.S., and M.B. developed the search strategy. M.B. and C.F. screened and reviewed articles. C.F., F.S., J.M., and M.B. wrote and edited the manuscript.

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IMPACT STATEMENT

Frailty is an important consideration in anticoagulation decision making for stroke prevention in patients with AF. There is scope to improve frailty screening and treatment in patients with AF. Frailty status is an important risk marker and should be considered when evaluating stroke risk, alongside CHA_2DS_2-VASc and HAS-BLED scores.

CONFLICT OF INTEREST

Nothing to disclose.

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APPENDIX A

Database	Search strategy (Searched on December 7, 2021) Terms	Results
Medline	(1) (atrial fibrillation* or atrial auricular fibrillation* or auricular fibrillation* or persistent atrial fibrillation* or familial atrial fibrillation* or paroxysmal atrial fibrillation* or permanent atrial fibrillation).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms) (2) (frailty* or frail elderly* or frailty syndrome* or asthenia*).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms) (3) (anticoagulant* or anticoagulation* or thrombin inhibitors* or direct thrombin inhibitors or non-vitamin K oral anticoagulants* or apixaban* or dabigatran* or edoxaban* or rivaroxaban*).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms) (4) limit 1 to (English language and full text and humans and year = "2005 - Current") (5) limit 2 to (English language and full text and humans and year = "2005 - Current") (6) limit 3 to (English language and full text and humans and year = "2005–2021") (7) 4 and 5 and 6	12
Cochrane Library	atrial fibrillation* or atrial auricular fibrillation* or auricular fibrillation* or persistent atrial fibrillation* or familial atrial fibrillation* or paroxysmal atrial fibrillation* or permanent atrial fibrillation* in Title Abstract Keyword AND frailty* or frail elderly* or frailty syndrome* or asthenia* in Title Abstract Keyword AND anticoagulant* or anticoagulation* or thrombin inhibitors* or direct thrombin inhibitors or non-vitamin K oral anticoagulants* or apixaban* or dabigatran* or edoxaban* or rivaroxaban* in Title Abstract Keyword - with Cochrane Library publication date Between January 2005 and January 2021 (Word variations have been searched)	16
Web of Science	#1 (TI = (atrial fibrillation* or atrial auricular fibrillation* or auricular fibrillation* or persistent atrial fibrillation* or familial atrial fibrillation* or paroxysmal atrial fibrillation* or permanent atrial fibrillation)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article) INDEXES = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 2005–2021) #2 (TI = (frailty* or frail elderly* or frailty syndrome* or asthenia*)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article) INDEXES = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 2005–2021) #3 (TI = [anticoagulant* or anticoagulation* or thrombin inhibitors* or direct thrombin inhibitors or non-vitamin K oral anticoagulants or apixaban* or dabigatran* or edoxaban* or rivaroxaban*]) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article) INDEXES = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 2005–2021) #4 - #3 and #2 and #1	28
Embase	(1) (atrial fibrillation* or atrial auricular fibrillation* or auricular fibrillation* or persistent atrial fibrillation* or familial atrial fibrillation* or paroxysmal atrial fibrillation* or permanent atrial fibrillation).mp. (2) limit 1 to (English language and full text and humans and year = "2005 - Current") (3) (frailty* or frail elderly* or frailty syndrome* or asthenia*).mp. (4) limit 3 to (English language and full text and humans and year = "2005 - Current") (5) (anticoagulant* or anticoagulation* or thrombin inhibitors* or direct thrombin inhibitors or non-vitamin K oral anticoagulants or apixaban* or dabigatran* or edoxaban* or rivaroxaban*).mp. (6) limit 5 to (English language and full text and humans and year = "2005 - Current") (7) 2 and 4 and 6	24
Scopus	TITLE (atrial fibrillation* OR atrial auricular fibrillation* OR auricular fibrillation* OR persistent atrial fibrillation* OR familial atrial fibrillation* OR paroxysmal atrial fibrillation* OR permanent atrial fibrillation).mp. AND (TITLE [frailty* OR frailty syndrome* OR asthenia* OR frail elderly*]).mp. AND (TITLE [anticoagulant* OR anticoagulation* OR thrombin inhibitors* OR direct thrombin inhibitors* OR non-vitamin K oral anticoagulants OR apixaban* OR dabigatran* OR edoxaban* OR rivaroxaban*]).mp. AND (LIMIT-TO (PUBYEAR,2021) OR LIMIT-TO (PUBYEAR,2020) OR LIMIT-TO (PUBYEAR,2019) OR LIMIT-TO (PUBYEAR,2018) OR LIMIT-TO (PUBYEAR,2017) OR LIMIT-TO (PUBYEAR,2016) OR LIMIT-TO (PUBYEAR,2015) OR LIMIT-TO (PUBYEAR,2014) OR LIMIT-TO (PUBYEAR,2013) OR LIMIT-TO (PUBYEAR,2012) OR LIMIT-TO (PUBYEAR,2011) OR LIMIT-TO (PUBYEAR,2010) OR LIMIT-TO (PUBYEAR,2009) OR LIMIT-TO (PUBYEAR,2008) OR LIMIT-TO (PUBYEAR,2007) OR LIMIT-TO (PUBYEAR,2006) OR LIMIT-TO (PUBYEAR,2005) AND (LIMIT-TO[ENGLISH])	5
CINAHL	TI (atrial fibrillation* OR atrial auricular fibrillation* OR auricular fibrillation* OR persistent atrial fibrillation* OR familial atrial fibrillation* OR paroxysmal atrial fibrillation* OR permanent atrial fibrillation) AND TI (frailty* OR frailty syndrome* OR asthenia* OR frail elderly*) AND TI (anticoagulant* OR anticoagulation* OR thrombin inhibitors* OR direct thrombin inhibitors* OR non-vitamin K anticoagulants OR apixaban* OR dabigatran* OR edoxaban* OR rivaroxaban*). Limiters - Linked Full Text; Published Date: 2005–2021-; English Language.	5