Experimental Gerontology

Describing the Relationship between Atrial Fibrillation and Frailty: Clinical Implications and Open Research Questions

--Manuscript Draft--

Manuscript Number:	EXG-D-21-00412
Article Type:	VSI: Cardiovascular disease
Section/Category:	Demography, Epidemiology and Population Genetics
Keywords:	atrial fibrillation; frailty; oral anticoagulation; outcomes
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Abstract:	In the recent years a lot of attention has been gathered by the issue of frailty outside the boundaries of the geriatric medicine, for example in the field of cardiovascular medicine. Atrial fibrillation (AF) is known as a very common cardiological condition, often burdened by high level of clinical complexity. Aim of this narrative review is to examine the most relevant evidence about the relationship between frailty and AF, focusing also on its impact on clinical management and natural history of patients with this condition. Data reported underline how a relevant relationship exists between these two conditions, even though the burden of frailty among AF cohorts is still unclear. Frailty seems to affect the clinical management, even though no definitive data are yet available. Lastly, frailty significantly increases the risk of all-cause mortality but its still unclear the impact on thromboembolic and bleeding events. Despite several data are already available, more research is still needed to fully elucidate the relationship between these two clinical entities.
Suggested Reviewers:	
Opposed Reviewers:	

UNIVERSITÀ DEGLI STUDI DI MILANO

Istituti Clinici Scientifici Maugeri

Milan, 20th May 2021

To Hélio José Coelho Júnior

To Emanuele Marzetti

Guest Editors

Experimental Gerontology

Dear Friends,

RE: **Describing the Relationship between Atrial Fibrillation and Frailty: Clinical Implications and Open Research Questions**

We are pleased to submit our paper, "*Describing the Relationship between Atrial Fibrillation and Frailty: Clinical Implications and Open Research Questions*" to contribute to your special issue "Cardiovascular disease and frailty: beyond physical performance and cognition" for which you kindly invited us to contribute.

In this narrative review we describe the most relevant evidence regarding the relationship between frailty and AF, underlining the impact of frailty on clinical management and determining the risk of adverse outcome. While it clearly emerges a strong relationship between those two conditions, it appears also strongly evident how more research is still needed to be produced to fully elucidate all the open questions.

We do apologize for the delay in submitting the manuscript, due to the overload of clinical and academic work.

We confirm the following: 1) the paper is not under consideration elsewhere, 2) none of the paper's contents have been previously published, 3) all authors had access to all the study data, take responsibility for the accuracy of the analysis, had authority over manuscript preparation and the decision to submit the manuscript for publication and 4) have read and approved the manuscript; 4) the full disclosure of any potential conflict of interest has been made.

Yours sincerely

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Describing the Relationship between Atrial Fibrillation and Frailty: Clinical Implications and Open Research Questions

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ABSTRACT

In the recent years a lot of attention has been gathered by the issue of frailty outside the boundaries of the geriatric medicine, for example in the field of cardiovascular medicine. Atrial fibrillation (AF) is known as a very common cardiological condition, often burdened by high level of clinical complexity. Aim of this narrative review is to examine the most relevant evidence about the relationship between frailty and AF, focusing also on its impact on clinical management and natural history of patients with this condition. Data reported underline how a relevant relationship exists between these two conditions, even though the burden of frailty among AF cohorts is still unclear. Frailty seems to affect the clinical management, even though no definitive data are yet available. Lastly, frailty significantly increases the risk of all-cause mortality but its still unclear the impact on thromboembolic and bleeding events. Despite several data are already available, more research is still needed to fully elucidate the relationship between these two clinical entities.

KEYWORDS: atrial fibrillation; frailty; oral anticoagulation; outcomes.

INTRODUCTION

Atrial fibrillation (AF) epidemiology is strictly connected to older age and progressive population aging[1]. This close relationship between AF and older age is expressed in a close correlation between this condition and several characteristics usually considered purely geriatric. Indeed, various studies underlined how AF patients often report multimorbidity[2,3], polypharmacy[4,5], and an increased risk of falls[6].

Frailty is a medical syndrome characterized by a reduced physical capacity and physiological reserve. It exposes the individual to an increased vulnerability to internal and external stressors, leading to an increased risk for dependency, disability, and death[7,8]. In the last years, growing evidence has been underlining that frailty is not exclusively peculiar to older subjects, describing higher levels of frailty in patients affected by diverse specific conditions, including cardiovascular diseases[9–11].

Hence, even AF has been associated with frailty. The latter seems to substantiallyinfluence the clinical management and course of patients with AF, although evidence is still sparce and controversial[12–14]. Aim of this paper is to present a narrative review of the most relevant evidence regarding the relationship between AF and frailty coming from the currently available literature.

Association between Atrial Fibrillation and Frailty

Looking at the current evidence regarding the relationship between AF and frailty, we can immediately note how data appear sparse and heterogeneous. To date, the vast majority of the studies investigating this relationship refers to retrospective/post-hoc cross-sectional evaluations of the frailty prevalence in cohorts of patients with AF. The most relevant are reported in Table 1. Looking at the table, it is evident that most of the data are coming from the US, and that a minority is based on multinational experiences. Furthermore, there is considerable heterogeneity across studies for what concerns their eligibility criteria. The number of patients recruited in the original studies also presents a quite wide range.

A specific consideration is needed about the tool used to assess frailty in the various cohorts. As known, many tools exist to define and evaluate frailty[15]. Some of the tools are focused exclusively on the “physical” frailty, while others recognize a multidimensional approach and stem from a more comprehensive evaluation of the subject[15]. Not surprisingly, the prevalence of (pre-frailty and) frailty significantly varies across the studies considered.

In the study by Pilotto and colleagues[16], frailty was retrospectively assessed by a modified version of the multidimensional prognostic index (MPI). This standardized evaluation proposes the assessment of cognitive function, pressure sore risk, autonomy in activities of daily living, mobility, and presence of social support. Accordingly, one-quarter of patients (26.7%) was found to be frail and 34.7% to be prefrail. Hohmann and colleagues[17], which investigated frailty in a cohort of patients with AF treated with non-vitamin K antagonist oral anticoagulants (NOACs) derived

from a administrative database, used a claim-based Frailty Index. Frailty was here defined according to the median value of the cohort (≥0.78), explaining the reported high prevalence of the condition of interest. In the studies by Madhavan[18] and Saczynski[19], the frailty phenotype was used, reporting different prevalence of frailty (5.9% and 13.8%, respectively), likely reflecting the differences in the inclusion criteria. Indeed, while all patients ≥18 years old were included in the first study, whereas only those ≥65 years were considered in the second one.

Four studies[20–23] used a Frailty Index to evaluate the presence of frailty. The four studies adopted the same cumulative deficit model proposed by Rockwood and Mitnitski[24,25]. The Frailty Indexes computed in the four studies considered different number of deficits, and retrieved data from different sources (i.e., clinical charts, electronic records, hospital-based electronic dataset). Furthermore, the studies included patients according to different inclusion criteria and followed different studies design (Table 1). All these differences might explain the heterogeneousproportions of frail subjects (ranging from 1.6% in the study by Yang and colleagues[22] to 59.1% in the study by Wilkinson and colleagues[20]).

In the study by Lip and colleagues, while using a similar claim frailty index, a different number of items was considered, and a different cut-off was considered, with only 37.2% of subjects considered frail[26].

In another recent study, a prospective observational registry of patients with AF treated with edoxaban, a total of 1,392 (10.6%) patients over 13,092 were considered frailty according to the physicians' discretion[27].

In another study involving a small group of 200 patients with AF undergoing an electrical cardioversion procedure, the presence of frailty was found to be inversely associated with the maintenance of sinus rhythm over a six-months follow-up observation. It was reported that patients with frailty were 60% less likely to maintain sinus rhythm compared to the robust ones (OR 0.41, 95% CI 0.29-0.59). In this study, the presence of frailty was evaluated according to the Tilburg Frailty Indicator and an overall prevalence of frailty of 34.2% was documented[28].

Furthermore, Orkaby and colleagues investigated the Framingham Study Offspring Cohort to evaluate if frailty was associated with incident AF[29]. In a cohort of 2,053 patients (mean age 69.7 [standard deviation 6.9] years), frailty was evaluated according to both the frailty phenotype and the Rockwood and Mitnitski's Frailty Index. The prevalence of frailty was found to be 6.4% and 19.2%, respectively. Over an almost 6-years follow-up time observation, the presence of frailty according to frailty phenotype was found to be not associated with the occurrence of AF both at univariate and multivariate analysis. Differently, the Frailty Index presented a trend in the association with incident AF at univariate analysis, which was not confirmed by the multivariate analysis[29].

Relationship between Frailty and OAC in Patients with AF

The prescription of oral anticoagulant (OAC) drugs is pivotal in the treatment of the thromboembolic risk in patients with AF[1]. It is already known that the clinical decision of prescribing OAC is influenced by several factors[30]. So far, it remains unclear

whether the presence of frailty can directly affect the clinical decision-making process to prescribe or not an OAC and which kind of OAC.

In the study by Pilotto and colleagues, patients prescribed with warfarin reported an overall lower MPI score compared to those not prescribed, a lower prevalence of frailty was observed in those receiving the prescription[16]. Notwithstanding, the authors did not perform any adjusted analysis regarding the prescription of warfarin. When analysing the impact of warfarin treatment on outcomes, they reported a lower risk of death in the treated vs. untreated patients[16]. Similarly, Madhavan et al. documented a lower rate of OAC prescription in frail patients compared to the non-frail ones (67.5% vs. 76.9%, $p<0.0001$); also in this case, adjusted analyses were not conducted[18]. Conversely, in a secondary analysis derived from the 'Systematic Assessment of Geriatric Elements in Atrial Fibrillation' (SAGE-AF) database, no relationship was found between the burden of frailty and the prescription of OAC, both in unadjusted and adjusted analyses[19].

In the nationwide primary care cohort analysed by Wilkinson and colleagues[21], a progressively higher burden of frailty was associated with a higher prescription of OAC[21]. In the study by Gugganig et al., while no difference was found in the overall OAC prescription, frail patients were found more likely to receive a vitamin K antagonist (VKA) rather than a NOAC, although (again) no adjusted analysis was performed[23].

In a systematic review and meta-analysis that examined the association between frailty and OAC prescription, a total of 7 studies were pooled for a total of 2,742

patients[14]. Despite being performed in an accurate and methodologically sound way, the study provided inconsistent results[14]. Three of the studies reported data from hospitalised patients examining the prescription of OAC according to frailty at the time of admission. In those studies, the authors found that frailty was inversely associated with OAC prescription (OR= 0.45, 95% CI= 0.22-0.93) [Figure 1]. Three other studies examined the prescription of OAC according to frailty at the hospital discharge, finding no difference between frail and no frail patients (OR= 0.40, 95% CI= 0.13-1.23) [Figure 1]. The last study included in the systematic review examined the prescription of OAC according to the frailty status in a small sample of community-dwelling persons. Here, the authors found that frail patients were more likely to be treated with OAC than those who were not frail[14] [Figure 1].

Only limited evidence exists about a differential effect of NOACs vs VKA in frail patients compared to those without frailty. In the secondary analysis of the ENGAGE AF-TIMI 48 trial, while a significant benefit regarding the major bleeding risk was found for both Edoxaban 30 mg and Edoxaban 60 mg compared to warfarin in patients with mild-to-moderate frailty, no difference was found in terms of thromboembolic events risk (irrespective of burden of frailty and edoxaban dose)[20]. Looking at the secondary outcomes, patients with mild-to-moderate frailty showed a significantly lower risk for all the composite clinical endpoints as well as for death risk[20]. Regarding the patients found to be severely frail, no difference was shown for any of the outcomes, except for the composite endpoint including disabling stroke, life-threatening bleeding, and/or death in edoxaban 60 mg users compared to warfarin users[20] (HR= 0.66, 95% CI= 0.39-0.99).

In the sub-analysis performed in the ARISTOPHANES registry, the authors tested the impact of differential OAC drugs in frail patients on determining the risk of adverse outcomes[26]. Compared to patients prescribed with warfarin, those prescribed with apixaban showed a consistently lower risk for all the examined outcomes (i.e., thromboembolic events, ischemic stroke, hemorrhagic stroke, systemic embolism, major bleeding, gastrointestinal bleeding, intracranial hemorrhage, other bleeding)[26]. While the lower risk of intracranial hemorrhage was found for all the examined NOACs (i.e., apixaban, dabigatran, rivaroxaban), a differential risk was found for the various outcomes across the different NOACs (with a particularly high risk for rivaroxaban users compared to warfarin user in the incidence of gastrointestinal bleeding)[26]. Comparing the various NOACs, apixaban showed a better profile in terms of effectiveness and safety compared to rivaroxaban, while dabigatran showed to be safer compared to rivaroxaban. In the comparison between apixaban and dabigatran, while no difference was found in terms of effectiveness, apixaban showed a significant lower risk for major and gastrointestinal bleeding[26].

Impact of Frailty on Adverse Outcomes in AF

Examining the impact of frailty on adverse outcomes a clear relationship with the occurrence of all-cause mortality emerges. In the analysis performed by Pilotto and colleagues, an increasing number of death events occurred for increasing levels of frailty[16]. In the analysis performed on the ORBIT-AF registry, while frailty was associated with an increased risk for all the outcomes examined in the unadjusted analysis, after multiple adjustments only the relationship with all-cause death (HR= 1.29, 95% CI= 1.08-1.55) remained statistically significant[18]. Wilkinson and

colleagues reported a progressively increasing risk of death by increasing levels of frailty[21]. Furthermore, they reported an increased risk of gastrointestinal bleeding for patients with severe frailty[21]. In the sub-analysis performed in the ENGAGE AF-TIMI 48 trial, a positive association was reported between the frailty burden and the risk of primary endpoints (i.e., thromboembolic events and major bleeding), secondary composite endpoints, and all-cause mortality[20]. Even in the analysis performed by Gugganig and colleagues, frailty was associated with higher risk of stroke, bleeding, and death[23].

Yang et al. examined whether a clinical management strategy resembling the 'Atrial fibrillation Better Care' (ABC) pathway (a structured model proposed to streamline the integrated holistic management of AF patients[31]) would be effective in reducing the risk of adverse outcomes in frail patients with AF[22]. The authors documented a progressively lower risk of mortality and incident adverse outcomes, especially among individuals with particularly high levels of frailty[22].

Discussion and Synthesis

In this narrative review about the relationship between AF and frailty, we reported substantial evidence regarding their close association. Frailty appears substantially prevalent in patients with AF. In the clinical management of these patients, frailty can influence the prescription of OAC, although its impact may differ according to the clinical setting. Frailty is strongly associated with an increased risk of all-cause mortality in patients with AF. Still, conflicting evidence has been found for other adverse outcomes. Despite these data, several open questions are still unanswered.

The prevalence reported across the studies is extremely heterogeneous. Part of such heterogeneity is surely related to the high number of instruments designed to measure frailty. Interestingly, the agreement of tools for the assessment of frailty has shown to be relatively modest. This particularly challenges the comparability of findings among studies and complicates the delivery of straightforward conclusions on the topic.

Another unclear issue is whether or not frailty significantly affects the prescription of OAC in AF patients. In particular, it is yet to be defined which factors can influence this prescription patterns and the subsequent clinical outcomes. Regarding the risk of adverse events, while the increased risk of death is clearly reported by all the studies, it is not demonstrated if frailty can also substantially affect the risk of incident thromboembolic and bleeding events.

Over the last years, a lot of research has been conducted to explore the impact of the clinical complexity on the determination of adverse events in patients with AF. For example, work has been done on the role of multimorbidity. The Framingham Heart Study previously showed that comorbidities may increase the risk for cardiovascular events and all-cause mortality in patients with AF[32]. An analysis from the ORBIT-AF registry showed that patients with AD clustered in a ‘low-comorbidity’ group showed the lowest risk of major cardiovascular and neurological adverse events than all the other identified clusters[33]. In the analysis of a time-dependent Charlson Comorbidity Index , the increasing burden of multimorbidity was associated with the incidence of stroke, major bleeding, and all-cause mortality[2].

In this context, the relationship between frailty and AF extends further the concept that those patients are not simply characterized by a mere abnormality of the heart. They need to be more comprehensively and exhaustively assessed. The idea that a patient with AF is often a patient who reports a low physiological reserve and is exposed to important clinical complications has extremely relevant implications. Indeed, while the presence of AF increases the risk of several adverse clinical events, the presence of frailty put the patients at an even higher risk of not being able to cope with stressors and face the clinical consequences.

In the last version of the European Society of Cardiology - AF Clinical Guidelines, the integration of care was put at the very basis of the clinical approach. The aim was to promote a holistic management of the patient with AF by considering the most relevant aspects of this clinical condition: i) management of OAC; ii) management of symptoms by rate/rhythm control therapy; iii) management of risk factors and comorbidities. As mentioned above, the ABC pathway has been suggested as a possible strategy to streamline this approach and facilitate the implementation of these pivotal clinical aspects[31]. A clinical management adherent to the ABC pathway has been found to reduce significantly the risk of all the outcomes in patients with AF[34], even among those who are most clinically complex[35,36].

We can postulate that even in frail patients with AF, the application of an integrated holistic care management can improve the risk of adverse clinical outcomes and obtain a global improvement of functions. We may also hypothesize that a geriatric approach may further enhance the benefits of the ABC pathway by supporting a more comprehensive evaluation of the individual and his/her environment.

It clearly emerges from our work that more research on the topic is needed. A clear evaluation of the actual burden of frailty as well as other solid epidemiological data are essential to better elucidate the intricate relationship between frailty and AF. Also, it is essential to understand how much frailty affects the prescription of OAC, their effectiveness and safety.

FUNDING

No funding has been used in the process of preparing this manuscript.

FIGURE LEGENDS

Figure 1: Association between Frailty and Anticoagulation status

Legend: CI= Confidence Interval; IV= Inverse Variance; Figure taken from *Wilkinson et al. Age Ageing. 2019 Mar 1;48(2):196-203. doi: 10.1093/ageing/afy180*, published under **Creative Commons CC BY** license, with no permission needed for reproduction.

Table 1 – Main Characteristics of the Studies Included in the Systematic Review

STUDY	YEAR	GEOGRAPHIC LOCATION	STUDY TYPE	INCLUSION CRITERIA	FRAILTY ASSESSMENT	N	PREFRAIL	FRAIL	AGE (mean)	CHA_2DS_2-VASC (mean)	OAC (%)
Pilotto[16]	2016	Italy	Observational Multicentre	AF ≥65 years	MPI	1827	634 (34.7%)	488 (26.7%)	84.4	3.8	43.7
Hohmann[17]	2019	Germany	Administrative Database	AF ≥18 years on OAC	CFI	70501	N/A	36267 (51.4%)	74	3.7	100
Madhavan[18]	2019	US	Observational Multicentre	AF ≥18 years	FP	9749	N/A	575 (5.9%)	75*	4*	76.4
Saczynski[19]	2020	US	Observational Multicentre	AF ≥65 years with High TE Risk	FP	1244	659 (53.0)	172 (13.8%)	75.5	4*	85.5
Wilkinson[20]	2020	Multinational	RCT	AF ≥21 years	Frailty Index	20867	12326 (59.1)	4082 (19.6%)	N/A	N/A	100
Wilkinson 2[21]	2020	UK	Cohort Study	AF ≥65 years	Frailty Index	61177	20352 (33.3%)	34382 (56.2%)	79.7	3.8	53.1
Yang PS[22]	2020	Korea	Cohort Study	AF ≥18 years CHA_2DS_2-VASc ≥1	Frailty Index	262987	37341 (14.2%)	4104 (1.6%)	58*	1.8	100
Gugganig[23]	2021	Switzerland	Observational Multicentre	AF ≥65 years	Frailty Index	2369	1436 (60.6%)	252 (10.6%)	73	3.5	90.4
Lip[26]	2021	US	Administrative Database	AF ≥65 years on OAC	CFI	404798	N/A	150487 (37.2%)	N/A	N/A	N/A

Legend: *median values; AF= Atrial Fibrillation; CFI= Claim Frailty Index; CFS= Clinical Frailty Scale; FP= Frailty phenotype; MPI= Multidimensional Prognostic Index; N/A= Not Available; NOACs= Non-Vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulant; RCT= Randomised Controlled Trial; TFI= Tilburg Frailty Indicator; UK= United Kingdom; US= United States.

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Figure 1

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