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CLINICAL RESEARCH
Atrial fibrillation

Perceived vs. objective frailty in patients with atrial fibrillation and impact on anticoagulant dosing: an ETNA-AF-Europe sub-analysis

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Aims Frailty is common in patients with atrial fibrillation (AF), with possible impact on therapies and outcomes. However, definitions of frailty are variable, and may not overlap with frailty perception among physicians. We evaluated the prevalence of frailty as perceived by enrolling physicians in the Edoxaban Treatment in Routine Clinical Practice for Patients With Non-Valvular AF (ETNA-AF)-Europe registry (NCT02944019), and compared it with an objective frailty assessment.

Methods and results ETNA-AF-Europe is a prospective, multi-centre, post-authorization, observational study. There we assessed the presence of frailty according to (i) a binary subjective investigators' judgement and (ii) an objective measure, the Modified Frailty Index. Baseline data on frailty were available in 13 621/13 980 patients. Prevalence of perceived frailty was 10.6%, with high variability among participating countries and healthcare settings (range 5.9–19.6%). Conversely, only 5.0% of patients had objective frailty, with minimal variability (range 4.5–6.7%); and only <1% of patients were identified as frail by both approaches. Compared with non-frailty-perceived, perceived frail patients were older, more frequently female, and with lower body weight; conversely, objectively frail patients had more comorbidities. Non-recommended edoxaban dose regimens were more frequently prescribed in both frail patient categories.

Conclusions Physicians' perception of frailty in AF patients is variable, mainly driven by age, sex, and weight, and quite different compared with the results of an objective frailty assessment. Whatever the approach, frailty appears to be associated with non-recommended anticoagulant dosages. Whether this apparent inappropriateness influences hard outcomes remains to be assessed.

Keywords Frailty • Perceived frailty • Objective frailty • Non-vitamin K antagonist oral anticoagulants • Atrial fibrillation

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What's new?

- Frailty is common in patients with atrial fibrillation (AF), with possible impact on therapies and outcomes. We evaluated the prevalence of frailty as perceived by enrolling physicians and an objective frailty assessment in the Edoxaban Treatment in Routine Clinical Practice for Patients With Non-Valvular Atrial Fibrillation-Europe registry, with data available in 13 621/13 980 patients enrolled.
- Prevalence of perceived frailty was >10%, with high variability among participating countries and healthcare settings. Conversely, only 5% of patients had objective frailty, with minimal variability. Only <1% of patients were identified as frail by both approaches.
- Both frail patient categories were more frequently associated with non-recommended edoxaban dose regimens.

Introduction

The progressive aging of populations and improvements in medical therapy are leading to an important increase of elderly patients presenting with clinically relevant arrhythmias, and especially with atrial fibrillation (AF).[1] Aging is frequently characterized by the coexistence of comorbidities and changes in body functions, such as sub-clinical malnutrition, inactivity, and inflammation ('inflamm-aging'), partly overlapping with the concept of frailty.[2] Frailty is, however, a complex syndrome, usually defined as an increased vulnerability to stressors coupled with a decreased ability to maintain homeostasis,[3,4] only partially overlapping with aging and comorbidities. Frailty is likely to be an important factor in the management of patients, and several reports have highlighted its importance in tailoring treatment of AF patients.[3–5]

Difficulties in defining frailty as a specific entity are reflected by the high variability in the assessment of this condition by different physicians. For this reason, several tests and scales have been created to objectively assess presence of frailty. Whether objective assessment of frailty may be overcome by a quick, yes-or-no bird's eye assessment by the physician is currently unknown.

Against this background, the aim of the present analysis was to evaluate the prevalence of frailty as perceived by the enrolling physician participating in a large European registry in AF (clinician-perceived frailty), to compare such subjective evaluation with an objective frailty evaluation based on a validated scale, the 'Modified Frailty Index' (MFI, algorithmic frailty), and to assess the impact of the two on the dosing patterns of anticoagulation.

Methods

Patient population

We pursued this investigation within the Edoxaban Treatment in Routine Clinical Practice for Patients With Non-Valvular AF (ETNA-AF)-Europe registry. ETNA-AF-Europe was designed as part of the risk management plan of edoxaban in order to assess risks and benefits of the drug in routine care in unselected European patients with AF. The ETNA-AF-Europe is part of the global ETNA-AF initiative, which comprises three separate, non-interventional prospective registries in Europe, East Asia, and Japan. The final ETNA-AF-Europe protocol was developed and approved based on consultations with the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency. The rationale and design of the study, including the statistical methodology here planned, have been previously published.[6] In short, ETNA-AF-Europe is a multinational, multi-centre, post-authorization, registered (Clinicaltrials.gov: NCT02944019) observational study conducted at 825 sites from 10 European countries, including cohorts from the clustered regions of Belgium, the Netherlands, and Luxembourg (BENELUX); Austria, Germany, and Switzerland (DACH); Spain and Portugal (IBERIA); Italy (not clustered); the United Kingdom (UK) and Ireland (IRL). All patients with 'non-valvular' AF treated with edoxaban according to the indications as per the summary of product characteristics, were eligible to participate if not simultaneously participating in another interventional study and after providing written informed consent. No explicit exclusion criteria were defined. The ETNA-AF-Europe enrolled 13 980 patients with AF confirmed within the last 12 months before enrolment. Detailed information on the principal baseline data have been previously published.[7]

Perceived frailty and frailty scale

Among the several items included in the case report form (CRF), the investigators had to provide a binary subjective judgement on the presence/absence of frailty for each patient based on their own clinical judgement. This item was included under the 'general' clinical data section without any specific suggestion on how to assess presence of the condition. For the specific purposes of this sub-analysis and to have a parallel objective measure of frailty as a comparator, we calculated, using the existing clinical variables, the MFI,[8] a simplified, validated, shortened version of the Rockwood's Frailty Index.[9] The calculation was performed *post-hoc* by two experts in geriatric medicine (S.F. and A.M., among the authors of this study) on the basis of items already included in the original CRF, with slight adaptations, as detailed in see Supplementary material online, *Table S1*. In brief, one point was assigned for each of the following conditions: non-independent functional status; diabetes mellitus; chronic obstructive pulmonary disease (COPD); congestive heart failure; myocardial infarction; history of coronary intervention; hypertension requiring the use of medications; peripheral vascular disease; history of transient ischaemic attack; history of ischaemic stroke. The total score was then divided by the total number ($N = 11$) of variables, with frailty identified as having a score >0.36.[8]

Statistical analysis

Continuous variables are expressed as mean ± standard deviation if presenting with a normal distribution in the kurtosis and Kolmogorov–Smirnov tests. Discrete variables are expressed as frequencies and percentages. To identify parameters significantly associated with the presence of frailty according to either the investigators' personal judgement or the MFI in the population enrolled, a multi-variable logistic regression analysis was performed inserting variables that achieved a significance threshold (set at $P < 0.05$) at the univariable logistic regression analysis. Receiver operating characteristic (ROC) curves were then produced to compare the different models used to generate an area under the curve (AUC).

The statistical analysis was done using SAS V. 9.4 (SAS Institute Inc., Cary, NC, USA); *P*-values <0.05 were considered statistically significant. Data used in this analysis are from a snapshot of the ETNA-AF-Europe study data base as of 31 October 2019.

Results

A total of 13 980 patients were enrolled in ETNA-AF-Europe between November 2016 and February 2018. Three-hundred and fifty-nine patients (2.6%) were excluded from the analysis because of missing baseline data, missing information on edoxaban treatment, or absence of eligibility criteria.[7] Per-country split of patients were as follows: Austria [$n = 295$ (2.2%)], Belgium [$n = 1315$ (9.6%)], Germany [$n = 5288$ (38.8%)], Ireland [$n = 168$ (1.2%)], Italy [$n = 3509$ (25.7%)], the Netherlands [$n = 1263$ (9.3%)], Portugal [$n = 108$ (0.8%)], Spain [$n = 838$ (6.1%)], Switzerland [$n = 156$ (1.1%)], and the UK [$n = 698$ (5.1%)]. Most patients (77.2%) were enrolled and assessed by cardiologists, whereas the remaining 22.8% were enrolled and assessed by non-cardiologists, here including internal medicine specialists, geriatricians, neurologists, and general practitioners.

Prevalence of perceived and objective frailty in the atrial fibrillation population enrolled

Analysis of the baseline data showed that 10.6% ($n = 1443$) of patients were perceived as frail as assessed by the investigators. This number contrasts with a figure of 5.0% ($n = 679$) objectively considered frail according to the adopted MFI scoring system (*Table 1*). While the prevalence of objective frailty did not vary much across geographic areas, clinical settings, and enrolling physicians (ranging between 4.5% and 6.7%), perceived frailty greatly differed, ranging between 5.9% and 19.6% (*Figures 1* and *2*). There was also a minimal overlap (~1%) between the two methods of evaluating the presence of frailty (*Figures 1* and *2*).

Characteristics of patients with perceived vs. objective frailty

Because very few patients (~1% overall) were identified as frail by both approaches, we analysed the different baseline characteristics of the enrolled population within each of the two subgroups (*Table 1*). Compared with the overall study population, frail patients were older, especially in the perceived frailty subgroup, with a higher prevalence of renal failure and higher values of the CHA_2DS_2-VASc and HAS-BLED scores. Women were more prevalent in the perceived frailty group, 58.4% of all cases. Conversely, female patients were less prevalent than male patients in the overall study population (43.4%) and among the objectively frail patients (31.0%). As expected, comorbidities were closely associated with any frailty classification, with a higher prevalence among the objective frail. Prescriptions of edoxaban 30 mg were more frequent in the perceived frailty group of patients than in the objective frailty and the overall study populations. Concomitant with this finding, there was a higher prevalence of criteria for edoxaban dose reduction, namely a CrCl ≤50 mL/min and/or a body weight ≤60 kg in the perceived frail patients.

Parameters associated with perception of frailty in atrial fibrillation patients

To better understand factors associated with the perception of frailty by enrolling physicians, we analysed the clinical characteristics of this subgroup of patients according to the enrolment region (see Supplementary material online, *Table S2*). Despite huge differences in the prevalence of perceived frailty in different geographic areas and clinical settings, patients within this subgroup shared a quite similar clinical profile, suggesting that the approach adopted by enrolling physicians was quite homogeneous. Finally, we performed a logistic regression analysis inserting the main factors associated with perceived frailty to identify the leading factors driving frailty perception. Independent factors identified after the multi-variable analysis (all with $P < 0.0001$) were: age >85 years (OR 3.833, 95% CI 3.291–4.466); female sex (OR 1.459, 95% CI 1.279–1.663); low body weight (<60 kg, OR 1.855, 95% CI 1.567–2.193): presence of congestive heart failure (OR 2.072, 95% CI 1.697–2.529); history of diabetes (OR 1.407, 95% CI 1.224–1.618); impaired renal function (CrCl <50 mL/min, OR 2.488, 95% CI 2.164–2.865); and presence of COPD (OR 1.877, 95% CI 1.573–2.239). Age was clearly the most relevant factor associated with perceived frailty. The contribution of comorbidities and CrCl was of limited importance, as exemplified by the small decrease in the AUC of the ROC curve after their deletion. More specifically, only small reductions in AUC values (from 0.764 to 0.741) were observed after removing CrCl, and only a reduction to 0.703 occurred when analysis was limited only to age, sex, and weight (*Figure 3*).

Association of perceived and objectively assessed frailty with prescription patterns of edoxaban

Focusing on thromboembolic prophylaxis, frail patients were more frequently prescribed the 30 mg daily dose of edoxaban, and this was especially the case for perceived frailty, where the prevalence of the 30 mg daily dose use more than doubled compared with the overall population (*Table 1*). Since this finding could be driven by the clinical characteristics of frail patients (i.e. a higher prevalence of CrCl ≤50 mL/min and/or a body weight ≤60 kg), we calculated the prevalence of recommended/non-recommended edoxaban dosing (according to the summary of product characteristics, as approved by the European Medicines Agency) in categories of perceived vs. objective frailty. This analysis (*Figure 4*) evidenced that the non-recommended low dose was more frequently prescribed in both frail subgroups. Notably, the perceived frailty subgroup also more frequently received the non-recommended 60 mg daily dosing. Considering the possibility of mistakes in the CrCl calculation that might affect, at least partially, the non-recommended dose prescription, we verified the concordance of the CrCl directly reported by the investigators with the value obtained by a recalculation based on data included in the case report form. We found that allocation to non-recommended dosages because of miscalculations of classes of CrCl above or below 50 mL/min (for which dose changes were to be enacted) occurred only in a minority of cases (ranging from 21.2% to 29.0% of the non-recommended dose prescriptions), demonstrating that frailty—both perceived and objective—influenced edoxaban dosing by prescribing physicians independent of recommended dose reduction criteria.

Discussion

This study, conducted on the data base of a large prospective non-interventional study, shows that the prevalence of perceived frailty

Table 1 Baseline demographics and characteristics according to frailty status

	Total [*N* = 13 621]	Perceived Frailty [*N* = 1443]	Objective Frailty [*N* = 679]
Male, *n* (%)	7706 (56.6%)	600 (41.6%)	468 (69.0%)
Age (years), mean (SD)	73.6 (9.5)	81.6 (7.1)	75.1 (8.2)
By age sub-groups, *n* (%)			
<65 years	2088 (15.3)	30 (2.1)	68 (10.0)
65–74 years	4601 (33.8)	173 (12.0)	219 (32.3)
75–84 years	5495 (40.3)	736 (51.0)	312 (46.0)
≥85 years	1435 (10.5)	503 (34.9)	79 (11.7)
Body weight (kg), mean (SD)	81.0 (17.3)	73.0 (16.5)	84.2 (17.8)
Body weight ≤60 kg, *n* (%)	1373 (10.4)	355 (25.2)	52 (7.8)
BMI (kg/m^2), mean (SD)	28.1 (5.1)	26.7 (5.3)	29.1 (5.3)
Smokers (current), *n* (%)	854 (6.3)	65 (4.5)	74 (10.9)
CrCl (calculated, mL/min), mean (SD)	74.4 (30.5)	54.3 (22.2)	68.2 (30.0)
Subgroups by (calculated) CrCl, *n* (%)			
<15	3 (0.0)	1 (0.1)	0 (0.0)
[15, 30)	298 (2.5)	120 (8.7)	28 (4.4)
[30, 50]	2188 (18.5)	573 (41.7)	178 (27.9)
[50, 80)	5048 (42.7)	518 (37.7)	241 (37.8)
≥80	4281 (36.2)	163 (11.9)	190 (29.8)
$CHADS_2$, mean (SD, calculated)	1.7 (1.1)	2.4 (1.1)	3.2 (1.1)
CHA_2DS_2-VASc, mean (SD, calculated)[a]	3.1 (1.4)	4.1 (1.3)	5.0 (1.3)
Mod. HAS-BLED, mean (SD)[b]	2.5 (1.1)	3.1 (1.0)	3.4 (1.0)
Perceived frailty (investigator judgement), *n* (%)	1443 (10.6)	1443 (100)	146 (21.5)
If frail: risk of fall, *n* (%)	942 (65.3)	942 (65.3)	100 (68.5)
Objective frailty, *n* (%)[c]	679 (5.0)	146 (10.1)	679 (100)
History of CV disease, *n* (%)			
Hypertension	10 482 (77.0)	1187 (82.3)	649 (95.6)
Congestive heart failure	802 (5.9)	181 (12.5)	226 (33.3)
Myocardial infarction	583 (4.3)	77 (5.3)	251 (37.0)
Angina pectoris	202 (1.5)	32 (2.2)	38 (5.6)
Valvular disease	2419 (17.8)	396 (27.4)	175 (25.8)
Peripheral artery disease	457 (3.4)	84 (5.8)	162 (23.9)
History of diabetes, *n* (%)	2989 (21.9)	401 (27.8)	485 (71.4)
History of COPD, *n* (%)	1248 (9.2)	221 (15.3)	299 (44.0)
History of dys-/hyperlipidaemia, *n* (%)	5816 (42.7)	639 (44.3)	476 (70.1)
History of hyper-/hypo-thyroidism, *n* (%)	1673 (12.3)	215 (14.9)	103 (15.2)
History of digestive tract disease, *n* (%)	1122 (8.2)	209 (14.5)	84 (12.4)
History of stroke and ICH, *n* (%)			
Ischaemic stroke	808 (5.9)	172 (11.9)	146 (21.5)
Stroke, unknown	79 (0.6)	9 (0.6)	16 (2.4)
Transient ischaemic attack	464 (3.4)	78 (5.4)	101 (14.9)
Intracranial haemorrhage	67 (0.5)	16 (1.1)	9 (1.3)
History of bleeding, *n* (%)			
Major	134 (1.0)	37 (2.6)	18 (2.7)
CRNM	148 (1.1)	29 (2.0)	21 (3.1)
GI bleeding (major or CRNM)	111 (0.8)	28 (1.9)	16 (2.4)
History of chronic hepatic disease, *n* (%)	191 (1.4)	40 (2.8)	19 (2.8)
Current AF type, *n* (%)			
Paroxysmal	7292 (53.7)	597 (41.4)	299 (44.1)
Persistent	3307 (24.3)	309 (21.4)	177 (26.1)
Long-standing persistent	334 (2.5)	59 (4.1)	8 (1.2)
Permanent	2655 (19.5)	477 (33.1)	194 (28.6)

Continued

Table 1 *Continued*

	Total [*N* = 13 621]	Perceived Frailty [*N* = 1443]	Objective Frailty [*N* = 679]
Time since first AF diagnosis (months), mean (SD)	25.7 (46.8)	29.5 (51.6)	28.6 (46.6)
Current AF symptoms, *n* (%)	3307 (24.3)	344 (23.9)	254 (37.4)
Edoxaban dose at baseline, *n* (%)			
60 (mg), OD	10 405 (76.4)	636 (44.1)	423 (62.3)
30 (mg), OD	3216 (23.6)	807 (55.9)	256 (37.7)

[a]Calculated based on characteristics as declared by the investigators in the eCRF.
[b]Not including labile INR, alcohol use was defined as ≥1 unit/day, and defining the presence or absence of renal or hepatic disease was left to the discretion of the enrolling physician.
[c]As assessed by a modified MFI score.
AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRNM, clinically relevant non-major; CV, cardiovascular; eCRF, electronic Case Report Form; GI, gastro-intestinal; ICH, intra-cranial haemorrhage; LVEF, left ventricular ejection fraction; OD, once daily; SD, standard deviation.

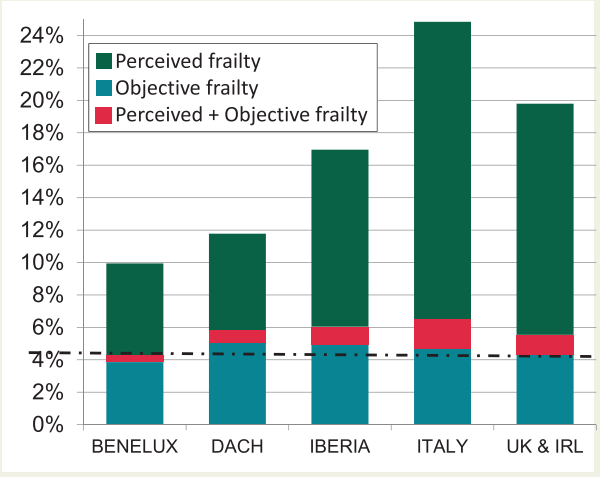

Figure 1 Prevalence of perceived and objective frailty among enrolled patients according to geographic areas. BENELUX, comprises Belgium, the Netherlands, and Luxembourg; DACH, comprises Austria, Germany, and Switzerland; IBERIA, comprises Spain and Portugal; UK, United Kingdom; IRL, Ireland.

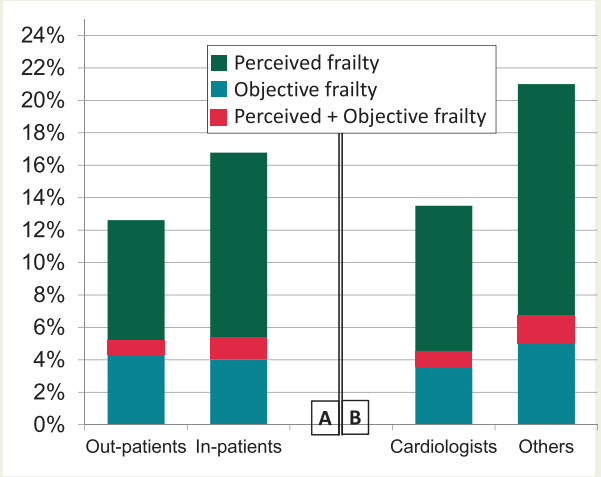

Figure 2 Prevalence of perceived and objective frailty among enrolled patients according to (A) clinical settings and (B) enrolling physicians.

varies widely according to geographical areas in the study and the settings of patient management. On the contrary, objective frailty (algorithmic frailty) is quite consistent among AF patients across the different trial centres and categories of managing clinicians. Perceived frailty appears to be more likely driven by demographic and anthropometric variables than by the presence of comorbidities. Conversely, comorbidities exert a greater influence on objective frailty estimated with the frailty score here used. These two approaches identify two subgroups of patients with limited overlapping characteristics ('clinical frailty mismatch'), both presenting, however, a worse clinical profile compared with the overall study population and both affecting management decisions in terms of anticoagulant dosing.

Our findings on the wide variability of perceived frailty are in line with the results of a previously published systematic review that showed, among 11 selected studies, a very wide range in the prevalence of frailty in AF patients—from 4.4% to 75.4%—also estimating that AF prevalence in the frail population ranged from 48.2% to 75.4%.[5] Age of the enrolled populations was thought to contribute the most to the dispersion of AF prevalence among the included studies.[5] Importantly, while the identification of frailty among AF patients was felt to be an important task for physicians in charge of tailoring AF management, no clear approach to define frailty was there provided, and the authors advocated the need for additional studies on this topic.[3] Accordingly, a recent survey by the European Heart Rhythm Association (EHRA) advocated the involvement of a multi-disciplinary team in the management of AF patients with complex problems such as frailty.[10] The many different ways to conceive and define frailty clearly vouch for a multi-specialists' approach, although information on frailty provided by non-specialists, despite limitations, still appears relevant.[11]

Patients in the perceived frailty group were older than the objective frailty group, with a higher proportion of women and a relatively

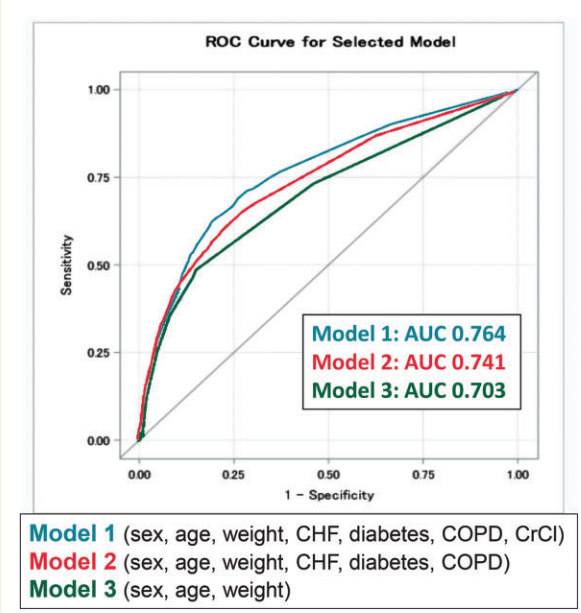

Figure 3 Receiver operating characteristic curves of three different models to predict the identification of perceived frailty in the enrolled population. The three lines present the ROC curves according to three different models each including the variables presented in the box. AUC, area under the curve; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; ROC, receiver operating characteristic curve.

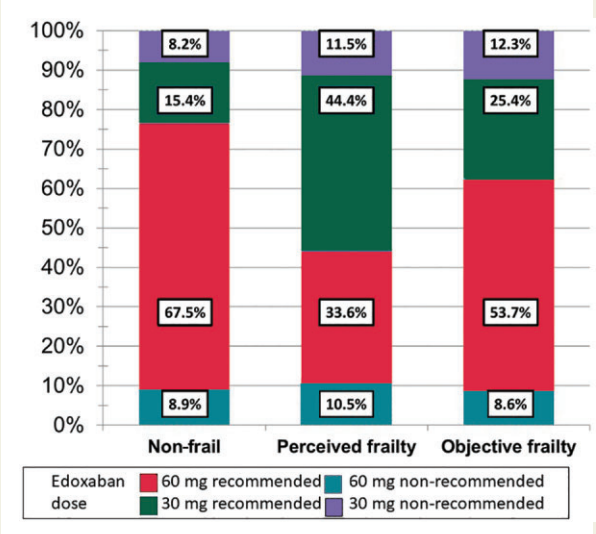

Figure 4 Dose of edoxaban prescribed to frail and non-frail patients considering presence/absence of dose-reduction criteria. Dose reduction criteria follow SmPC approved by the European Medicines Agency.

lower body mass index (BMI). This suggests that such parameters were the leading factors influencing the ETNA-AF-Europe investigators' judgement for the presence/absence of frailty, in a homogenous manner across the different geographic areas of the study. The 'homogeneous mismatch' between perceived and objectively assessed frailty, which at first sight appears to conflict with previously mentioned literature, can be justified considering that multi-morbidity, which explains large part of the MFI score, usually—but not always—contributes to frailty, with several subjects that can be frail without overt disease. Moreover, the principal drivers we found for perceived frailty, namely older age, female gender, and reduced body weight—a possible expression of sarcopenia—are extremely common in frail individuals.[12,13] Last, according to Rockwood *et al.*,[14] it could be paradoxically hypothesized that a subjective-based scale should be more appropriately used by experienced physicians, while other more complex tools, which also allows a more accurate quantification, should be necessarily used in settings of care where a specialist's approach to frailty is unavailable. Also, the specific context of the present analysis—where only AF patients receiving a direct oral anticoagulant were investigated—could explain the discrepancies between perceived and objective frailty. Indeed, advanced age, low body weight, and female gender are often associated with limited use or a low dose prescription of oral anticoagulants for the common perception of an increased risk of bleeding, and many physicians translate this risk into a diagnosis of frailty.[3,15]

Another relevant finding of our study is about the role of CrCl in the definition of frailty in AF patients. The logistic regression analysis evidenced a statistical association of CrCl with perceived frailty. However, the contribution of CrCl to perceived frailty appeared to be minimal, as other factors, such as age, sex, and BMI, were, in this sense, much more predominant. The association between reduced CrCl and frailty is debated, but both renal dysfunction and frailty are of paramount importance for the pre-anticoagulant prescription. Other investigators previously assessed the association of reduced renal function with frailty in participants to the Cardiovascular Health Study.[16] They found that a lower GFR estimated on the basis of cystatin C was associated with a higher risk of prevalent and incident frailty, whereas a lower CrCl based on serum creatinine concentration was found not to be significantly associated with frailty, even providing opposite results. The authors of that report remarked the influence of muscle mass on both serum creatinine concentration and the development of the frailty syndrome. Indeed, renal function assessments based on creatinine appear to be particularly inaccurate in elderly adults, especially in the case of sarcopenia.[16] Independent of the different ways to evaluate renal function, it should be remembered that the prevalence of frailty is extremely high (>40%) in subjects with end-stage renal disease, where a frailty diagnosis portends a worse prognosis.[17]

In our study, more patients with perceived frailty were treated with edoxaban 30 mg than those with objective frailty (55.9% vs. 37.7%, respectively). A sub-analysis of the ENGAGE AF-TIMI 48 clinical trial, using the Rockwood cumulative deficit model showed a clear association between the use of edoxaban 30 mg and a lower incidence of major bleeding compared with warfarin, not only in patients classified as 'fit', but also in pre-frail and mildly-to-moderately frail patients.[18] The same was observed for pre-frail and mildly-to-moderately frail subjects treated with edoxaban 60 mg. Importantly, no differences in the relative incidence of stroke or systemic embolism with edoxaban vs. warfarin were observed across classes of frailty.[18] These results emphasize that, under the conditions of a

randomized controlled clinical trial, the usefulness of the direct oral anticoagulant (DOAC) here used, edoxaban, is not limited to 'fit' patients.[18] The impact of perceived frailty was not, however, assessed in that study. In the ETNA-AF-Europe registry, patients both in the perceived and objective frailty groups more frequently received non-recommended doses according to edoxaban approved summary of product characteristics, namely 22.0% and 20.9%, respectively (compared with 17.1% of non-frail patients, see *Figure 4*). According to our analysis, this seems due to a physician's decision in about three quarter of the cases rather than due to issues in CrCl calculation, which can occur especially in elderly subjects with low body weight. An additional explanation for the more frequent prescription of the non-recommended dosage in frail patients may be due to a higher variability in CrCl (less often weight), which is certainly not infrequent in these subjects, prompting physicians to prescribe the safer—albeit possibly less effective—dosage. Whatever the underlying reasons, a main finding of our study is the documentation that frailty, both perceived and objectively assessed, is associated, and probably influences the decision to go for a non-officially recommended, usually lower, anticoagulant dosage. Additional analysis will address the implication of these findings on clinical outcomes, showing whether the trend to play safer in terms of anticoagulant dosing by prescribing doctors in case of frailty is an error to avoid or something to encourage because associated with improved net clinical benefit. In this regard, the strong association between AF, frailty, and dementia should also be considered. This relatively novel, intriguing relation is probably due to the interaction of cerebral hypoperfusion, inflammatory mediators, and prothrombotic state promoted by AF.[19] Indeed, antithrombotic drugs proved to mitigate the development of AF-related cognitive decline, in both vascular and degenerative forms, with data favouring DOACs over vitamin K antagonists.[20] However, further studies are needed to identify the most appropriate antithrombotic regimen able to maximize the overall net clinical benefit also beyond acute ischaemic and haemorrhagic events.

Limitations

Our measure of 'objective' frailty, the MFI, is a simplified, shortened, version of the Rockwood Frailty Index. We decided to use this validated tool not only to limit the missing values derived from the CRF, but also to compare perceived frailty with a tool simple enough to be practically applied in current practice by many physicians beyond geriatricians. Accordingly, we cannot exclude that our results could have been different by using the original, extended tool, containing 70 variables, or other more precise albeit more complex models, but this was beyond the scope and the possibilities of our analysis. The present report still does not address the relevance of perceived vs. objectively estimated frailty on clinical ischaemic and haemorrhagic events. Such evaluations are ongoing and will evaluate the complex interaction of frailty assessments on AF outcomes, with important, practical, consequences for issuing recommendations on thromboembolic prophylaxis in such challenging situations.

Conclusions

Perceived and objectively assessed frailty appear to characterize minimally overlapping categories of patients with AF, both with a worse clinical profile compared with the overall AF population. Perception of frailty varies widely across different countries and physicians' categories. Because of their association with the use of lower, and in general non-recommended, DOAC doses, both perceived and objectively assessed frailty warrant consideration in the management of AF.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: I.D. reports having received speaker fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Medtronic, Boston Scientific, and Biotronik. A.B. reports being involved in research sponsored by and is a member of advisory panels and speakers' bureau for Daiichi Sankyo, Pfizer, BMS, Bayer, and Boehringer Ingelheim. P.-E.R., M.C.M., and J.A.G.d.S. are employees of Daiichi Sankyo Europe GmbH. L.P. has received fees and honoraria from Daiichi-Sankyo, SOTIO Biotech, and Beckman-Coulter. P.K. receives research support from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies. He is listed as inventor on two patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). He is co-principal investigator of ETNA-AF-Europe. R.D.C. co-authored ESC Guidelines on Atrial Fibrillation 2010–2012; acted as a Steering Committee member and National Coordinator for Italy, and co-authored manuscripts published on APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE AF-TIMI 48, and Re-DUAL PCI. R.D.C. has received fees, honoraria, and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Novartis, Portola, Roche, and Merck. He is co-principal investigator of ETNA-AF-Europe. All remaining authors have declared no conflicts of interest.

Data availability

The data underlying this article are available in the article and in Supplementary material online. Further data underlying this article will be shared on reasonable request to the corresponding author.

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