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

Short title: **Perceived frailty in atrial fibrillation**

Igor Diemberger,[a] Stefano Fumagalli,[b] Anna Maria Mazzone,[c] Ameet Bakhai,[d] Paul-Egbert Reimitz,[e] Ladislav Pecen,[f] Marius Constantin Manu,[e] José Antonio Gordillo de Souza,[e] Paulus Kirchhof,[g] and Raffaele De Caterina[h]

[a]Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Policlinico S.Orsola-Malpighi, via Massarenti 9 40138 Bologna, Italy. igor.diemberger@unibo.it

[b]Geriatric Intensive Care Unit, University of Florence and AOU Careggi Florence Italy, Florence, Italy. stefano.fumagalli@unifi.it

[c]Cardiology Department "G. Pasquinucci" Heart Hospital, "G. Monasterio" Foundation, Massa, Italy. annamaria.mazzone@ftgm.it

[d]Royal Free London NHS Foundation Trust, Barnet General Hospital Cardiology Department, Barnet General Hospital, Thames House, Wellhouse Lane, Barnet, Enfield, UK. asbakhai@nhs.net

[e]Daiichi Sankyo Europe GmbH, Zielstattstraße 48, 81379 Munich, Germany. Paul-Egbert.Reimitz@daiichi-sankyo.eu; Marius.Manu@daiichi-sankyo.eu; Jose.Souza@daiichi-sankyo.eu

[f]Institute of Computer Science of the Czech Academy of Sciences (Pod Vodárenskou věží 271/2, 182 07 Prague 8, Czech Republic). Ladislav.Pecen@seznam.cz

[g]Department of Cardiology, University Heart and Vascular Centre UKE Hamburg, Hamburg, Germany; Institute of Cardiovascular Sciences, University of Birmingham, SWBH and UHB NHS Trusts, Birmingham, UK; The Atrial Fibrillation NETwork (AFNET), Münster, Germany. p.kirchhof@uke.de

[h]Chair of Cardiology, University of Pisa, Pisa; Division of Cardiology, Azienda Ospedaliero-Universitaria Pisana, Pisa; and Fondazione VillaSerena per la Ricerca, Città Sant'Angelo-Pescara;; C/o Pisa University Hospital, via Paradisa, 2, 56124 Pisa, Italy. raffaele.decaterina@unipi.it

Online Supplemental Material

Correspondence:

Professor Raffaele De Caterina

Division of Cardiology, Pisa University Hospital

Via Paradisa 2 - 56124 Pisa, Italy

Phone no: +39-050-315-2714 - E-mail: raffaele.decaterina@unipi.it

Online Supplementary Table 1: A comparison of variables included in the *adapted Modified Frailty Index,* used in this study, and the original *Modified Frailty Index*

Adapted Modified Frailty Index[a]	**Modified Frailty Index[b]**
1. Surrogates for a non-independent functional status: Current AF symptoms: fatigue frequency ≥1/ day **OR** dyspnea frequency ≥1/ day **OR** dizziness frequency ≥1/ day	1. Non-independent functional status
2. History of diabetes mellitus	2. History of diabetes mellitus
3. History of chronic obstructive pulmonary disease	3. History of either chronic obstructive pulmonary disease or pneumonia
4. History of congestive heart failure	4. History of congestive heart failure
5. History of myocardial infarction	5. History of myocardial infarction
6. History of coronary intervention	6. History of percutaneous coronary intervention, cardiac surgery, or angina
7. Hypertension requiring the use of medications	7. Hypertension requiring the use of medications
8. Peripheral artery disease	8. Peripheral vascular disease or rest pain
9. *Impaired sensorium	9. Impaired sensorium
10. History of transient ischemic attack	10. Transient ischemic attack or cerebrovascular accident without residual deficit
11. History of ischemic stroke	11. Cerebrovascular accident with deficit

Footnote: *Modified Frailty Index* (MFI) as described by Ethun et al., with differences in red. *This patient characteristic was not monitored in ETNA-AF, so that all patients attained 0 points for this variable.

[a,b]Both the *adapted Modified Frailty Index* and the *Modified Frailty Index* are computed as (total number of variables present)/11 total variables.

Online Supplementary Table 2: Demographics and clinical baseline characteristics of perceived frail patients according to geographic region [N=1443]

	BENELUX [N=2578]	DACH [N=5729]	IBERIA [N=947]	ITALY [N=3499]	UK & IRELAND [N=868]
Perceived frailty, n (%)	**153 (5.9%)**	**362 (6.3%)**	**110 (11.6%)**	**687 (19.6%)**	**131 (15.1%)**
Male, n (%)	56 (36.6%)	152 (42.0%)	41 (37.3%)	282 (41.0%)	69 (52.7%)
Age, years, mean (SD)	81.1 (7.9)	81.2 (7.2)	82.2 (8.6)	81.8 (6.7)	81.5 (6.7)
By age sub-groups, n (%)					
<65 years	4 (2.6%)	9 (2.5%)	5 (4.5%)	11 (1.6%)	1 (0.8%)
65–74 years	25 (16.3%)	38 (10.5%)	9 (8.2%)	79 (11.5%)	22 (16.8%)
75–84 years	69 (45.1%)	191 (52.8%)	51 (46.4%)	357 (52.0%)	68 (51.9%)
≥85 years	55 (35.9%)	124 (34.3%)	45 (40.9%)	239 (34.8%)	40 (30.5%)
Body weight, kg, mean (SD)	70.5 (15.9)	75.8 (17.6)	70.0 (14.9)	71.8 (15.3)	76.6 (19.7)
Body weight ≤60 kg, n (%)	49 (33.3%)	73 (20.4%)	28 (26.2%)	178 (26.3%)	27 (22.0%)
BMI, kg/m^2, mean (SD)	25.7 (4.7)	27.3 (5.7)	27.7 (5.6)	26.3 (5.0)	27.4 (6.3)
Smokers (current), n (%)	11 (7.2%)	19 (5.2%)	3 (2.7%)	25 (3.6%)	7 (5.3%)
CrCl (calc.°), mL/min, mean (SD)	53.5 (23.2)	54.2 (22.7)	55.4 (23.7)	54.0 (21.5)	56.6 (23.0)
By (recalc.) CrCl subgroups, n (%)					
<15	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
[15, 30)	16 (11.3%)	38 (11.3%)	7 (6.5%)	48 (7.2%)	11 (8.9%)
[30, 50]	53 (37.6%)	130 (38.6%)	48 (44.9%)	297 (44.5%)	45 (36.6%)
[50, 80)	54 (38.3%)	129 (38.3%)	38 (35.5%)	249 (37.3%)	48 (39.0%)
≥80	18 (12.8%)	39 (11.6%)	14 (13.1%)	73 (10.9%)	19 (15.4%)
$CHADS_2$, mean (SD) (calculated)	2.4 (1.2)	2.5 (1.1)	2.5 (1.1)	2.4 (1.1)	2.2 (1.0)
CHA_2DS_2-VASc, mean (SD)(calculated)†	4.1 (1.4)	4.2 (1.3)	4.2 (1.2)	4.1 (1.3)	3.8 (1.3)
Mod. HAS-BLED, mean (SD)‡	3.1 (1.0)	3.2 (1.1)	2.7 (0.9)	3.1 (1.1)	3.1 (1.0)
Risk of fall, n (%)					
No	52 (34.0%)	89 (24.6%)	27 (24.5%)	239 (34.8%)	29 (22.1%)
Yes	90 (58.8%)	258 (71.3%)	80 (72.7%)	417 (60.7%)	97 (74.0%)
Unknown	11 (7.2%)	15 (4.1%)	3 (2.7%)	31 (4.5%)	5 (3.8%)
History of CV disease, n (%)					
Hypertension	117 (76.5%)	315 (87.0%)	83 (75.5%)	583 (84.9%)	89 (67.9%)
CHF	18 (11.8%)	36 (9.9%)	10 (9.1%)	103 (15.0%)	14 (10.7%)
MI	10 (6.5%)	15 (4.1%)	3 (2.7%)	35 (5.1%)	14 (10.7%)
Angina pectoris	5 (3.3%)	10 (2.8%)	1 (0.9%)	15 (2.2%)	1 (0.8%)
Valvular disease	34 (22.2%)	105 (29.0%)	19 (17.3%)	213 (31.0%)	25 (19.1%)
Peripheral artery disease	6 (3.9%)	43 (11.9%)	5 (4.5%)	23 (3.3%)	7 (5.3%)
History of diabetes, n (%)	35 (22.9%)	125 (34.5%)	36 (32.7%)	174 (25.3%)	31 (23.7%)
History of COPD, n (%)	27 (17.6%)	53 (14.6%)	12 (10.9%)	112 (16.3%)	17 (13.0%)
History of dys-/hyperlipidemia, n (%)	73 (47.7%)	166 (45.9%)	55 (50.0%)	291 (42.4%)	54 (41.2%)
History of hyper-/ hypo-thyroidism, n (%)	27 (17.6%)	65 (18.0%)	13 (11.8%)	87 (12.7%)	23 (17.6%)
History of digestive tract disease, n (%)	17 (11.1%)	48 (13.3%)	16 (14.5%)	99 (14.4%)	29 (22.1%)
History of stroke and ICH, n (%)					
Ischemic stroke	28 (18.3%)	42 (11.6%)	19 (17.3%)	69 (10.0%)	14 (10.7%)
Stroke, unknown	0 (0.0%)	5 (1.4%)	1 (0.9%)	1 (0.1%)	2 (1.5%)
TIA	11 (7.2%)	13 (3.6%)	9 (8.2%)	38 (5.5%)	7 (5.3%)
ICH	1 (0.7%)	6 (1.7%)	2 (1.8%)	6 (0.9%)	1 (0.8%)
History of bleeding, n (%)					
Major	2 (1.3%)	11 (3.0%)	4 (3.6%)	10 (1.5%)	2 (1.5%)
CRNM	2 (1.3%)	4 (1.1%)	1 (0.9%)	14 (2.0%)	3 (2.3%)
GI bleeding (major or CRNM)	2 (1.3%)	9 (2.5%)	4 (3.6%)	11 (1.6%)	2 (1.5%)
History of chronic hepatic disease, n (%)	4 (2.6%)	13 (3.6%)	5 (4.5%)	20 (2.9%)	1 (0.8%)
Current AF type, n (%)					
Paroxysmal	85 (55.9%)	166 (45.9%)	28 (25.5%)	275 (40.0%)	43 (32.8%)
Persistent	43 (28.3%)	68 (18.8%)	23 (20.9%)	136 (19.8%)	39 (29.8%)
Long-standing persistent	3 (2.0%)	14 (3.9%)	6 (5.5%)	23 (3.3%)	13 (9.9%)
Permanent	21 (13.8%)	114 (31.5%)	53 (48.2%)	253 (36.8%)	36 (27.5%)
Time since first AF diagnosis, months, mean (SD)	21.6 (44.3)	33.5 (52.6)	43.9 (54.8)	24.1 (50.2)	36.5 (55.5)
Current AF symptoms, n (%)	49 (32.2%)	91 (25.1%)	16 (14.5%)	137 (19.9%)	51 (38.9%)
Edoxaban dose at baseline, n (%):					
60 mg, OD	80 (52.3%)	171 (47.2%)	52 (47.3%)	272 (39.6%)	61 (46.6%)
30 mg, OD	73 (47.7%)	191 (52.8%)	58 (52.7%)	415 (60.4%)	70 (53.4%)

Footnote: †Calculated based on characteristics as declared by the investigators in the eCRF.

°Cockroft-Gault formula; ‡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 physician.

AF, atrial fibrillation; BENELUX, comprises Belgium, the Netherlands and Luxembourg; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRNM, clinically relevant non major; CV, cardiovascular; DACH, comprises Austria, Germany and Switzerland; eCRF, electronic Case Report Form; GI, gastro-intestinal; IBERIA comprises Spain and Portugal; ICH, intracranial hemorrhage; IRL, Ireland; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OD, once daily; SD, standard deviation; TIA, transient ischaemic attack.