

Supplementary Material

Symptom Burden of Atrial Fibrillation and its Relation to Interventions and Outcome in Europe

Renate B. Schnabel ^a, MD, MSc, Ladislav Pecen ^b, Nargiz Rzayeva ^a, MSc, Markus Lucerna ^c,
Yanish Purmah ^d, Francisco M. Ojeda ^a, PhD, Raffaele De Caterina ^e, Paulus Kirchhof ^d

^a University Heart Center Hamburg Eppendorf, Hamburg, Germany, German Center for Cardiovascular Research (DZHK) partner site Hamburg/Kiel/Lübeck; ^b Medical faculty Pilsen of Charles University, Czech Republic; ^c Daiichi Sankyo Europe, Munich, Germany; ^d Institute of Cardiovascular Sciences, University of Birmingham and SWBH and UHB NHS Trust, Birmingham, UK; ^e G. d'Annunzio University, Chieti, Italy, and Fondazione G. Monasterio, Pisa, Italy

Supplementary Methods Literature evidence for the selection of predictor variables and potential confounders

Variables	Reference
Age	1-4
Gender	1-4
Body mass index	5-7
Systolic blood pressure	5,6
Hypertension	1,4
Smoking	8,9
Alcohol intake	9-11
Diabetes mellitus	1,4
Dyslipidaemia	8,9
History of myocardial infarction	3,5
Heart failure	1,12
History of ischemic stroke/TIA	1,4,13
History of cardioversion and/or ablation	1

Supplementary Table 1. Selected items from the EQ-5D-5L Questionnaire

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities

I have slight problems doing my usual activities

I have moderate problems doing my usual activities

I have severe problems doing my usual activities

I am unable to do my usual activities

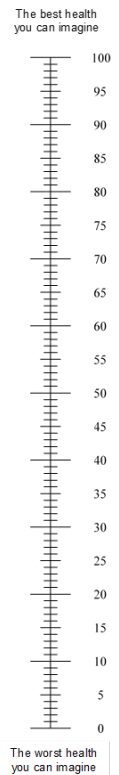
We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100. 100 means the best health you can imagine.

0 means the worst health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



EQ-5D™ is a trade mark of the EuroQol Group.

Supplementary Table 2. Selected items from the Perception of Anticoagulant Treatment Questionnaire (PACT-Q)¹⁴

B1 - How difficult is it to take your anticoagulant treatment (e.g., pills or injections, number of pills or injections, frequency of intake ...)?

1	2	3	4	5
Not at all	A little	Moderately	Very	Extremely

C1 - Because of potential side effects (e.g., minor bruises, bleeding...), do you limit your usual activities (i.e., work, leisure, social, or physical activities...)?

1	2	3	4	5
Not at all	A little	Moderately	A lot	Completely

D1 - How reassured do you feel by your anticoagulant treatment?

1	2	3	4	5
Not at all	A little	Somewhat	Very	Completely

D3 - How did your experience with side effects such as minor bruises or bleeding (e.g., while shaving, cooking, after small cuts...) compare to what you expected?

1	2	3	4	5
It is much worse than what I expected	It is worse than what I expected	It is exactly what I expected	It is better than what I expected	It is much better than what I expected

D7 - Overall, how satisfied are you with your anticoagulant treatment?

1	2	3	4	5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

Supplementary Table 3 Baseline characteristics of the patients entering the analyses compared to patients excluded from the analyses due to missing follow-up information or missing EHRA data at baseline

Variables	Study sample	Excluded due to	P Value
	N= 6196	missing N=1047*	
Age, years (SD)	71.8±10.4	70.7±12.1	0.13
Female gender, N (%)	2460 (39.7)	426 (41.4)	0.32
Body mass index, kg/m ² (SD)	27.9±5.0	28.0±5.0	0.68
Systolic blood pressure, mm Hg (SD)	131.5±16.5	132.1±17.6	0.11
Hypertension, N (%)	4514 (73.3)	727 (71.2)	0.16
Ever smoking, N (%)	2331 (39.7)	382 (39.2)	0.61
Alcohol abuse, N (%)	157 (2.6)	25 (2.6)	0.99
Diabetes mellitus, N (%)	1368 (22.3)	249 (24.4)	0.14
Dyslipidaemia, N (%)	2697 (44.5)	436 (43.6)	0.61
History of myocardial infarction, N (%)	663 (10.7)	110 (10.7)	0.97
Heart failure, N (%)	1723 (28.6)	263 (26.4)	0.17
History of ischemic stroke/TIA/other ischemic-thromboembolic event, N (%)	924 (15.1)	149 (14.9)	0.91
EHRA score ≥2, N (%)	5695 (91.9)	889 (92.9)	0.30
History of cardioversion and/or ablation, N (%)	2147 (34.7)	381 (37.6)	0.07

Data are presented as mean and standard deviation for continuous and percentages for discrete variables.

Supplementary Table 4 Multivariable stepwise selection model for variables correlates of EHRA score at baseline

Variables	Partial R²	Model R²	β	F Value	P Value	P Value*
Female gender	0.0230	0.0590	0.361±0.025	139.47	<0.0001	<0.0001
Ever smoking	0.0104	0.0694	0.190±0.026	62.68	<0.0001	<0.0001
History of cardioversion and/or ablation	0.0043	0.0737	0.124±0.024	26.21	<0.0001	0.001
Body mass index, kg/m²	0.0031	0.0769	0.011±0.002	18.87	<0.0001	0.005
Diabetes mellitus	0.0008	0.0776	- 0.065±0.029	4.73	0.03	0.06
History of myocardial infarction	0.0008	0.0785	0.086±0.038	5.03	0.03	0.04
Heart failure	0.0360	0.0360	0.387±0.026	208.49	<0.0001	<0.0001

All variables from Table 1 were permitted to enter the analysis. Partial R² is provided for the variation in EHRA score explained by the clinical variable. β, the regression coefficient, shows estimated change in EHRA score for one unit increment in body mass index or the condition present for categorical variables. *P Value derived by bootstrapping. At 91% of stepwise selection models from 1000 runs of bootstrapping a subset of presented variables was selected.

Supplementary Table 5 Multivariable-adjusted logistic regression analyses for EHRA score and EHRA symptom dimensions separately in relation to interventions to restore sinus rhythm at one year

Variable	Odds ratio EHRA 3/4 versus 1/2	95% Confidence interval		P Value	P Value adjusted logistic regression. across all 4 categories	AUC – resubstitution	AUC – 10-fold cross validation	P- Value 10-fold cross validation
<i>Cardioversio, N=701 (11.3%)</i>								
Palpitations	1.32	1.08	1.61	0.007	<0.0001	0.682/0.548	0.621/0.539	0.009
Fatigue	1.16	0.97	1.39	0.11	0.18	0.678/0.520	0.601/0.513	0.19
Dizziness	1.27	0.98	1.64	0.07	0.32	0.678/0.508	0.560/0.506	0.39
Dyspnea	1.05	0.86	1.27	0.65	0.79	0.676/0.507	0.592/0.506	0.76
Chest pain	1.37	0.97	1.93	0.08	0.20	0.679/0.510	0.604/0.509	0.23
Anxiety	0.79	0.63	0.99	0.04	0.08	0.677/0.507	0.603/0.506	0.35
EHRA score	1.21	1.01	1.45	0.040	0.07	0.679/0.534	0.616/0.533	0.04
<i>Catheter-based ablation, N=226 (3.4%)</i>								
Palpitations	2.02	1.48	2.76	<0.0001	<0.0001	0.808/0.599	0.715/0.574	<0.0001
Fatigue	1.67	1.23	2.26	0.0009	0.002	0.800/0.545	0.691/0.535	0.007
Dizziness	1.11	0.70	1.75	0.65	0.90	0.796/0.504	0.688/0.503	0.91
Dyspnea	1.19	0.84	1.68	0.26	0.008	0.796/0.511	0.690/0.509	0.27
Chest pain	1.41	0.79	2.52	0.24	0.25	0.797/0.510	0.689/0.507	0.34
Anxiety	1.26	0.88	1.80	0.21	0.20	0.797/0.521	0.692/0.518	0.23
EHRA score	1.97	1.44	2.69	<0.0001	<0.0001	0.804/0.568	0.708/0.550	0.0003
<i>Sinus rhythm at one year, N=2022 (32.6%)</i>								
Palpitations	1.51	1.30	1.76	<0.0001	<0.0001	0.706/0.551	0.651/0.550	0.0004
Fatigue	0.98	0.86	1.12	0.76	0.93	0.702/0.520	0.640/0.514	0.83
Dizziness	0.90	0.74	1.10	0.31	0.75	0.702/0.514	0.638/0.510	0.84
Dyspnea	0.86	0.74	0.99	0.033	0.003	0.703/0.538	0.644/0.530	0.04
Chest pain	1.44	1.90	1.10	0.009	0.01	0.703/0.505	0.641/0.504	0.54
Anxiety	1.04	0.89	1.22	0.60	0.007	0.702/0.512	0.641/0.510	0.61
EHRA score	1.06	0.93	1.20	0.40	0.048	0.702/0.501	0.628/0.501	0.97
<i>Adequate heart rate control, N=2734 (44.1%)</i>								
Palpitations	0.81	0.68	0.95	0.012	0.03	0.565/0.516	0.550/0.515	0.05
Fatigue	0.86	0.74	0.99	0.04	0.03	0.560/0.511	0.544/0.510	0.18
Dizziness	1.00	0.82	1.23	0.97	0.23	0.558/0.501	0.537/0.501	0.99

Variable	Odds ratio EHRA 3/4 versus 1/2	95% Confidence interval		P Value	P Value adjusted logistic regression. across all 4 categories	AUC – resubstitution	AUC – 10-fold cross validation	P- Value 10-fold cross validation
Dyspnea	0.88	0.76	1.02	0.10	0.16	0.559/0.508	0.541/0.506	0.44
Chest pain	0.84	0.62	1.14	0.27	0.51	0.559/0.505	0.540/0.504	0.61
Anxiety	0.91	0.76	1.07	0.25	0.51	0.560/0.502	0.538/0.502	0.82
EHRA score	0.80	0.70	0.92	0.001	0.005	0.565/0.521	0.551/0.519	0.04

Odds ratios are provided for EHRA score category 3/4 versus 1/2. P-values across all 4 categories are from logistic regression analyses as implemented in SAS proc logistic. All models are adjusted for age, sex, country, body mass index, systolic blood pressure, hypertension, diabetes mellitus, smoking, heart failure, history of myocardial infarction. AUCs (area under the curve) are for the whole model/ partial EHRA component.

Supplementary Table 6 Multivariable-adjusted logistic regression- and area under the curve analysis for EHRA score and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 3/4 versus 1/2	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories	AUC – resubstitution	AUC – 10-fold cross validation	P-value 10-fold cross validation
<u>Stroke/TIA/arterial thromboembolic events, N=136 (2.2%)</u>								
Palpitations	0.92	0.58	1.46	0.72	0.29	0.707/0.502	0.641/0.502	0.86
Fatigue	1.04	0.72	1.51	0.82	0.92	0.706/0.535	0.639/0.517	0.88
Dizziness	1.32	0.82	2.13	0.26	0.002	0.706/0.526	0.642/0.521	0.36
Dyspnea	1.04	0.71	1.53	0.84	0.59	0.706/0.547	0.643/0.527	0.55
Chest pain	1.69	0.92	3.10	0.09	0.002	0.704/0.526	0.645/0.522	0.14
Anxiety	0.55	0.32	0.93	0.03	0.08	0.711/0.521	0.653/0.520	0.06
EHRA score	1.02	0.70	1.49	0.92	0.05	0.706/0.540	0.646/0.519	0.88
<u>Coronary events, N=140 (2.3%)</u>								
Palpitations	0.98	0.60	1.60	0.95	0.21	0.725/0.515	0.645/0.512	0.97
Fatigue	1.09	0.75	1.58	0.64	0.73	0.724/0.533	0.649/0.520	0.65
Dizziness	1.16	0.70	1.91	0.57	0.72	0.725/0.512	0.647/0.510	0.59
Dyspnea	1.32	0.90	1.93	0.16	0.024	0.726/0.559	0.654/0.532	0.18
Chest pain	2.45	1.42	4.22	0.001	<0.0001	0.734/0.546	0.657/0.543	0.02
Anxiety	1.41	0.91	2.18	0.13	0.33	0.727/0.513	0.652/0.511	0.40
EHRA score	1.45	0.99	2.13	0.06	0.12	0.727/0.560	0.654/0.542	0.07
<u>Heart failure, N=155 (2.5%)</u>								
Palpitations	1.14	0.74	1.76	0.56	0.42	0.639/0.508	0.568/0.506	0.71
Fatigue	1.84	1.30	2.60	0.0006	0.0006	0.656/0.576	0.609/0.557	0.005
Dizziness	1.50	0.93	2.41	0.10	0.19	0.644/0.523	0.588/0.518	0.21
Dyspnea	2.33	1.63	3.33	<0.0001	<0.0001	0.669/0.598	0.615/0.580	<0.0001
Chest pain	1.25	0.57	2.75	0.58	0.42	0.637/0.502	0.570/0.502	0.94
Anxiety	1.72	1.16	2.55	0.007	0.032	0.648/0.545	0.590/0.543	0.04
EHRA score	1.65	1.16	2.34	0.005	0.005	0.653/0.567	0.592/0.555	0.02

Variable	Odds ratio EHRA 3/4 versus 1/2	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories	AUC – resubstitution	AUC – 10-fold cross validation	P-value 10-fold cross validation
<u>Major bleeding,</u>								
<u>N=168 (2.7%)</u>								
Palpitations	0.88	0.55	1.41	0.59	0.78	0.651/0.516	0.581/0.513	0.67
Fatigue	1.27	0.90	1.79	0.17	0.28	0.656/0.541	0.592/0.531	0.20
Dizziness	1.08	0.67	1.74	0.74	0.90	0.650/0.509	0.582/0.507	0.78
Dyspnea	0.92	0.64	1.34	0.67	0.61	0.651/0.520	0.583/0.512	0.73
Chest pain	0.91	0.42	1.98	0.81	0.74	0.651/0.501	0.578/0.500	0.98
Anxiety	1.21	0.80	1.83	0.36	0.46	0.651/0.517	0.584/0.516	0.40
EHRA score	1.09	0.77	1.54	0.64	0.60	0.652/0.529	0.583/0.514	0.69

Odds ratios are provided for EHRA score category 3/4 versus 1/2. P-values across all 4 categories are from logistic regression analyses and **additionally from 10-fold cross validation** implemented in SAS proc logistic. All models are adjusted for age, sex, country, body mass index, systolic blood pressure, hypertension, diabetes mellitus, smoking, heart failure, history of myocardial infarction. AUCs (area under the curve) are for the whole model/ partial EHRA component **and measured for resubstitution and 10-fold cross validation.**

Supplementary Table 7. Baseline characteristics of individuals excluded due to missing information on any EHRA score

Variables	N=216
Age, years (SD)	70.4±11.4
Female gender, N (%)	39.8% (86)
Body mass index, kg/m ² (SD)	28.8±5.7
Systolic blood pressure, mm Hg (SD)	129±21
Hypertension, N (%)	66.7% (144)
Ever smoking, N (%)	45.5% (75)
Alcohol abuse, N (%)	3.4% (6)
Diabetes mellitus, N (%)	25.0% (54)
Dyslipidaemia, N (%)	41.7% (83)
History of myocardial infarction, N (%)	12.5% (27)
Heart failure, N (%)	41.5% (80)
History of ischemic stroke/TIA/other ischemic-thromboembolic event, N (%)	18.5% (37)

Data are presented as mean and standard deviation for continuous variables and number and percentages. Other variables were also partly incomplete in these patients as seen from the numbers.

Supplementary Table 8. Spearman correlation coefficients for the EHRA score and its components with PACT- Q items

EHRA Score	Anxiety	Chest pain	Palpitations	Dyspnoea	Fatigue	Dizziness
[B1] How difficult is it to take your anticoagulant treatment (e.g., pills or injections, number of pills or injections, frequency of intake ...)?						
0.10546 <0.0001	0.16633 <0.0001	0.10594 <0.0001	0.17954 <0.0001	0.10539 <0.0001	0.09543 <0.0001	0.09072 <0.0001
[B2] How bothered are you by taking your anticoagulant treatment?						
0.12898 <0.0001	0.19448 <0.0001	0.12898 <0.0001	0.20222 <0.0001	0.10518 <0.0001	0.11116 <0.0001	0.07323 <0.0001
[B3] Some anticoagulant treatments may need dose adjustments; how difficult is this for you?						
0.12773 <0.0001	0.19594 <0.0001	0.12075 <0.0001	0.19115 <0.0001	0.10951 <0.0001	0.12683 <0.0001	0.09478 <0.0001
[B4] Certain medications cannot be taken at all while you are on anticoagulant treatments; how difficult is this for you?						
0.12383 <0.0001	0.20048 <0.0001	0.10256 <0.0001	0.20647 <0.0001	0.11369 <0.0001	0.12825 <0.0001	0.09460 <0.0001
[B5] It is recommended that certain foods be avoided while taking an anticoagulant treatment; how difficult is this for you?						
0.07683 <0.0001	0.18530 <0.0001	0.11705 <0.0001	0.18827 <0.0001	0.07738 <0.0001	0.10838 <0.0001	0.09460 <0.0001
[B6] How difficult is it for you to take your anticoagulant treatment when you are away from home?						
0.10162 <0.0001	0.16068 <0.0001	0.12057 <0.0001	0.10201 <0.0001	0.09191 <0.0001	0.10385 <0.0001	0.06483 <0.0001
[B7] How difficult is it for you to plan your time around your anticoagulant treatment (e.g., appointments with nurses, doctors or labs...)?						
0.14566 <0.0001	0.17336 <0.0001	0.14388 <0.0001	0.21822 <0.0001	0.12125 <0.0001	0.13797 <0.0001	0.06483 <0.0001

Supplementary Table 8. Spearman correlation coefficients for the EHRA score and its components with PACT- Q items (continued)

EHRA Score	Anxiety	Chest pain	Palpitations	Dyspnoea	Fatigue	Dizziness
[B8] How bothered are you by the medical follow-up required with your anticoagulant treatment?						
0.08453 <0.0001	0.18823 <0.0001	0.11752 <0.0001	0.20081 <0.0001	0.05842 <0.0001	0.09220 <0.0001	0.08461 <0.0001
[B9] How difficult is it for you to take your anticoagulant treatment as directed on a regular basis?						
0.12537 <0.0001	0.16171 <0.0001	0.11651 <0.0001	0.21103 <0.0001	0.09063 <0.0001	0.10710 <0.0001	0.08525 <0.0001
[B10] Do you feel more dependent on others (e.g., partner, family, nurse) because of your anticoagulant treatment?						
0.17240 <0.0001	0.18311 <0.0001	0.12693 <0.0001	0.16914 <0.0001	0.17195 <0.0001	0.16955 <0.0001	0.08525 <0.0001
[B11] How worried are you about having to interrupt or stop your anticoagulant treatment?						
0.13061 <0.0001	0.20338 <0.0001	0.12549 <0.0001	0.15611 <0.0001	0.17195 <0.0001	0.11834 <0.0001	0.08525 <0.0001
[C1] Because of potential side effects (e.g., minor bruises, bleeding...), do you limit your usual activities (i.e., work, leisure, social, or physical activities...)?						
0.15334 <0.0001	0.18924 <0.0001	0.14262 <0.0001	0.18691 <0.0001	0.15104 <0.0001	0.15889 <0.0001	0.14754 <0.0001
[D1] How reassured do you feel by your anticoagulant treatment?						
-0.07108 <0.0001	-0.10681 <0.0001	-0.10686 <0.0001	-0.10521 <0.0001	-0.7081 <0.0001	-0.08733 <0.0001	-0.07081 <0.0001
[D2] Do you feel that your anticoagulant treatment has decreased your symptoms (e.g., leg pain or swelling, palpitations, shortness of breath, or chest pain...)?						
-0.05842 <0.0001	-0.06600 <0.0001	0.00986 0.5077	-0.05842 <0.0001	-0.02086 <0.0001	-0.06279 <0.0001	0.04011 <0.0001

Supplementary Table 8. Spearman correlation coefficients for the EHRA score and its components with PACT- Q items (continued)

EHRA Score	Anxiety	Chest pain	Palpitations	Dyspnoea	Fatigue	Dizziness
[D3] How did your experience with side effects such as minor bruises or bleeding (e.g., while shaving, cooking, after small cuts) compare to what you expected?						
-0.13079 <0.0001	-0.13910 <0.0001	-0.09285 <0.0001	-0.12041 <0.0001	0.11865 <0.0001	-0.12903 <0.0001	-0.07451 <0.0001
[D4] Regarding the follow-up of your disease and anticoagulant treatment, how satisfied are you with your level of independence?						
-0.15334 <0.0001	-0.15450 <0.0001	-0.13176 <0.0001	-0.14687 <0.0001	-0.12468 <0.0001	-0.13208 <0.0001	-0.08783 <0.0001
[D5] How satisfied are you with the methods (e.g., appointments with nurses, doctors, labs) used to ensure the follow-up of your disease and anticoagulant treatment?						
-0.08021 <0.0001	-0.11282 <0.0001	-0.12734 <0.0001	-0.14360 <0.0001	-0.07482 <0.0001	-0.07624 <0.0001	-0.07045 <0.0001
[D6] How satisfied are you with the form of your anticoagulant treatment (oral pill / injection)?						
-0.11068 <0.0001	-0.14048 <0.0001	-0.14555 <0.0001	-0.14001 <0.0001	-0.09524 <0.0001	-0.10708 <0.0001	-0.06141 <0.0001
[D7] Overall, how satisfied are you with your anticoagulant treatment?						
-0.11068 <0.0001	-0.15982 <0.0001	-0.12879 <0.0001	-0.15225 <0.0001	-0.11041 <0.0001	-0.11477 <0.0001	-0.05738 0.0001

Spearman's r_s is provided in the upper, the corresponding P-value in the lower row.

Supplementary Table 9. Unadjusted logistic regression analyses for EHRA score (Categories 3/4 versus 1/2) and EHRA symptom dimensions separately in relation to interventions to restore sinus rhythm at one year

Variable	Odds ratio EHRA 3/4 versus 1/2	95% Confidence interval		P Value	P Value unadjusted logistic regression across all 4 categories
Cardioversion, N=701					
Palpitations	1.75	1.46	2.10	<0.0001	<0.0001
Fatigue	1.19	1.01	1.40	0.04	0.02
Dizziness	1.17	0.92	1.47	0.20	0.08
Dyspnea	1.07	0.90	1.27	0.45	0.74
Chest pain	1.45	1.06	1.98	0.02	0.13
Anxiety	0.91	0.74	1.12	0.36	0.24
EHRA score	1.32	1.12	1.55	0.0008	0.009
Catheter-based ablation, N=226					
Palpitations	2.76	2.09	3.65	<0.0001	<0.0001
Fatigue	1.47	1.12	1.92	0.005	0.04
Dizziness	1.08	0.72	1.61	0.73	0.68
Dyspnea	0.90	0.67	1.21	0.48	0.41
Chest pain	1.42	0.84	2.40	0.19	0.57
Anxiety	1.30	0.94	1.80	0.11	0.46
EHRA score	1.76	1.33	2.34	<0.0001	0.0003
Sinus rhythm at one year, N=2022					
Palpitations	1.91	1.67	2.18	<0.0001	<0.0001
Fatigue	0.84	0.75	0.94	0.003	0.002
Dizziness	0.75	0.63	0.90	0.002	0.002
Dyspnea	0.69	0.61	0.78	<0.0001	<0.0001
Chest pain	1.22	0.96	1.55	0.11	0.06
Anxiety	1.17	1.02	1.34	0.03	0.0009
EHRA score	0.99	0.89	1.10	0.84	0.01
Adequate heart rate control, N=2734					
Palpitations	0.81	0.70	0.95	0.01	0.01
Fatigue	0.91	0.80	1.03	0.14	0.21
Dizziness	0.99	0.81	1.20	0.90	0.28
Dyspnea	0.93	0.81	1.06	0.28	0.70
Chest pain	0.81	0.61	1.07	0.14	0.25
Anxiety	0.97	0.83	1.14	0.72	0.10
EHRA score	0.85	0.75	0.96	0.008	0.02

Odds ratios are provided for EHRA score category 3/4 versus 1/2 in an unadjusted model.

Supplementary Table 10. Unadjusted logistic regression analyses for EHRA score (Categories 3/4 versus 1/2) and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 3/4 versus 1/2	95% Confidence interval		P Value	P Value unadjusted logistic regression across all 4 categories
Stroke/TIA/arterial thromboembolic events, N=136					
Palpitations	1.04	0.67	1.60	0.87	0.12
Fatigue	1.35	0.95	1.91	0.09	0.40
Dizziness	1.52	0.97	2.40	0.07	0.0002
Dyspnea	1.51	1.07	2.14	0.02	0.08
Chest pain	2.13	1.21	3.75	0.009	<0.0001
Anxiety	0.73	0.45	1.19	0.21	0.09
EHRA score	1.39	0.98	1.97	0.07	0.06
Coronary events, N=140					
Palpitations	0.81	0.51	1.29	0.38	0.52
Fatigue	1.33	0.94	1.87	0.11	0.32
Dizziness	1.24	0.77	2.00	0.38	0.51
Dyspnea	1.68	1.19	2.36	0.0029	<0.0001
Chest pain	3.15	1.94	5.13	<0.0001	<0.0001
Anxiety	1.19	0.79	1.80	0.42	0.72
EHRA score	1.65	1.16	2.35	0.005	0.009
Heart failure, N=155					
Palpitations	1.11	0.74	1.66	0.61	0.68
Fatigue	1.96	1.42	2.71	<0.0001	0.0002
Dizziness	1.53	0.97	2.41	0.07	0.08
Dyspnea	2.53	1.82	3.51	<0.0001	<0.0001
Chest pain	1.10	0.51	2.39	0.81	0.40
Anxiety	1.73	1.20	2.50	0.004	0.02
EHRA score	1.72	1.24	2.39	0.001	0.001
Major bleeding, N=168					
Palpitations	0.80	0.52	1.22	0.30	0.63
Fatigue	1.42	1.04	1.95	0.03	0.05
Dizziness	1.18	0.75	1.85	0.47	0.73
Dyspnea	1.20	0.87	1.66	0.26	0.09
Chest pain	1.03	0.52	2.03	0.94	0.67
Anxiety	1.24	0.85	1.81	0.26	0.33
EHRA score	1.26	0.92	1.72	0.15	0.11

Odds ratios are provided for EHRA score category 3/4 versus 1/2 in an unadjusted model. Coronary events comprised acute coronary syndrome and coronary revascularization. The model for incident heart failure does not include adjustment for heart failure.

Supplementary Table 11. Multivariable-adjusted logistic regression analyses for EHRA score (category 2 versus 1) and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 2 versus 1	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories
<i>Stroke/TIA/arterial thromboembolic events, N=136</i>					
Palpitations	1.41	0.93	2.12	0.11	0.29
Fatigue	0.89	0.55	1.44	0.63	0.92
Dizziness	1.77	1.19	2.62	0.005	0.002
Dyspnea	0.85	0.53	1.37	0.51	0.59
Chest pain	1.94	1.32	2.84	0.0008	0.002
Anxiety	1.29	0.88	1.91	0.20	0.08
EHRA score	0.43	0.23	0.81	0.009	0.05
<i>Coronary events, N=140</i>					
Palpitations	1.43	0.96	2.14	0.08	0.21
Fatigue	0.81	0.51	1.30	0.38	0.73
Dizziness	1.22	0.82	1.80	0.32	0.72
Dyspnea	1.10	0.68	1.78	0.69	0.02
Chest pain	1.51	1.01	2.24	0.04	<0.0001
Anxiety	1.14	0.76	1.72	0.53	0.33
EHRA score	0.84	0.40	1.77	0.64	0.12
<i>Heart failure, N=155</i>					
Palpitations	1.06	0.72	1.55	0.77	0.42
Fatigue	0.70	0.45	1.10	0.12	0.0006
Dizziness	1.28	0.88	1.86	0.20	0.19
Dyspnea	1.26	0.81	1.95	0.30	<0.0001
Chest pain	1.10	0.73	1.65	0.65	0.42
Anxiety	1.02	0.68	1.53	0.94	0.032
EHRA score	0.54	0.30	0.99	0.05	0.005
<i>Major bleeding, N=168</i>					
Palpitations	1.04	0.72	1.49	0.85	0.78
Fatigue	1.42	0.88	2.29	0.15	0.28
Dizziness	1.13	0.78	1.62	0.53	0.90
Dyspnea	1.10	0.72	1.68	0.66	0.61
Chest pain	1.14	0.78	1.66	0.50	0.74
Anxiety	1.08	0.74	1.59	0.69	0.46
EHRA score	1.49	0.70	3.18	0.30	0.60

Odds ratios are provided for EHRA score category 2 versus 1 in a multivariable-adjusted model. Covariates are age, sex, country, body mass index, systolic blood pressure, hypertension, diabetes mellitus, smoking, heart failure, history of myocardial infarction. Coronary events comprised acute coronary syndrome and coronary revascularization. The model for incident heart failure does not include adjustment for heart failure.

Supplementary Table 12. Multivariable-adjusted logistic regression analyses for EHRA score (category 3 versus 1) and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 3 versus 1	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories
Stroke/TIA/arterial thromboembolic events, N=136					
Palpitations	1.29	0.73	2.29	0.38	0.29
Fatigue	1.01	0.60	1.69	0.97	0.92
Dizziness	1.28	0.68	2.41	0.45	0.002
Dyspnea	1.06	0.64	1.77	0.81	0.59
Chest pain	2.37	1.24	4.55	0.01	0.002
Anxiety	0.61	0.32	1.17	0.14	0.08
EHRA score	0.58	0.31	1.07	0.08	0.05
Coronary events, N=140					
Palpitations	1.02	0.54	1.93	0.95	0.21
Fatigue	0.91	0.55	1.51	0.71	0.73
Dizziness	1.30	0.73	2.32	0.37	0.72
Dyspnea	1.01	0.57	1.78	0.97	0.02
Chest pain	1.93	0.96	3.88	0.06	<0.0001
Anxiety	1.35	0.78	2.34	0.28	0.33
EHRA score	1.10	0.52	2.32	0.80	0.12
Heart failure, N=155					
Palpitations	0.95	0.53	1.71	0.88	0.42
Fatigue	1.29	0.81	2.06	0.28	0.0006
Dizziness	1.52	0.85	2.72	0.15	0.19
Dyspnea	2.69	1.70	4.26	<0.0001	<0.0001
Chest pain	0.92	0.33	2.55	0.87	0.42
Anxiety	1.54	0.94	2.52	0.09	0.03
EHRA score	0.92	0.51	1.65	0.77	0.005
Major bleeding, N=168					
Palpitations	0.78	0.43	1.41	0.41	0.78
Fatigue	1.54	0.92	2.57	0.10	0.28
Dizziness	1.11	0.64	1.95	0.71	0.90
Dyspnea	0.85	0.50	1.43	0.53	0.61
Chest pain	0.80	0.32	2.00	0.63	0.74
Anxiety	1.43	0.88	2.3	0.15	0.46
EHRA score	1.40	0.65	3.01	0.39	0.60

Odds ratios are provided for EHRA score category 3 versus 1 in a multivariable-adjusted model. Covariates are age, sex, country, body mass index, systolic blood pressure, hypertension, diabetes mellitus, smoking, heart failure, history of myocardial infarction. Coronary events comprised acute coronary syndrome and coronary revascularization. The model for incident heart failure does not include adjustment for heart failure.

Supplementary Table 13. Multivariable-adjusted logistic regression analyses for EHRA score (category 4 versus 1) and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 4 versus 1	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories
Stroke/TIA/arterial thromboembolic events, N=136					
Palpitations	0.77	0.29	2.01	0.59	0.29
Fatigue	0.89	0.47	1.67	0.71	0.92
Dizziness	3.42	1.62	7.20	0.001	0.002
Dyspnoea	0.73	0.38	1.40	0.35	0.59
Chest pain	1.18	0.16	8.87	0.87	0.002
Anxiety	0.65	0.25	1.66	0.37	0.08
EHRA score	0.46	0.24	0.89	0.02	0.05
Coronary events, N=140					
Palpitations	1.75	0.79	3.86	0.17	0.21
Fatigue	1.08	0.60	1.94	0.80	0.73
Dizziness	1.12	0.39	3.17	0.84	0.72
Dyspnoea	2.09	1.19	3.66	0.01	0.02
Chest pain	8.46	3.48	20.56	<0.0001	<0.0001
Anxiety	1.85	0.91	3.75	0.09	0.33
EHRA score	1.50	0.70	3.20	0.29	0.12
Heart failure, N=155					
Palpitations	1.71	0.88	3.32	0.11	0.42
Fatigue	2.10	1.22	3.63	0.008	0.0006
Dizziness	1.98	0.88	4.47	0.10	0.19
Dyspnoea	2.50	1.34	4.67	0.004	<0.0001
Chest pain	2.76	0.81	9.42	0.10	0.42
Anxiety	2.24	1.21	4.16	0.01	0.032
EHRA score	1.25	0.67	2.32	0.49	0.005
Major bleeding, N=168					
Palpitations	1.24	0.58	2.66	0.59	0.78
Fatigue	1.77	0.98	3.20	0.06	0.28
Dizziness	1.22	0.48	3.10	0.67	0.90
Dyspnoea	1.23	0.70	2.16	0.48	0.61
Chest pain	1.78	0.42	7.56	0.44	0.74
Anxiety	0.83	0.35	1.95	0.66	0.46
EHRA score	1.74	0.79	3.83	0.17	0.60

Odds ratios are provided for EHRA score category 4 versus 1 in a multivariable-adjusted model. Covariates are age, sex, country, body mass index, systolic blood pressure, hypertension, diabetes mellitus, smoking, heart failure, history of myocardial infarction. Coronary events comprised acute coronary syndrome and

coronary revascularization. The model for incident heart failure does not include adjustment for heart failure.

Supplementary Table 14. Unadjusted logistic regression analyses for EHRA score (category 2 versus 1) and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 2 versus 1	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories
<i>Stroke/TIA/arterial thromboembolic events, N=136</i>					
Palpitations	1.54	1.04	2.29	0.03	0.12
Fatigue	1.01	0.65	1.59	0.96	0.40
Dizziness	1.94	1.34	2.82	0.0005	0.0002
Dyspnoea	1.00	0.64	1.54	0.99	0.08
Chest pain	2.19	1.52	3.16	<0.0001	<0.0001
Anxiety	1.50	1.04	2.17	0.03	0.09
EHRA score	0.52	0.28	0.95	0.03	0.06
<i>Coronary events, N=140</i>					
Palpitations	1.20	0.83	1.73	0.35	0.52
Fatigue	0.92	0.60	1.43	0.72	0.32
Dizziness	1.26	0.87	1.82	0.22	0.51
Dyspnoea	1.32	0.85	2.06	0.22	<0.0001
Chest pain	2.03	1.41	2.94	0.0002	<0.0001
Anxiety	1.48	0.76	2.91	0.73	0.72
EHRA score	0.92	0.44	1.92	0.83	0.009
<i>Heart failure, N=155</i>					
Palpitations	0.98	0.69	1.41	0.92	0.68
Fatigue	0.78	0.51	1.19	0.25	0.0002
Dizziness	1.30	0.91	1.86	0.15	0.08
Dyspnoea	1.37	0.90	2.07	0.14	<0.0001
Chest pain	1.13	0.77	1.66	0.54	0.40
Anxiety	1.05	0.72	1.55	0.79	0.02
EHRA score	0.57	0.32	1.01	0.05	0.001
<i>Major bleeding, N=168</i>					
Palpitations	0.92	0.66	1.29	0.64	0.63
Fatigue	1.44	0.94	2.22	0.10	0.05
Dizziness	1.14	0.81	1.60	0.45	0.73
Dyspnoea	1.23	0.84	1.81	0.28	0.09
Chest pain	1.22	0.86	1.73	0.26	0.67
Anxiety	1.12	0.79	1.60	0.51	0.33
EHRA score	1.62	0.77	3.40	0.21	0.11

Odds ratios are provided for EHRA score category 2 versus 1 in an unadjusted model. Coronary events comprised acute coronary syndrome and coronary revascularization. The model for incident heart failure does not include adjustment for heart failure.

Supplementary Table 15. Unadjusted logistic regression analyses for EHRA score (category 3 versus 1) and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 3 versus 1	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories
<i>Stroke/TIA/arterial Thromboembolic events, N=136</i>					
Palpitations	1.51	0.89	2.58	0.13	0.12
Fatigue	1.39	0.86	2.23	0.18	0.40
Dizziness	1.59	0.88	2.88	0.13	0.0002
Dyspnoea	1.67	1.06	2.62	0.0258	0.08
Chest pain	3.08	1.68	5.64	0.0003	<0.0001
Anxiety	0.84	0.46	1.53	0.56	0.09
EHRA score	0.88	0.49	1.57	0.65	0.06
<i>Coronary events, N=140</i>					
Palpitations	0.80	0.44	1.45	0.46	0.52
Fatigue	1.16	0.73	1.87	0.53	0.32
Dizziness	1.40	0.81	2.43	0.23	0.51
Dyspnoea	1.28	0.76	2.16	0.35	<0.0001
Chest pain	3.04	1.66	5.56	0.0003	<0.0001
Anxiety	1.12	0.67	1.87	0.68	0.72
EHRA score	1.31	0.64	2.68	0.47	0.009
<i>Heart failure, N=155</i>					
Palpitations	0.96	0.57	1.62	0.87	0.68
Fatigue	1.52	0.99	2.35	0.06	0.0002
Dizziness	1.46	0.83	2.56	0.19	0.08
Dyspnoea	2.97	1.93	4.57	<0.0001	<0.0001
Chest pain	0.80	0.29	2.19	0.66	0.40
Anxiety	1.60	1.01	2.53	0.05	0.02
EHRA score	0.96	0.55	1.69	0.90	0.001
<i>Major bleeding, N=168</i>					
Palpitations	0.70	0.41	1.19	0.19	0.63
Fatigue	1.71	1.07	2.71	0.02	0.05
Dizziness	1.18	0.70	2.00	0.54	0.73
Dyspnoea	1.09	0.68	1.72	0.73	0.09
Chest pain	1.00	0.46	2.17	0.99	0.67
Anxiety	1.47	0.95	2.28	0.08	0.33
EHRA score	1.66	0.79	3.52	0.18	0.11

Odds ratios are provided for EHRA score category 3 versus 1 in an unadjusted model. Coronary events comprised acute coronary syndrome and coronary revascularization. The model for incident heart failure does not include adjustment for heart failure.

Supplementary Table 16. Unadjusted logistic regression analyses for EHRA score (category 4 versus 1) and EHRA symptom dimensions separately in relation to cardiovascular outcomes at one year

Variable	Odds ratio EHRA 4 versus 1	95% Confidence interval		P Value	P Value adjusted logistic regression across all 4 categories
Stroke/TIA/arterial thromboembolic events, N=136					
Palpitations	0.90	0.35	2.29	0.82	0.12
Fatigue	1.30	0.72	2.36	0.39	0.40
Dizziness	3.65	1.77	7.54	0.0004	0.0002
Dyspnoea	1.23	0.68	2.21	0.49	0.08
Chest pain	1.20	0.16	8.83	0.86	<0.0001
Anxiety	0.97	0.42	2.26	0.94	0.09
EHRA score	0.77	0.41	1.45	0.42	0.06
Coronary events, N=140					
Palpitations	1.16	0.54	2.46	0.71	0.52
Fatigue	1.48	0.85	2.56	0.16	0.32
Dizziness	1.21	0.44	3.35	0.72	0.51
Dyspnoea	3.17	1.96	5.15	<0.0001	<0.0001
Chest pain	9.42	4.11	21.59	<0.0001	<0.0001
Anxiety	1.48	0.76	2.91	0.25	0.72
EHRA score	1.92	0.93	3.95	0.08	0.009
Heart failure, N=155					
Palpitations	1.44	0.76	2.72	0.26	0.68
Fatigue	2.17	1.31	3.61	0.003	0.0002
Dizziness	2.36	1.11	5.01	0.03	0.08
Dyspnoea	2.89	1.66	5.04	0.0002	<0.0001
Chest pain	2.59	0.78	8.59	0.12	0.40
Anxiety	2.17	1.20	3.91	0.01	0.03
EHRA score	1.36	0.77	2.42	0.29	0.001
Major bleeding, N=168					
Palpitations	0.94	0.46	1.90	0.86	0.63
Fatigue	2.00	1.17	3.42	0.01	0.05
Dizziness	1.45	0.63	3.37	0.38	0.73
Dyspnoea	1.82	1.13	2.93	0.01	0.09
Chest pain	1.52	0.37	6.32	0.57	0.67
Anxiety	0.88	0.40	1.92	0.74	0.33
EHRA score	2.26	1.06	4.82	0.04	0.11

Odds ratios are provided for EHRA score category 4 versus 1 in an unadjusted model. Coronary events comprised acute coronary syndrome and coronary revascularization. The model for incident heart failure does not include adjustment for heart failure

Reference List

1. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, Gupta D. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace* 2014;16:965-972.
2. Rabin R, de CF. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337-343.
3. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Dan GA, Kalarus Z, Tavazzi L, Maggioni AP, Lip GY. 'Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) General Pilot Registry. *Europace* 2016;18:648-657.
4. Vermond RA, Crijns HJ, Tijssen JG, Alings AM, van den Berg MP, Hillege HL, van Veldhuisen DJ, Van Gelder IC, Rienstra M. Symptom severity is associated with cardiovascular outcome in patients with permanent atrial fibrillation in the RACE II study. *Europace* 2014;16:1417-1425.
5. Schnabel RB, Aspelund T, Li G, et al. Validation of an atrial fibrillation risk algorithm in whites and african americans. *Arch Intern Med* 2010;170:1909-1917.
6. Schnabel RB, Rienstra M, Sullivan LM, et al. Risk assessment for incident heart failure in individuals with atrial fibrillation. *Eur J Heart Fail* 2013;15:843-849.
7. Sandhu RK, Ezekowitz J, Andersson U, Alexander JH, Granger CB, Halvorsen S, Hanna M, Hijazi Z, Jansky P, Lopes RD, Wallentin L. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *Eur Heart J* 2016;37:2869-2878.
8. Alonso A, Krijthe BP, Aspelund T, et al. Simple Risk Model Predicts Incidence of Atrial Fibrillation in a Racially and Geographically Diverse Population: the CHARGE-AF Consortium. *J Am Heart Assoc* 2013;2:e000102.
9. Freeman JV, Simon DN, Go AS, et al. Association Between Atrial Fibrillation Symptoms, Quality of Life, and Patient Outcomes: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes* 2015;8:393-402.
10. Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. *JAMA* 2008;300:2489-2496.
11. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol* 2014;64:281-289.

12. Sandhu RK, Hohnloser SH, Pfeffer MA, Yuan F, Hart RG, Yusuf S, Connolly SJ, McAlister FA, Healey JS. Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. *Stroke* 2015;46:667-672.
13. Boriani G, Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Ricci R, Biffi M, De ST, Corbucci G, Lip GY. Improving Stroke Risk Stratification Using the CHADS2 and CHA2DS2-VASc Risk Scores in Patients With Paroxysmal Atrial Fibrillation by Continuous Arrhythmia Burden Monitoring. *Stroke* 2011;42:1768-1770.
14. Prins MH, Guillemin I, Gilet H, Gabriel S, Essers B, Raskob G, Kahn SR. Scoring and psychometric validation of the Perception of Anticoagulant Treatment Questionnaire (PACT-Q). *Health Qual Life Outcomes* 2009;7:30.