

SUPPLEMENTARY MATERIAL

Persistence with Anticoagulation for Atrial fibrillation. Report from the GLORIA-AF Phase III 1-year follow-up

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Table S1: Clinical characteristics of all eligible patients treated (or on) NOAC or VKA

	NOAC	VKA	Standardized difference
Patients, n (%)	12,492 (100.0)	4,774 (100.0)	
Age, mean (SD), yrs	71.0 (10.2)	71.2 (10.3)	-0.014
Age $\geq$ 75 yrs, n (%)	4922 (39.4)	1928 (40.4)	-0.020
Body mass index, mean (SD), kg/m ²	29.0 (6.6)	28.6 (6.1)	0.061
Gender male, n (%)	6849 (54.8)	2648 (55.5)	-0.013
Type of atrial fibrillation, n (%)			
Paroxysmal	7049 (56.4)	2149 (45.0)	0.230
Persistent	4290 (34.3)	1949 (40.8)	-0.134
Permanent	1153 (9.2)	676 (14.2)	-0.154
Categorization of atrial fibrillation, n (%)			
Symptomatic	3748 (30.0)	1602 (33.6)	-0.076
Minimally symptomatic	4139 (33.1)	1615 (33.8)	-0.015
Asymptomatic	4605 (36.9)	1557 (32.6)	0.089
Medical history, n (%)			
Previous stroke	1328 (10.6)	457 (9.6)	0.035
Unknown	6 (0.0)	1 (0.0)	0.015
Myocardial infarction	1048 (8.4)	542 (11.4)	-0.100
Unknown	9 (0.1)	3 (0.1)	0.004

Coronary artery disease	2110 (16.9)	910 (19.1)	-0.057
Unknown	280 (2.2)	164 (3.4)	-0.072
Congestive heart failure	2459 (19.7)	1365 (28.6)	-0.209
Unknown	94 (0.8)	45 (0.9)	-0.021
Ejection fraction $\leq 40\%$	1025 (8.2)	517 (10.8)	0.090
Unknown	290 (11.8)	204 (14.9)	-0.093
Diabetes mellitus	2905 (23.3)	1213 (25.4)	-0.050
Unknown	0 (0.0)	0 (0.0)	
Prior bleeding	609 (4.9)	248 (5.2)	-0.015
Unknown	282 (2.3)	65 (1.4)	0.067
Renal impairment	105 (0.8)	165 (3.5)	-0.181
Unknown	124 (1.0)	93 (1.9)	-0.079
Hypertension, n (%)			
Uncontrolled hypertension	1078 (8.6)	463 (9.7)	-0.037
Controlled hypertension	8267 (66.2)	3060 (64.1)	0.044
Unknown	170 (1.8)	79 (2.2)	-0.029
Creatinine clearance (measured), mean (SD), ml/min	83.0 (72.4)	76.9 (35.4)	0.109
CHA ₂ DS ₂ -VASc score, median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	-0.069
HAS-BLED risk score, median (Q1, Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	-0.014
Cardioversion, n (%)	2467 (19.7)	677 (14.2)	0.149

Unknown	134 (1.1)	38 (0.8)	0.029
Atrial fibrillation ablation n, (%)	248 (2.0)	81 (1.7)	0.022
Unknown	106 (0.8)	40 (0.8)	0.001
Medications, n (%)			
Antiplatelet drug	2172 (17.4)	897 (18.8)	-0.036
Medication usage predisposing to bleeding	2507 (20.1)	978 (20.5)	-0.010
Number of concomitant medications, mean (SD)	3.48 (1.80)	3.53 (1.84)	-0.027
Physician specialty, n (%)			
Cardiologist	10655 (85.3)	3907 (81.8)	0.093
General practitioner / Primary care physician /Geriatrician	580 (4.6)	218 (4.6)	0.004
Internist	407 (3.3)	316 (6.6)	-0.156
Neurologist	391 (3.1)	69 (1.4)	0.113
Angiologist	2 (0.0)	1 (0.0)	-0.004
Other	408 (3.3)	254 (5.3)	-0.102
Missing	49 (0.4)	9 (0.2)	0.038
Medical treatment reimbursed by:			
Private insurance	2034 (16.3)	482 (10.1)	0.184
Statutory / federal insurance	8972 (71.8)	3765 (78.9)	-0.164
Self-pay / no coverage	618 (4.9)	220 (4.6)	0.016

Unknown	868 (6.9)	307 (6.4)	0.021
Region (N [%])			
Asia	1794 (14.4)	787 (16.5)	-0.059
Europe	6354 (50.9)	2721 (57.0)	-0.123
North America	3483 (27.9)	725 (15.2)	0.313
Latin America	861 (6.9)	541 (11.3)	-0.155
Race (N [%])			
Amer.Indian/Amer.Native/Alaska Native	78 (0.6)	29 (0.6)	0.002
Black/African American	229 (1.8)	81 (1.7)	0.010
White	9205 (73.7)	3574 (74.9)	-0.027
Asian	1731 (13.9)	754 (15.8)	-0.055
Native Hawaiian/Other Pacific Islander	1 (0.0)	0 (0.0)	
Arab/Middle East	16 (0.1)	7 (0.1)	-0.005
African	6 (0.0)	2 (0.0)	0.002
Missing	847 (6.8)	195 (4.1)	0.119
Smoking status (N [%])			
Non-smoker	7065 (56.6)	2722 (57.0)	-0.009
Current smoker	1090 (8.7)	437 (9.2)	-0.015
Past smoker	3932 (31.5)	1477 (30.9)	0.012
Unknown	405 (3.2)	138 (2.9)	0.020

Alcohol abuse (N [%])			
No (<8U/wk)	10813 (86.6)	4176 (87.5)	-0.027
Yes (≥8U/wk)	937 (7.5)	303 (6.3)	0.046
Unknown	742 (5.9)	295 (6.2)	-0.010
Alcohol use (N [%])			
Never	5069 (40.6)	2149 (45.0)	-0.090
<1 drink/week	3078 (24.6)	1150 (24.1)	0.013
1-7 drinks/week	2666 (21.3)	877 (18.4)	0.075
≥8 drinks/week	937 (7.5)	303 (6.3)	0.046
Unknown	742 (5.9)	295 (6.2)	-0.010
Type of site (N [%])			
General practice/primary care	678 (5.4)	254 (5.3)	0.005
Specialist office	4060 (32.5)	1083 (22.7)	0.221
Community hospital	4111 (32.9)	1239 (26.0)	0.153
University hospital	3355 (26.9)	1922 (40.3)	-0.287
Out-patient health care center	98 (0.8)	162 (3.4)	-0.183
Anticoagulation clinics	45 (0.4)	57 (1.2)	-0.003
Other	145 (1.2)	57 (1.2)	-0.003

Transient ischaemic attack (N [%])			
Yes	634 (5.1)	196 (4.1)	0.046
Unknown	37 (0.3)	19 (0.4)	-0.017
Pulmonary embolism (N [%])			
Yes	84 (0.7)	25 (0.5)	0.019
Unknown	164 (1.3)	34 (0.7)	0.060
Deep vein thrombosis (N [%])			
Yes	157 (1.3)	65 (1.4)	-0.009
Unknown	190 (1.5)	38 (0.8)	0.068
Angina pectoris (N [%])			
Yes	971 (7.8)	440 (9.2)	-0.052
Unknown	122 (1.0)	48 (1.0)	-0.003
Rheumatic Heart Disease (N [%])			
Yes	45 (0.4)	31 (0.6)	-0.041
Unknown	154 (1.2)	31 (0.6)	0.061
Additional antiplateletes (N [%])			
	1691 (13.5)	726 (15.2)	-0.048
Peripheral artery disease (N [%])			
Yes	360 (2.9)	153 (3.2)	-0.019
Unknown	80 (0.6)	58 (1.2)	-0.060
Cancer (N [%])			
Yes	1320 (10.6)	471 (9.9)	0.023

Unknown	191 (1.5)	69 (1.4)	0.007
Hyperlipidemia (N [%])			
Yes	5233 (41.9)	1831 (38.4)	0.072
Unknown	286 (2.3)	141 (3.0)	-0.042
Hepatic disease (N [%])			
Yes	166 (1.3)	65 (1.4)	-0.003
Unknown	183 (1.5)	57 (1.2)	0.024
Non-central nervous system arterial embolism (N [%])			
Yes	48 (0.4)	21 (0.4)	-0.009
Unknown	42 (0.3)	11 (0.2)	0.019
Presence of complex aortic plaque (N [%])			
Yes	112 (0.9)	56 (1.2)	-0.027
Unknown	205 (1.6)	130 (2.7)	-0.074

CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischaemic attack, vascular disease, age 65 to 74 years, sex category, HAS-BLED, hypertension, abnormal renal/ liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly, drugs or alcohol concomitantly, NOAC, non-vitamin K antagonist oral anticoagulants, SD, standard deviation, VKA, vitamin K antagonists. Medication usage predisposing to bleeding is defined as antiplatelet therapy or inhibitors of cyclooxygenase 2 or other non-steroidal anti-inflammatory drugs (NSAIDs).

Table S2: Baseline characteristics of all eligible patients on once daily regimen (rivaroxaban or edoxaban) or twice daily regimen (dabigatran or apixaban)

	Once daily	Twice daily	Standardized difference
Patients, n (%)	4277 (100.0)	8215 (100.0)	
Age, mean (SD), yrs	70.5 (10.2)	71.3 (10.2)	-0.077
Age $\geq$ 75 yrs, n (%)	1605 (37.5)	3317 (40.4)	-0.059
Body mass index, mean (SD), kg/m ²	29.4 (6.5)	28.8 (6.6)	0.082
Gender, male, n (%)	2399 (56.1)	4450 (54.2)	0.039
Type of atrial fibrillation, n (%)			
Paroxysmal	2439 (57.0)	4610 (56.1)	0.018
Persistent	1486 (34.7)	2804 (34.1)	0.013
Permanent	352 (8.2)	801 (9.8)	-0.053
Categorization of atrial fibrillation, n (%)			
Symptomatic	1312 (30.7)	2436 (29.7)	0.022
Minimally symptomatic	1410 (33.0)	2729 (33.2)	-0.005
Asymptomatic	1555 (36.4)	3050 (37.1)	-0.016
Medical history, n (%)			
Previous stroke	326 (7.6)	1002 (12.2)	-0.154
Unknown	2 (0.0)	4 (0.0)	-0.001
Myocardial infarction	366 (8.6)	682 (8.3)	0.009
Unknown	3 (0.1)	6 (0.1)	-0.001

Coronary artery disease	745 (17.4)	1365 (16.6)	0.021
Unknown	132 (3.1)	148 (1.8)	0.083
Congestive heart failure	846 (19.8)	1613 (19.6)	-0.004
Unknown	37 (0.9)	57 (0.7)	0.019
Ejection fraction $\leq 40\%$	351 (8.2)	674 (8.2)	0.000
Unknown	85 (10.0)	205 (12.7)	-0.084
Diabetes mellitus	1052 (24.6)	1853 (22.6)	0.048
Unknown	0 (0.0)	0 (0.0)	
Prior bleeding	219 (5.1)	390 (4.7)	0.017
Unknown	124 (2.9)	158 (1.9)	0.064
Renal impairment	29 (0.7)	76 (0.9)	-0.028
Unknown	56 (1.3)	68 (0.8)	0.047
Hypertension, n (%)			
Uncontrolled hypertension	311 (7.3)	767 (9.3)	-0.075
Controlled hypertension	2872 (67.1)	5395 (65.7)	-0.031
Unknown	53 (1.6)	117 (1.9)	-0.017
Creatinine clearance (measured), mean (SD), ml/min	85.0 (40.1)	82.0 (84.8)	0.046
CHA ₂ DS ₂ -VASc score, median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	-0.116
HAS-BLED risk score, median (Q1, Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	-0.075
Cardioversion, n (%)	967(22.6)	1500 (18.3)	0.108

Unknown	43 (1.0)	91 (1.1)	-0.010
Atrial fibrillation ablation, n (%)	59 (1.4)	189 (2.3)	-0.069
Unknown	34 (0.8)	72 (0.9)	-0.009
Medications, n (%)			
Antiplatelet drug	777 (18.2)	1395 (17.0)	0.312
Medication usage predisposing to bleeding	906 (21.2)	1601 (19.5)	0.042
Number of concomitant medications, mean (SD)	3.52 (1.84)	3.47 (1.78)	0.029
Physician specialty, n (%)			
Cardiologist	3709 (86.7)	6946 (84.6)	0.062
General practitioner / Primary care physician /Geriatrician	203 (4.7)	377 (4.6)	0.007
Internist	149 (3.5)	258 (3.1)	0.019
Neurologist	64 (1.5)	327 (4.0)	-0.153
Angiologist	1 (0.0)	1 (0.0)	0.008
Other	142 (3.3)	266 (3.2)	0.005
Missing	9 (0.2)	40 (0.5)	-0.047
Region (N [%])			
Asia	503 (11.8)	1291 (15.7)	-0.115
Europe	2156 (50.4)	4198 (51.1)	-0.014
North America	1336 (31.2)	2147 (26.1)	0.113
Latin America	282 (6.6)	579 (7.0)	-0.018

Race (N [%])

Amer.Indian/Amer.Native/Alaska Native	31 (0.7)	47 (0.6)	0.019
Black/African American	69 (1.6)	160 (1.9)	-0.025
White	3277 (76.6)	5928 (72.2)	0.102
Asian	501 (11.7)	1230 (15.0)	-0.096
Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.0)	
Arab/Middle East	7 (0.2)	9 (0.1)	-0.015
African	2 (0.0)	4 (0.0)	-0.001
Missing	254 (5.9)	593 (7.2)	-0.052

Smoking status (N [%])

Non-smoker	2349 (54.9)	4716 (57.4)	-0.050
Current smoker	343 (8.0)	747 (9.1)	-0.038
Past smoker	1440 (33.7)	2492 (30.3)	0.071
Unknown	145 (3.4)	260 (3.2)	0.013

Alcohol abuse (N [%])

No (<8U/wk)	3674 (85.9)	7139 (86.9)	-0.029
Yes (>=8U/wk)	345 (8.1)	592 (7.2)	0.032
Unknown	258 (6.0)	484 (5.9)	0.006

Alcohol use (N [%])

Never	1620 (37.9)	3449 (42.0)	-0.084
<1 drink/week	1101 (25.7)	1977 (24.1)	0.039
1-7 drinks/week	953 (22.3)	1713 (20.9)	0.035

>=8 drinks/week	345 (8.1)	592 (7.2)	0.032
Unknown	258 (6.0)	484 (5.9)	0.006
Type of site (N [%])			
General practice /primary care	256 (6.0)	422 (5.1)	0.037
Specialist office	1536 (35.9)	2524 (30.7)	0.110
Community hospital	1337 (31.3)	2774 (33.8)	-0.054
University hospital	1034 (24.2)	2321 (28.3)	-0.093
Out-patient health care center	28 (0.7)	70 (0.9)	-0.023
Anticoagulation clinics	19 (0.4)	26 (0.3)	0.021
Transient ischaemic attack (N [%])			
Yes	189 (4.4)	445 (5.4)	-0.046
Unknown	12 (0.3)	25 (0.3)	-0.004
Pulmonary embolism (N [%])			
Yes	40 (0.9)	44 (0.5)	0.047
Unknown	71 (1.7)	93 (1.1)	0.045
Deep vein thrombosis (N [%])			
Yes	62 (1.4)	95 (1.2)	0.026
Unknown	81 (1.9)	109 (1.3)	0.045
Angina pectoris (N [%])			
Yes	298 (7.0)	673 (8.2)	-0.046
Unknown	61 (1.4)	61 (0.7)	0.066
Rheumatic Heart Disease (N [%])			

Yes	11 (0.3)	34 (0.4)	-0.027
Unknown	81 (1.9)	73 (0.9)	0.086
Additional antiplatelets (N [%])			
	608 (14.2)	1083 (13.2)	0.300
Peripheral artery disease (N [%])			
Yes	118 (2.8)	242 (2.9)	-0.011
Unknown	30 (0.7)	50 (0.6)	0.012
Cancer (N [%])			
Yes	441 (10.3)	879 (10.7)	-0.013
Unknown	90 (2.1)	101 (1.2)	0.068
Hyperlipidemia (N [%])			
Yes	1815 (42.4)	3418 (41.6)	0.017
Unknown	116 (2.7)	170 (2.1)	0.042
Hepatic disease (N [%])			
Yes	65 (1.5)	101 (1.2)	0.025
Unknown	78 (1.8)	105 (1.3)	0.044
Non-central nervous system arterial embolism (N [%])			
Yes	17 (0.4)	31 (0.4)	0.003
Presence of complex aortic plaque (N [%])			
Yes	32 (0.7)	80 (1.0)	-0.024
Proton Pump inhibitors (N [%])			

Yes	1073 (25.1)	2113 (25.7)	-0.015
Chronic gastrointestinal diseases (N [%])			
Yes	639 (14.9)	1094 (13.3)	0.047
Unknown	79 (1.8)	117 (1.4)	0.033
Vascular disease (N [%])			
Yes	479 (11.2)	938 (11.4)	-0.007
Dementia (N [%])			
Yes	25 (0.6)	54 (0.7)	-.009
Missing	81 (1.9)	96 (1.2)	0.059

CHA₂DS₂-VASc, congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, stroke/
transient ischaemic attack, vascular disease, age 65 to 74 years, sex category, HAS-BLED,
hypertension, abnormal renal/ liver function, stroke, bleeding history or predisposition, labile
International Normalised Ratio, elderly, drugs or alcohol concomitantly, NOAC, non-vitamin
K antagonist oral anticoagulants, SD, standard deviation, VKA, vitamin K antagonists.

Medication usage predisposing to bleeding is defined as antiplatelet therapy or inhibitors of
cyclooxygenase 2 or other non-steroidal anti-inflammatory drugs (NSAIDs).

Table S3: Multivariate Cox regression model of 1-year persistence with NOAC or VKA

		95% CI	
Parameter	Hazard ratio	Lower limit	Upper limit
Myocardial infarction (MI) (yes vs. no)	0.81	0.65	1.01
Congestive heart failure (yes vs. no)	0.93	0.85	1.01
Diabetes mellitus (Inclusion criteria) (yes vs. no)	0.95	0.88	1.04
Previous stroke (yes vs. no)	0.96	0.86	1.08
Creatinine clearance (measured) class 1 (<30 vs. ≥80)	1.14	0.84	1.53
Creatinine clearance (measured) class 1 (30-<50 vs. ≥80)	1.03	0.90	1.19
Creatinine clearance (measured) class 1 (50-<80 vs. ≥80)	0.99	0.90	1.08
Type of AF (Persistent vs. paroxysmal)	1.00	0.93	1.08
Prior bleeding (yes vs. no)	1.14	0.98	1.33
Hepatic disease (yes vs. no)	1.08	0.81	1.43
Alcohol use (1-7 drinks/week vs. never)	0.97	0.88	1.07
Alcohol use (≥8 drinks/week vs. never)	0.91	0.79	1.05
Smoking status (Past smoker vs. non-smoker)	1.08	0.99	1.17
Coronary artery disease (CAD) (yes vs. no)	1.01	0.91	1.13
Chronic gastrointestinal diseases (yes vs. no)	0.99	0.89	1.09
Cancer (yes vs. no)	1.08	0.97	1.21

		95% CI	
Parameter	Hazard ratio	Lower limit	Upper limit
Dementia (yes vs. no)	1.07	0.66	1.72
Vascular disease defined as prior myocardial infarction, peripheral artery disease, complex aortic plaque (yes vs. no)	1.17	0.97	1.41
Systolic blood pressure (>160 mmHg vs. ≤160 mmHg)	0.96	0.82	1.11

AF; atrial fibrillation

Table S4: Multivariate Cox regression model of 1-year persistence with NOAC's once daily vs twice daily

Parameter	Hazard ratio	95% CI	
		Lower limit	Upper limit
Diabetes mellitus (inclusion criteria) (yes vs. no)	0.94	0.85	1.05
Prior bleeding (yes vs. no)	1.18	0.98	1.42
Previous stroke (yes vs. no)	0.93	0.8	1.08
Congestive heart failure (yes vs. no)	0.97	0.87	1.08
Creatinine clearance (measured) class 1 (<30 vs. ≥80)	1.06	0.71	1.59
Creatinine clearance (measured) class 1 (30-<50 vs. ≥80)	1.01	0.85	1.20
Creatinine clearance (measured) class 1 (50-<80 vs. ≥80)	0.93	0.83	1.04
Type of AF (persistent vs. paroxysmal)	1.00	0.92	1.10
Type of AF (permanent vs. paroxysmal)	0.92	0.78	1.09
Hepatic disease (yes vs. no)	1.05	0.76	1.47
Alcohol use (<1 drink / week vs. never)	0.91	0.81	1.01
Alcohol use (1-7 drinks/week vs. never)	0.94	0.84	1.05
Alcohol use (≥8 drinks/week vs. never)	0.90	0.76	1.07
Smoking status (Past smoker vs. non-smoker)	1.04	0.94	1.15
Proton Pump inhibitors (yes vs. no)	1.10	0.99	1.22

		95% CI	
Parameter	Hazard ratio	Lower limit	Upper limit
Coronary artery disease (CAD) (yes vs. no)	1.11	0.98	1.27
Chronic gastrointestinal diseases (yes vs. no)	0.91	0.81	1.03
Medical treatment reimbursed by (private insurance vs. statutory/federal insurance)	1.06	0.95	1.20
Body mass index (<18.5 kg/m ² vs ≥ 18.5 kg/m ²)	0.94	0.87	1.02
Number of concomitant medications (≥ median vs. < median)	0.93	0.84	1.03
Cancer (yes vs. no)	1.06	0.93	1.21
Dementia (yes vs. no)	0.90	0.51	1.58
Vascular disease defined as prior myocardial infarction, peripheral artery disease, complex aortic plaque (yes vs. no)	1.11	0.87	1.43
Systolic blood pressure (>160 mmHg vs. ≤160 mmHg)	1.10	0.92	1.31

AF; atrial fibrillation

Table S5: Clinical characteristics of restricted patients treated (or on) NOAC or VKA

	NOAC	VKA	Standardized difference
Patients, n (%)	11945	4478	
Age, mean (SD), yrs	71.1 (10.2)	71.2 (10.3)	-0.013
Age $\geq$ 75 yrs, n (%)	4711 (39.4)	1819 (40.6)	-0.024
Body mass index, mean (SD), kg/m ²	29.0 (6.6)	28.6 (6.1)	0.064
Gender male, n (%)	6473 (54.2)	2446 (54.6)	-0.009
Type of atrial fibrillation, n (%)			
Paroxysmal	6736 (56.4)	2002 (44.7)	0.235
Persistent	4091 (34.2)	1831 (40.9)	-0.137
Permanent	1118 (9.4)	645 (14.4)	-0.156
Categorization of atrial fibrillation, n (%)			
Symptomatic	3550 (29.7)	1484 (33.1)	-0.074
Minimally symptomatic	3986 (33.4)	1540 (34.4)	-0.022
Asymptomatic	4409 (36.9)	1454 (32.5)	0.093
Medical history, n (%)			
Previous stroke	1252 (10.5)	412 (9.2)	0.043
Unknown	6 (0.1)	1 (0.0)	0.015
Myocardial infarction	972 (8.1)	464 (10.4)	-0.77
Unknown	8 (0.1)	1 (0.0)	0.021

Coronary artery disease	1963 (16.4)	792 (17.7)	-0.033
Unknown	253 (2.1)	150 (3.3)	-0.076
Congestive heart failure	2308 (19.3)	1248 (27.9)	-0.202
Unknown	86 (0.7)	27 (0.8)	-0.12
Ejection fraction $\leq 40\%$	964 (41.8)	463 (37.1)	0.096
Unknown	274 (11.9)	190 (15.2)	-0.098
Diabetes mellitus	2762 (23.1)	1109 (24.8)	-0.039
Unknown	0 (0.0)	0 (0.0)	
Prior bleeding	572 (4.8)	220 (4.9)	-0.006
Unknown	255 (2.1)	52 (1.2)	0.077
Renal impairment	19 (0.2)	18 (0.4)	-0.046
Unknown	110 (0.9)	81 (1.8)	-0.077
Hypertension, n (%)			
Uncontrolled hypertension	930 (10.3)	385 (11.5)	-0.039
Controlled hypertension	7984 (88.3)	2904 (86.7)	0.048
Unknown	0 (0.0)	0 (0.0)	
Creatinine clearance (measured), mean (SD), ml/min	83.3 (73.6)	78.2 (34.5)	0.089
CHA ₂ DS ₂ -VASc score, median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	-0.057
HAS-BLED risk score, median (Q1, Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	-0.018
Cardioversion, n (%)	2354 (19.7)	627 (14.0)	0.153

Unknown	122 (1.0)	33 (0.7)	0.031
Atrial fibrillation ablation n, (%)	234 (2.0)	69 (1.5)	0.032
Unknown	96 (0.8)	35 (0.8)	0.002
Medications, n (%)			
Antiplatelet drug	2064 (17.3)	812 (18.1)	-0.022
Medication usage predisposing to bleeding	2383 (19.9)	888 (19.8)	0.003
Number of concomitant medications, mean (SD)	3.5 (1.8)	3.5 (1.8)	-0.015
Physician specialty, n (%)			
Cardiologist	10175 (85.2)	3677 (82.1)	0.083
General practitioner / Primary care physician /Geriatrician	559 (4.7)	199 (4.4)	0.011
Internist	397 (3.3)	297 (6.6)	-0.153
Neurologist	375 (3.1)	60 (1.3)	0.122
Angiologist	2 (0.0)	1 (0.0)	-0.004
Other	389 (3.3)	236 (5.3)	-0.099
Missing	48 (0.4)	8 (0.2)	0.042
Medical treatment reimbursed by:			
Private insurance	1919 (16.1)	439 (9.8)	0.187
Statutory / federal insurance	8619 (72.2)	3546 (79.2)	-0.164
Self-pay / no coverage	819 (6.9)	289 (6.5)	0.016
Unknown	819 (6.9)	289 (6.5)	0.016

Region (N [%])			
Asia	1644 (13.8)	730 (16.3)	-0.071
Europe	6149 (51.5)	2575 (57.5)	-0.121
North America	3345 (28.0)	666 (14.9)	0.324
Latin America	807 (6.8)	507 (11.3)	-0.159
Race (N [%])			
Amer.Indian/Amer.Native/Alaska Native	76 (0.6)	27 (0.6)	0.004
Black/African American	222 (1.9)	70 (1.6)	0.023
White	8862 (74.2)	3379 (75.5)	-0.029
Asian	1587 (13.3)	698 (15.6)	-0.066
Native Hawaiian/Other Pacific Islander	1 (0.0)	0 (0.0)	
Arab/Middle East	16 (0.1)	6 (0.1)	0.000
African	5 (0.0)	1 (0.0)	0.011
Missing	824 (6.9)	176 (3.9)	0.131
Smoking status (N [%])			
Non-smoker	6794 (56.9)	2576 (57.5)	-0.013
Current smoker	1028 (8.6)	405 (9.0)	-0.015
Past smoker	3765 (31.5)	1371 (30.6)	0.019
Unknown	358 (3.0)	126 (2.8)	0.011
Alcohol abuse (N [%])			
No (<8U/wk)	10441 (87.4)	3932 (87.8)	-0.012

Yes (≥ 8 U/wk)	835 (7.0)	279 (6.2)	0.031
Unknown	669 (5.6)	267 (6.0)	-0.016
Alcohol use (N [%])			
Never	4885 (40.9)	2014 (45.0)	-0.083
<1 drink/week	2978 (24.9)	1088 (24.3)	0.015
1-7 drinks/week	2578 (21.6)	830 (18.5)	0.076
≥ 8 drinks/week	835 (7.0)	279 (6.2)	0.031
Unknown	669 (5.6)	267 (6.0)	-0.016
Type of site (N [%])			
General practice/primary care	648 (5.4)	233 (5.2)	0.009
Specialist office	3912 (32.8)	1012 (22.6)	0.228
Community hospital	3939 (33.0)	1162 (25.9)	0.155
University hospital	3166 (26.5)	1809 (40.4)	-0.298
Out-patient health care center	98 (0.8)	155 (3.5)	-0.183
Anticoagulation clinics	41 (0.3)	51 (1.1)	-0.093

Transient ischaemic attack (N [%])	606 (5.1)	185 (4.1)	0.045
Unknown	6 (0.1)	1 (0.0)	0.014
Pulmonary embolism (N [%])	81 (0.7)	24 (0.5)	0.018
Unknown	139 (1.2)	27 (0.6)	0.060
Deep vein thrombosis (N [%])	143 (1.2)	62 (1.4)	-0.017
Unknown	253 (2.1)	150 (3.3)	0.065
Angina pectoris (N [%])	897 (7.5)	391 (8.7)	-0.045
Unknown	102 (0.9)	41 (0.9)	-0.006
Rheumatic heart disease (N [%])	44 (0.4)	29 (0.6)	-0.39
Unknown	126 (1.1)	21 (0.5)	0.067
Additional antiplatelets (N [%])	1602 (13.4)	563 (14.6)	-0.034
Peripheral artery disease (N [%])	328 (2.7)	125 (2.8)	-0.003
Unknown	76 (0.6)	47 (1.0)	-0.045
Cancer (N [%])	1259 (10.5)	435 (9.7)	0.027
Unknown	170 (1.4)	59 (1.3)	0.009
Hyperlipidemia (N [%])	4986 (41.7)	1698 (37.9)	0.008
Unknown	265 (2.2)	129 (2.9)	-0.042
Hepatic disease (N [%])	117 (1.0)	50 (1.1)	-0.014
Unknown	163 (1.4)	49 (1.1)	0.025

Non-central nervous system arterial embolism (N [%])	46 (0.4)	21 (0.5)	-0.013
Unknown	36 (0.3)	9 (0.2)	0.020
Presence of complex aortic plaque (N [%])	101 (0.8)	44 (1.0)	-0.014
Unknown	189 (1.6)	103 (2.3)	-0.052

CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischaemic attack, vascular disease, age 65 to 74 years, sex category, HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly, drugs or alcohol concomitantly, NOAC, non-vitamin K antagonist oral anticoagulants, SD, standard deviation, VKA, vitamin K antagonists.

Medication usage predisposing to bleeding is defined as antiplatelet therapy or inhibitors of cyclooxygenase 2 or other non-steroidal anti-inflammatory drugs (NSAIDs).

Table S6: Baseline characteristics of restricted patients on once daily regimen (rivaroxaban or edoxaban) or twice daily regimen (dabigatran or apixaban)

	Once daily	Twice daily	Standardized difference
Patients, n (%)	4097	7855	
Age, mean (SD), yrs	70.6 (10.2)	71.3 (10.1)	-0.073
Age $\geq$ 75 yrs, n (%)	1545 (37.7)	3164 (40.3)	-0.053
Body mass index, mean (SD), kg/m ²	29.4 (6.5)	28.8 (6.6)	0.088
Gender, male, n (%)	2268 (55.4)	4209 (53.6)	0.036
Type of atrial fibrillation, n (%)			
Paroxysmal	2339 (57.1)	4425 (56.3)	0.015
Persistent	1415 (34.5)	2660 (33.9)	0.014
Permanent	343 (8.4)	770 (9.8)	-0.050
Categorization of atrial fibrillation, n (%)			
Symptomatic	1253 (30.6)	2315 (29.5)	0.024
Minimally symptomatic	1353 (33.0)	2618 (33.3)	-0.007
Asymptomatic	1491 (36.4)	2922 (37.2)	-0.017
Medical history, n (%)			
Previous stroke	305 (7.4)	950 (12.1)	-0.157
Unknown	2 (0.0)	4 (0.1)	-0.001
Myocardial infarction	336 (8.2)	631 (8.0)	0.006
Unknown	2 (0.0)	4 (0.1)	-0.001

Coronary artery disease	696 (17.0)	1283 (16.3)	0.018
Unknown	119 (2.9)	131 (1.7)	0.083
Congestive heart failure	783 (19.1)	1519 (19.3)	-0.006
Ejection fraction $\leq 40\%$	322 (41.1)	632 (41.6)	0.010
Unknown	79 (10.1)	193 (12.7)	-0.082
Diabetes mellitus	968 (23.6)	1729 (22.0)	0.039
Unknown	0 (0.0)	0 (0.0)	
Prior bleeding	203 (5.0)	360 (4.6)	0.017
Unknown	110 (2.7)	144 (1.8)	0.057
Renal impairment	14 (0.3)	19 (0.2)	0.019
Unknown	48 (1.2)	64 (0.8)	0.036
Hypertension, n (%)			
Uncontrolled hypertension	281 (6.9)	646 (8.2)	-0.052
Controlled hypertension	2766 (67.5)	5232 (66.6)	0.019
Unknown	51 (1.6)	109 (1.8)	-0.013
Creatinine clearance (measured), mean (SD), ml/min	84.8 (39.4)	82.1 (36.2)	0.040
CHA ₂ DS ₂ -VASc score, median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	-0.117
HAS-BLED risk score, median (Q1, Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	-0.063
Cardioversion, n (%)	926 (22.6)	1427 (18.2)	0.110
Unknown	40 (0.1)	86 (1.1)	-0.012

Atrial fibrillation ablation, n (%)	57 (1.4)	170 (2.2)	-0.059
Unknown	32 (0.8)	68 (0.9)	-0.009
Medications, n (%)			
Antiplatelet drug	738 (18.0)	1303 (16.6)	0.038
Medication usage predisposing to bleeding	859 (21.0)	1495 (19.0)	0.048
Number of concomitant medications, mean (SD)	3.50 (1.8)	3.45 (1.8)	0.029
Physician specialty, n (%)			
Cardiologist	3550 (86.6)	6647 (84.6)	0.058
General practitioner / Primary care physician /Geriatrician	197 (4.8)	356 (4.5)	0.013
Internist	144 (3.5)	250 (3.2)	0.018
Neurologist	61 (1.5)	312 (4.0)	-0.153
Angiologist	1 (0.0)	1 (0.0)	0.009
Other	136 (3.3)	250 (3.2)	0.008
Missing	8 (0.2)	39 (0.5)	-0.051
Region (N [%])			
Asia	470 (11.5)	1228 (15.6)	-0.122
Europe	2064 (50.4)	4039 (51.4)	-0.021
North America	1294 (31.6)	2044 (26.0)	0.123
Latin America	269 (6.6)	544 (6.9)	-0.014
Race (N [%])			

Amer.Indian/Amer.Native/Alaska Native	31 (0.8)	47 (0.6)	0.019
Black/African American	66 (1.6)	148 (1.9)	-0.021
White	3153 (77.0)	5671 (72.2)	0.109
Asian	468 (11.4)	1175 (15.0)	-0.105
Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.0)	
Arab/Middle East	7 (0.2)	9 (0.1)	0.015
African	2 (0.0)	4 (0.1)	-0.001
Smoking status (N [%])			
Non-smoker	2277 (55.6)	4548 (57.9)	-0.047
Current smoker	324 (7.9)	699 (8.9)	-0.036
Past smoker	1357 (33.1)	2357 (30.0)	0.067
Unknown	139 (3.4)	251 (3.2)	0.011
Alcohol abuse (N [%])			
No (<8U/wk)	3542 (86.5)	6854 (87.3)	-0.024
Yes (>=8U/wk)	312 (7.6)	540 (6.9)	0.029
Unknown	243 (5.9)	461 (5.9)	0.003
Alcohol use (N [%])			
Never	1564 (38.2)	3295 (41.9)	-0.077
<1 drink/week	1055 (25.8)	1903 (24.2)	0.035
1-7 drinks/week	923 (22.5)	1656 (21.1)	0.035
>=8 drinks/week	312 (7.6)	540 (6.9)	0.029
Unknown	243 (5.9)	461 (5.9)	0.003

Type of site (N [%])			
General practice /primary care	246 (6.0)	401 (5.1)	0.039
Specialist office	1479 (36.1)	2413 (30.7)	0.114
Community hospital	1267 (30.9)	2659 (33.9)	-0.063
University hospital	993 (24.2)	2217 (28.2)	-0.091
Out-patient health care center	28 (0.7)	68 (0.9)	-0.021
Anticoagulation clinics	19 (0.5)	24 (0.3)	0.026
Missing	8 (0.2)	39 (0.5)	-0.051
Transient ischaemic attack (N [%])	183 (4.5)	423 (5.4)	-0.042
Unknown	2 (0.0)	4 (0.1)	-0.001
Pulmonary embolism (N [%])	39 (1.0)	41 (0.5)	0.050
Unknown	59 (1.4)	84 (1.1)	0.033
Deep vein thrombosis (N [%])	60 (1.5)	90 (1.1)	0.028
Unknown	69 (1.7)	99 (1.3)	0.035
Angina pectoris (N [%])	280 (6.8)	631 (8.0)	-0.046
Unknown	55 (1.3)	53 (0.7)	0.067
Congestive heart failure (N [%])	783 (19.1)	1519 (19.3)	-0.006
Unknown	35 (0.9)	52 (0.7)	0.022
Rheumatic heart disease (N [%])	11 (0.3)	34 (0.4)	-0.028
Unknown	66 (1.6)	63 (0.8)	0.074
Additional antiplatelets (N [%])	578 (14.1)	1012 (12.9)	0.036
Peripheral artery disease (N [%])	99 (2.4)	196 (2.5)	-0.005

Unknown	28 (0.7)	47 (0.6)	0.011
Cancer (N [%])	417 (10.2)	840 (10.7)	-0.017
Unknown	79 (1.9)	91 (1.2)	0.063
Hyperlipidemia (N [%])	1734 (42.3)	3249 (41.4)	0.019
Unknown	104 (2.5)	159 (2.0)	0.034
Hepatic disease (N [%])	41 (1.0)	77 (1.0)	0.002
Unknown	66 (1.6)	97 (1.2)	0.032
Non-central nervous system arterial embolism (N [%])	17 (0.4)	30 (0.4)	0.005
Unknown	16 (0.4)	22 (0.3)	0.019
Presence of complex aortic plaque (N [%])	26 (0.6)	61 (0.8)	-0.017
Unknown	57 (1.4)	131 (1.7)	-0.022
Proton Pump inhibitors (N [%])	1023 (25.0)	2022 (25.7)	-0.018
Chronic gastrointestinal diseases (N [%])	603 (14.7)	1042 (13.3)	0.042
Unknown	67 (1.6)	108 (1.4)	0.021
Vascular disease (N [%])	433 (10.6)	843 (10.7)	-0.005
Dementia (N [%])	25 (0.6)	51 (0.6)	-0.005
Missing	70 (1.7)	86 (1.1)	0.052

CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischaemic attack, vascular disease, age 65 to 74 years, sex category, HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly, drugs or alcohol concomitantly, NOAC, non-

vitamin K antagonist oral anticoagulants, SD, standard deviation, VKA, vitamin K antagonists.

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