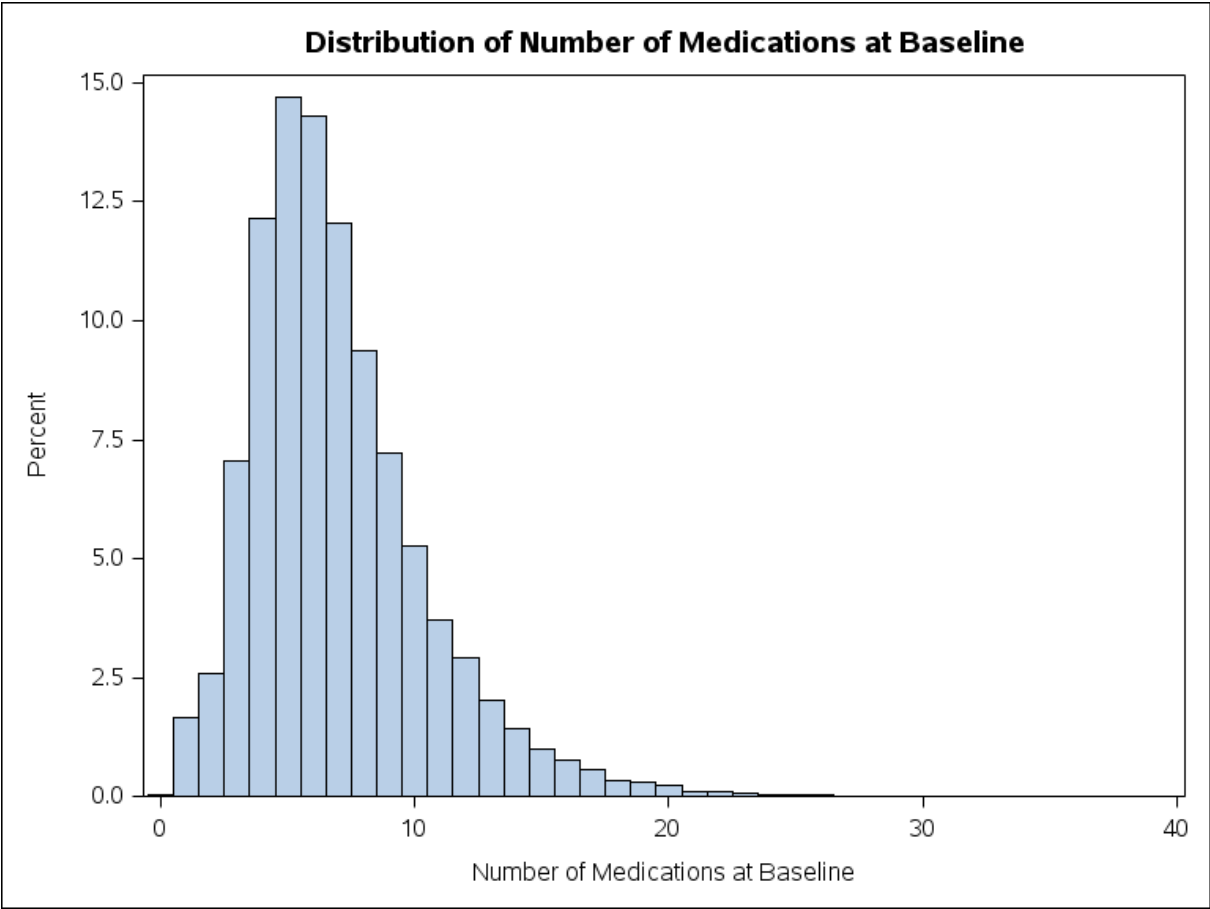**Web appendix: Supplementary materials**

Supplementary Figure 1

Supplementary figure 1. Distribution of number of medications at baseline.

Supplementary Table 1. Baseline characteristics by number of baseline concomitant medications subcategorized by treatment allocation

Characteristic	0-5 Meds		6-8 Meds		9 or More Meds	
	Apixaban (N=3424)	Warfarin (N=3519)	Apixaban (N=3320)	Warfarin (N=3182)	Apixaban (N=2376)	Warfarin (N=2380)
Age, mean (SD), yrs	68, (10)	68, (10)	69, (9)	69, (10)	71, (9)	71, (9)
Male, no, (%)	2320 (67.8%)	2367 (67.3%)	2076 (62.5%)	2031 (63.8%)	1490 (62.7%)	1501 (63.1%)
Weight, mean (SD), kg	81, (19)	81, (18)	84, (21)	84, (21)	89, (23)	89, (23)
Body mass index, mean (SD), kg/m^2	28.2, (5.3)	28.3, (5.4)	29.4, (6.0)	29.6, (6.1)	30.7, (6.5)	30.8, (6.6)
Prior use of Vitamin K antagonists for >30 days, no (%)	1759 (51.4%)	1796 (51.0%)	1852 (55.8%)	1804 (56.7%)	1597 (67.2%)	1593 (66.9%)
Creatinine, mean (SD)	1.01, (0.24)	1.02, (0.25)	1.06, (0.28)	1.06, (0.28)	1.12, (0.32)	1.12, (0.32)
Region of enrollment, no. (%)						
North America	362 (10.6%)	374 (10.6%)	702 (21.1%)	651 (20.5%)	1185 (49.9%)	1200 (50.4%)
Latin America	905 (26.4%)	904 (25.7%)	670 (20.2%)	636 (20.0%)	168 (7.1%)	185 (7.8%)
Europe	1549 (45.2%)	1579 (44.9%)	1409 (42.4%)	1402 (44.1%)	714 (30.1%)	690 (29.0%)
Asia	608 (17.8%)	662 (18.8%)	539 (16.2%)	493 (15.5%)	309 (13.0%)	305 (12.8%)
HAS-BLED score, mean (SD)	1.46, (0.96)	1.45, (0.96)	1.78, (1.01)	1.76, (1.03)	2.23, (1.06)	2.27, (1.04)
CHADS$_2$ score, mean (SD)	1.87, (1.02)	1.88, (1.02)	2.15, (1.08)	2.14, (1.09)	2.41, (1.15)	2.46, (1.19)
CHADS$_2$ score, no (%)						
≤1	1533 (44.8%)	1560 (44.3%)	1037 (31.2%)	1020 (32.1%)	530 (22.3%)	503 (21.1%)
2	1139 (33.3%)	1170 (33.2%)	1217 (36.7%)	1183 (37.2%)	906 (38.1%)	901 (37.9%)
≥3	752 (22.0%)	789 (22.4%)	1066 (32.1%)	979 (30.8%)	940 (39.6%)	976 (41.0%)
Low dose apixaban/placebo (2.5 mg bid) received	122 (3.6%)	131 (3.7%)	166 (5.0%)*	122 (3.8%)*	140 (5.9%)	150 (6.3%)
Comorbidities organized by organ system, no. (%)						
Cardiovascular						
CAD	897 (26.2%)	898 (25.6%)	1118 (33.7%)	1066 (33.6%)	1032 (43.5%)	1031 (43.3%)
Prior MI	295 (8.6%)	269 (7.7%)	501 (15.1%)	484 (15.2%)	523 (22.0%)	513 (21.6%)
History of PCI/CABG	192 (5.6%)	177 (5.0%)	430 (13.0%)	385 (12.1%)	653 (27.5%)	639 (26.8%)
Congestive Heart Failure within 3 Months	958 (28.0%)	973 (27.6%)	1127 (33.9%)	1067 (33.5%)	699 (29.4%)	717 (30.1%)
At Least Moderate Valvular Heart Disease	458 (13.4%)	468 (13.3%)	611 (18.4%)	581 (18.3%)	560 (23.6%)	556 (23.4%)
Syncope in Last 5 years	136 (4.0%)	122 (3.5%)	147 (4.4%)	132 (4.2%)	153 (6.4%)	169 (7.1%)
Hypertension with Pharmacological Treatment	2893 (84.5%)	2951 (83.9%)	2941 (88.6%)	2821 (88.7%)	2128 (89.6%)*	2182 (91.7%)*
PAD	88 (2.6%)	105 (3.0%)	150 (4.6%)	140 (4.4%)	204 (8.7%)	197 (8.4%)
Aortic Aneurysm	26 (0.8%)	20 (0.6%)	50 (1.5%)	34 (1.1%)	65 (2.8%)	74 (3.1%)
Neurological/Cerebrovascular						
Carotid Stenosis	29 (0.8%)	25 (0.7%)	48 (1.4%)	45 (1.4%)	103 (4.3%)	87 (3.7%)
TIA	138 (4.0%)	164 (4.7%)	164 (4.9%)	151 (4.7%)	158 (6.7%)	179 (7.5%)
Stroke	383 (11.2%)	425 (12.1%)	385 (11.6%)	365 (11.5%)	277 (11.7%)	292 (12.3%)
Dementia	10 (0.3%)	12 (0.4%)	18 (0.6%)	11 (0.4%)	21 (0.9%)	24 (1.1%)
Epilepsy	10 (0.3%)	12 (0.4%)	22 (0.7%)	27 (0.9%)	21 (0.9%)	20 (0.9%)

Supplementary Table 1. Baseline characteristics by number of baseline concomitant medications subcategorized by treatment allocation

Characteristic	0-5 Meds		6-8 Meds		9 or More Meds	
	Apixaban (N=3424)	Warfarin (N=3519)	Apixaban (N=3320)	Warfarin (N=3182)	Apixaban (N=2376)	Warfarin (N=2380)
Pulmonary						
COPD	211 (6.2%)	224 (6.4%)	317 (9.6%)	309 (9.8%)	442 (18.6%)	447 (18.8%)
Asthma	77 (2.3%)	80 (2.3%)	122 (3.7%)	128 (4.0%)	211 (8.9%)	251 (10.6%)
Sleep Apnea	72 (2.1%)	73 (2.1%)	138 (4.2%)	124 (3.9%)	310 (13.1%)	296 (12.5%)
Gastrointestinal						
Dyspepsia	193 (5.6%)	181 (5.2%)	229 (6.9%)	216 (6.8%)	272 (11.5%)	284 (11.9%)
GE Reflux Disease	164 (4.8%)	151 (4.3%)	253 (7.7%)	274 (8.6%)	540 (22.8%)	534 (22.5%)
Peptic Ulcer Disease	193 (5.6%)	190 (5.4%)	211 (6.4%)	206 (6.5%)	210 (8.8%)	196 (8.2%)
GI Surgery	246 (7.2%)	263 (7.5%)	316 (9.5%)	290 (9.1%)	298 (12.5%)	277 (11.7%)
Chronic Liver Disease	94 (2.7%)	96 (2.7%)	106 (3.2%)	87 (2.7%)	65 (2.7%)	56 (2.4%)
Endocrine						
Hypo/Hyperthyrodism	210 (6.2%)	219 (6.2%)	389 (11.7%)	344 (10.8%)	450 (19.0%)	428 (18.0%)
Diabetes	403 (11.8%)	403 (11.5%)	827 (24.9%)	776 (24.4%)	1054 (44.4%)	1084 (45.5%)
End organ Damage due to DM	32 (0.9%)	43 (1.2%)	108 (3.3%)	111 (3.5%)	229 (9.7%)	230 (9.7%)
Musculoskeletal						
Falls within 1 year	81 (2.7%)*	59 (1.9%)*	96 (3.2%)	119 (4.1%)	209 (9.3%)	189 (8.4%)
Previous Non-Traumatic Fracture	147 (4.3%)	152 (4.3%)	171 (5.2%)	168 (5.3%)	229 (9.7%)	207 (8.7%)
Osteoporosis	75 (2.2%)	76 (2.2%)	146 (4.4%)	152 (4.8%)	266 (11.2%)	255 (10.7%)
Renal						
Chronic Kidney Disease	218 (6.4%)	216 (6.1%)	260 (7.8%)	260 (8.2%)	270 (11.4%)	283 (11.9%)
Creatine Clearance < 50 mL/min	444 (13.0%)	483 (13.8%)	573 (17.3%)	539 (17.0%)	479 (20.2%)	491 (20.7%)
Hematological						
History of Anemia	97 (2.8%)	113 (3.2%)	199 (6.0%)	160 (5.0%)	354 (14.9%)	322 (13.5%)
Thrombocytopenia (platelet at baseline < 150)	261 (7.8%)	249 (7.3%)	245 (7.6%)	222 (7.1%)	177 (7.7%)	155 (6.7%)
Bleeding History	392 (11.4%)	387 (11.0%)	543 (16.4%)	486 (15.3%)	590 (24.8%)	642 (27.0%)
Number of organ systems affected (median, 25th-75th)	2, 1-3	2, 1-3	2, 2-3	2, 2-3	3, 2-4	3, 3-4

*P-value<0.05 between apixaban and warfarin allocation;
Abbreviations: n = number of patients, sd = standard deviation, yrs = years, no = number, kg = kilogram, m = meter, CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, PAD = peripheral artery disease, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, GE = gastroesophageal reflux disease, GI = gastrointestinal, DM = diabetes mellitus, mL = milliliter, min = minute.

Supplementary Table 2A. Distribution of Drug Classes by Number of Medications Used – <u>U.S. Patients</u>

Drug Class	All (N=3417)	Number of Medications 0-5 (N=467)	6-8 (N=970)	9 or more (N=1980)	p-value
A. Alimentary tract and metabolism	2508 (73%)	100 (21.4%)	603 (62.2%)	1805 (91.2%)	<.0001
B. Blood and blood forming organs [excluding apixaban/warfarin]	2722 (80%)	209 (44.8%)	720 (74.2%)	1793 (90.6%)	<.0001
C. Cardiovascular system	3323 (97%)	400 (85.7%)	956 (98.6%)	1967 (99.3%)	<.0001
D. Dermatologicals	270 (8%)	8 (1.7%)	44 (4.5%)	218 (11.0%)	<.0001
G. Genito-urinary system and sex hormones	717 (21%)	29 (6.2%)	146 (15.1%)	542 (27.4%)	<.0001
H. Systemic hormonal preparations, excluding sex hormones and insulins	528 (15%)	19 (4.1%)	87 (9.0%)	422 (21.3%)	<.0001
J. Antiinfectives for systemic use	214 (6%)	3 (0.6%)	36 (3.7%)	175 (8.8%)	<.0001
L. Antineoplastic and immunomodulating agents	95 (3%)	4 (0.9%)	18 (1.9%)	73 (3.7%)	0.0004
M. Musculo-skeletal system	824 (24%)	18 (3.9%)	154 (15.9%)	652 (32.9%)	<.0001
N. Nervous system	1529 (45%)	63 (13.5%)	340 (35.1%)	1126 (56.9%)	<.0001
P. Antiparasitic products, insecticides and repellents	20 (0.6%)	0 (0.0%)	1 (0.1%)	19 (1.0%)	0.0034
R. Respiratory system	850 (25%)	19 (4.1%)	145 (14.9%)	686 (34.6%)	<.0001
S. Sensory organs	207 (6%)	4 (0.9%)	34 (3.5%)	169 (8.5%)	<.0001
V. Various	400 (12%)	10 (2.1%)	52 (5.4%)	338 (17.1%)	<.0001
Interacting drugs					
≥1 combined PGP and weak-moderate-strong CYP3A4 inhibitor	913 (26.7%)	87 (18.6%)	244 (25.2%)	582 (29.4%)	<.0001
≥1 combined PGP and weak-moderate-strong CYP3A4 inducer	12 (0.4%)	1 (0.2%)	4 (0.4%)	7 (0.4%)	0.9
≥1 highly probable VKA inhibiting drug	24 (0.7%)	1 (0.2%)	6 (0.6%)	17 (0.9%)	0.3
≥1 highly probable VKA potentiating drug	772 (22.6%)	45 (9.6%)	167 (17.2%)	560 (28.3%)	<.0001
Use of ASA,NSAIDs and/or Prednisone	1555 (45.5%)	91 (19.5%)	371 (38.2%)	1093 (55.2%)	<.0001

Abbreviations: n = number of patients, PGP = P-Glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist, ASA = acetylsalicylic acid, NSAID = non-steroidal anti-inflammatory drug.

Supplementary table 2B. Distribution of Drug Classes by Number of Medications Used - <u>non-U.S. Patients</u>

Drug Class	All (N=14784)	Number of Medications 0-5 (N=6476)	6-8 (N=5532)	9 or more (N=2776)	p-value
A. Alimentary tract and metabolism	5593 (38%)	862 (13.3%)	2442 (44.1%)	2289 (82.5%)	<.0001
B. Blood and blood forming organs [excluding apixaban/warfarin]	7998 (54%)	2073 (32.0%)	3602 (65.1%)	2323 (83.7%)	<.0001
C. Cardiovascular system	14342 (97%)	6060 (93.6%)	5512 (99.6%)	2770 (99.8%)	<.0001
D. Dermatologicals	206 (1.4%)	26 (0.4%)	52 (0.9%)	128 (4.6%)	<.0001
G. Genito-urinary system and sex hormones	902 (6%)	144 (2.2%)	364 (6.6%)	394 (14.2%)	<.0001
H. Systemic hormonal preparations, excluding sex hormones and insulins	1013 (7%)	162 (2.5%)	421 (7.6%)	430 (15.5%)	<.0001
J. Antiinfectives for systemic use	338 (2%)	41 (0.6%)	125 (2.3%)	172 (6.2%)	<.0001
L. Antineoplastic and immunomodulating agents	131 (0.9%)	10 (0.2%)	42 (0.8%)	79 (2.8%)	<.0001
M. Musculo-skeletal system	1416 (10%)	184 (2.8%)	534 (9.7%)	698 (25.1%)	<.0001
N. Nervous system	2818 (19%)	460 (7.1%)	1108 (20.0%)	1250 (45.0%)	<.0001
P. Antiparasitic products, insecticides and repellents	39 (0.3%)	0 (0.0%)	12 (0.2%)	27 (1.0%)	<.0001
R. Respiratory system	1250 (8%)	145 (2.2%)	455 (8.2%)	650 (23.4%)	<.0001
S. Sensory organs	249 (1.7%)	37 (0.6%)	81 (1.5%)	131 (4.7%)	<.0001
V. Various	603 (4%)	116 (1.8%)	195 (3.5%)	292 (10.5%)	<.0001
Interacting drugs					
≥1 combined PGP and weak-moderate-strong CYP3A4 inhibitor	2947 (19.9%)	1041 (16.1%)	1187 (21.5%)	719 (25.9%)	<.0001
≥1 combined PGP and weak-moderate-strong CYP3A4 inducer	81 (0.5%)	11 (0.2%)	30 (0.5%)	40 (1.4%)	<.0001
≥1 highly probable VKA inhibiting drug	36 (0.2%)	7 (0.1%)	13 (0.2%)	16 (0.6%)	0.0002
≥1 highly probable VKA potentiating drug	2994 (20.3%)	928 (14.3%)	1239 (22.4%)	827 (29.8%)	<.0001
Use of ASA,NSAIDs and/or Prednisone	3827 (25.9%)	865 (13.4%)	1693 (30.6%)	1269 (45.7%)	<.0001

Abbreviations: n = number of patients, PGP = P-Glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist, ASA = acetylsalicylic acid, NSAID = non-steroidal anti-inflammatory drug.