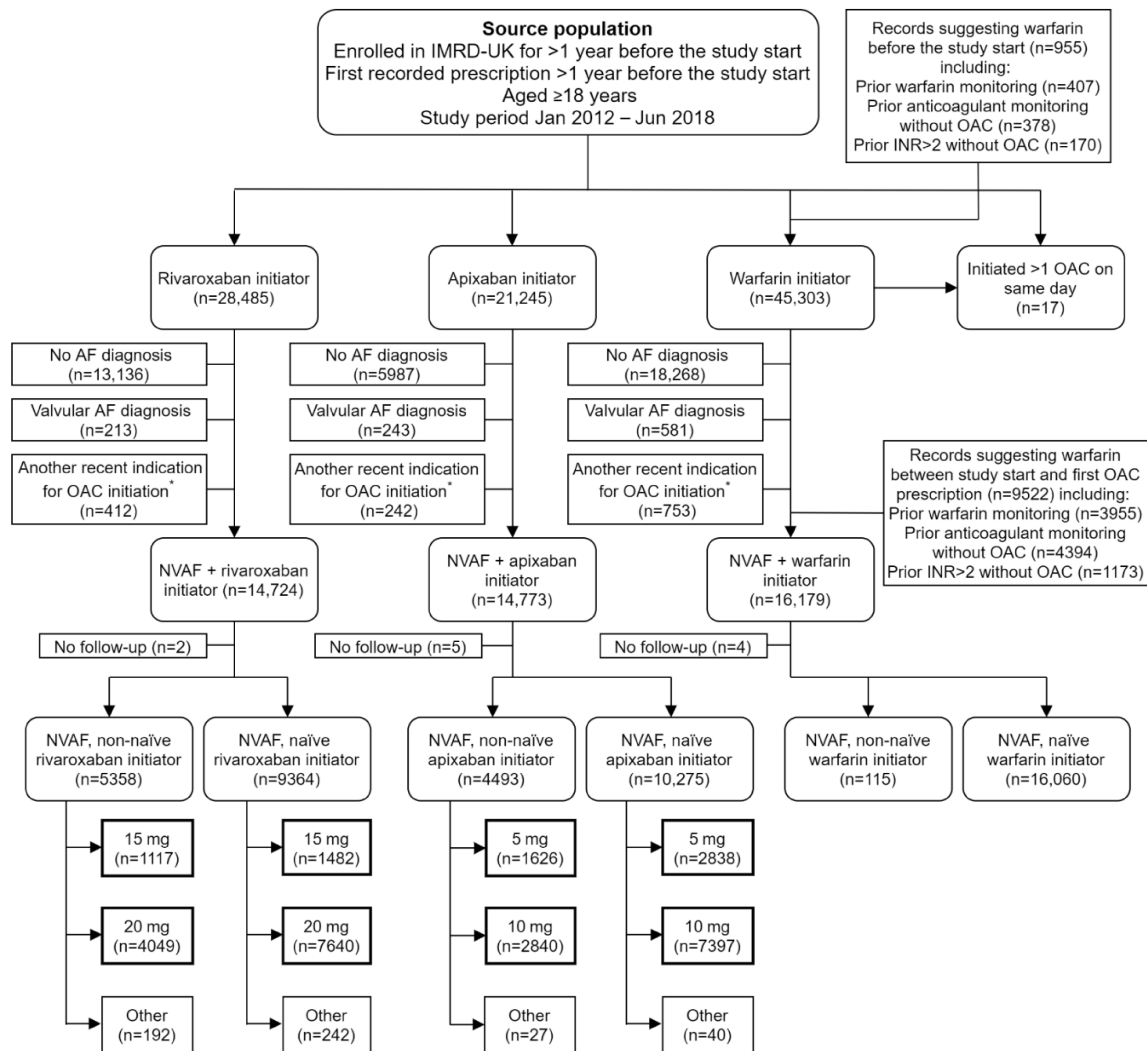


SUPPLEMENTARY METHODS

Additional inclusion/exclusion criteria

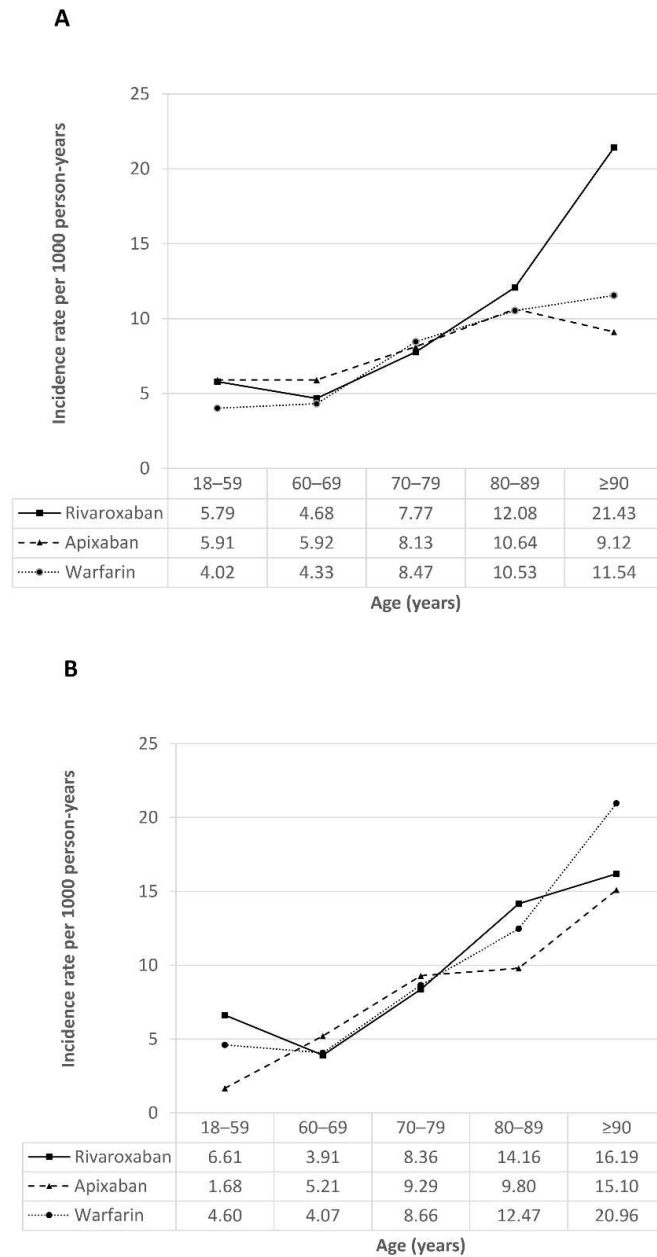
Individuals were required to have been registered with their general practice for at least 1 year following their first primary care health contact and before their first study drug prescription (start date). Patients with a first prescription for more than one of the study drugs on the same day were excluded, and those with a first prescription for different study drugs on different days were assigned to the cohort of the first prescribed drug. We also excluded new users of apixaban/rivaroxaban if the daily dose of the first prescription was not 5 mg/10 mg (apixaban) or 15 mg/20 mg (rivaroxaban). We also excluded patients with evidence of another recent indication for oral anticoagulation (OAC) initiation, i.e. those with a record of venous thromboembolism or orthopaedic arthroplasty in the 3 months before the first prescription for the study drug or in the week after.



Supplementary Figure 1. Identification of the study cohorts.

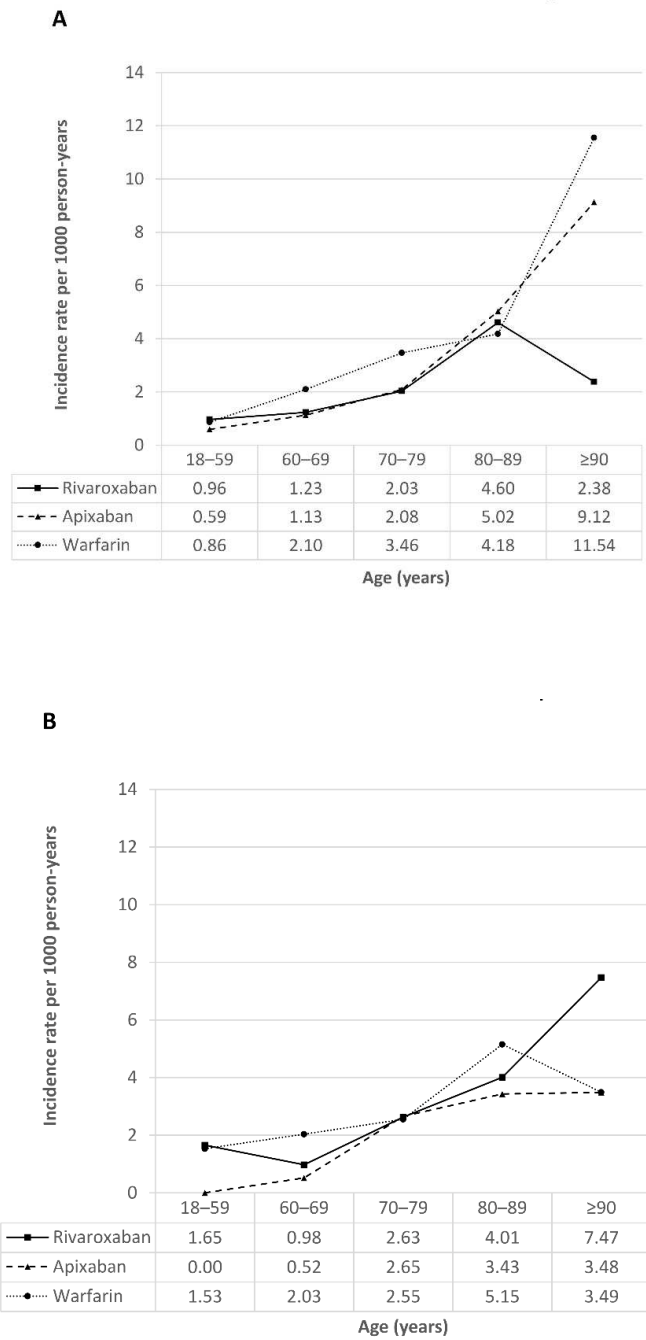
* A record of VTE or orthopaedic arthroplasty in the 3 months before the first OAC prescription or in the week after.

AF, atrial fibrillation; DVT, deep vein thrombosis; INR, international normalised ratio; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulation, PE, pulmonary embolism, VTE, venous thromboembolism



Supplementary Figure 2. Crude incidence of IS/SE per 1000 person-years by age in (A) males, (B) females.

IS/SE, ischemic stroke/systemic embolism



Supplementary Figure 3. Crude incidence of ICB per 1000 person years in (A) males, (B) females. ICB, intracranial bleeding

Supplementary Table 1. Appropriate/inappropriate DOAC dosing* (first DOAC prescription) in patients with NVAF **prescribed** standard/reduced apixaban/rivaroxaban.

	DOAC prescribed			
	Apixaban standard dose (prescribed dose) N=10,237 n (%)	Apixaban reduced dose N=4464 (prescribed dose) n (%)	Rivaroxaban standard dose N=11,689 (prescribed dose) n (%)	Rivaroxaban standard dose N=2599 (prescribed dose) n (%)
Underdosed	0 (0)	2339 (52.4)	0 (0)	888 (34.2)
Correct dose	9910 (96.8)	1907 (42.7)	10,882 (93.1)	1708 (65.7)
Overdosed	196 (1.9)	0 (0)	806 (6.9)	0 (0)
Contraindicated	131 (1.3)	218 (4.9)	1 (0.01)	3 (0.1)

*Based on the instructions on the respective drug label.

DOAC, direct oral anticoagulant; NVAF, non-valvular atrial fibrillation

Supplementary Table 2. Appropriate/inappropriate DOAC dosing* (first DOAC prescription) in patients with NVAF according to their **eligibility** to receive a standard/reduced dose.

Daily DOAC dose prescribed	Patient eligibility*			Total
	Eligible for Standard dose	Eligible for Reduced dose	Ineligible due to a contra-indication	
Rivaroxaban	N=11,770	N=2514	N=4	N=14,288
Recommended	10,882 (92.5)	1708 (67.9)	NA	12,590 (88.1)
Lower than recommended	888 (7.5)	0 (0.0)	NA	888 (6.2)
Higher than recommended	0 (0.0)	806 (32.1)	NA	806 (5.6)
Prescribed a DOAC when contraindicated	NA	NA	4 (100.0)	4 (0.0)
Higher than recommended	0 (0.0)	806 (32.1)	4 (100.0)	810 (5.7)
Apixaban	N=12,249	N=2103	N=349	N=14,701
Recommended	9910 (80.9)	1907 (90.7)	NA	11,817 (80.4)
Lower than recommended	2339 (19.1)	0 (0.0)	NA	2339 (15.9)
Higher than recommended	0 (0.0)	196 (9.3)	NA	196 (1.3)
Prescribed a DOAC when contraindicated	NA	NA	349 (100.0)	349 (2.4)
Higher than recommended/contraindicated	0 (0.0)	196 (9.3)	349 (100.0)	545 (3.7)

Data are n (column %).

*Based on the instructions on the respective drug label.

DOAC, direct oral anticoagulant; NA, not applicable; NVAF, non-valvular atrial fibrillation

Supplementary Table 3. ORs (95% CI) for risk of the **primary outcomes** of IS/SE and ICB, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Ischemic stroke/systemic embolism*						
Any dose	185 (22.7)	594 (24.3)	1.14 (0.90–1.45)	187 (22.9)	624 (25.5)	1.11 (0.87–1.40)
Appropriate dose	146 (17.9)	451 (18.5)	1.19 (0.92–1.52)	150 (18.4)	528 (21.6)	1.07 (0.83–1.37)
Inappropriate dose	39 (4.8)	143 (5.9)	1.01 (0.67–1.51)	35 (4.3)	96 (3.9)	1.21 (0.78–1.88)
Reduced dose	56 (6.9)	228 (9.3)	0.85 (0.60–1.20)	46 (5.6)	153 (6.3)	1.06 (0.72–1.56)
Appropriate dose	26 (3.2)	97 (4.0)	0.86 (0.53–1.40)	25 (3.1)	95 (3.9)	1.00 (0.61–1.64)
Inappropriate dose (underdosed)	30 (3.7)	131 (5.4)	0.84 (0.54–1.32)	21 (2.6)	58 (2.4)	1.16 (0.67–2.03)
Standard dose	129 (15.8)	366 (15.0)	1.33 (1.03–1.74)	139 (17.1)	471 (19.3)	1.10 (0.85–1.42)
Appropriate dose	120 (14.7)	354 (14.5)	1.29 (0.99–1.69)	125 (15.3)	433 (17.7)	1.08 (0.83–1.41)
Inappropriate dose (overdosed)	9 (1.1)	12 (0.5)	2.72 (1.06–6.95)	14 (1.7)	38 (1.6)	1.25 (0.65–2.40)
Intracranial bleeding†						
Any dose	58 (20.3)	281 (24.6)	0.62 (0.42–0.91)	67 (23.4)	263 (23)	0.86 (0.60–1.25)
Appropriate dose	48 (16.8)	218 (19.1)	0.67 (0.44–1.00)	54 (18.9)	226 (19.8)	0.81 (0.55–1.20)
Inappropriate dose	10 (3.5)	63 (5.5)	0.45 (0.21–0.95)	13 (4.5)	37 (3.2)	1.14 (0.56–2.31)
Reduced dose	23 (8.0)	101 (8.8)	0.63 (0.36–1.09)	21 (7.3)	79 (6.9)	0.87 (0.49–1.52)
Appropriate dose	14 (4.9)	45 (3.9)	0.76 (0.38–1.52)	12 (4.2)	52 (4.5)	0.77 (0.39–1.55)
Inappropriate dose (underdosed)	9 (3.1)	56 (4.9)	0.50 (0.23–1.09)	9 (3.1)	27 (2.4)	1.02 (0.45–2.34)
Standard dose	35 (12.2)	180 (15.7)	0.61 (0.39–0.95)	46 (16.1)	184 (16.1)	0.87 (0.57–1.31)
Appropriate dose	34 (11.9)	173 (15.1)	0.63 (0.41–0.99)	42 (14.7)	174 (15.2)	0.83 (0.54–1.26)
Inappropriate dose (overdosed)	1 (0.3)	7 (0.6)	0.21 (0.02–1.95)	4 (1.4)	10 (0.9)	1.51 (0.44–5.19)

*ORs were adjusted for matching factors (OAC naive at start date, sex, and year of birth), frailty, use of health services (hospitalizations, referrals), BMI, alcohol abuse, polymedication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

†ORs were adjusted for matching factors (OAC naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin.

BMI, body mass index; CI, confidence interval; IS/SE, ischemic stroke/systemic embolism; OR, odds ratio

Supplementary Table 4. ORs (95% CI) for risk of the **secondary outcomes** of haemorrhagic stroke, myocardial infarction and all-cause mortality, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR* (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Haemorrhagic stroke*						
Any dose	35 (21.1)	149 (22.4)	0.83 (0.50–1.36)	45 (27.1)	158 (23.8)	1.15 (0.71–1.84)
Appropriate dose	30 (18.1)	121 (18.2)	0.89 (0.53–1.50)	35 (21.1)	140 (21.1)	0.98 (0.59–1.63)
Inappropriate dose	5 (3.0)	28 (4.2)	0.55 (0.19–1.59)	10 (6.0)	18 (2.7)	2.39 (1.00–5.72)
Reduced dose	11 (6.6)	46 (6.9)	0.68 (0.31–1.48)	14 (8.4)	39 (5.9)	1.35 (0.66–2.79)
Appropriate dose	6 (3.6)	22 (3.3)	0.64 (0.23–1.77)	7 (4.2)	24 (3.6)	1.02 (0.40–2.64)
Inappropriate dose (underdosed)	5 (3.0)	24 (3.6)	0.68 (0.23–2.00)	7 (4.2)	15 (2.3)	1.83 (0.67–4.96)
Standard dose	24 (14.5)	103 (15.5)	0.91 (0.52–1.59)	31 (18.7)	119 (17.9)	1.07 (0.63–1.81)
Appropriate dose	24 (14.5)	99 (14.9)	0.96 (0.55–1.69)	28 (16.9)	116 (17.5)	0.97 (0.56–1.66)
Inappropriate dose (overdosed)	0 (0)	4 (0.6)	–	3 (1.8)	3 (0.5)	5.77 (1.02–32.54)
Myocardial infarction†						
Any dose	179 (29.4)	476 (26.1)	1.37 (1.04–1.81)	160 (26.3)	468 (25.6)	1.30 (0.98–1.73)
Appropriate dose	130 (29.4)	371 (20.3)	1.29 (0.96–1.73)	118 (19.4)	393 (21.5)	1.21 (0.89–1.64)
Inappropriate dose	49 (8.0)	104 (5.7)	1.73 (1.12–2.67)	38 (6.2)	72 (3.9)	1.68 (1.04–2.70)
Reduced dose	73 (12.0)	166 (9.1)	1.63 (1.12–2.38)	59 (9.7)	108 (5.9)	1.72 (1.14–2.60)
Appropriate dose	30 (4.9)	69 (3.8)	1.58 (0.93–2.68)	37 (6.1)	66 (3.6)	1.77 (1.07–2.92)
Inappropriate dose (underdosed)	43 (7.1)	97 (5.3)	1.69 (1.07–2.67)	22 (3.6)	42 (2.3)	1.69 (0.93–3.05)
Standard dose	106 (16.4)	309 (16.9)	1.27 (0.93–1.73)	97 (15.9)	357 (19.5)	1.15 (0.84–1.57)
Appropriate dose	100 (16.4)	302 (16.5)	1.22 (0.89–1.68)	81 (13.3)	327 (17.9)	1.07 (0.77–1.50)
Inappropriate dose (overdosed)	6 (1.0)	7 (0.4)	2.67 (0.81–8.79)	16 (2.6)	30 (1.6)	1.76 (0.88–3.53)
All-cause mortality‡						
Any dose	1621 (23.3)	1840 (26.4)	1.17 (1.05–1.31)	1647 (23.7)	1902 (27.3)	1.32 (1.18–1.47)
Appropriate dose	1056 (15.2)	1333 (19.2)	1.08 (0.95–1.22)	1194 (17.2)	1498 (21.5)	1.25 (1.11–1.41)
Inappropriate dose	562 (8.1)	507 (7.3)	1.41 (1.20–1.66)	440 (6.3)	386 (5.5)	1.58 (1.33–1.89)
Reduced dose	937 (13.5)	822 (11.8)	1.39 (1.22–1.60)	679 (9.8)	551 (7.9)	1.60 (1.37–1.86)
Appropriate dose	458 (6.6)	371 (5.3)	1.38 (1.15–1.65)	395 (5.7)	322 (4.6)	1.51 (1.25–1.82)
Inappropriate dose (underdosed)	479 (6.9)	451 (6.5)	1.42 (1.20–1.68)	284 (4.1)	229 (3.3)	1.76 (1.42–2.18)
Standard dose	681 (9.8)	1018 (14.6)	0.98 (0.86–1.13)	955 (13.7)	1333 (19.2)	1.20 (1.06–1.36)
Appropriate dose	598 (8.6)	962 (13.8)	0.94 (0.82–1.09)	799 (11.5)	1176 (16.9)	1.17 (1.02–1.33)
Inappropriate dose (overdosed)	83 (1.2)	56 (0.8)	1.53 (1.04–2.26)	156 (2.2)	157 (2.3)	1.40 (1.08–1.82)

*ORs were adjusted for the matching factors (OAC naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin.

†ORs were adjusted for the matching factors (OAC naive at start date, sex, and year of birth), frailty, health services utilization (hospitalizations, referrals), BMI, alcohol abuse, polymedication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

‡ORs were adjusted for matching factors (naive at start date, sex, and year of birth), polymedication, frailty, health services utilization, alcohol, BMI, history of heart failure, cancer, diabetes, peripheral artery disease, stroke, MI, and use of oral steroids, statins, antihypertensives, parenteral anticoagulants, other DOAC, digoxin, and CYP-inducing drugs.

BMI, body mass index; CI, confidence interval; CYP, cytochrome P450; IS/SE, ischemic stroke/systemic embolism; OR, odds ratio

Supplementary Table 5. ORs (95% CI) for the risk of study outcomes, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification, in the CKD subgroup.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR* (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Ischemic stroke/systemic embolism*						
Any dose	78 (24.5)	253 (27.8)	1.00 (0.68–1.47)	67 (21)	225 (24.7)	0.91 (0.61–1.36)
Appropriate dose	57 (17.9)	171 (18.8)	1.10 (0.72–1.67)	44 (13.8)	168 (18.5)	0.83 (0.53–1.31)
Inappropriate dose	21 (6.6)	82 (9.0)	0.79 (0.44–1.42)	22 (6.9)	57 (6.3)	1.05 (0.58–1.92)
Standard dose	44 (13.8)	114 (12.5)	1.34 (0.84–2.12)	33 (10.4)	112 (12.3)	0.88 (0.54–1.44)
Appropriate dose	37 (11.6)	106 (11.6)	1.22 (0.75–1.98)	19 (6)	74 (8.1)	0.76 (0.41–1.39)
Inappropriate dose	7 (2.2)	8 (0.9)	2.82 (0.89–8.92)	14 (4.4)	38 (4.2)	1.11 (0.55–2.23)
Reduced dose	34 (10.7)	139 (15.3)	0.72 (0.44–1.19)	33 (10.4)	113 (12.4)	0.89 (0.53–1.48)
Appropriate dose	20 (6.3)	65 (7.1)	0.91 (0.49–1.71)	25 (7.9)	94 (10.3)	0.88 (0.51–1.53)
Inappropriate dose	14 (4.4)	74 (8.1)	0.57 (0.29–1.12)	8 (2.5)	19 (2.1)	0.95 (0.36–2.50)
Intracranial bleeding†						
Any dose	29 (25.4)	124 (26.8)	0.76 (0.41–1.41)	25 (21.9)	110 (23.8)	0.82 (0.44–1.52)
Appropriate dose	22 (19.3)	91 (19.7)	0.79 (0.41–1.52)	16 (14.0)	90 (19.4)	0.64 (0.32–1.29)
Inappropriate dose	7 (6.1)	33 (7.1)	0.72 (0.27–1.92)	9 (7.9)	20 (4.3)	1.61 (0.62–4.15)
Standard dose	12 (10.5)	66 (14.3)	0.67 (0.31–1.45)	8 (7.0)	48 (10.4)	0.68 (0.28–1.66)
Appropriate dose	11 (9.6)	29 (6.3)	0.70 (0.32–1.53)	4 (3.5)	38 (8.2)	0.42 (0.13–1.35)
Inappropriate dose	1 (0.9)	4 (0.9)	0.47 (0.04–4.92)	4 (3.5)	10 (2.2)	1.63 (0.45–5.93)
Reduced dose	17 (14.9)	58 (12.5)	0.88 (0.41–1.87)	17 (14.9)	62 (13.4)	0.92 (0.45–1.88)
Appropriate dose	11 (9.6)	29 (6.3)	0.95 (0.38–2.38)	12 (10.5)	52 (11.2)	0.79 (0.36–1.74)
Inappropriate dose	6 (5.3)	29 (6.3)	0.80 (0.29–2.26)	5 (4.4)	10 (2.2)	1.61 (0.46–5.68)
Haemorrhagic stroke†						
Any dose	14 (22.6)	66 (25.3)	0.82 (0.35–1.94)	16 (25.8)	51 (19.5)	1.42 (0.61–3.28)
Appropriate dose	10 (16.1)	49 (18.8)	0.86 (0.34–2.20)	10 (16.1)	44 (16.9)	0.99 (0.39–2.52)
Inappropriate dose	4 (6.5)	17 (6.5)	0.80 (0.20–3.16)	6 (9.7)	7 (2.7)	4.94 (1.26–19.38)
Standard dose	7 (11.3)	37 (14.2)	0.90 (0.31–2.58)	6 (9.7)	23 (8.8)	1.30 (0.41–4.12)
Appropriate dose	7 (11.3)	34 (13.2)	1.15 (0.39–3.35)	3 (4.8)	20 (7.8)	0.71 (0.17–3.01)
Inappropriate dose	0 (0)	0 (0)	–	3 (4.8)	3 (1.2)	6.51 (0.98–43.40)
Reduced dose	7 (11.3)	29 (11.1)	0.75 (0.25–2.30)	10 (16.1)	28 (10.7)	1.51 (0.56–4.07)
Appropriate dose	3 (4.8)	15 (5.8)	0.45 (0.10–2.08)	7 (11.3)	24 (9.3)	1.14 (0.38–3.44)

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR* (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Inappropriate dose	4 (6.5)	14 (5.4)	1.12 (0.28–4.49)	3 (4.8)	4 (1.6)	3.48 (0.57–21.39)
Myocardial infarction*						
Any dose	71 (26.0)	189 (28.3)	1.30 (0.84–2.03)	83 (30.4)	171 (25.6)	1.55 (1.01–2.40)
Appropriate dose	41 (15.0)	125 (18.8)	1.13 (0.68–1.86)	54 (19.8)	119 (17.9)	1.44 (0.89–2.34)
Inappropriate dose	30 (11.0)	63 (9.5)	1.72 (0.95–3.10)	28 (10.3)	51 (7.7)	1.74 (0.96–3.15)
Standard dose	27 (9.9)	84 (12.6)	1.18 (0.67–2.06)	33 (12.1)	83 (12.5)	1.30 (0.76–2.24)
Appropriate dose	23 (8.4)	80 (12.0)	1.03 (0.57–1.87)	17 (6.2)	53 (8.0)	1.05 (0.54–2.07)
Inappropriate dose	4 (1.5)	4 (0.6)	4.09 (0.87–19.22)	16 (5.9)	30 (4.5)	1.73 (0.82–3.65)
Reduced dose	44 (16.1)	104 (15.6)	1.45 (0.86–2.43)	49 (17.9)	87 (13.1)	1.79 (1.07–2.98)
Appropriate dose	18 (6.6)	45 (6.8)	1.30 (0.65–2.60)	37 (13.6)	66 (9.9)	1.79 (1.02–3.16)
Inappropriate dose	26 (9.5)	59 (8.9)	1.59 (0.85–2.95)	12 (4.4)	21 (3.2)	1.79 (0.78–4.13)
All-cause mortality†						
Any dose	860 (24.3)	823 (28.1)	1.05 (0.89–1.23)	793 (22.4)	806 (27.5)	1.11 (0.94–1.31)
Appropriate dose	513 (14.5)	550 (18.8)	0.93 (0.78–1.12)	532 (15.0)	544 (18.6)	1.10 (0.92–1.32)
Inappropriate dose	346 (9.8)	273 (9.3)	1.26 (1.02–1.57)	254 (7.2)	254 (8.7)	1.13 (0.90–1.42)
Standard dose	262 (7.4)	356 (12.2)	0.75 (0.61–0.93)	293 (8.3)	379 (12.9)	0.98 (0.79–1.20)
Appropriate dose	198 (5.6)	313 (10.7)	0.69 (0.54–0.87)	137 (3.9)	222 (7.6)	0.81 (0.62–1.06)
Inappropriate dose	64 (1.8)	43 (1.5)	1.14 (0.73–1.77)	156 (4.4)	157 (5.4)	1.20 (0.91–1.57)
Reduced dose	597 (16.9)	467 (15.9)	1.28 (1.07–1.54)	493 (13.9)	419 (14.3)	1.24 (1.03–1.50)
Appropriate dose	315 (8.9)	237 (8.1)	1.25 (1.00–1.57)	395 (11.2)	322 (11.0)	1.30 (1.06–1.60)
Inappropriate dose	282 (8.0)	230 (7.9)	1.32 (1.05–1.66)	98 (2.8)	97 (3.3)	1.05 (0.75–1.48)

*ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, health services utilization (hospitalizations, referrals), BMI, alcohol abuse, poly medication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

†ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin.

‡ORs were adjusted for matching factors (naive at start date, sex, and year of birth), poly medication, frailty, health services utilization, alcohol, BMI, history of heart failure, cancer, diabetes, peripheral artery disease, stroke, myocardial infarction, and use of oral steroids, statins, antihypertensives, parenteral anticoagulants, other DOAC, digoxin, and cytochrome P450-inducing drugs

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; OR, odds ratio
Note: CKD was determined based on estimated glomerular filtration rate values.

Supplementary Table 6. ORs (95% CI) for the risk of study outcomes, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification, in the diabetes subgroup.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Ischemic stroke/systemic embolism*						
Any dose	52 (26.1)	147 (25.9)	1.27 (0.78–2.07)	39 (19.6)	144 (25.4)	1.12 (0.67–1.88)
Appropriate dose	40 (20.1)	99 (17.4)	1.37 (0.81–2.33)	32 (16.1)	127 (22.4)	1.09 (0.63–1.88)
Inappropriate dose	12 (6.0)	48 (8.5)	1.02 (0.47–2.19)	7 (3.5)	17 (3.0)	1.27 (0.47–3.46)
Standard dose	37 (18.6)	80 (14.1)	1.63 (0.94–2.85)	29 (14.6)	104 (18.3)	1.14 (0.64–2.01)
Appropriate dose	33 (16.6)	77 (13.6)	1.52 (0.86–2.68)	26 (13.1)	95 (16.7)	1.23 (0.68–2.23)
Inappropriate dose	4 (2.0)	3 (0.5)	5.91 (1.03–33.88)	3 (1.5)	9 (1.6)	0.76 (0.18–3.15)
Reduced dose	15 (7.5)	67 (11.8)	0.82 (0.41–1.66)	10 (5.0)	40 (7.0)	1.06 (0.46–2.41)
Appropriate dose	7 (3.5)	22 (3.9)	1.04 (0.39–2.83)	6 (3.0)	32 (5.6)	0.79 (0.29–2.14)
Inappropriate dose	8 (4.0)	45 (7.9)	0.72 (0.30–1.72)	4 (2.0)	8 (1.4)	2.13 (0.56–8.13)
Intracranial bleeding†						
Any dose	20 (31.7)	54 (23.1)	1.03 (0.45–2.39)	8 (12.7)	49 (20.9)	0.46 (0.18–1.21)
Appropriate dose	16 (25.4)	40 (17.9)	1.34 (0.55–3.26)	8 (12.7)	39 (17.4)	0.55 (0.21–1.46)
Inappropriate dose	4 (6.3)	14 (6.3)	0.43 (0.10–1.84)	0 (0)	0 (0)	–
Standard dose	9 (14.3)	37 (15.8)	0.75 (0.27–2.09)	4 (6.3)	29 (12.4)	0.42 (0.12–1.46)
Appropriate dose	9 (14.3)	34 (15.4)	0.92 (0.33–2.57)	4 (6.3)	25 (11.3)	0.44 (0.12–1.58)
Inappropriate dose	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Reduced dose	11 (17.5)	17 (7.3)	1.59 (0.52–4.89)	4 (6.3)	20 (8.5)	0.57 (0.16–1.99)
Appropriate dose	7 (11.1)	6 (2.7)	3.30 (0.75–14.47)	4 (6.3)	14 (6.3)	0.78 (0.21–2.88)
Inappropriate dose	4 (6.3)	11 (5.0)	0.71 (0.16–3.16)	0 (0)	0 (0)	–
Haemorrhagic stroke†						
Any dose	13 (39.4)	32 (22.7)	1.02 (0.32–3.30)	3 (9.1)	28 (19.9)	0.31 (0.07–1.40)
Appropriate dose	10 (30.3)	26 (19.1)	1.37 (0.40–4.71)	3 (9.1)	23 (16.9)	0.37 (0.08–1.69)
Inappropriate dose	3 (9.1)	6 (4.4)	0.39 (0.05–2.86)	0 (0)	0 (0)	–
Standard dose	7 (21.2)	25 (20.3)	0.74 (0.18–3.01)	0 (0)	0 (0)	–
Appropriate dose	7 (21.2)	23 (19.8)	1.16 (0.28–4.81)	0 (0)	0 (0)	–
Inappropriate dose	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Reduced dose	6 (18.2)	7 (5.7)	1.53 (0.30–7.70)	3 (9.1)	10 (8.1)	0.80 (0.15–4.10)
Appropriate dose	3 (9.1)	3 (2.6)	1.77 (0.21–14.97)	3 (9.1)	4 (4.3)	1.31 (0.20–8.55)

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Inappropriate dose	3 (9.1)	4 (3.4)	1.10 (0.14–8.82)	0 (0)	0 (0)	–
Myocardial infarction*						
Any dose	62 (29.7)	97 (26.1)	1.54 (0.90–2.61)	59 (28.2)	111 (29.9)	1.52 (0.90–2.57)
Appropriate dose	44 (21.2)	73 (19.7)	1.49 (0.84–2.65)	44 (21.2)	93 (25.1)	1.38 (0.79–2.42)
Inappropriate dose	18 (8.7)	23 (6.2)	1.69 (0.75–3.84)	14 (6.7)	18 (4.9)	2.11 (0.89–5.03)
Standard dose	39 (18.8)	63 (17.0)	1.63 (0.91–2.94)	34 (16.3)	85 (23.0)	1.25 (0.70–2.25)
Appropriate dose	36 (17.3)	62 (16.8)	1.53 (0.84–2.79)	26 (12.5)	72 (19.5)	1.13 (0.60–2.13)
Inappropriate dose	3 (1.4)	1 (0.3)	5.69 (0.52–62.14)	8 (3.8)	13 (3.5)	1.84 (0.64–5.32)
Reduced dose	23 (11.1)	33 (8.9)	1.41 (0.66–3.00)	24 (11.5)	26 (7.0)	2.23 (1.05–4.73)
Appropriate dose	8 (3.8)	11 (3.0)	1.29 (0.40–4.19)	18 (8.7)	21 (5.7)	2.14 (0.93–4.94)
Inappropriate dose	15 (7.2)	22 (5.9)	1.49 (0.63–3.55)	6 (2.9)	5 (1.4)	2.73 (0.69–10.77)
All-cause mortality†						
Any dose	514 (24.4)	457 (29.3)	0.97 (0.78–1.20)	476 (22.6)	430 (27.5)	1.11 (0.89–1.38)
Appropriate dose	334 (15.9)	325 (20.8)	0.90 (0.71–1.14)	353 (16.8)	353 (22.6)	1.01 (0.80–1.28)
Inappropriate dose	178 (8.5)	132 (8.5)	1.15 (0.85–1.56)	120 (5.7)	77 (4.9)	1.49 (1.04–2.14)
Standard dose	249 (11.9)	257 (15.3)	0.87 (0.67–1.12)	268 (12.8)	284 (18.2)	1.00 (0.78–1.28)
Appropriate dose	206 (9.8)	239 (15.3)	0.79 (0.61–1.03)	216 (10.3)	251 (16.1)	0.94 (0.72–1.22)
Inappropriate dose	43 (2.0)	18 (1.2)	1.78 (0.94–3.38)	52 (2.5)	33 (2.1)	1.33 (0.80–2.21)
Reduced dose	263 (12.5)	200 (12.8)	1.11 (0.85–1.46)	205 (9.8)	146 (9.4)	1.31 (0.98–1.76)
Appropriate dose	128 (6.1)	86 (5.5)	1.18 (0.83–1.68)	137 (6.5)	102 (6.5)	1.18 (0.84–1.65)
Inappropriate dose	135 (6.4)	114 (7.3)	1.06 (0.77–1.48)	68 (3.2)	44 (2.8)	1.66 (1.05–2.63)

*ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, health services utilization (hospitalizations, referrals), BMI, alcohol abuse, poly medication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

†ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin.

‡ORs were adjusted for matching factors (naive at start date, sex, and year of birth), poly medication, frailty, health services utilization, alcohol, BMI, history of heart failure, cancer, peripheral artery disease, stroke, myocardial infarction, and use of oral steroids, statins, antihypertensives, parenteral anticoagulants, other DOAC, digoxin, and CYP-inducing drugs.

BMI, body mass index; CI, confidence interval; CYP, cytochrome P450; DOAC, direct oral anticoagulant; OR, odds ratio Note: Diabetes was determined based on coded entries.

Supplementary Table 7. ORs (95% CI) for the risk of study outcomes, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification, among individuals with CHA₂DS₂-VASc score >4.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Ischemic stroke/systemic embolism*						
Any dose	72 (24.5)	199 (29.2)	0.98 (0.64–1.50)	68 (23.1)	185 (27.2)	0.99 (0.65–1.52)
Appropriate dose	54 (18.4)	134 (19.7)	1.06 (0.67–1.67)	54 (18.4)	143 (21)	1.01 (0.64–1.60)
Inappropriate dose	18 (6.1)	65 (9.5)	0.81 (0.42–1.54)	13 (4.4)	42 (6.2)	0.84 (0.40–1.78)
Standard dose	45 (15.4)	83 (12.2)	1.34 (0.81–2.21)	40 (13.7)	107 (15.7)	0.86 (0.52–1.41)
Appropriate dose	40 (13.7)	79 (11.6)	1.25 (0.75–2.08)	37 (12.6)	92 (13.5)	0.95 (0.57–1.59)
Inappropriate dose	5 (1.7)	4 (0.6)	4.27 (0.90–20.28)	3 (1)	15 (2.2)	0.45 (0.12–1.69)
Reduced dose	27 (9.2)	116 (17)	0.69 (0.40–1.20)	27 (9.2)	78 (11.5)	1.19 (0.67–2.10)
Appropriate dose	14 (4.8)	55 (8.1)	0.79 (0.39–1.61)	17 (5.8)	51 (7.5)	1.24 (0.63–2.42)
Inappropriate dose	13 (4.4)	61 (9)	0.63 (0.31–1.28)	10 (3.4)	27 (4)	1.16 (0.49–2.77)
Intracranial bleeding†						
Any dose	21 (25.3)	92 (29.5)	0.58 (0.28–1.20)	11 (13.3)	71 (22.8)	0.45 (0.20–1.04)
Appropriate dose	16 (19.3)	64 (20.5)	0.66 (0.30–1.45)	8 (9.6)	58 (18.6)	0.38 (0.15–0.96)
Inappropriate dose	5 (6)	28 (9)	0.43 (0.13–1.40)	3 (3.6)	13 (4.2)	0.83 (0.18–3.72)
Standard dose	8 (9.6)	47 (15.1)	0.36 (0.13–0.96)	6 (7.2)	41 (13.1)	0.41 (0.14–1.15)
Appropriate dose	8 (9.6)	43 (14)	0.43 (0.16–1.16)	4 (4.8)	38 (12.3)	0.27 (0.08–0.88)
Inappropriate dose	0 (0)	0 (0)	–	2 (2.4)	3 (1)	5.40 (0.67–43.83)
Reduced dose	13 (15.7)	45 (14.4)	0.90 (0.37–2.17)	5 (6)	30 (9.6)	0.56 (0.18–1.75)
Appropriate dose	8 (9.6)	21 (6.8)	1.20 (0.40–3.62)	4 (4.8)	20 (6.5)	0.80 (0.23–2.81)
Inappropriate dose	5 (6)	24 (7.8)	0.62 (0.18–2.08)	1 (1.2)	10 (3.2)	0.20 (0.02–2.20)
Haemorrhagic stroke†						
Any dose	11 (23.9)	46 (26)	0.46 (0.17–1.31)	6 (13)	37 (20.9)	0.45 (0.14–1.47)
Appropriate dose	7 (15.2)	33 (18.6)	0.44 (0.14–1.45)	5 (10.9)	29 (16.4)	0.48 (0.14–1.65)
Inappropriate dose	4 (8.7)	13 (7.3)	0.51 (0.11–2.28)	1 (2.2)	8 (4.5)	0.33 (0.03–4.18)
Standard dose	4 (8.7)	23 (13)	0.34 (0.08–1.47)	2 (4.3)	21 (11.9)	0.25 (0.05–1.35)
Appropriate dose	4 (8.7)	21 (12.5)	0.45 (0.10–2.06)	1 (2.2)	20 (11.9)	0.12 (0.01–1.09)
Inappropriate dose	0 (0)	0 (0)	–	1 (2.2)	1 (0.6)	12.72 (0.35–463.14)
Reduced dose	7 (15.2)	23 (13)	0.61 (0.17–2.14)	4 (8.7)	16 (9)	0.85 (0.20–3.69)
Appropriate dose	3 (6.5)	12 (7.1)	0.41 (0.07–2.28)	4 (8.7)	9 (5.4)	2.18 (0.43–11.16)

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Inappropriate dose	4 (8.7)	11 (6.5)	0.85 (0.17–4.19)	0 (0)	0 (0)	–
Myocardial infarction*						
Any dose	82 (34.9)	127 (28.7)	1.84 (1.11–3.04)	58 (24.7)	134 (30.3)	1.22 (0.72–2.07)
Appropriate dose	56 (23.8)	85 (19.3)	1.91 (1.11–3.30)	45 (19.1)	107 (24.3)	1.20 (0.68–2.10)
Inappropriate dose	26 (11.1)	41 (9.3)	1.73 (0.86–3.50)	13 (5.5)	27 (6.1)	1.30 (0.56–3.01)
Standard dose	42 (17.9)	55 (12.5)	1.97 (1.10–3.54)	27 (11.5)	89 (20.2)	0.84 (0.45–1.55)
Appropriate dose	37 (15.7)	53 (12)	1.77 (0.97–3.25)	19 (8.1)	73 (16.6)	0.74 (0.38–1.46)
Inappropriate dose	5 (2.1)	2 (0.5)	6.79 (1.14–40.42)	8 (3.4)	16 (3.6)	1.22 (0.43–3.44)
Reduced dose	40 (17)	71 (16.1)	1.84 (0.99–3.42)	31 (13.2)	45 (10.2)	2.15 (1.09–4.24)
Appropriate dose	19 (8.1)	32 (7.3)	2.33 (1.06–5.14)	26 (11.1)	34 (7.7)	2.38 (1.14–4.97)
Inappropriate dose	21 (8.9)	39 (8.8)	1.49 (0.70–3.17)	5 (2.1)	11 (2.5)	1.55 (0.45–5.33)
All-cause mortality†						
Any dose	720 (25.6)	663 (30.4)	1.08 (0.90–1.30)	692 (24.6)	662 (30.4)	1.18 (0.98–1.42)
Appropriate dose	444 (15.8)	450 (20.7)	0.99 (0.81–1.21)	471 (16.8)	487 (22.4)	1.08 (0.88–1.32)
Inappropriate dose	273 (9.7)	213 (9.8)	1.27 (1.00–1.62)	211 (7.5)	171 (7.9)	1.44 (1.10–1.87)
Standard dose	236 (8.4)	293 (13.5)	0.83 (0.65–1.05)	322 (11.5)	388 (17.8)	1.01 (0.81–1.25)
Appropriate dose	198 (7)	265 (12.2)	0.80 (0.63–1.03)	254 (9)	315 (14.5)	1.00 (0.79–1.26)
Inappropriate dose	38 (1.4)	28 (1.3)	1.05 (0.60–1.82)	68 (2.4)	73 (3.4)	1.06 (0.72–1.56)
Reduced dose	481 (17.1)	370 (17)	1.29 (1.05–1.59)	360 (12.8)	270 (12.4)	1.41 (1.12–1.76)
Appropriate dose	246 (8.8)	185 (8.5)	1.27 (0.98–1.65)	217 (7.7)	172 (7.9)	1.23 (0.95–1.60)
Inappropriate dose	235 (8.4)	185 (8.5)	1.32 (1.03–1.71)	143 (5.1)	98 (4.5)	1.76 (1.28–2.42)

*ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, health services utilization (hospitalizations, referrals), BMI, alcohol abuse, poly medication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

†ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin. ‡ORs were adjusted for matching factors (naive at start date, sex, and year of birth), poly medication, frailty, health services utilization, alcohol, BMI, history of heart failure, cancer, peripheral artery disease, stroke, myocardial infarction, and use of oral steroids, statins, antihypertensives, parenteral anticoagulants, other DOAC, digoxin, and CYP-inducing drugs
BMI, body mass index; CI, confidence interval; CYP, cytochrome P450; DOAC, direct oral anticoagulant; OR, odds ratio

Supplementary Table 8. ORs (95% CI) for the risk of study outcomes, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification, among individuals with HAS-BLED score >2.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Ischemic stroke/systemic embolism*						
Any dose	60 (24.5)	117 (22.9)	1.33 (0.84–2.10)	54 (22)	125 (24.4)	1.10 (0.70–1.73)
Appropriate dose	47 (19.2)	87 (17)	1.44 (0.88–2.34)	44 (18)	97 (18.9)	1.15 (0.71–1.87)
Inappropriate dose	13 (5.3)	30 (5.9)	0.99 (0.45–2.17)	10 (4.1)	28 (5.5)	0.89 (0.38–2.06)
Standard dose	36 (14.7)	68 (13.3)	1.50 (0.88–2.56)	37 (15.1)	78 (15.2)	1.10 (0.66–1.84)
Appropriate dose	33 (13.5)	65 (12.7)	1.45 (0.84–2.50)	34 (13.9)	69 (13.5)	1.14 (0.67–1.95)
Inappropriate dose	3 (1.2)	3 (0.6)	2.50 (0.39–15.92)	3 (1.2)	9 (1.8)	0.84 (0.20–3.41)
Reduced dose	24 (9.8)	49 (9.6)	1.10 (0.58–2.07)	17 (6.9)	47 (9.2)	1.06 (0.53–2.11)
Appropriate dose	14 (5.7)	22 (4.3)	1.40 (0.63–3.12)	10 (4.1)	28 (5.5)	1.19 (0.52–2.76)
Inappropriate dose	10 (4.1)	27 (5.3)	0.84 (0.36–1.98)	7 (2.9)	19 (3.7)	0.91 (0.34–2.48)
Intracranial bleeding†						
Any dose	21 (25)	68 (27.9)	0.36 (0.16–0.81)	13 (15.5)	51 (20.9)	0.42 (0.18–0.97)
Appropriate dose	18 (21.4)	52 (21.3)	0.38 (0.16–0.90)	8 (9.5)	44 (18)	0.30 (0.11–0.79)
Inappropriate dose	3 (3.6)	16 (6.6)	0.26 (0.06–1.17)	5 (6)	7 (2.9)	1.17 (0.29–4.68)
Standard dose	10 (11.9)	37 (15.2)	0.27 (0.10–0.73)	7 (8.3)	29 (11.9)	0.36 (0.13–1.04)
Appropriate dose	10 (11.9)	33 (13.8)	0.33 (0.12–0.89)	5 (6)	24 (10)	0.29 (0.09–0.94)
Inappropriate dose	0(0)	0 (0)	–	2 (2.4)	5 (2.1)	0.81 (0.13–4.91)
Reduced dose	11 (13.1)	31 (12.7)	0.55 (0.19–1.60)	6 (7.1)	22 (9)	0.53 (0.17–1.66)
Appropriate dose	8 (9.5)	19 (7.9)	0.54 (0.16–1.88)	3 (3.6)	20 (8.3)	0.34 (0.08–1.39)
Inappropriate dose	3 (3.6)	12 (5)	0.50 (0.10–2.46)	3 (3.6)	2 (0.8)	2.13 (0.23–19.67)
Haemorrhagic stroke†						
Any dose	12 (23.5)	31 (23.5)	0.29 (0.10–0.88)	9 (17.6)	32 (24.2)	0.30 (0.10–0.97)
Appropriate dose	10 (19.6)	26 (19.7)	0.28 (0.09–0.92)	4 (7.8)	29 (22)	0.11 (0.02–0.50)
Inappropriate dose	2 (3.9)	5 (3.8)	0.18 (0.02–1.60)	5 (9.8)	3 (2.3)	2.53 (0.40–15.79)
Standard dose	7 (13.7)	19 (14.4)	0.30 (0.09–1.08)	4 (7.8)	19 (14.4)	0.18 (0.04–0.84)
Appropriate dose	7 (13.7)	17 (13.1)	0.34 (0.09–1.29)	2 (3.9)	18 (13.8)	0.07 (0.01–0.52)
Inappropriate dose	0 (0)	0 (0)	–	2 (3.9)	1 (0.8)	4.27 (0.21–88.11)
Reduced dose	5 (9.8)	12 (9.1)	0.28 (0.06–1.41)	5 (9.8)	13 (9.8)	0.51 (0.12–2.14)
Appropriate dose	3 (5.9)	9 (6.9)	0.18 (0.03–1.24)	2 (3.9)	11 (8.5)	0.22 (0.03–1.56)

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Inappropriate dose	2 (3.9)	3 (2.3)	0.42 (0.03–5.07)	3 (5.9)	2 (1.5)	1.67 (0.16–17.05)
Myocardial infarction*						
Any dose	59 (33.3)	92 (22.8)	1.60 (0.92–2.77)	40 (22.6)	106 (26.2)	1.03 (0.59–1.81)
Appropriate dose	41 (23.2)	69 (17.1)	1.64 (0.90–2.97)	34 (19.2)	85 (21.1)	1.15 (0.64–2.08)
Inappropriate dose	18 (10.2)	22 (5.5)	1.54 (0.67–3.55)	6 (3.4)	21 (5.2)	0.65 (0.23–1.85)
Standard dose	29 (16.4)	51 (12.7)	1.60 (0.84–3.03)	23 (13)	71 (17.6)	0.95 (0.50–1.82)
Appropriate dose	26 (14.7)	50 (12.4)	1.46 (0.75–2.83)	19 (10.7)	61 (15.1)	0.98 (0.49–1.94)
Inappropriate dose	3 (1.7)	1 (0.2)	4.99 (0.47–53.01)	4 (2.3)	10 (2.5)	0.87 (0.24–3.21)
Reduced dose	30 (16.9)	40 (9.9)	1.67 (0.82–3.41)	17(9.6)	35 (8.7)	1.19 (0.54–2.60)
Appropriate dose	15 (8.5)	19 (4.7)	2.07 (0.82–5.19)	15 (8.5)	24 (6)	1.60 (0.67–3.83)
Inappropriate dose	15 (8.5)	21 (5.2)	1.37 (0.56–3.33)	2 (1.1)	11 (2.7)	0.47 (0.09–2.39)
All-cause mortality†						
Any dose	460(23.8)	472 (29.6)	0.98(0.80–1.21)	396 (20.5)	400 (25.1)	1.09 (0.88–1.36)
Appropriate dose	276 (14.3)	325 (20.4)	0.89 (0.70–1.13)	275 (14.3)	314 (19.7)	0.95 (0.75–1.20)
Inappropriate dose	182 (9.4)	147 (9.2)	1.17 (0.87–1.56)	119 (6.2)	83(5.2)	1.70 (1.19–2.42)
Standard dose	159 (8.3)	229 (14.4)	0.78 (0.59–1.03)	188 (9.8)	249 (15.6)	0.87 (0.67–1.13)
Appropriate dose	129 (6.7)	205 (12.9)	0.76 (0.57–1.02)	152 (7.9)	212 (13.3)	0.82 (0.62–1.09)
Inappropriate dose	30 (1.6)	24 (1.5)	0.91 (0.49–1.67)	36 (1.9)	37 (2.3)	1.15 (0.67–1.97)
Reduced dose	299 (15.5)	243 (15.3)	1.18 (0.92–1.52)	206 (10.7)	148 (9.3)	1.49 (1.12–1.98)
Appropriate dose	147 (7.6)	120 (7.5)	1.11 (0.80–1.53)	123 (6.4)	102 (6.4)	1.21 (0.87–1.69)
Inappropriate dose	152 (7.9)	123 (7.7)	1.26 (0.92–1.72)	83 (4.3)	46 (2.9)	2.22 (1.43–3.43)

*ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, health services utilization (hospitalizations, referrals), BMI, alcohol abuse, polymedication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

†ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin. ‡ORs were adjusted for matching factors (naive at start date, sex, and year of birth), polymedication, frailty, health services utilization, alcohol, BMI, history of heart failure, cancer, peripheral artery disease, stroke, myocardial infarction, and use of oral steroids, statins, antihypertensives, parenteral anticoagulants, other DOAC, digoxin, and CYP-inducing drugs

BMI, body mass index; CI, confidence interval; CYP, cytochrome P450; DOAC, direct oral anticoagulant; OR, odds ratio

Supplementary Table 9. ORs (95% CI) for the risk of study outcomes, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification, among individuals with severe frailty.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Ischemic stroke/systemic embolism*						
Any dose	41 (25.2)	111 (29.4)	1.22 (0.66–2.25)	44 (27)	108 (28.6)	1.34 (0.72–2.50)
Appropriate dose	29 (17.8)	63 (16.7)	1.49 (0.77–2.91)	34 (20.9)	80 (21.2)	1.42 (0.73–2.76)
Inappropriate dose	12 (7.4)	48 (12.7)	0.84 (0.36–1.95)	10 (6.1)	28 (7.4)	1.14 (0.45–2.88)
Standard dose	23 (14.1)	40 (10.6)	1.79 (0.86–3.69)	24 (14.7)	61 (16.2)	1.09 (0.53–2.22)
Appropriate dose	18 (11)	36 (9.5)	1.58 (0.73–3.39)	20 (12.3)	49 (13)	1.18 (0.55–2.54)
Inappropriate dose	5 (3.1)	4 (1.1)	3.87 (0.78–19.18)	4 (2.5)	12 (3.2)	0.82 (0.22–3.06)
Reduced dose	18 (11)	71 (18.8)	0.83 (0.40–1.75)	20 (12.3)	47 (12.5)	1.67 (0.78–3.57)
Appropriate dose	11 (6.7)	27 (7.2)	1.30 (0.52–3.27)	14 (8.6)	31 (8.2)	1.84 (0.79–4.30)
Inappropriate dose	7 (4.3)	44 (11.7)	0.54 (0.20–1.45)	6 (3.7)	16 (4.2)	1.47 (0.46–4.74)
Intracranial bleeding†						
Any dose	19 (31.1)	49 (29.7)	1.09 (0.43–2.78)	10 (16.4)	41 (24.8)	0.53 (0.18–1.52)
Appropriate dose	14 (23)	26 (15.8)	1.48 (0.53–4.11)	9 (14.8)	27 (16.4)	0.71 (0.23–2.15)
Inappropriate dose	5 (8.2)	23 (13.9)	0.58 (0.16–2.11)	1 (1.6)	14 (8.5)	0.14 (0.01–1.46)
Standard dose	8 (13.1)	16 (9.7)	1.17 (0.36–3.83)	7 (11.5)	19 (11.5)	0.65 (0.19–2.22)
Appropriate dose	7 (11.5)	13 (8.4)	1.43 (0.41–4.96)	6 (9.8)	16 (10.4)	0.65 (0.18–2.36)
Inappropriate dose	1 (1.6)	3 (1.9)	0.35 (0.02–5.17)	1 (1.6)	3 (1.9)	0.64 (0.04–10.53)
Reduced dose	11 (18)	33 (20)	1.04 (0.36–3.01)	3 (4.9)	22 (13.3)	0.38 (0.08–1.67)
Appropriate dose	7 (11.5)	13 (8.4)	1.52 (0.42–5.52)	3 (4.9)	11 (7.1)	0.87 (0.17–4.34)
Inappropriate dose	4 (6.6)	20 (13)	0.65 (0.17–2.56)	0 (0)	0 (0)	1.00 (–)
Haemorrhagic stroke†						
Any dose	9 (23.7)	18 (22.5)	0.74 (0.21–2.63)	7 (18.4)	20 (25)	0.48 (0.13–1.80)
Appropriate dose	6 (15.8)	10 (12.5)	0.95 (0.22–4.03)	6 (15.8)	14 (17.5)	0.57 (0.14–2.30)
Inappropriate dose	3 (7.9)	8 (10)	0.47 (0.08–2.81)	1 (2.6)	6 (7.5)	0.18 (0.01–2.66)
Standard dose	3 (7.9)	7 (8.8)	0.44 (0.08–2.50)	4 (10.5)	9 (11.3)	0.61 (0.13–2.91)
Appropriate dose	3 (8.1)	5 (7.1)	0.81 (0.13–5.16)	3 (8.1)	9 (12.9)	0.46 (0.09–2.40)
Inappropriate dose	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Reduced dose	6 (15.8)	11 (13.8)	1.06 (0.24–4.66)	3 (7.9)	11 (13.8)	0.35 (0.06–2.05)
Appropriate dose	3 (8.1)	5 (7.1)	0.86 (0.11–6.73)	3 (8.1)	4 (5.7)	0.82 (0.11–6.22)

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Inappropriate dose	3 (8.1)	6 (8.6)	0.90 (0.15–5.50)	0 (0)	0 (0)	–
Myocardial infarction*						
Any dose	56 (31.6)	72 (29.4)	2.29 (1.16–4.51)	51 (28.8)	82 (33.5)	2.11 (1.05–4.22)
Appropriate dose	39 (22.3)	47 (19.2)	2.68 (1.29–5.59)	36 (20.6)	65 (26.5)	1.79 (0.86–3.75)
Inappropriate dose	17 (9.7)	25 (10.2)	1.65 (0.66–4.15)	13 (7.4)	17 (6.9)	2.78 (1.01–7.62)
Standard dose	23 (13.1)	33 (13.5)	2.15 (0.95–4.84)	24 (13.7)	47 (19.2)	1.93 (0.87–4.25)
Appropriate dose	20 (11.4)	30 (12.2)	2.02 (0.87–4.71)	18 (10.3)	39 (15.9)	1.64 (0.69–3.86)
Inappropriate dose	3 (1.7)	3 (1.2)	3.13 (0.49–19.90)	6 (3.4)	8 (3.3)	3.32 (0.89–12.34)
Reduced dose	33 (18.9)	39 (15.9)	2.46 (1.12–5.39)	25 (14.3)	35 (14.3)	2.17 (0.93–5.05)
Appropriate dose	19 (10.9)	17 (6.9)	4.06 (1.55–10.65)	18 (10.3)	26 (10.6)	2.05 (0.81–5.24)
Inappropriate dose	14 (8)	22 (9)	1.47 (0.55–3.92)	7 (4)	9 (3.7)	2.46 (0.65–9.26)
All-cause mortality†						
Any dose	572 (27.8)	416 (33)	1.10 (0.87–1.39)	537 (26.1)	381 (30.2)	1.31 (1.03–1.66)
Appropriate dose	349 (17)	270 (21.4)	1.03 (0.79–1.33)	352 (17.2)	273 (21.7)	1.16 (0.90–1.50)
Inappropriate dose	221 (10.8)	146 (11.6)	1.23 (0.91–1.66)	180 (8.8)	103 (8.2)	1.76 (1.27–2.45)
Standard dose	187 (9.1)	161 (12.8)	0.89 (0.66–1.20)	242 (11.8)	193 (15.3)	1.16 (0.87–1.54)
Appropriate dose	147 (7.2)	144 (11.4)	0.81 (0.59–1.11)	189 (9.2)	152 (12.1)	1.13 (0.83–1.53)
Inappropriate dose	40 (1.9)	17 (1.3)	1.46 (0.77–2.75)	53 (2.6)	41 (3.3)	1.30 (0.80–2.12)
Reduced dose	383 (18.7)	255 (20.2)	1.23 (0.95–1.60)	290 (14.1)	183 (14.5)	1.48 (1.12–1.95)
Appropriate dose	202 (9.8)	126 (10)	1.29 (0.94–1.77)	163 (7.9)	121 (9.6)	1.20 (0.87–1.65)
Inappropriate dose	181 (8.8)	129 (10.2)	1.19 (0.87–1.63)	127 (6.2)	62 (4.9)	2.08 (1.42–3.05)

*ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, health services utilization (hospitalizations, referrals), BMI, alcohol abuse, poly medication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

†ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin. ‡ORs were adjusted for matching factors (naive at start date, sex, and year of birth), poly medication, frailty, health services utilization, alcohol, BMI, history of heart failure, cancer, peripheral artery disease, stroke, myocardial infarction, and use of oral steroids, statins, antihypertensives, parenteral anticoagulants, other DOAC, digoxin, and CYP-inducing drugs

BMI, body mass index; CI, confidence interval; CYP, cytochrome P450; DOAC, direct oral anticoagulant; OR, odds ratio

Supplementary Table 10. ORs (95% CI) for the risk of study outcomes, associated with apixaban vs. warfarin and with rivaroxaban vs. warfarin, according to dose classification, among individuals without missing data on eGFR or BMI.

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Ischemic stroke/systemic embolism*						
Any dose	167 (23.7)	522 (24.8)	1.13 (0.88–1.45)	155 (22.0)	546 (26.0)	1.00 (0.78–1.29)
Appropriate dose	129 (18.4)	394 (18.7)	1.16 (0.89–1.52)	122 (17.4)	474 (22.5)	0.92 (0.70–1.21)
Inappropriate dose	38 (5.4)	128 (6.1)	1.04 (0.68–1.58)	31 (4.4)	72 (3.4)	1.37 (0.85–2.21)
Standard dose	112 (16.0)	317 (15.1)	1.29 (0.97–1.70)	111 (15.8)	415 (19.7)	0.94 (0.71–1.25)
Appropriate dose	104 (14.8)	306 (14.6)	1.25 (0.94–1.66)	97 (13.8)	379 (18.0)	0.91 (0.68–1.22)
Inappropriate dose	8 (1.1)	11 (0.5)	2.42 (0.90–6.51)	14 (2.0)	36 (1.7)	1.28 (0.66–2.47)
Reduced dose	55 (7.8)	205 (9.8)	0.90 (0.63–1.29)	42 (6.0)	131 (6.2)	1.11 (0.74–1.68)
Appropriate dose	25 (3.6)	88 (4.2)	0.91 (0.55–1.51)	25 (3.6)	95 (4.5)	0.98 (0.60–1.61)
Inappropriate dose	30 (4.3)	117 (5.6)	0.90 (0.57–1.42)	17 (2.4)	36 (1.7)	1.46 (0.77–2.77)
Intracranial bleeding†						
Any dose	48 (20.3)	236 (24.3)	0.58 (0.38–0.89)	53 (22.4)	233 (24.0)	0.74 (0.49–1.12)
Appropriate dose	40 (16.9)	186 (19.2)	0.62 (0.40–0.97)	43 (18.1)	199 (20.5)	0.71 (0.46–1.09)
Inappropriate dose	8 (3.4)	50 (5.1)	0.45 (0.19–1.03)	10 (4.2)	34 (3.5)	0.91 (0.41–2.01)
Standard dose	28 (11.8)	152 (15.7)	0.55 (0.33–0.91)	34 (14.3)	157 (16.2)	0.73 (0.45–1.16)
Appropriate dose	27 (11.4)	145 (14.9)	0.57 (0.35–0.95)	31 (13.1)	147 (15.1)	0.70 (0.43–1.14)
Inappropriate dose	1 (0.4)	7 (0.7)	0.21 (0.02–1.94)	3 (1.3)	10 (1.0)	1.04 (0.26–4.13)
Reduced dose	20 (8.4)	84 (8.7)	0.64 (0.35–1.17)	19 (8.0)	76 (7.8)	0.78 (0.43–1.41)
Appropriate dose	13 (5.5)	41 (4.2)	0.73 (0.35–1.53)	12 (5.1)	52 (5.4)	0.73 (0.36–1.47)
Inappropriate dose	7 (3.0)	43 (4.4)	0.52 (0.22–1.25)	7 (3.0)	24 (2.5)	0.87 (0.34–2.20)
Haemorrhagic stroke†						
Any dose	28 (20.6)	127 (22.5)	0.71 (0.41–1.24)	35 (25.7)	136 (24.1)	0.98 (0.57–1.66)
Appropriate dose	24 (17.6)	103 (18.3)	0.77 (0.43–1.38)	27 (19.9)	119 (21.1)	0.83 (0.47–1.47)
Inappropriate dose	4 (2.9)	24 (4.3)	0.46 (0.14–1.53)	8 (5.9)	17 (3.0)	2.03 (0.78–5.27)
Standard dose	18 (13.2)	87 (15.4)	0.75 (0.39–1.42)	23 (16.9)	98 (17.4)	0.92 (0.50–1.66)
Appropriate dose	18 (13.2)	83 (14.8)	0.80 (0.42–1.52)	20 (14.7)	95 (17.0)	0.79 (0.43–1.48)
Inappropriate dose	0	0	–	3 (2.2)	3 (0.5)	5.20 (0.92–29.37)
Reduced dose	10 (7.4)	40 (7.1)	0.66 (0.28–1.52)	12 (8.8)	38 (6.7)	1.13 (0.52–2.46)
Appropriate dose	6 (4.4)	20 (3.6)	0.66 (0.23–1.90)	7 (5.1)	24 (4.3)	0.93 (0.36–2.46)

	Apixaban vs. warfarin			Rivaroxaban vs. warfarin		
	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)	Exposed cases, n (%)	Exposed controls, n (%)	OR (95% CI)
Inappropriate dose	4 (2.9)	20 (3.6)	0.60 (0.18–2.01)	5 (3.7)	14 (2.5)	1.42 (0.45–4.45)
Myocardial infarction*						
Any dose	157 (29.0)	393 (25.9)	1.45 (1.08–1.95)	148 (27.4)	402 (26.4)	1.36 (1.00–1.83)
Appropriate dose	115 (21.3)	307 (20.2)	1.36 (0.99–1.87)	108 (20.0)	333 (21.9)	1.25 (0.91–1.73)
Inappropriate dose	42 (7.8)	85 (5.6)	1.84 (1.15–2.96)	36 (6.7)	66 (4.3)	1.75 (1.07–2.87)
Standard dose	95 (17.6)	255 (16.8)	1.40 (1.00–1.95)	89 (16.5)	300 (19.7)	1.19 (0.85–1.67)
Appropriate dose	89 (16.5)	249 (16.4)	1.33 (0.95–1.87)	73 (13.5)	271 (17.8)	1.11 (0.78–1.58)
Inappropriate dose	6 (1.1)	6 (0.4)	3.38 (0.98–11.67)	16 (3.0)	29 (1.9)	1.79 (0.89–3.60)
Reduced dose	62 (11.5)	137 (9.0)	1.60 (1.06–2.41)	55 (10.2)	99 (6.5)	1.77 (1.15–2.72)
Appropriate dose	26 (4.8)	58 (3.8)	1.46 (0.83–2.58)	35 (6.5)	62 (4.1)	1.79 (1.07–3.01)
Inappropriate dose	36 (6.7)	79 (5.2)	1.74 (1.06–2.88)	20 (3.7)	37 (2.4)	1.77 (0.94–3.32)
All-cause mortality†						
Any dose	1424 (23.6)	1604 (27.1)	1.17 (1.04–1.32)	1428 (23.7)	1616 (27.3)	1.32 (1.17–1.49)
Appropriate dose	934 (15.5)	1174 (19.8)	1.07 (0.94–1.22)	1051 (17.4)	1280 (21.6)	1.27 (1.12–1.45)
Inappropriate dose	488 (8.1)	430 (7.3)	1.42 (1.20–1.69)	365 (6.0)	322 (5.4)	1.50 (1.23–1.81)
Standard dose	601 (10.0)	896 (15.1)	0.97 (0.83–1.12)	825 (13.7)	1126 (19.0)	1.21 (1.06–1.38)
Appropriate dose	522 (8.7)	845 (14.3)	0.92 (0.79–1.07)	676 (11.2)	975 (16.4)	1.17 (1.01–1.35)
Inappropriate dose	79 (1.3)	51 (0.9)	1.54 (1.03–2.31)	149 (2.5)	151 (2.5)	1.43 (1.10–1.87)
Reduced dose	821 (13.6)	708 (11.9)	1.41 (1.22–1.64)	591 (9.8)	476 (8.0)	1.58 (1.34–1.86)
Appropriate dose	412 (6.8)	329 (5.5)	1.41 (1.16–1.70)	375 (6.2)	305 (5.1)	1.57 (1.30–1.91)
Inappropriate dose	409 (6.8)	379 (6.4)	1.43 (1.19–1.72)	216 (3.6)	171 (2.9)	1.60 (1.25–2.05)

*ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, health services utilization (hospitalizations, referrals), BMI, alcohol abuse, poly medication, history of ischemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

†ORs were adjusted for matching factors (naive at start date, sex, and year of birth), frailty, hospitalizations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin.

‡ORs were adjusted for matching factors (naive at start date, sex, and year of birth), poly medication, frailty, health services utilization (hospitalizations, referrals), alcohol, BMI, history of peripheral artery disease, ischemic stroke, myocardial infarction, tachycardia,

hyperlipidemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics.

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio