Online Appendix

Appendix Methods

Exposure to oral anticoagulants

The length of an individual prescription in IMRD-UK was based on the number of tablets prescribed and the dosing instructions. For OAC prescriptions in the National Danish Prescription Registry, and for OAC prescriptions in IMRD-UK with unclear dosing instructions, the length of a prescription for warfarin, phenprocoumon or rivaroxaban was based on the number of tablets prescribed (UK)/dispensed (Denmark), and for apixaban, dabigatran and edoxaban it was based on the number of tablets prescribed divided by two, as per the posology on the respective drug labels.

Comorbidities

For all incident IS cases and their controls, we obtained data on comorbidities any time before the index date. In Denmark, we identified comorbidities from the National Danish Patient Registry[1] with additional information obtained from the National Danish Prescription Registry[2] to identify certain conditions (hypertension, diabetes, myocardial infarction, chronic obstructive pulmonary disease and peripheral artery disease). We calculated the CHA_2DS_2Vasc score for stroke risk using patients' recorded history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke/transient ischaemic attack. Renal function was ascertained using data on the most recent estimated glomerular filtration rate (eGFR, expressed as ml/min/1.73m2) from the Register of Laboratory Results for Research in Denmark, and from recorded serum creatinine values in the IMRD-UK applying the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation,[3] but omitting ethnicity because this is not routinely recorded in UK primary care. Coded clinical entries indicating CKD stage, acute or chronic dialysis were also used to determine renal function among UK patients. To obtain the eGFR values, we also accessed data from the Register of Laboratory Results for Research, which holds information on results of blood tests reported by medical laboratories at Danish hospitals performed for both inpatients and outpatients as well as covering blood tests ordered by general practitioners.

We determined whether cases and controls had a history of stroke (IS or intracranial bleeding) any time before the start date (before the start of follow-up), in addition to any time before the index date. In Denmark, stroke history was determined from both the Patient Registry and the Stroke Registry. This was because while the Stroke Registry data for IS outcome identification has a higher positive predictive value (and thus was used for incident IS case identification during follow-up), the Patient Registry contains data back to 1977.

Demographics, lifestyle factors and healthcare use

We obtained data on demographics (age and sex), current smoking status (UK only; using the most recent status before the index date), and healthcare use (0, 1, 2 or ≥3 hospitalizations in the year before the index date; 0–1, 2–4, 5–9, 10–14, 15–19, ≥20 referrals/outpatient contacts in the year before the index date), which were obtained from the Patient Registry for Denmark. Use of drugs other than OACs, including low-dose aspirin, digoxin, anti-arrhythmic drugs, statins, proton pump inhibitors, selective serotonin re-uptake inhibitors, and nonsteroidal anti-inflammatory drugs was determined using the same categories as those described for OACs, with the exception of non-use which was defined as no use of the drug in the year before the index date.

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Calculation of potentially preventable IS cases nationwide among patients receiving OAC therapy if OAC discontinuation was avoided

We used the number of incident cases of IS who were OAC discontinuers at the time of their stroke during the last full year of the follow-up period (2017 UK; 2018 Denmark). These numbers were then multiplied by a factor of 26.1 for the UK and by a factor of 4.7 for Denmark, which represent the magnitude greater the nationwide population aged 20–89 years was to the population of the respective data source (IMRD-UK/RSD) of the same age range. We calculated these multiplicative factors using population estimates from the Office for National Statistics in the UK (mid-2017 estimates),[4] from Statistics Denmark (first quarter of 2018).[5] The estimates were based on the assumption that the number of IS cases across the country did not vary substantially by region.

Sensitivity analysis

In a sensitivity analysis of the UK data, we repeated our main analyses after removing all OAC discontinuers among IS cases and controls where the reason to discontinue OAC therapy was recorded as due to a major bleeding event (including intracranial, gastrointestinal, urogenital, hemothorax, epistaxis or subconjunctival). These patients were identified through a manual review of the relevant patients' EHRs by one investigator (LAGR).

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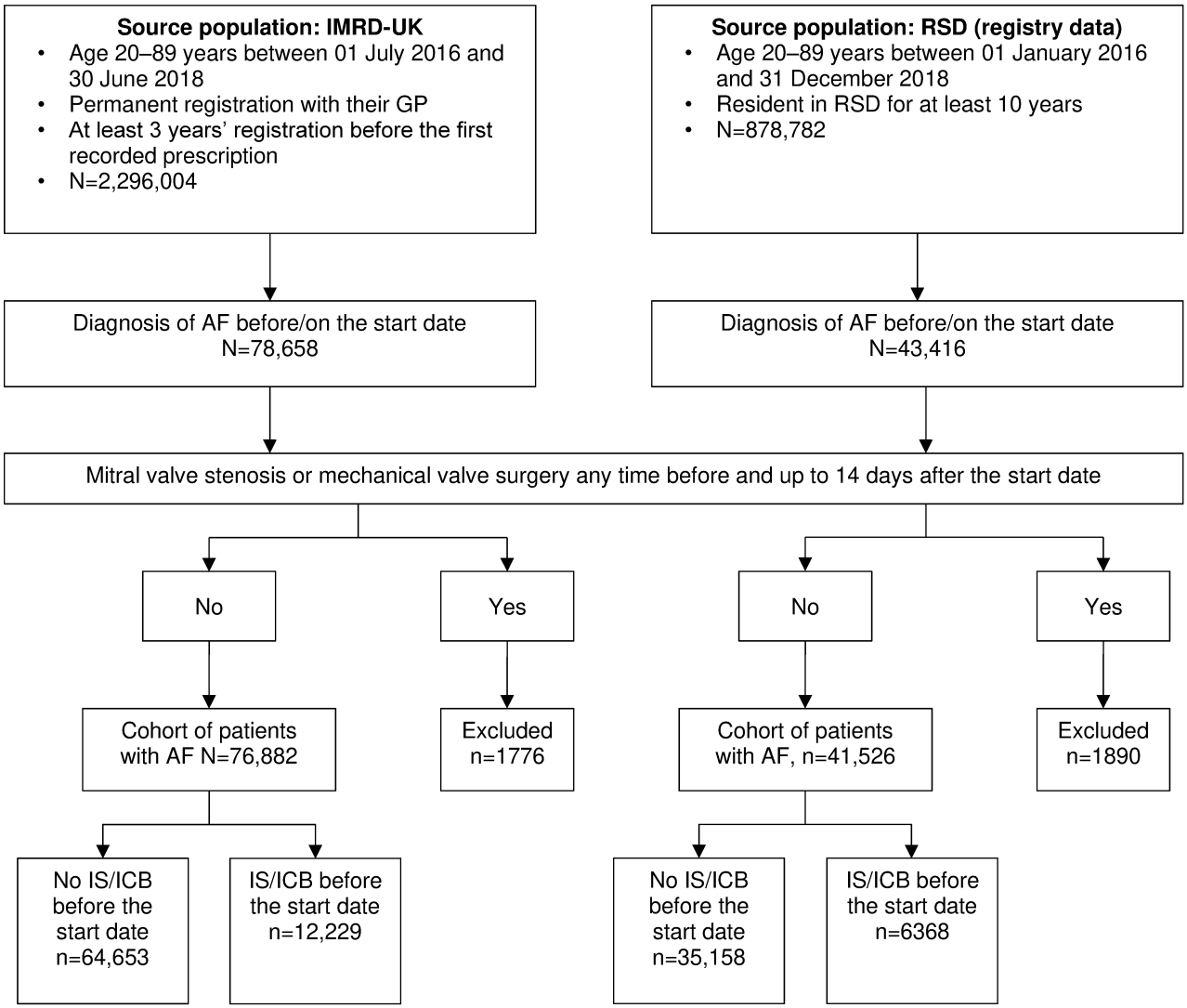
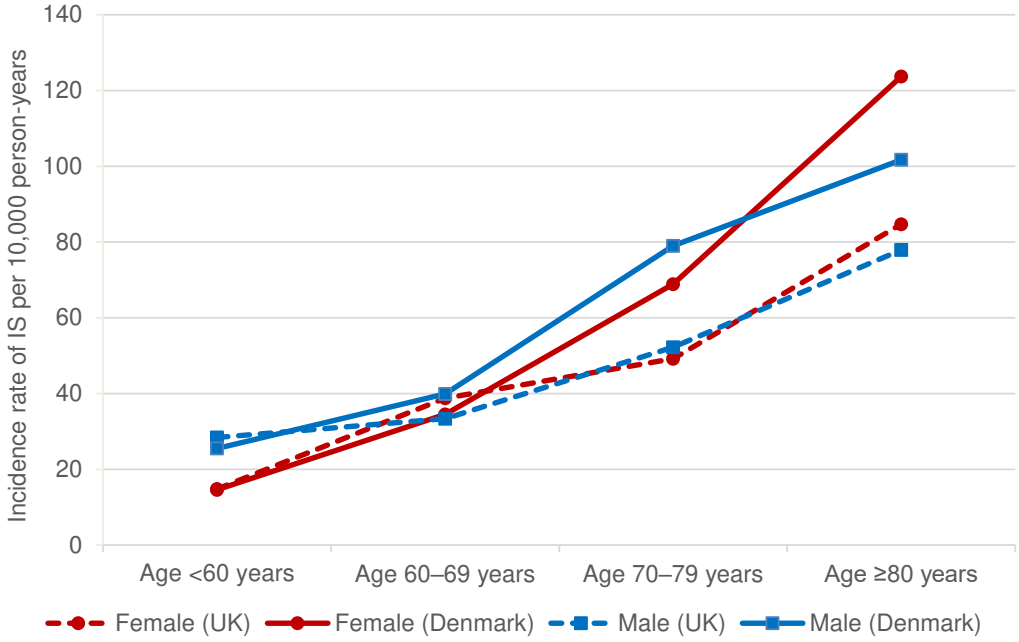


Appendix Figure 1. Identification of the AF study cohort in the UK and Denmark datasets. AF, atrial fibrillation; GP, general practitioner; ICB, intracranial bleeding; IMRD, IQVIA medical research databases; IS, ischaemic stroke; RSD, Region of Southern Denmark; UK, United Kingdom



Appendix Figure 2. Age- and sex-specific incidence rate of IS per 10,000 person-years among patients with AF in the UK and Denmark.
AF, atrial fibrillation; IS, ischaemic stroke; UK, United Kingdom

Appendix Table 1. Incidence rate of IS per 10,000 person-years by age and sex.

	Incidence rate per 10,000 person-years			
Age (years)	**Female (UK)**	**Female (Denmark)**	**Male (UK)**	**Male (Denmark)**
<60	14.8	14.6	28.4	25.5
60–69	38.8	34.5	33.4	39.9
70–79	49.2	68.9	52.2	79.0
≥80	84.7	123.7	77.9	101.7

IS, ischaemic stroke; UK, United Kingdom

Appendix Table 2. Characteristics of incident IS cases and controls, and odds ratios (95% CI) for their association their association with IS.
Note: Adjusted ORs shown in bold italics are those considered significant at the 5% significance level.

	UK (IMRD-UK)					Denmark (RSD)				
	Cases N=615		Controls N=3075		Adjusted OR (95% CI)[a]	Cases N=643		Controls N=6430		Adjusted OR (95% CI)[*]
	n	%	n	%		n	%	n	%	
Demographics										
Males	345	56.1	1725	56.1	NA	358	55.7	3580	55.7	NA
Females	270	43.9	1350	43.9	NA	285	44.3	2850	44.3	NA
Age <60 years	35	5.7	171	5.6	NA	24	3.7	244	3.8	NA
Age 60–69 years	79	12.8	342	11.1	NA	78	12.1	778	12.1	NA
Age 70–79 years	198	32.2	981	31.9	NA	235	36.5	2320	36.2	NA
Age ≥80 years	303	49.3	1581	51.4	NA	306	47.6	3078	47.9	NA
Referrals (UK) / outpatient visits (Denmark)[†]										
0–1	58	9.4	365	11.9	1.00 (reference)	157	24.4	1879	29.2	1.00 (reference)
2–4	94	15.3	643	20.9	0.87 (0.60 to 1.25)	125	19.4	1429	22.2	0.98 (0.77 to 1.27)
5–9	150	24.4	794	25.8	0.98 (0.70 to 1.38)	136	21.2	1380	21.5	1.09 (0.85 to 1.40)
10–14	113	18.4	564	18.3	0.95 (0.66 to 1.37)	77	12.0	650	10.1	1.24 (0.91 to 1.68)
15–19	88	14.3	335	10.9	1.09 (0.73 to 1.61)	51	7.9	399	6.2	1.31 (0.92 to 1.88)
≥20	112	18.2	374	12.2	1.04 (0.70 to 1.54)	97	15.1	693	10.8	1.28 (0.93 to 1.75)
Hospitalizations[†]										–
None	283	46.0	2134	69.4	1.00 (reference)	347	54.0	4223	65.7	1.00 (reference)
1	157	25.5	457	14.9	***2.50 (1.98 to 3.17)***	128	19.9	1078	16.8	***1.34 (1.07 to 1.68***)

	UK (IMRD-UK)					Denmark (RSD)				
	Cases N=615		Controls N=3075		Adjusted OR (95% CI)[a]	Cases N=643		Controls N=6430		Adjusted OR (95% CI)[*]
	n	%	n	%		n	%	n	%	
2	72	11.7	231	7.5	***2.23 (1.62 to 3.05)***	79	12.3	522	8.1	***1.64 (1.24 to 2.17)***
≥3	103	16.7	253	8.2	***2.79 (2.06 to 3.79)***	89	13.8	607	9.4	***1.43 (1.07 to 1.90)***
Current smoker‡	60	9.8	211	6.9	1.27 (0.90 to 1.79)	NA	NA	NA	NA	–
Cerebrovascular disease before the start date										
IS	127	20.7	350	11.4	***1.65 (1.34 to 2.04)***	209	32.5	1037	16.1	***2.33 (1.94 to 2.81)***
ICB	25	4.1	56	1.8	***1.92 (1.16 to 3.16)***	32	5.0	196	3.0	1.15 (0.78 to 1.72)
Comorbidities before the index date										
Myocardial infarction	94	15.3	398	12.9	0.96 (0.74 to 1.25)	107	16.6	856	13.3	1.07 (0.85 to 1.36)
Heart failure	139	22.6	656	21.3	0.94 (0.76 to 1.17)	139	21.6	1269	19.7	0.99 (0.81 to 1.21)
DVT/PE	73	11.79	385	12.5	0.86 (0.65 to 1.14)	44	6.8	483	7.5	0.87 (0.63 to 1.20)
PAD	52	8.5	201	6.5	0.98 (0.70 to 1.38)	90	14.0	547	8.5	***1.51 (1.17 to 1.94)***
Cancer	187	30.4	841	27.3	1.09 (0.89 to 1.33)	132	20.5	1300	20.2	0.95 (0.77 to 1.17)
Hypertension	441	71.7	2139	69.6	1.01 (0.82 to 1.24)	550	85.5	5350	83.2	1.01 (0.80 to 1.29)
Diabetes	170	27.6	734	23.9	1.11 (0.90 to 1.36)	164	25.5	1322	20.6	***1.21 (1.00 to 1.46)***
COPD	104	16.9	370	12.0	1.26 (0.98 to 1.63)	91	14.2	820	12.8	0.99 (0.78 to 1.27)
Dementia	39	6.3	158	5.1	1.02 (0.69 to 1.52)	36	5.6	321	5.0	0.92 (0.64 to 1.33)
Other comorbidities and comedications before the index date										
Urogenital bleeding	104	16.9	456	14.8	1.10 (0.86 to 1.41)	69	10.7	571	8.9	1.19 (0.91 to 1.56)

	UK (IMRD-UK)					Denmark (RSD)				
	Cases N=615		Controls N=3075		Adjusted OR (95% CI)[a]	Cases N=643		Controls N=6430		Adjusted OR (95% CI)[*]
	n	%	n	%		n	%	n	%	
Gastrointestinal bleeding	115	18.7	486	15.8	1.07 (0.85 to 1.25)	99	15.4	726	11.3	1.26 (1.00 to 1.60)
COPD	104	16.9	370	12.0	1.26 (0.98 to 1.63)	91	14.2	820	12.8	0.99 (0.78 to 1.27)
CHA_2DS_2-VASc score										
0–1	58	9.4	335	10.9	1.00 (reference)	51	7.9	726	11.3	1.00 (reference)
2	90	14.6	481	15.6	1.17 (0.76 to 1.78)	84	13.1	1040	16.2	1.29 (0.86 to 1.95)
3	95	15.4	603	19.6	0.85 (0.55 to 1.31)	94	14.6	1517	23.6	1.01 (0.66 to 1.56)
4	155	25.2	830	27.0	1.06 (0.68 to 1.66)	166	25.8	1519	23.6	***1.65 (1.06 to 2.58)***
5	112	18.2	491	16.0	1.12 (0.70 to 1.81)	126	19.6	856	13.3	***1.77 (1.08 to 2.90)***
6	62	10.1	230	7.5	1.18 (0.69 to 2.02)	70	10.9	521	8.1	1.28 (0.72 to 2.26)
7–9	43	7.0	105	3.4	1.39 (0.75 to 2.59)	52	8.1	251	3.9	1.69 (0.90 to 3.16)
eGFR (ml/min/1.73m^2)										
<30	17	2.8	73	2.4	0.84 (0.45 to 1.56)	36	5.6	242	3.8	0.93 (0.55 to 1.57)
30–59	170	27.6	866	28.2	0.92 (0.66 to 1.27)	208	32.3	2164	33.7	***0.65 (0.43 to 0.97)***
60–89	255	41.5	1234	40.1	1.03 (0.76 to 1.39)	292	45.4	2939	45.7	0.71 (0.49 to 1.05)
≥90 (reference)	71	11.5	367	11.9	1.00 (reference)	39	6.1	253	3.9	1.0 (reference)
Missing	102	16.6	535	17.4	1.05 (0.74 to 1.50)	68	10.6	832	12.9	0.70 (0.45 to 1.09)
Medication use[§]										
Antiplatelets	157	25.5	470	15.3	***1.85 (1.49 to 2.30)***	149	23.2	1124	17.5	***1.34 (1.10 to 1.64)***
Antiarrhythmics	40	6.5	357	11.6	***0.53 (0.37 to 0.75)***	41	6.4	492	7.7	0.76 (0.54 to 1.07)
Digoxin	101	16.4	500	16.3	1.06 (0.83 to 1.35)	136	21.2	1223	19.0	1.17 (0.95 to 1.44)

	UK (IMRD-UK)					Denmark (RSD)				
	Cases N=615		Controls N=3075		Adjusted OR (95% CI)[a]	Cases N=643		Controls N=6430		Adjusted OR (95% CI)[*]
	n	%	n	%		n	%	n	%	
Statins	292	47.5	1613	52.5	***0.70 (0.57 to 0.85)***	254	39.5	2656	41.3	0.83 (0.69 to 1.00)
Antihypertensives	495	80.5	2588	84.2	0.93 (0.65 to 1.35)	370	57.5	3691	57.4	0.99 (0.83 to 1.19)
NSAIDs	12	2.0	51	1.7	1.20 (0.61 to 2.35)	33	5.1	214	3.3	***1.69 (1.15 to 2.49)***
SSRI	61	9.9	228	7.4	1.12 (0.82 to 1.53)	69	10.7	532	8.3	1.10 (0.84 to 1.45)
PPIs	212	34.5	1036	33.7	0.84 (0.69 to 1.04)	197	30.6	1482	23.0	***1.27 (1.05 to 1.53)***

[*]Adjusted by the number of referrals/outpatient contacts in the year before the index date, the number of hospitalizations in the year before the index date, use of an antiplatelet medication 0–7 days before the index date, use of an antiarrhythmic medication 0–7 days before the index date (UK analysis only), and cerebrovascular disease before the start date.
[†]In the year before the index date.
[‡]The reference group for smoking was never smoker.
[§]Medication use was use on the index date or within 7 days before the index date; the reference group was non-use (no prescription before the index date).
Note: 615 incident cases of IS were available for the nested case–control analysis based on the most recent IMRD-UK data update at the time these analyses were performed (one case was no longer in the database).
AF, atrial fibrillation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; GIB, gastrointestinal bleeding; ICB, intracranial bleeding; IS, ischaemic stroke; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PAD, peripheral artery disease; PPI, proton pump inhibitor; PE, pulmonary embolism; SSRI, selective serotonin re-uptake inhibitor

Appendix Table 3. Odds ratios (95% CI) for the associations between previous duration of OAC use among discontinuers and the risk of IS among patients with AF.

	UK (IMRD-UK)						Denmark (RSD)					
	Cases N=615		Controls N=3075		Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Cases N=643		Controls N=6430		Crude OR (95% CI)	Adjusted OR[a] (95% CI)
	n	%	n	%			n	%	n	%		
Currently exposed to a NOAC/VKA	**267**	**43.4**	**1994**	**64.8**	1.0 (reference)	1.0 (reference)	339	52.7	4239	65.9	1.0 (reference)	1.0 (reference)
Any OAC discontinued												
Duration ≤120 days	48	7.8	120	3.9	3.02 (2.10–4.33)	2.59 (1.75–3.82)	51	7.9	268	4.2	2.29 (1.63–3.21)	2.58 (1.79–3.71)
Duration >120 days	89	14.5	193	6.3	3.40 (2.57–4.51)	3.22 (2.39–4.33)	80	12.4	515	8.0	2.02 (1.53–2.66)	2.04 (1.51–2.75)
Duration ≤365 days	90	14.6	201	6.5	3.36 (2.53–4.45)	3.12 (2.30–4.23)	97	15.1	561	8.7	2.26 (1.75–2.93)	2.43 (1.85–3.21)
Duration >365 days	47	7.6	112	3.6	3.09 (2.14–4.44)	2.75 (1.88–4.04)	34	5.3	222	3.5	1.82 (1.22–2.71)	1.83 (1.20–2.79)
VKA discontinued												
Duration ≤120 days	26	4.2	78	2.5	2.50 (1.58–3.96)	2.13 (1.31–3.47)	24	3.7	156	2.4	1.70 (1.07–2.70)	1.80 (1.09–2.96)
Duration >120 days	58	9.4	157	5.1	2.69 (1.94–3.73)	2.63 (1.86–3.71)	51	7.9	383	6.0	1.77 (1.27–2.45)	1.77 (1.24–2.54)
Duration ≤365 days	53	8.6	145	4.7	2.72 (1.94–3.83)	2.58 (1.80–3.70)	54	8.4	375	5.8	1.86 (1.35–2.57)	1.94 (1.36–2.77)
Duration >365 days	31	5.0	90	2.9	2.48 (1.62–3.80)	2.28 (1.46–3.56)	21	3.3	164	2.6	1.53 (0.94–2.49)	1.55 (0.93–2.60)
NOAC discontinued												
Duration ≤120 days	25	4.1	42	1.4	4.62 (2.74–7.78)	4.09 (2.33–7.18)	28	4.4	127	2.0	2.82 (1.77-4.48)	3.49 (2.15–5.67)
Duration >120 days	28	4.6	36	1.2	6.34 (3.73–10.76)	5.81 (3.33–10.13)	28	4.4	117	1.8	3.28 (2.03–5.30)	3.51 (2.13–5.80)
Duration ≤365 days	42	6.8	59	1.9	5.59 (3.46–8.59)	5.21 (3.28–8.27)	45	7.0	198	3.1	3.06 (2.09–4.49)	3.62 (2.43–5.38)
Duration >365 days	11	1.8	19	0.6	4.72 (2.20–10.15)	3.96 (1.79–8.76)	11	1.7	46	0.7	3.02 (1.44–6.36)	2.92 (1.33–6.39)

[*]Adjusted by number of referrals/outpatient visits in the year before the index date, the number of hospitalizations in the year before the index date, use of an antiplatelet medication 0–7 days before the index date, use of an antiarrhythmic medication 0–7 days before the index date (UK analysis only), and cerebrovascular disease before the start date.

AF, atrial fibrillation; CI, confidence interval; IS, ischaemic stroke, NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; RSD, Region of Southern Denmark; VKA, vitamin K antagonist; UK, United Kingdom

Appendix Table 4. Odds ratios (95% CI) for the association between OAC discontinuation and the risk of IS among patients with AF using never use of OAC as the reference group.

	UK (IMRD-UK)						Denmark (RSD)					
	Cases N=615		Controls N=3075		Crude OR (95% CI)	Adjusted OR* (95% CI)	Cases N=643		Controls N=6430		Crude OR (95% CI)	Adjusted OR* (95% CI)
	n	%	n	%			n	%	n	%		
Never use of OAC	176	28.6	640	20.8	1.0 (reference)	1.0 (reference)	142	22.1	1188	22.1	1.0 (reference)	1.0 (reference)
Currently exposed to an OAC (NOAC or VKA)	267	43.4	1994	64.8	0.48 (0.39–0.59)	0.50 (0.39–0.64)	339	52.7	4239	65.9	0.65 (0.52–0.80)	0.57 (0.48–0.72)
OAC discontinuation at any time	137	22.3	313	10.2	1.55 (1.19–2.03)	1.52 (1.14–2.01)	131	20.4	783	12.2	1.40 (1.08–1.81)	1.27 (0.98–1.66)

*Adjusted by number of referrals/outpatient visits in the year before the index date, the number of hospitalizations in the year before the index date, use of an antiplatelet medication 0–7 days before the index date, use of an antiarrhythmic medication 0–7 days before the index date (UK analysis only), and cerebrovascular disease before the start date.

Note: Cases and controls not included in the analysis were as follows: Denmark, 9/43 current switchers, 5/66 intermediate users of VKA and 17/111 intermediate users of NOAC; UK , 6/11 current switchers, 16/62 intermediate users of VKA and 13/55 intermediate users of NOAC.

AF, atrial fibrillation; CI, confidence interval; IS, ischaemic stroke, NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; RSD, Region of Southern Denmark; VKA, vitamin K antagonist; UK, United Kingdom