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Discontinuation of oral anticoagulation in atrial fibrillation and risk of ischaemic stroke

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ABSTRACT

Objective To evaluate associations between oral anticoagulant (OAC) discontinuation and risk of ischaemic stroke (IS) among patients with atrial fibrillation (AF).

Methods We undertook a population-based cohort study with nested case–control analysis using UK primary care electronic health records (IQVIA Medical Research Data-UK) and linked registries from the Region of Southern Denmark (RSD). Patients with AF (76 882 UK, 41 526 RSD) were followed to identify incident IS cases during 2016–2018. Incident IS cases were matched by age and sex to controls. Adjusted ORs for OAC discontinuation (vs current OAC use) were calculated using logistic regression.

Results We identified 616 incident IS cases in the UK and 643 in the RSD. ORs for IS with any OAC discontinuation were 2.99 (95% CI 2.31 to 3.86, UK) and 2.30 (95% CI 1.79 to 2.95, RSD), for vitamin K antagonist discontinuation they were 2.38 (95% CI 1.72 to 3.30, UK) and 1.83 (95% CI 1.34 to 2.49, RSD), and for non-vitamin K antagonist oral anticoagulant discontinuation they were 4.59 (95% CI 2.97 to 7.08, UK) and 3.37 (95% CI 2.35 to 4.85, RSD). ORs were unaffected by time since discontinuation and duration of use. Annually, up to 987 IS cases in the UK and 132 in Denmark could be preventable if OAC therapy is not discontinued.

Conclusions Our results suggest that patients with AF who discontinue OAC therapy have a significant twofold to threefold higher risk of IS compared with those who continue therapy. Addressing OAC discontinuation could potentially result in a significant reduction in AF-attributed IS.

INTRODUCTION

Atrial fibrillation (AF) is the most common chronic cardiac arrythmia affecting approximately 2%–3% of the population of Europe and the USA.[1] It is associated with a fivefold increased risk of ischaemic stroke (IS) across all ages.[2] Approximately one-third of IS events are attributed to AF, and these are frequently severe leading to death or significant disability.[3] However, there is clear evidence that they are preventable with oral anticoagulant (OAC) therapy. Vitamin K antagonists (VKAs) reduce the risk of stroke by around two-thirds compared with controls,[4] and non-vitamin K antagonist oral anticoagulants (NOACs) afford at least a comparable benefit but with the advantage of less intracranial bleeding.[5]

Clinical guidelines thus recommended life-long OAC therapy for patients with AF at increased stroke risk.[6 7] Continuous OAC therapy without interruption is necessary to maintain this benefit. Observational studies indicate that patients with AF who discontinue OAC therapy have an approximately twofold increased risk of stroke/transient ischaemic attack (TIA),[8 9] yet, 1-year OAC discontinuation rates are reportedly high—between 30% and 70%.[10 11] To help address this significant care gap, robust data from recent clinical practice are needed to better determine the magnitude of the potential benefit for the AF population if OAC discontinuation is avoided. Of the limited studies on this topic, few, if any, have explored whether the risk of ischaemic stroke varies by time since OAC discontinuation, duration of OAC use before discontinuation or OAC class. We therefore conducted a large population-based cohort study with nested case–control analysis, using two separate datasets from the UK and Denmark to evaluate associations between OAC discontinuation and risk of IS among patients with AF.

MATERIALS AND METHODS

Data sources

We used the IQVIA Medical Research Data-UK (IMRD-UK), formerly known as The Health Improvement Network (THIN). The IMRD-UK is a database of de-identified longitudinal primary care electronic health records (EHRs) reflecting routine patient care. The database covers approximately 6% of the UK population, to which it is generalisable in terms demography, prevalence of major diseases and death rates.[12] It includes coded entries (Read codes, the standard clinical coding system used by the UK's National Health Service) and captures all prescriptions issued in primary care. Information received from secondary care visits is entered retrospectively. We also accessed data from five linked registries covering the Region of Southern Denmark (RSD; population ~1.2 million), which is representative of the Danish population regarding demographics, healthcare and medication use.[13] Details on four of these registers—the National Danish Patient Registry, the Danish National Prescription Registry, the Danish Stroke Registry and the Danish Civil Registry—have been published previously.[14–17] We also used the Register of Laboratory Results for

Table 1 Characteristics of incident IS cases and controls

	UK (IMRD-UK)				Denmark (RSD)			
	Cases n=615		Controls n=3075		Cases n=643		Controls n=6430	
	N	%	N	%	N	%	N	%
Demographics								
Males	345	56.1	1725	56.1	358	55.7	3580	55.7
Females	270	43.9	1350	43.9	285	44.3	2850	44.3
Age <60 years	35	5.7	171	5.6	24	3.7	244	3.8
Age 60–69 years	79	12.8	342	11.1	78	12.1	778	12.1
Age 70–79 years	198	32.2	981	31.9	235	36.5	2320	36.2
Age ≥80 years	303	49.3	1581	51.4	306	47.6	3078	47.9
Referrals (UK)/outpatient visits (Denmark)*								
0–1	58	9.4	365	11.9	157	24.4	1879	29.2
2–4	94	15.3	643	20.9	125	19.4	1429	22.2
5–9	150	24.4	794	25.8	136	21.2	1380	21.5
10–14	113	18.4	564	18.3	77	12.0	650	10.1
15–19	88	14.3	335	10.9	51	7.9	399	6.2
≥20	112	18.2	374	12.2	97	15.1	693	10.8
Hospitalisations*								
None	283	46.0	2134	69.4	347	54.0	4223	65.7
1	157	25.5	457	14.9	128	19.9	1078	16.8
2	72	11.7	231	7.5	79	12.3	522	8.1
≥3	103	16.7	253	8.2	89	13.8	607	9.4
Cerebrovascular disease before the start date								
IS	127	20.7	350	11.4	209	32.5	1037	16.1
ICB	25	4.1	56	1.8	32	5.0	196	3.0
Comorbidities before the index date								
Myocardial infarction	94	15.3	398	12.9	107	16.6	856	13.3
Heart failure	139	22.6	656	21.3	139	21.6	1269	19.7
DVT/PE	73	11.79	385	12.5	44	6.8	483	7.5
PAD	52	8.5	201	6.5	90	14.0	547	8.5
Cancer	187	30.4	841	27.3	132	20.5	1300	20.2
Hypertension	441	71.7	2139	69.6	550	85.5	5350	83.2
Diabetes	170	27.6	734	23.9	164	25.5	1322	20.6
COPD	104	16.9	370	12.0	91	14.2	820	12.8
Dementia	39	6.3	158	5.1	36	5.6	321	5.0
Medication use†								
Antiplatelets	157	25.5	470	15.3	149	23.2	1124	17.5
Antiarrhythmics	40	6.5	357	11.6	41	6.4	492	7.7
Digoxin	101	16.4	500	16.3	136	21.2	1223	19.0
Statins	292	47.5	1613	52.5	254	39.5	2656	41.3
Antihypertensives	495	80.5	2588	84.2	370	57.5	3691	57.4
NSAIDs	12	2.0	51	1.7	33	5.1	214	3.3

Adjusted by the number of referrals/outpatient contacts in the year before the index date, the number of hospitalisations 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.
†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).
.COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ICB, intracranial bleeding; IMRD-UK, IQVIA Medical Research Data-UK; IS, ischaemic stroke; NSAID, non-steroidal anti-inflammatory drug; PAD, peripheral artery disease; ; PE, pulmonary embolism.

Research, which contains results of blood tests conducted within Danish hospitals for inpatients/outpatients and those requested by general practitioners.

Study design and source population

The study design is shown in online supplemental figure 1. The source populations included individuals aged 20–89 years between 1 January 2016 and 31 December 2018 (Denmark) or between 1 July 2016 and 30 June 2018 (UK). These study periods were based on obtaining a 2-year period defined by the latest available data updates. The upper age cut-off was applied due to the high proportion of people above this age living in long-term care facilities, and thus with potentially more incomplete medical records. Individuals in IMRD-UK were required to be permanently registered with their practice, and to have at least 3 years' registration before their first recorded prescription. In Denmark, individuals were required to have been residents of Southern Denmark for at least 10 years. We assigned each individual a 'start date' (start of follow-up) defined as the start of the study period or, for Denmark, the date of immigration to RSD (from elsewhere in Denmark or abroad) if this was later. We assigned a 'stop date' (end of follow-up), defined as the earliest of the following: the first coded entry of IS after the start date (using the Stroke Registry for Denmark, which records all IS hospitalisations), the emigration date from RSD (for Denmark), date of death or the end of the study period.

Table 2 OAC exposure among incident cases of IS in the UK and Denmark

	Incident cases of IS	
	UK (IMRD-UK) N=615 n (%)	Denmark (RSD) N=643 n (%)
Any OAC		
Current use†	267 (43.4)	339 (52.7)
Intermediate use	29 (4.7)	22 (3.4)
Discontinued	137 (22.3)	131 (20.4)
Non-use	176 (28.6)	142 (22.1)
Any VKA		
Current use†	141 (22.9)	164 (25.5)
Intermediate use	16 (2.6)	5 (0.8)
Discontinued	84 (13.7)	75 (11.7)
Non-use*	368 (59.8)	390 (60.7)
Any NOAC		
Current use†	126 (20.5)	175 (27.2)
Intermediate use	13 (2.6)	17 (2.6)
Discontinued	53 (13.7)	56 (8.7)
Non-use*	383 (62.3)	386 (60.0)

Definitions of OAC exposure were as follows: *current use*, when the prescription supply lasted until the index date or ended within the 7 days before the index date; *intermediate use*, when the prescription supply ended 8–30 days before the index date; *discontinued*, when the prescription supply ended ≥31 days before index date; *non-use*, when there was no prescription before the index date.
*Non-users of any VKA and non-users of any NOAC were not mutually exclusive categories.
†In the UK, six cases were current users of both a VKA and a NOAC and were not included. These six cases were considered 'OAC switchers' and not current users of one OAC class. In Denmark, 9 cases were considered 'OAC switchers' and not current users of one OAC class.
IMRD-UK, IQVIA Medical Research Data-UK; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; RSD, Region of Southern Denmark; VKA, vitamin K antagonist.

Public and patient involvement

No patients were involved in any aspect of the study design, implementation of the study or the interpretation and writing of the results. There are no plans to involve patients in the dissemination of the study results.

AF cohort

We restricted the source cohorts to patients with AF diagnosed before the start date (prevalent AF) and those with AF diagnosed between the start and stop date (incident AF). For the latter, the start date was reassigned to the date of AF diagnosis. For Denmark, AF was identified from the Danish National Patient Registry using International Classification of Diseases (ICD)−10 codes that have a 93% positive predictive value (PPV).[18] We are unaware of AF validation studies in IMRD-UK, yet a validation study of a similar primary care database reported a 92.6% PPV for AF Read code entries.[19] We excluded patients with a code for mitral valve stenosis or mechanical valve surgery any time before, and up to 14 days after, the start date.

Outcome identification

For the UK, patients were required to have a hospitalisation recorded between 15 days before and 30 days after the IS code entry date. This was determined through manual review of patients' EHR by one investigator (LCS) with review by a second investigator (LAGR) where necessary to ensure that the hospitalisation related to the first incident IS during follow-up. The date of hospitalisation was the index date. For Denmark, the PPV (90%) and sensitivity (91%) of the ICD-10 IS codes in the stroke registry are high.[20] We did not exclude patients with a history of stroke (ischaemic or haemorrhagic) before the start date, thus the stroke could have been either a first or recurrent event.

Control selection

Controls were randomly selected from the country-specific AF cohort by risk-set sampling and individually matched to cases (UK 5:1, Denmark 10:1) by age and sex. To do this, for each case, we identified all cohort members who were still at risk of a first IS and of the same age and sex (the case set). Within each case set, 5 controls (UK) or 10 controls (Denmark) were selected at random using the sttocc command in STATA. Matched controls were assigned the index date of their corresponding case. Cases were eligible to be controls for another case until the date of their IS. By this design, the OR is an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study based on the source population.

Exposure to oral anticoagulants

Exposure to OACs for IS cases and controls up to (and including) the index date was determined from prescription records in IMRD-UK and the Danish Prescription Registry (see online supplemental methods). Based on the most recent episode of OAC use before the index date, OAC exposure was categorised as follows: *current use*, when the prescription supply lasted until/over the index date or ended within the seven previous days; *intermediate use*, when the prescription supply ended 8–30 days before the index date; *discontinued*, when the prescription supply ended ≥31 days before the index date; and *non-use*, where there was no prescription before the index date. An OAC treatment episode comprised the length of consecutive

Table 3 Nationwide estimates for the UK and Denmark of the number of IS cases potentially occurring among patients with AF who had discontinued OAC therapy at the time of stroke

	IS cases in last full year of follow-up† who were OAC discontinuers at the time of stroke	Population of IMRD-UK/RSD aged 20–89 years	Nationwide population aged 20–89 years*	Multiplicative factor	Estimated number of IS cases nationwide among OAC discontinuers
UK	63	2 125 080	49 948 645	23.5 (49 948 645/2 125 080)	1481 (63×23.5)
Denmark	42	932 769	4 430 000	4.7 (4 430 000/932 769)	198 (42×4.7)

*Data for first quarter of 2018 used from Statistics Denmark.
†2017 UK, 2018 Denmark.
AF, atrial fibrillation; IMRD-UK, IQVIA Medical Research Data-UK; IS, ischaemic stroke; OAC, oral anticoagulant; RSD, Region of Southern Denmark.;

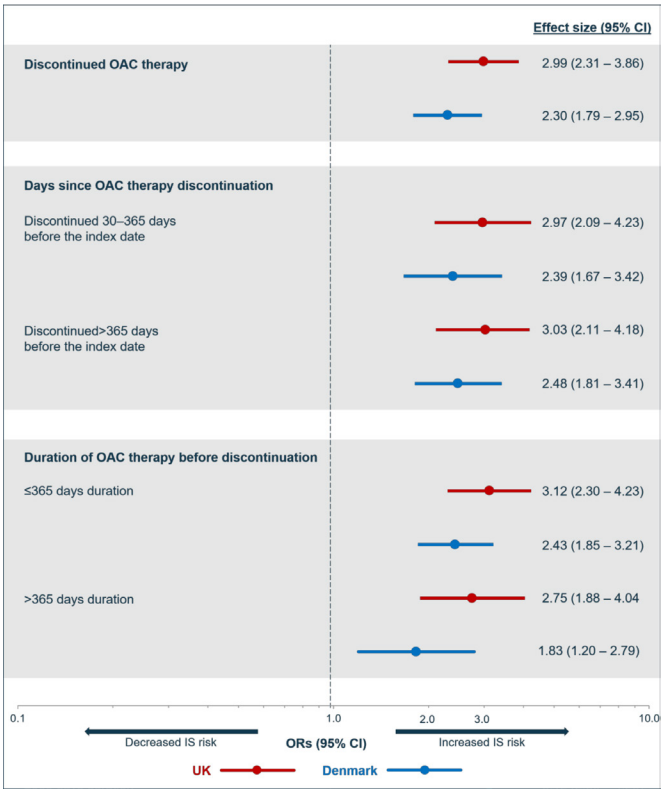

Figure 1 ORs (95% CI) for associations between oral anticoagulant (OAC) discontinuation and risk of ischaemic stroke (IS).

prescriptions disregarding gaps between prescriptions of ≤30 days (grace period). Current users of both a VKA and a NOAC (ie, switchers) were assigned to a separate category. Discontinuers of NOAC therapy were required to have no VKA use between the date of NOAC discontinuation and the index date, and vice versa.

Comorbidity and other potential confounders

We obtained data on comorbidities and other potential confounders as described in online supplemental methods.

Statistical analysis

Descriptive analyses were undertaken with categorical data presented using frequency counts and percentages, and continuous data using means with SD. Incidence rates were calculated as the number of incident IS cases during follow-up divided by the total person-years, with 95% CIs based on assuming a Poisson distribution. Incidence rates were stratified by age and sex. We estimated the annual number of potentially preventable IS cases among patients with AF that would occur nationwide in the absence of any episode of OAC discontinuation, based on data from the last complete year of the study period and population census data (see online supplemental methods). Nested case–control analyses were conducted using conditional logistic regression to calculate ORs as measures of the relative risk of IS with OAC discontinuation (vs current OAC use) adjusted for confounders. We used a stepwise approach retaining variables in the model that changed the OR by 10% or more. We included the number of referral/outpatient visits in the final model as an informative proxy variable for overall comorbidity. Stratified analyses were performed by time since OAC discontinuation (30–365 or ≥365 days before the index date) and by duration of the last episode of OAC use before discontinuation (≤120 or >120 days, ≤365 or >365 days). Sensitivity analysis of the UK data was performed to evaluate the effect of excluding patients who discontinued OAC therapy due to major bleeding (see online supplemental methods). We performed a post hoc analysis changing the reference group to 'never use of an OAC'.

Analyses were undertaken using Stata, V.12 (UK), V.16 (Denmark).

RESULTS

Incidence of IS

The AF study cohorts comprised 76 882 (UK) and 41 526 (Denmark) patients. Mean age (SD) at the start of follow-up was 72.9 years (±11.4, UK) and 71.8 years (±11.5, Denmark). Men accounted for 58.7% (UK) and 58.8% (Denmark) of the study cohort. We identified 616 incident IS cases during 114 461 person-years (UK) and 643 incident IS cases during 95 236 person-years (Denmark). Corresponding incidence rates of IS were 53.8 per 10 000 person-years (95% CI 49.7 to 58.2, UK) and 67.5 (95% CI 62.4 to 72.9, Denmark). The mean age of IS cases was 77.5 years (SD 9.2, UK) and 78.4 years (SD 9.0, Denmark). Men accounted for 56.0% (UK) and 55.7 (Denmark) of IS cases. Incidence rates of IS increased with age (online supplemental figure 2 and table 1).

Factors associated with incident IS

Characteristics of IS cases and controls in the UK and Danish cohorts are shown in table 1 and online supplemental table 2. In both UK and Danish cohorts, having at least one hospitalisation (due to any cause) in the year before the index date was associated with a higher risk of IS. Other factors shown to be associated with a higher risk of IS were having a history of IS, current use of antiplatelets and, for Denmark, a diagnosis of peripheral artery disease. Current use of antiarrhythmics was associated with a lower risk of IS.

Discontinuation (previous use) of OAC therapy among incident cases of hospitalised IS

The number of IS cases in each OAC exposure category is shown in table 2. A total of 28.6% (176/615) of UK IS cases and 22.1% (142/643) of Danish IS cases had no OAC prescription before their IS. Among IS cases who had ever used an OAC, 31.2% (UK, 137/439) and 26.1% (Denmark, 131/501) of cases discontinued OAC therapy before their hospitalisation. Among IS cases ever prescribed a VKA, 34.0% (UK, 84/247) and 29.6% (Denmark, 75/253) discontinued, while among IS cases ever prescribed a NOAC, 26.8% (UK, 53/198) and 21.8% (Denmark, 56/257) discontinued. Sixty-three IS cases 2017 (UK) and 42 IS cases in 2018 (Denmark) were OAC discontinuers. Using population estimates of the data sources and nationwide, we estimated that annually, 1481 IS cases in the UK and 198 IS cases in Denmark occurred among patients with AF who discontinued OAC therapy (table 3). As randomised controlled trials have documented that OAC therapy reduces IS risk by approximately two-thirds,[4 5] we estimated that 987 (ie, two-thirds of 1481) IS cases in the UK and 132 (two-thirds of 198) IS cases in Denmark are potentially preventable if OAC therapy is not discontinued.

OAC discontinuation and risk of IS

OAC discontinuation was associated with an increased risk of IS in both datasets (figure 1, table 4). For any OAC discontinuation, adjusted ORs were 2.99 (95% CI 2.31 to 3.86, UK) and 2.30 (95% CI 1.79 to 2.94, Denmark), for VKA discontinuation

Table 4 ORs (95% CI) for the association between time since OAC discontinuation 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* (95% CI)	Cases n=643		Controls n=6430	Crude OR (95% CI)	Adjusted OR* (95% CI)	
	N	%	N	%			N	%	N	%		
Currently exposed to an OAC	267	43.4	1994	64.8	1.0 (reference)	1.0 (reference)	339	52.7	4239	65.9	1.0 (reference)	1.0 (reference)
OAC discontinuation at any time												
Any OAC	137	22.3	313	10.2	3.25 (2.56 to 4.13)	2.99 (2.31 to 3.86)	131	20.4	783	12.2	2.18 (1.74 to 2.74)	2.30 (1.79 to 2.95)
VKA	84	13.7	235	7.6	2.89 (2.13 to 3.92)	2.38 (1.72 to 3.30)	75	11.7	539	8.4	1.77 (1.34 to 2.33)	1.83 (1.34 to 2.49)
NOAC	53	8.6	78	2.5	4.83 (3.21 to 7.26)	4.59 (2.97 to 7.08)	56	8.7	244	3.8	3.02 (2.14 to 4.25)	3.37 (2.35 to 4.85)
OAC discontinuation 30–365 days before the index date												
Any OAC	59	9.6	125	4.1	3.54 (2.53 to 4.95)	2.97 (2.09 to 4.23)	51	7.9	276	4.3	2.45 (1.74 to 3.45)	2.39 (1.67 to 3.42)
VKA	26	4.2	77	2.5	2.49 (1.57 to 3.94)	2.08 (1.29 to 3.35)	13	2.0	135	2.1	1.20 (0.66 to 2.20)	1.15 (0.62 to 2.15)
NOAC	33	5.4	48	1.6	5.61 (3.46 to 9.08)	4.78 (2.88 to 7.95)	38	5.9	141	2.2	3.84 (2.52 to 5.86)	3.82 (2.44 to 5.97)
OAC discontinuation >365 days before the index date												
Any OAC	78	12.7	188	6.1	3.07 (2.29 to 4.13)	3.03 (2.11 to 4.18)	80	12.4	507	7.9	2.08 (1.58 to 2.73)	2.48 (1.81 to 3.41)
VKA	58	9.4	158	5.1	2.70 (1.95 to 3.75)	2.72 (1.91 to 3.86)	62	9.6	404	6.3	1.95 (1.44 to 2.64)	2.21 (1.55 to 3.15)
NOAC	20	3.3	30	1.0	5.03 (2.70 to 9.07)	4.98 (2.63 to 9.43)	18	2.8	103	1.6	2.07 (1.19 to 3.62)	2.87 (1.60 to 5.15)
Intermediate use: discontinued 8–30 days before the index date												
Any OAC	29	4.7	117	3.8	1.84 (1.20 to 2.82)	1.51 (0.97 to 2.36)	22	3.4	177	2.8	1.71 (1.05 to 2.78)	1.41 (0.85 to 2.34)
VKA	16	2.6	62	2.0	2.08 (1.17 to 3.70)	1.59 (0.86 to 2.91)	5	0.8	66	1.0	1.17 (0.45 to 3.02)	0.78 (0.29 to 2.10)
NOAC	13	2.1	55	1.8	1.66 (0.88 to 3.12)	1.50 (0.77 to 2.88)	17	2.6	111	1.7	1.97 (1.11 to 3.47)	1.80 (1.00 to 3.24)

*Adjusted by number of referrals/outpatient visits in the year before the index date, the number of hospitalisations 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; IMRD-UK, IQVIA Medical Research Data-UK; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; RSD, Region of Southern Denmark; VKA, vitamin K antagonist.

they were 2.38 (95% CI 1.72 to 3.30, UK) and 1.83 (95% CI 1.34 to 2.48, Denmark), and for NOAC discontinuation they were 4.59 (95% CI 2.97 to 7.08, UK) and 3.37 (95% CI 2.35 to 4.84, Denmark). ORs from analyses stratified by time since OAC discontinuation (table 4) and duration of OAC use before discontinuation (figure 1, online supplemental file 1) were not significantly different from the main estimates. In the sensitivity analysis, after removing 25/137 (18.2%) IS cases and 34/313 (10.91%) controls in the UK who had discontinued OAC therapy due to bleeding, the OR for IS (2.88, 95% CI 2.19 to 3.78) was only minimally different from the main analysis estimate. In the post hoc analysis, using never use as the reference group, current OAC use was associated with a significantly reduced risk of IS, and OAC discontinuation was associated with an increased risk of IS (online supplemental table 4).

DISCUSSION

In our large population study using data from the UK and Denmark, we found that patients with AF who discontinue OAC therapy have a twofold to threefold higher risk of IS compared with those who maintain therapy. There was no evidence that this risk changed appreciably by time since OAC discontinuation or duration of OAC use or differed by OAC class. We estimated that close to 987 IS cases in the UK and 132 IS cases in Denmark could be preventable every year if OAC therapy was not discontinued.

A key strength of our study is the population-based settings in two European countries with different healthcare systems and the similar results observed from these two settings. Our findings have good generalisability because the study cohorts included elderly patients and those with multiple comorbidities, reflecting the spectrum of patients with AF in clinical practice, and the individuals in the IMRD-UK and the RSD are representative of their respective nationwide populations.[12 13] We evaluated both VKAs and NOACs—the latter being increasingly prescribed over the last decade,[21 22] and the OAC class recommended for stroke prevention in this patient population in American guidelines.[6] The nested case–control analysis enabled an accurate assessment of OAC exposure—a variable that changes over time. To further avoid misclassification of OAC therapy, we did not include patients who discontinued OAC therapy in the month before the index date in our main discontinuer category, that is, patients more prone to exposure misclassification. Discontinuation of OAC may represent an appropriate response to, for example, a major bleeding event, yet our sensitivity analysis indicated that the associations seen are not explained by bleeding occurrence. Although some misclassification of OAC exposure may still have occurred as we assumed that all patients took their medicine, any misclassification would have been non-differential between IS cases and controls and biased the risk estimates towards the null. Another limitation is that some IS cases in the UK may have been missed if information from secondary care was not recorded. This could be one reason why IS incidence rates in the UK were lower than those in RSD where stroke cases were identified from a hospital-based database. In addition, the percentage of IS cases with a previous IS (a risk factor for subsequent stroke) was lower in the IMRD-UK (20.7%) than in the RSD (32.5%), and incidence rates of IS in Denmark were notably higher than UK rates in the Global Burden of Disease study.[23] While we adjusted for confounding factors in our analyses, residual confounding cannot be excluded.

The twofold to threefold higher risk of IS associated with OAC discontinuation observed in our study is roughly the inverse of the benefit obtained with OAC use for stroke prevention in AF seen in randomised trials.[4 5] This level of increased IS risk is also consistent with previous smaller observational studies on this topic,[8 9 24 25] including those from Martinez *et al*[24] in the UK who similarly found that time since VKA discontinuation was not an influencing factor on IS risk. Other smaller observational studies have reported even high relative risks for stroke with VKA cessation.[26 27] Although the point estimates in our study suggest IS risk could be higher when the OAC discontinued is a NOAC, this could be explained by greater exposure misclassification for VKAs than NOACs. One could expect misclassification of VKA exposure to be more common because dosing is guided by the international normalised ratio. This could lead to greater inaccuracy in determining VKA prescription length using prescription data alone, thus diluting the true increased relative risk under a non-differential assumption.

Our findings have high clinical relevance as they point towards a significant potential to reduce AF-related IS if OAC discontinuation levels are reduced. OAC discontinuation is common—in our study, nearly one-third of IS cases in the UK and about a quarter of those in Denmark were classed as discontinuers at the time of their IS, and it should be noted that these patients may have had previous episodes of discontinuation. In addition, we found that a substantial percentage of IS cases (28.6% UK, 22.1% Denmark) were not prescribed OAC therapy before their stroke, in line with a previous study from Denmark.[28] Our estimates could help support physician–patient communication about the extent of IS risk if they were to discontinue OAC therapy. Encouraging therapy persistence is increasingly important as ageing populations will see greater numbers of people living with AF and requiring OAC therapy. So far, evidence regarding a potential benefit of educational/behavioural interventions on OAC persistence among patients with AF is lacking,[29 30] thus further research into ways of increasing therapy OAC persistence among patients with AF is needed. The quantitative evidence provided from our study, of the importance of continuing OAC therapy, may help towards greater prioritisation of this topic, as well as being helpful for physicians in their efforts to educate patients about the importance of OAC persistence.

Key messages

What is already known on this subject?

- The majority of patients with atrial fibrillation (AF) require long-term oral anticoagulant (OAC) therapy to reduce their risk of ischaemic stroke (IS), yet levels of OAC discontinuation among this patient population are high.

What might this study add?

- Our study suggests that patients who discontinued OAC therapy have a two- to three-fold higher IS risk than those who maintain therapy, irrespective of OAC class, time since discontinuation, or OAC duration.

How might this impact on clinical practice?

- Encouraging persistence with OAC therapy in patients with AF could potentially result in a significant reduction in AF-attributed IS.

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Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA.

Contributors LAGR, DG, YB, GB and PV contributed to the design of the study. LCS, LAGR and DG extracted the data and performed the statistical analysis. All authors contributed to the interpretation of the data and the review of manuscript drafts, and all approved the final manuscript. LAGR is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests LAGR works for CEIFE, which has received other research funding from Bayer AG. LAGR has also received honoraria for serving on advisory boards for Bayer AG. DG has received honoraria from AstraZeneca (Sweden) for participation as a co-investigator on a research project outside the submitted work, and receiving speaker honorarium from Bristol-Myers Squibb outside the submitted work. YB and PV are employees of Bayer AG. GB is an employee of Bayer AB. MS has served on the steering committees and led sub-studies from trials sponsored by Bayer and has served as a consultant and received speaker's honoraria from Bayer. MS has also served as a consultant to Portola, Bristol Myers Squibb and Janssen. LCS, SMH and JH report no potential conflicts of interest.

Patient consent for publication Not required.

Ethics approval The UK and Denmark studies were approved by the Independent Scientific Research Committee for IMRD-UK (reference no. 19THIN057) and the Danish Data Protection Agency, respectively. Data collection for IMRD-UK was approved by the South East Multicentre Research Ethics Committee in 2003 and individual studies using IMRD-UK data do not require separate ethical approval if only anonymised data are used. Danish law does not require approval from an ethics board or informed consent for register studies.

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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.

García Rodríguez LA, *et al. Heart* 2020;0:1–7. doi: 10.1136/heartjnl-2020-317887

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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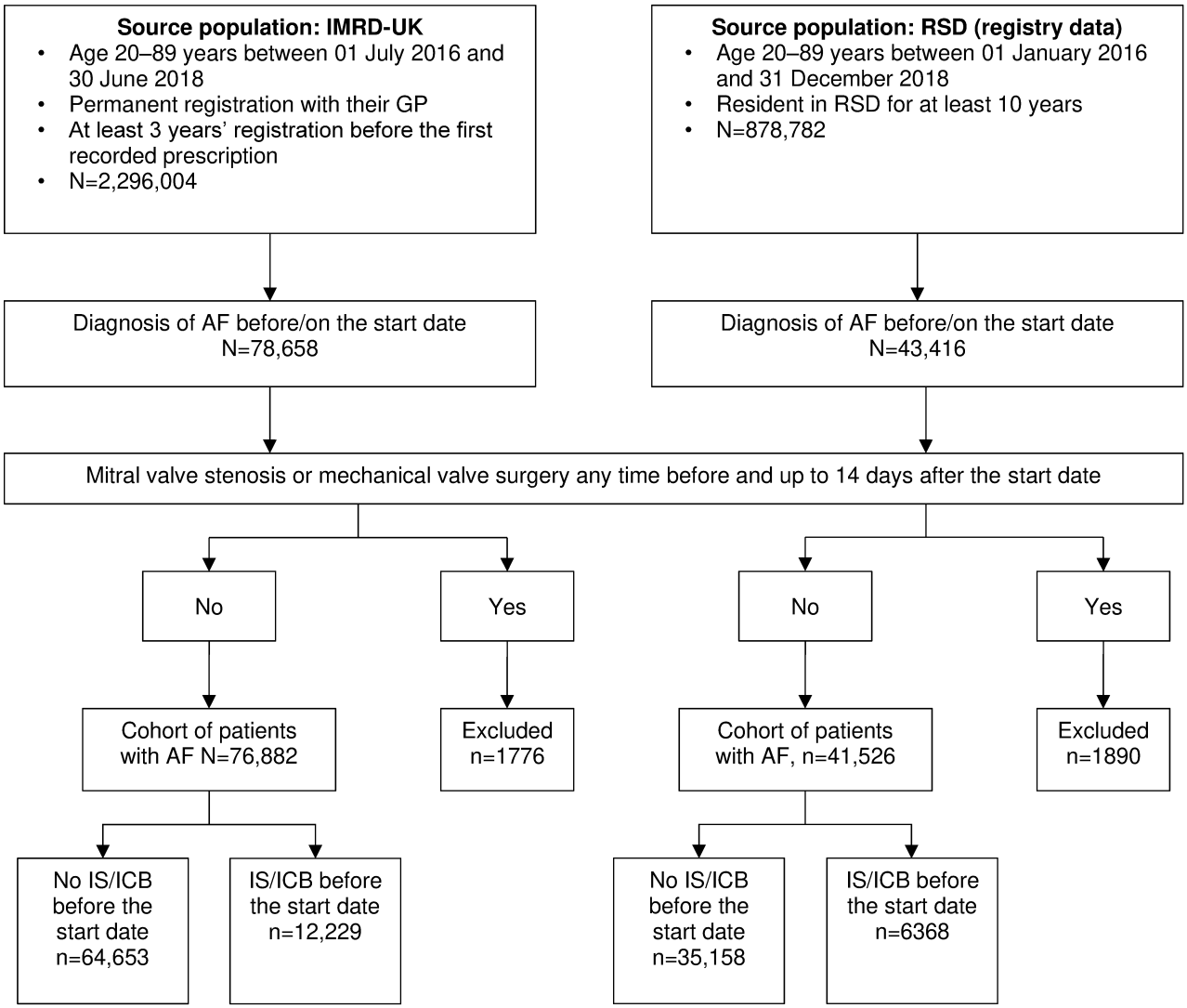
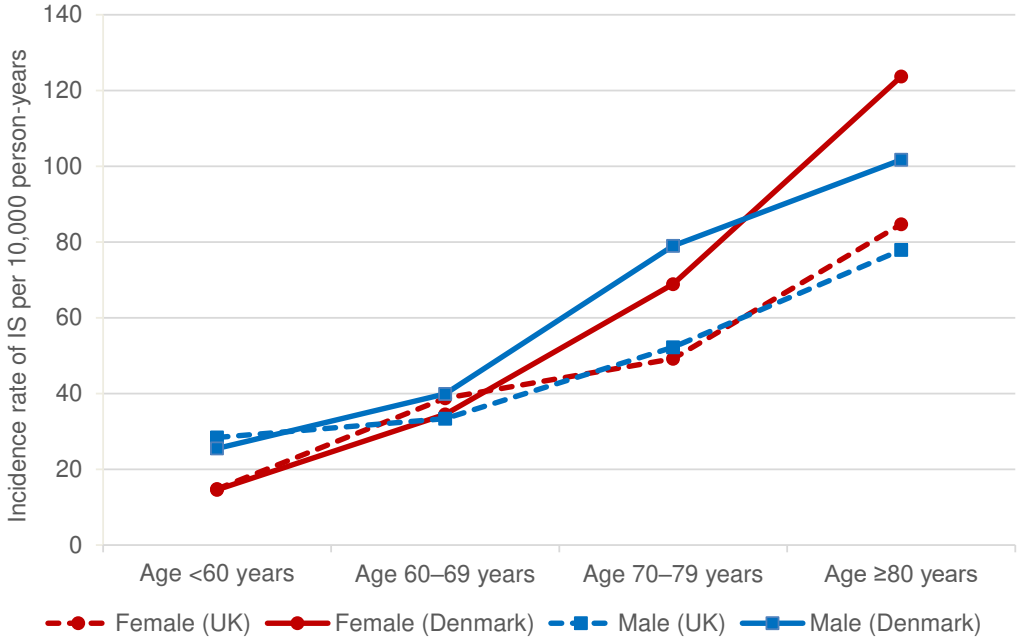


Appendix Figure 1. Identification of the AF study cohort in the UK and Denmark datasets. AF, atrial fibrillation; GP, general practitioner; ICB, intracranial bleeding; IMRD, IQVIA medical research databases; IS, ischaemic stroke; RSD, Region of Southern Denmark; UK, United Kingdom



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