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Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes

Laurent Azoulay[1,2], Sophie Dell'Aniello[1], Teresa A. Simon[3], Christel Renoux[1,4], and Samy Suissa[1,5]*

[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Côte-Sainte-Catherine, H-461, Montreal, QC, Canada H3T 1E2; [2]Department of Oncology, McGill University, Montreal, QC, Canada; [3]Bristol-Myers Squibb, Princeton, NJ, USA; [4]Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada; and [5]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada

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Aims An increased risk of stroke was observed in two atrial fibrillation (AF) trials of oral factor Xa inhibitors, when patients were transitioned to open label warfarin at the end of the study. The objective of this study is to determine whether initiation of warfarin is associated with an increased risk of stroke in patients with AF.

Methods and results Using the UK Clinical Practice Research Datalink, a nested case–control analysis was conducted within a cohort of 70 766 patients with AF between 1993 and 2008. Stroke cases were randomly matched with up to 10 controls on age, sex, date of AF diagnosis, and time since AF diagnosis. Conditional logistic regression was used to estimate adjusted rate ratios (RRs) with 95% confidence intervals (CIs) of stroke associated with current warfarin use classified according to time since initiation of treatment (<30 days, 31–90 days, and >90 days), when compared with non-use. A total of 5519 patients experienced a stroke during follow-up. Warfarin was associated with a 71% increased risk of stroke in the first 30 days of use (RR: 1.71, 95% CI: 1.39–2.12), while decreased risks were observed with initiation >30 days before the event (31–90 days: RR: 0.50, 95% CI: 0.34–0.75 and >90 days: RR: 0.55, 95% CI: 0.50–0.61, respectively).

Conclusion Patients initiating warfarin may be at an increased risk of stroke during the first 30 days of treatment, supporting the biological plausibility of a transient hypercoagulable state at the start of the treatment, although additional studies are needed to confirm these findings.

Keywords Atrial fibrillation • Stroke • Warfarin • Hypercoagulable state • Population-based

Introduction

Warfarin is highly effective in preventing thromboembolism in patients with atrial fibrillation (AF),[1,2] but is underutilized because of its many shortcomings.[3–5] Novel oral anticoagulants have been developed to overcome these challenges and are at least as effective as warfarin in preventing thromboembolism in patients with AF.[6–9] In the ROCKET-AF randomized controlled trial (RCT) of rivaroxaban, a factor Xa inhibitor, an increased risk of thromboembolic events was observed in the first 30 days after patients were transitioned from blinded rivaroxaban to open label warfarin at the end of the study.[7] These patients had an over three-fold increased risk [hazard ratio: 3.71, 95% confidence interval (CI): 1.51–9.16] of ischaemic stroke or systemic embolism, when compared with patients transitioned from blinded warfarin to open label warfarin.[10] This observation raised safety concerns that discontinuation of rivaroxaban may increase the risk of ischaemic stroke, which led to a boxed warning.[11] However in a *post hoc* analysis,[10] no increased risk was observed in patients who temporarily or permanently discontinued rivaroxaban during the study. A similar effect was observed in the ARISTOTLE trial of apixaban, where an increased risk of ischaemic stroke was observed in the first 30 days at the end of the study during when patients randomized to apixaban were transitioned to open label warfarin (4.02% per year for blinded apixaban to open label warfarin vs. 0.99% per year for blinded warfarin to open label warfarin).[12] Thus, these findings suggest a possible increased risk of ischaemic stroke early on during warfarin initiation. Indeed, it is well established that warfarin can theoretically lead to a transient

* Corresponding author. Tel: +1 514 340 7593, Fax: +1 514 340 7564, Email: samy.suissa@mcgill.ca

hypercoagulable state at treatment initiation due to differential depletion of certain vitamin k-dependent clotting factors.[13–15] Thus, the objective of this study is to determine whether the initiation of warfarin is associated with an increased risk of ischaemic stroke in patients with AF.

Methods

Data source

This study was conducted using the Clinical Practice Research Datalink (CPRD) (previously known as the General Practice Research Database), a primary care database from the UK.[16] The CPRD is the world's largest computerized database of longitudinal records from primary care. It contains the complete primary care medical record for more than 12 million people enrolled in more than 650 general practices. The geographic distribution of the practices participating in the CPRD has been shown to be representative of the UK population, and age and sex distributions of patients in the CPRD are similar to those reported by the National Population Census.[17] Participating general practitioners have been trained to record medical information including demographic data, medical diagnoses and procedures, and deaths using a standardized form. Prescriptions written by CPRD physicians in the outpatient setting are automatically transcribed into the computer record. In addition, the CPRD collects information regarding lifestyle variables such as body mass index (BMI), and quantitative and qualitative data pertaining to smoking and excessive alcohol use. The Read classification is used to enter medical diagnoses and procedures, and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions. The recorded information on drug exposures and diagnoses has been validated and proved to be of high quality.[18–21]

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada.

Study population

The study cohort is described elsewhere.[22,23] Briefly, we identified all patients, at least 18 years of age, diagnosed for the first time with AF between 1 January 1993 and 31 December 2008. Patients with paroxysmal or non-permanent AF were not included, leaving a cohort of patients primarily diagnosed with chronic AF. We excluded patients with less than 1 year of medical history in the CPRD before cohort entry, as well as patients with a history of mitral/aortic valve repair/replacement, or hyperthyroidism at any time before cohort entry. Patients were followed until an ischaemic stroke, death, end of registration with the practice, or end of the study period (31 December 2008), whichever came first.

Case–control selection

A nested case–control analysis was conducted within the cohort defined above. This analytic approach was chosen because of the time-varying nature of exposure, the size of the cohort, and the long duration of follow-up.[24] In comparison with a time-dependent survival analysis, a nested case–control analysis is computationally more efficient,[25] while producing odds ratios that are unbiased estimators of incidence rate ratios (RRs), with little or no loss in precision.[24–26]

Cases consisted of all patients who experienced an ischaemic stroke during follow-up, which were identified on the basis of Read codes. The date of the event was defined as the index date. Using risk set sampling, up to 10 controls were randomly selected from the case's risk set (i.e. the subset of the cohort still at risk of experiencing the outcome at the time of the case's event date) and matched on year of birth (age) $\pm$ 1 year, sex, date of the AF diagnosis, and time since the AF diagnosis (duration of follow-up), and thus cases and matched controls had equal duration of follow-up at the risk set date.

Warfarin exposure

Exposure to warfarin was assessed using an algorithm that simultaneously estimates warfarin exposure and therapeutic range. This algorithm is an adaptation of two algorithms commonly used in AF studies, one devised by Go *et al.*[27] (warfarin exposure status) and Rosendaal *et al.*[28] (time in therapeutic range), which has been previously described[22] and used elsewhere.[23] Briefly, patients were considered exposed to warfarin in the presence of a prescription and/or an international normalized ratio (INR) measurement performed in the outpatient setting. The latter was also used to bridge gaps between any two warfarin prescription coverage periods [when gaps occurred, we searched for the last INR occurring prior to the end of a warfarin exposure period, and extended that exposure period to an additional 45 days (30-day grace period plus a 15-day elimination period) from the date of that last INR. Multiple INR measurements $\leq$45 days apart were bridged and defined a more extended period of warfarin exposure].[22]

Using the algorithm above, cases and controls were classified into one of the following eight mutually exclusive groups based on their exposure at index date: (i) *current* use (defined as a prescription coverage overlapping the index date) of warfarin monotherapy initiated $\leq$30 days before index date, (ii) *current use* of warfarin monotherapy initiated 31–90 days before index date, and (iii) current use of warfarin monotherapy initiated $>$90 days before index date. All of the aforementioned groups were considered the primary exposure groups, and warfarin had to be the only antithrombotic therapy used in the year before index. The other exposure groups consisted of other antithrombotic therapies and treatment combinations. These consisted of (iv) *current use* of warfarin monotherapy but with evidence of aspirin and/or clopidogrel use in the year before index date (i.e. switchers to warfarin), (v) *current use* of aspirin or clopidogrel monotherapy (defined as prescriptions in the 90 days before index date), (vi) *current use* of antithrombotic combinations (including warfarin with antiplatelets), (vii) *past use* of any of these drugs in the year before index date, and (viii) no use of any antithrombotic therapy for at least 1 year before index date. The latter group served as the reference category in the models.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cohort, cases, and matched controls. We also calculated crude incidence rates for ischaemic stroke, along with 95% CIs based on the Poisson distribution. Conditional logistic regression was used to estimate RRs with 95% CIs of ischaemic stroke associated with *current use* of warfarin monotherapy, categorized according to timing of treatment initiation ($\leq$30 days, 31–90 days, and $>$90 days), when compared with non-use of any antithrombotic therapy for at least 1 year prior to index date.

We conducted two secondary analyses. In the first analysis, we further explored the timing of ischaemic strokes after warfarin initiation in the first 30 days of use. For this analysis, a cubic spline model was used to produce a smooth curve of the RR (with 95% CIs) as a function of the first 30 days of warfarin use. In the second analysis, we assessed whether patients with a history of ischaemic stroke prior to cohort entry (AF diagnosis) modified the association between warfarin initiation and the risk of ischaemic stroke. Effect modification was assessed by including interaction terms between the three primary warfarin exposure groups and prior history of ischaemic strokes in the models.

In addition to the matching factors (year of birth, sex, date of the AF diagnosis, and time since the AF diagnosis) on which the logistic

regression was conditioned, all models were adjusted for the following potential confounders measured at index date: excessive alcohol use (based on alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and failure, and other related disorders), smoking status, obesity (BMI $\geq$30 kg/m^2), $CHADS_2$ score,[29] peripheral artery disease, myocardial infarction, previous cancer (other than non-melanoma skin cancer), prior bleeds, venous thromboembolism, valvular disease, and current use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, antidepressants, antipsychotics, non-steroidal anti-inflammatory drugs (NSAIDs), and statins.

Sensitivity analyses

We conducted three sensitivity analyses to assess the robustness of the findings. For the first analysis, we assessed the impact of residual confounding by comparing current users of warfarin monotherapy who initiated the treatment $\leq$30 days before index date to current users of warfarin monotherapy who initiated the treatment >90 days before index date. In contrast to non-users, these two patient populations are likely to be similar on a number of measured and unmeasured characteristics. Furthermore, patients who initiated warfarin >90 days before index date more closely resemble the comparator group of patients who were transitioned from blinded warfarin to open label warfarin in the previous RCTs.[10,12] In the second analysis, we assessed the potential role of reverse causation on the association, a situation where the prescribing of warfarin may have been influenced by neurological signs of an ischaemic event. Thus, for this analysis, the primary analysis was repeated after excluding cases and matched controls that had a recorded diagnosis of transient ischaemic attack (TIA) or ischaemic stroke in the 30 days prior to index date. Finally, for the third sensitivity analysis, we repeated the primary analysis substituting warfarin with low dose aspirin (75–16 mg) as a negative control exposure. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The cohort included 70 766 patients newly diagnosed with AF (*Figure 1*). At cohort entry, the mean age was 74.1 (SD: 11.8) years, 51.8% were males, and the mean duration of follow-up was 3.9 (SD: 3.3) years. With respect to $CHADS_2$ score at baseline, 21.6% had a score of 0, 33.9% had a score of 1, 26.0% had a score of 2, 10.5% had a score of 3, and 7.9% had a score of $\geq$4. During the 275 987 person-years of follow-up, 5519 patients experienced an ischaemic stroke, yielding an overall rate of 2.0% (95% CI: 1.9–2.1) per year.

The characteristics of the cases and matched controls overall and across the primary warfarin exposure groups are presented in *Table 1*. As expected, cases were more likely to have had higher $CHADS_2$ score, peripheral artery disease, and had greater use of antidepressants, antipsychotics, and NSAIDs compared with controls. In contrast, controls were more likely to have been obese, and to have used ACE inhibitors, and angiotensin receptor blockers compared with cases. These differences were consistent across the warfarin exposure groups. The median time from the diagnosis of AF to warfarin initiation between cases and controls was similar (30 and 34 days, respectively).

Table 2 presents the results of the primary analysis. During the first 30 days of warfarin initiation, a 71% increased risk of ischaemic stroke was observed, when compared with no use of any antithrombotic therapy (*Table 2*). In a cubic spline model, the risk was highest in the first week of use, peaking at 3 days after initiation (adjusted RR: 2.33, 95% CI: 1.50–3.61) (*Figure 2*). In contrast, the risk of ischaemic stroke was significantly decreased beyond 30 days after initiation of warfarin (*Table 2*).

A history of ischaemic stroke prior to cohort entry modified the association between warfarin use and the risk of ischaemic stroke during follow-up (*P*-value for interaction: <0.001). Specifically, in patients with a history of ischaemic stroke, an increased risk of was observed in the first 30 days of warfarin use (adjusted RR: 2.45, 95% CI: 1.72–3.49), while a null association in patients who initiated warfarin 30–90 before index date, and a decreased risk in patients who initiated warfarin >90 before index date (adjusted RR: 0.95, 95% CI: 0.49–1.86 and adjusted RR: 0.54, 95% CI: 0.43–0.68, respectively). In contrast, in patients with no history of ischaemic stroke, an increased risk was observed in the first 30 days of use (adjusted RR: 1.30, 95% CI: 1.04–1.63), and a decreased risk in the two other warfarin exposure groups (initiation 30–90 before index date, adjusted RR: 0.43, 95% CI: 0.27–0.68 and initiation >90 days before index date, adjusted RR: 0.62, 95% CI: 0.56–0.69).

In sensitivity analyses, an over three-fold increased risk of ischaemic stroke was observed when comparing current users of warfarin who initiated the treatment within 30 days before index to current users of warfarin who initiated the treatment >90 days before index date (adjusted RR: 3.11, 95% CI: 2.49–3.90). Overall, 438 cases and 337 controls had a TIA or an ischaemic stroke in the 30 days immediately prior to index date. Excluding such patients from the analysis resulted in RRs similar in magnitude as that observed in the primary analysis ($\leq$30 days, RR: 1.52, 95% CI: 1.20–1.93; 31–90 days, RR: 0.55, 95% CI: 0.37–0.81; >90 days, RR: 0.55, 95% CI: 0.50–0.62). Finally, repeating the analyses using low-dose aspirin yielded non-significant results ($\leq$30 days, adjusted RR: 1.22, 95% CI: 0.98–1.51; 31–90 days, adjusted RR: 1.19, 95% CI: 0.98–1.44; >90 days, adjusted RR: 0.98, 95% CI: 0.91–1.07).

Discussion

The results of this large population-based study indicate that, compared with non-users, patients initiating warfarin had a nearly two-fold increased risk of ischaemic stroke in the first 30 days of use. Furthermore, this risk was highest in the first week of warfarin initiation. In contrast, warfarin was strongly associated with a decreased risk of ischaemic stroke in patients who have used warfarin for more than 30 days. A history of ischaemic stroke prior to AF appeared to modify this association, and the results remained consistent in sensitivity analyses. To our knowledge, this is the first population-based study to investigate whether the initiation of warfarin is associated with an increased risk of ischaemic stroke.

The paradoxical procoagulant effect of warfarin observed in the early days of the treatment is biologically plausible. While warfarin blocks the activation of clotting factors II, VII, IX, and X, it also deactivates protein C and protein S, two endogenous anticoagulants.[13] Protein C has a short half-life (8 h), and thus rapid depletion of this protein can theoretically lead to a transient hypercoagulable state.[13] Supporting this hypothesis is the increased risk observed in the first 7 days of use, which also concordant with the time of onset of warfarin-induced skin necrosis,[30] another known but rare manifestation of this hypercoagulable state.

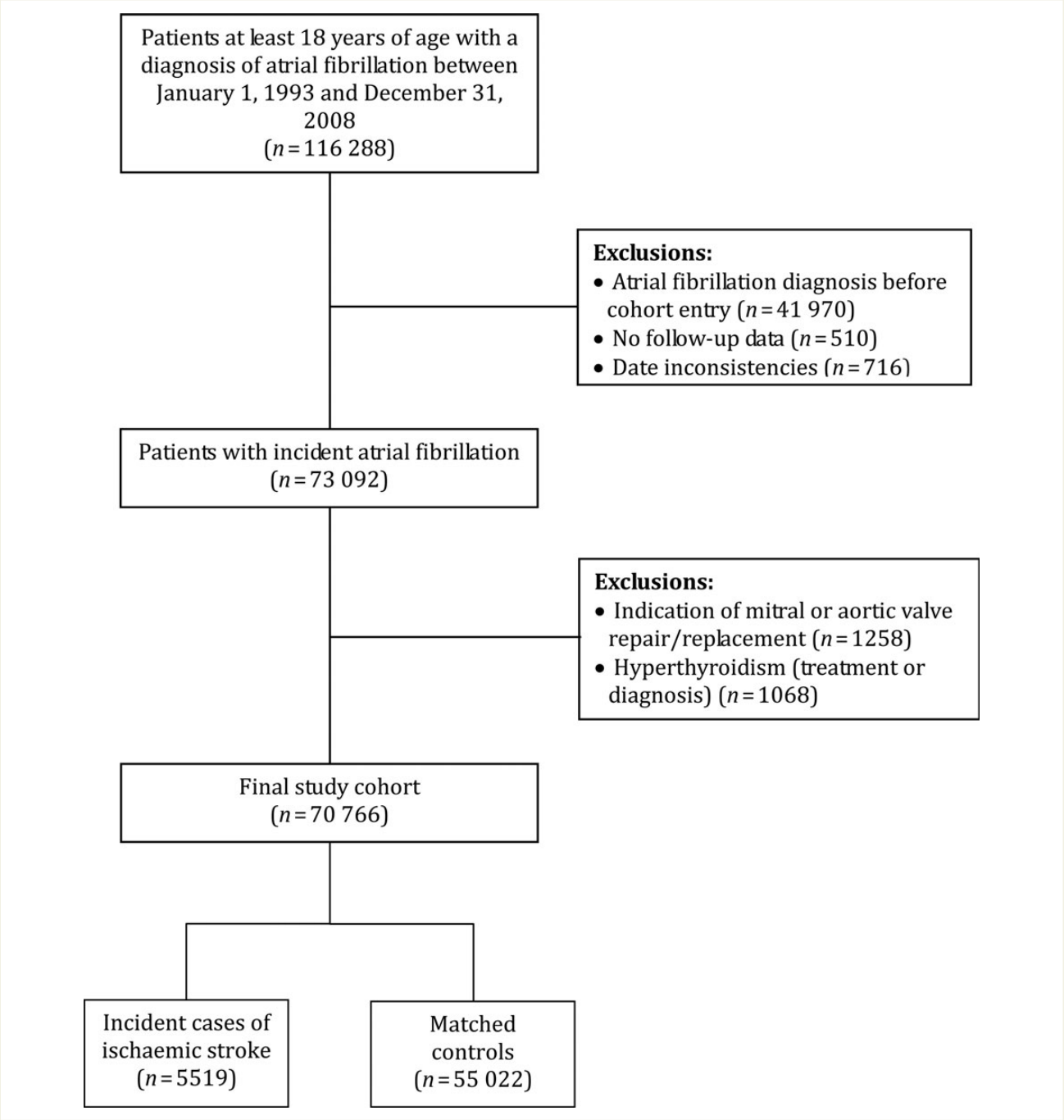

Figure 1 Study flow chart.

In previous placebo-controlled RCTs, warfarin was shown to be highly effective in preventing ischaemic stroke and systemic embolism by over 60%.[1,2] However, these RCTs had small sample sizes (ranging between 378 and 1007 patients), although they were adequately powered to detect large treatment effects.[31–36] However, these RCTs were not designed to assess whether the risk varied with duration of warfarin use. Furthermore, few events occurred during follow-up,[31–36] likely rendering secondary analyses of these RCTs unfeasible. In contrast, with sample sizes ranging between 14 264 and 18 201 patients,[6–8] RCTs of novel anticoagulants are better powered to detect whether the use of warfarin is associated with an initial transient increased risk of ischaemic stroke.[10,12] Indeed, the ARISTOTLE trial of apixaban and the ROCKET-AF trial of rivaroxaban found an increased risk of ischaemic stroke in the first 30 days at the end of the study when patients were transitioned from apixaban or rivaroxaban to open label warfarin.[10,12] It is important to note, however, that the short bridging time (2 days) between the study drugs and warfarin may not have been adequate to provide optimal anticoagulation, and thus it is possible that longer bridging times would have abrogated the transient increased risk observed with

Table 1 Characteristics of cases of ischaemic stroke and matched controls overall and across the primary warfarin exposure duration groups

Characteristics at index date	Cases of ischaemic stroke				Controls			
		Warfarin				Warfarin		
	Overall (n = 5519)	First 30 days (n = 117)	≥30 days (n = 637)	Non-use[a] (n = 1513)	Overall (n = 55 022)	First 30 days (n = 732)	≥30 days (n = 10 689)	Non-use[a] (n = 15 499)
Age, years, mean (SD)	79.5 (9.2)	74.8 (8.9)	77.1 (8.9)	79.0 (10.1)	79.5 (9.1)	73.9 (9.1)	77.9 (8.2)	79.0 (10.3)
Males, *n* (%)	2503 (45.4)	58 (49.6)	359 (56.4)	661 (43.7)	24 979 (45.4)	388 (53.0)	5429 (50.8)	6500 (41.9)
Excessive alcohol use, *n* (%)	76 (1.4)	0 (0.0)	13 (2.0)	19 (1.3)	643 (1.2)	9 (1.2)	104 (1.0)	154 (1.0)
Smoking status, *n* (%)								
Ever	2253 (40.8)	46 (39.3)	313 (49.1)	495 (32.7)	22 044 (40.1)	304 (41.5)	4765 (44.6)	5004 (32.3)
Never	2709 (49.1)	58 (49.6)	283 (44.4)	791 (52.3)	28 181 (51.2)	373 (51.0)	5372 (50.3)	8312 (53.6)
Unknown	557 (10.1)	13 (11.1)	41 (6.4)	227 (15.0)	4797 (8.7)	55 (7.5)	552 (5.2)	2183 (14.1)
Obesity, *n* (%)								
BMI <30 kg/m^2	3407 (61.7)	69 (59.0)	410 (64.4)	841 (55.6)	34 630 (62.9)	443 (60.5)	7058 (66.0)	8968 (57.9)
BMI ≥ 30 kg/m^2	810 (14.7)	19 (16.2)	112 (17.6)	190 (12.6)	8716 (15.8)	151 (20.6)	2045 (19.1)	1982 (12.8)
Unknown	1302 (23.6)	29 (24.8)	115 (18.1)	482 (31.9)	11 676 (21.2)	138 (18.9)	1586 (14.8)	4549 (29.4)
$CHADS_2$ score, *n* (%)								
0	390 (7.1)	20 (17.1)	44 (6.9)	181 (12.0)	5593 (10.2)	137 (18.7)	1055 (9.9)	2373 (15.3)
1	1301 (23.6)	28 (23.9)	124 (19.5)	494 (32.7)	16 626 (30.2)	298 (40.7)	3043 (28.5)	5636 (36.4)
≥2	3828 (69.4)	69 (59.0)	469 (73.6)	838 (55.4)	32 803 (59.6)	297 (40.6)	6591 (61.7)	7490 (48.3)
Peripheral artery disease, *n* (%)	297 (5.4)	2 (1.7)	44 (6.9)	45 (3.0)	2275 (4.1)	15 (2.1)	432 (4.0)	389 (2.5)
Myocardial infarction, *n* (%)	696 (12.6)	5 (4.3)	93 (14.6)	90 (6.0)	6554 (11.9)	30 (4.1)	1255 (11.7)	721 (4.7)
Previous cancer, *n* (%)	1003 (18.2)	20 (17.1)	133 (20.9)	237 (15.7)	10 605 (19.3)	114 (15.6)	2109 (19.7)	2744 (17.7)
History of bleeds, *n* (%)	1304 (23.6)	21 (18.0)	194 (30.5)	269 (17.8)	12 358 (22.5)	111 (15.2)	2789 (26.1)	2875 (18.6)
Venous thromboembolism, *n* (%)	421 (7.6)	10 (8.6)	77 (12.1)	83 (5.5)	4094 (7.4)	62 (8.5)	1255 (11.7)	680 (4.4)
Valvular disease	388 (7.0)	4 (3.4)	96 (15.1)	64 (4.2)	3946 (7.2)	42 (5.7)	1389 (13.0)	615 (4.0)
ACE inhibitors, *n* (%)	1738 (31.5)	21 (18.0)	288 (45.2)	244 (16.1)	18 237 (33.1)	216 (29.5)	4614 (43.2)	2837 (18.3)
Angiotensin receptor blockers, *n* (%)	397 (7.2)	7 (6.0)	58 (9.1)	53 (3.5)	4572 (8.3)	54 (7.4)	1268 (11.9)	606 (3.9)
Antidepressants, *n* (%)	706 (12.8)	12 (10.3)	76 (11.9)	162 (10.7)	5404 (9.8)	56 (7.7)	879 (8.2)	1390 (9.0)
Antipsychotics, *n* (%)	555 (10.1)	9 (7.7)	52 (8.2)	144 (9.5)	3858 (7.0)	33 (4.5)	508 (4.8)	1177 (7.6)
NSAIDs, *n* (%)	981 (17.8)	15 (12.8)	59 (9.3)	291 (19.2)	9102 (16.5)	171 (23.4)	882 (8.3)	2996 (9.3)
Statins, *n* (%)	1294 (23.4)	16 (13.7)	218 (34.2)	100 (6.6)	12 503 (22.7)	110 (15.0)	3243 (30.3)	936 (6.0)

SD, standard deviation; BMI, body mass index; ACE, angiotensin-converting enzyme; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Defined as no use of any antithrombotic therapy for at least one year before index date.

Table 2 Timing of warfarin initiation and the risk of ischaemic stroke

Current use of warfarin monotherapy	Cases ($n = 5519$)	Controls[a] ($n = 55\,022$)	Crude RR	Adjusted RR (95% CI)[b]
No use of any antithrombotic therapy for at least 1 year, *n* (%)	1513 (27.4)	15 499 (28.2)	1.00	1.00 (reference)
Time since initiation of warfarin, *n* (%)				
≤30 days	117 (2.1)	732 (1.3)	1.74	1.71 (1.39–2.12)
31–90 days	27 (0.5)	544 (1.0)	0.52	0.50 (0.34–0.75)
≥90 days	610 (11.1)	10 145 (18.4)	0.57	0.55 (0.49–0.61)

RR, rate ratio; CI, confidence interval.
Current users of warfarin monotherapy who had used aspirin and/or clopidogrel in the year prior to index date, current users of aspirin or clopidogrel monotherapy, current users of antithrombotic combinations (including warfarin), and past users of any of these drugs in the year before index date are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects (representing 3252 cases and 28 102 controls).
[a]Cases and controls were matched on age, sex, and date of atrial fibrillation diagnosis, and time since atrial fibrillation diagnosis.
[b]Adjusted for excessive alcohol use, smoking status, obesity, $CHADS_2$ score, peripheral artery disease, myocardial infarction, previous cancer, prior bleeds, venous thromboembolism, valvular disease, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, antipsychotics, non-steroidal anti-inflammatory drugs, and statins.

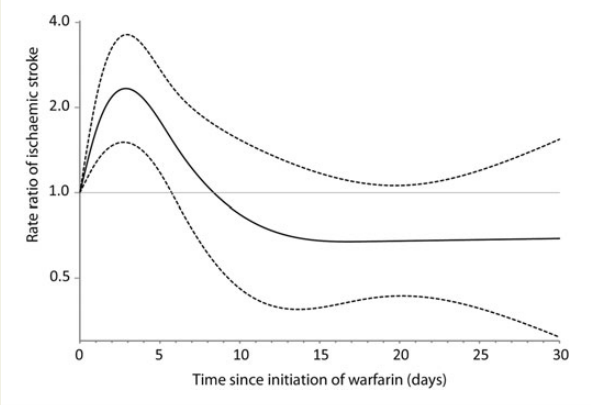

Figure 2 Smooth cubic spline curve of the adjusted rate ratio of ischaemic stroke (solid line) and 95% confidence limits (dashed lines) as a function of the time since initiation of warfarin.

warfarin. While this may have contributed to the observed signals, the ARISTOTLE investigators did report an increased risk in the first 30 days of the trial among patients warfarin-naïve at baseline [warfarin-naïve to warfarin (17/3888) vs. warfarin-naïve to apixaban (3/3912)].[12] Finally, while further analyses of these RCTs can provide insight, well-designed observational studies should be conducted in parallel to confirm these findings and identify high-risk individuals.

This study has a number of strengths and some limitations. First, we assembled a large population-based cohort of patients with AF, followed for up to 16 years. Second, the study exposure and covariate variables were time-dependent, as a result of the risk set sampling scheme used to select the controls. Moreover, because CPRD data are prospectively collected, the possibility of recall bias was eliminated. However, drug information in the CPRD represents written prescriptions. As such, it is unknown whether these prescriptions were actually filled and used by the patient. As a result, it is possible that some unexposed patients were misclassified as exposed which would have biased the estimates towards the null. Another limitation is that stroke events may be underreported in the CPRD, which would lead to an underestimation of the treatment effects. Furthermore, ischaemic strokes were defined on the basis of a specific diagnostic code for this event or a diagnostic code of 'stroke' with no mention of the subtype. Since stroke subtypes are not always specified in the CPRD files, it is possible that some haemorrhagic strokes were misclassified as being ischaemic. However, this potential bias is likely to have been minimal as the vast majority of strokes are ischaemic (>80%), and our overall rate was very similar to the one reported in other studies (2.0% per year vs. 2.1% per year in the ATRIA cohort, respectively).[37] In addition, it is important to consider reverse causality, a situation where warfarin may have been initiated at the time of a TIA or shortly after an initial stroke. However, in a sensitivity analysis, excluding cases and controls with a TIA or stroke diagnosis in the 30 days prior to index yielded similar RRs, although the point estimate for the first 30 days of use was lower than the one estimated in the primary analysis (RR: 1.52 vs. RR: 1.71). Furthermore, the fact that our results corroborate those of RCTs, which were not subjected to such reverse causality, provides some reassurance that this bias was likely minimal. Finally, because of the observational nature of the study, confounding by indication needs to be considered. In particular, the baseline stroke risk may be higher among treated compared with non-treated patients. However, we adjusted the models for 15 potential confounders, including $CHADS_2$ score which is a composite score of congestive heart failure, hypertension, age ≥75 years, diabetes, and a history of ischaemic stroke or TIA. Adjustment for these covariates did not materially affect the RRs (crude RR: 1.74 vs. adjusted RR: 1.71), suggesting that confounding had a limited role. Furthermore, when we compared patients who initiated warfarin within 30 days before index date to patients who initiated the treatment >90 days before index, we observed an over three-fold increased risk of ischaemic stroke, an estimate similar in magnitude to the ones reported in the previous RCTs.[10,12] Moreover, given the large estimated RRs, any unknown or unmeasured confounder would need to be strongly associated with both the exposure and outcome, which is unlikely beyond those considered (Supplementary material online). Finally, the initial increased risk observed may have been due to inadequate warfarin control, and thus it would have been informative to correlate INR fluctuations with the outcome during each exposure time period. However, this was not possible because INR information is not consistently recorded in the

CPRD,[22] and as such, future studies are needed to assess whether the observed increased risk correlates with INR control.

In summary, the findings of this large population-based study indicate that the initiation of warfarin is associated with an increased risk of ischaemic stroke. These results corroborate with those observed in *post hoc* analyses of two large trials of novel oral anticoagulants.[10,12] While one hypothesis is that warfarin may induce a transient hypercoagulable state at the start of the treatment, additional well-conducted studies are needed to confirm these findings and determine whether a heparin bridging strategy at the initial phase of the treatment reduces this risk.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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