

# Increased short-term risk of thrombo-embolism or death after interruption of warfarin treatment in patients with atrial fibrillation

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## Aims

It is presently unknown whether patients with atrial fibrillation (AF) are at increased risk of thrombo-embolic adverse events after interruption of warfarin treatment. The purpose of this study was to assess the risk and timing of thrombo-embolism after warfarin treatment interruption.

## Methods and results

A retrospective, nationwide cohort study of all patients in Denmark treated with warfarin after a first hospitalization with AF in the period 1997–2008. Incidence rate ratios (IRRs) of thrombo-embolic events and all-cause mortality were calculated using the Poisson regression analyses. In total, 48 989 AF patients receiving warfarin treatment were included. Of these, 35 396 patients had at least one episode of warfarin treatment interruption. In all, 8255 deaths or thrombo-embolic events occurred during treatment interruption showing an initial clustering of events with 2717, 835, 500, and 427 events occurring during 0–90, 91–180, 181–270, and 271–360 days after treatment interruption, respectively. Correspondingly, the crude incidence rates were 31.6, 17.7, 12.3, and 11.4 events per 100 patient-years. In a multivariable analysis, the first 90-day interval of treatment interruption was associated with a markedly higher risk of death or thrombo-embolism (IRR 2.5; 95% confidence interval 2.3–2.8) vs. the interval of 271–360 days.

## Conclusion

In patients with AF, an interruption of warfarin treatment is associated with a significantly increased short-term risk of death or thrombo-embolic events within the first 90 days of treatment interruption.

## Keywords

Warfarin • Atrial fibrillation • Rebound • Thrombo-embolism

## Introduction

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia and a major risk factor for thrombo-embolic complications and death.<sup>1–5</sup> Warfarin therapy substantially reduces the risk of AF-related thrombo-embolic complications and patients eligible for anticoagulant therapy should be considered for long-term treatment.<sup>1–3</sup> However, patients who receive anticoagulant therapy commonly interrupt treatment

either due to lack of compliance, need for surgery, or conversion to apparently stable sinus rhythm. The rate of thrombo-embolism in patients with AF who interrupt ongoing warfarin treatment is uncertain and this important question needs to be addressed. In the present study, 149 151 patients with a first-time hospitalization for AF in Denmark were identified to analyse the association between interruption of warfarin therapy and risk and timing of thrombo-embolic complications.

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## Methods

### Patient population

All 5.5 million Danish citizens have a unique and permanent personal registration number which enables cross-linkage of nationwide administrative registers holding information on health-care usage. The Danish National Patient Registry contains administrative data for all hospitalizations in the country since 1978. Each admission is registered with one primary and, if appropriate, one or more secondary diagnoses using the International Classification of Diseases (ICD) version 8 until 1994 succeeded by ICD-10. Diagnosis codes used in this study are listed in the Supplementary material online. From the register, we identified all Danish residents with a first-time hospitalization for AF or atrial flutter as the primary or secondary diagnosis between 1 January 1997 and 31 December 2008. All patients alive at discharge and aged 30 years or older were included. We excluded patients with valvular AF having previous diagnoses of mitral or aortic valve disease and previous mitral or aortic valve surgery (Nordic Medical Statistics Committees Classification of Surgical Procedures: KFK, KFM, KFP), as done previously.<sup>6</sup> Prior cancer diagnoses or liver disease were also excluded due to probable confounding effects in the analysis. Follow-up was started 7 days after discharge because medication could have been changed or intensified in relation to the index admission. Patients experiencing outcome events during the 7 days were not included in the study. Finally, patients receiving other anticoagulant treatment than warfarin (e.g. phenprocoumon) were excluded. The study population has previously been described in detail.<sup>7</sup>

### Pharmacotherapy

The Danish Registry of Medicinal Product Statistics includes information of all prescriptions dispensed from Danish pharmacies since 1995. Each prescribed drug is coded according to the international Anatomical Therapeutic Chemical (ATC) classification. The register also includes information about date of dispensing, strength, and quantity dispensed but not the prescribed dosage of the drug. The register has been found to be accurate and has been described previously.<sup>8,9</sup> The patients' baseline medication was recorded as claimed prescriptions between 180 days before index admission and 7 days after discharge.

### Warfarin use and warfarin interruption

By individual-level cross-linkage between the Danish National Patient Registry and The Danish Registry of Medicinal Product Statistics, patients with a first hospitalization for AF and their subsequent prescription claims of warfarin therapy (ATC code B01AA03) were identified. Treatment with warfarin was estimated based on prescription claims which included information on tablet strength and the number of tablets. If only one prescription was available, a typical dose of 5 mg daily was assumed. If previous prescriptions were available, the dose and duration was based on the average dose from up to four consecutive prescription claims. Treatment was assumed to continue until no more tablets were available. If a patient was admitted to hospital during treatment, we assumed that the hospital continued treatment and provided tablets during the stay. A warfarin interruption was assumed to start when a patient by the above calculations did not have available tablets for treatment. This method of quantifying pharmaceutical treatment doses has been described previously.<sup>10</sup>

### Co-morbidity, concomitant medical therapy, and thrombo-embolic risk assessment

Congestive heart failure was identified as a combination of previous congestive heart failure and loop-diuretic treatment, as previously described.<sup>11</sup> Hypertension patients were defined as using at least two classes of anti-hypertensive drugs, as validated previously.<sup>12</sup> Diabetes mellitus was defined as a claimed prescription of glucose-lowering medication (ATC code A10). Additional co-morbidity diagnoses comprised the following: ischaemic stroke and transitory ischaemic attacks, peripheral artery embolism, and acute and chronic renal failure. Bleeding episodes comprised gastrointestinal bleedings, intracranial bleedings, bleedings in the urinary tract, and bleedings in the airways. All diagnosis codes used for the analyses are listed in the Supplementary material online.

Thrombo-embolic risk of all patients was evaluated using the CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age  $\geq$ 75 years, Diabetes, previous Stroke) according to the present guidelines and previously described.<sup>3,12–14</sup>

Prescriptions filled of renin–angiotensin system inhibitors (ATC code C09A),  $\beta$ -blockers (C07), calcium channel blockers (C08), digoxin (C01A), amiodarone (C01BD01), and class 1C anti-arrhythmics (C01BC), statins (C10AA), diuretics (C03), and aspirin (B01AC06) between 180 days before index admission and 7 days after discharge were identified and classified as concomitant medical therapy.

### Outcomes

The primary outcome was the combined endpoint of hospitalization with thrombo-embolism or death of all causes. Thrombo-embolism was defined as an ischaemic cerebral event (ischaemic stroke, transient ischaemic attack, unspecified stroke), pulmonary embolism or systemic arterial embolism. Only the first episode of thrombo-embolism was included in the outcome analysis.

### Statistical analyses

Patients were included on the day of warfarin treatment initiation. The statistical analyses were performed independently for treatment periods and interruption periods. For each patient, the frequency and duration of treatment periods and treatment interruptions were recorded. Thus, every patient could contribute with treatment or interruption periods several times. Patients ended participation in the analysis at the first episode of thrombo-embolism and were censored at death from any cause or at the end of the follow-up period (31 December 2008).

Patient baseline characteristics are presented as percentages or as medians with 25th–75th percentile range. Differences in baseline characteristics between patients with no interruptions and at least one interruption were assessed by  $\chi^2$  tests (categorical variables) and the Kruskal–Wallis test (age).

The crude event incidence rate was assessed for each day, in time intervals of 90 days, and for the total period of interruption. The rate was calculated as the number of events per 100 patient-years.

Multivariable Cox's regression models were constructed to obtain risk-adjusted instantaneous incidence rates using kernel hazard functions.

To assess the association between time interval after warfarin interruption and risk of thrombo-embolism or death, we used Poisson's regression analysis to calculate incidence rate ratios (IRRs). In these models, the primary independent variable of interest was the risk of outcome events in the first interval of 0–90 days after warfarin interruption compared with the interval of 271–360 days. This comparison was chosen because the incidence rate had dropped to a constant level during the final 90 days of the observation year. The Cox and Poisson regression models were adjusted for year of index admission, total

**Table 1** Baseline characteristics of the study cohort

	All (n = 102 591) (100%)	Warfarin treated (n = 48 989) (48%)	Patients with interruption (n = 35 396) (35%)	Patients without interruption (n = 13 593) (13%)	P-value (interruption vs. non-interruption)
Male gender	54%	61%	61%	60%	0.22
Age (years) (25th–75th percentile)	75 (65–83)	71 (63–78)	71 (62–78)	72 (65–79)	<0.001
Medical history					
Congestive heart failure	16%	16%	16%	16%	0.57
Vascular disease	16%	14%	13%	15%	<0.001
Stroke	16%	14%	13%	19%	<0.001
Hypertension	41%	48%	47%	51%	<0.001
Diabetes	8.7%	8.8%	8.5%	9.4%	0.004
Renal disease	5.2%	3.7%	3.5%	4.3%	<0.001
Previous bleed	7.0%	4.4%	4.0%	5.3%	<0.001
CHADS <sub>2</sub> score					
0	24%	26%	28%	21%	<0.001
1	32%	33%	33%	32%	<0.001
≥2	44%	42%	40%	47%	<0.001
Medication at discharge					
β-Blocker	46%	56%	55%	58%	<0.001
Diuretic	30%	31%	30%	32%	<0.001
RAS inhibitor	33%	39%	37%	43%	<0.001
Calcium channel blocker	28%	31%	32%	30%	0.002
Digoxin	44%	49%	51%	44%	<0.001
Amiodarone	3.2%	4.0%	4.0%	4.0%	0.56
Class 1C anti-arrhythmic therapy	1.4%	1.7%	1.9%	1.3%	<0.001
Statin	16%	19%	17%	24%	<0.001
Acetylic salicylic acid	35%	30%	29%	35%	<0.001

RAS, renin–angiotensin system.

duration of warfarin therapy, and baseline variables listed in Table 1. Age had a non-linear distribution and was included in the analyses as age groups of 10-year interval. The models were tested for interactions. A level of 5% was considered statistically significant in all analyses.

## Secondary and sensitivity analyses

We performed several secondary analyses to validate the final result.

First, we reanalysed the data in a specific subgroup of patients with no prior hospitalizations to minimize hidden bias through possible co-morbidities. Additionally, we analysed specific subgroups according to gender, age, the presence of risk factors for thrombo-embolic complications (diabetes, congestive heart failure, and previous stroke), and for the subgroup of patients with AF as the primary diagnosis at index admission.

Secondly, we calculated the risk only using each patient's first interruption period to exclude skewing of the data by few patients with many interruption periods.

Thirdly, we assessed the importance of warfarin treatment duration before interruption. We stratified the data in two groups with warfarin treatment duration above and below 180 days and repeated the multivariable analysis.

Fourthly, we repeated the analyses with an arbitrary time shift of 7, 14, and 30 days from the interruption start date. This was done

to test for interruption date inaccuracy and event-triggered interruptions.

Fifthly, we excluded all patients using heparins or anti-platelet treatment and reanalysed the data to test for confounding effects of other antithrombotics.

Sixthly, with the event rate during warfarin treatment serving as reference, we calculated a hazard ratio using Cox's regression analysis, comparing the rate of events following warfarin treatment initiation with the rate of events after interruption of treatment (including and excluding all-cause mortality). This is to give an indication of the hazard of interruption compared with continuing warfarin treatment.

Finally, to test whether the results were mainly carried by all-cause mortality, we reanalysed the data using only thrombo-embolic events as the primary endpoint.

All statistical calculations were performed using the SAS statistical software package, version 9.1 for windows servers (SAS Institute Inc., Cary, NC, USA) and STATA software version 10.1 (StataCorp, College Station, TX, USA).

## Ethics

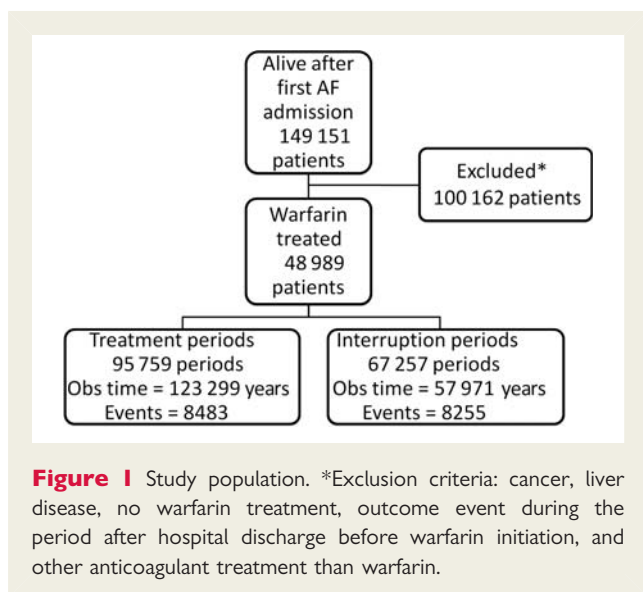
The Danish Data Protection Agency approved the study (ref. 2007-41-1667). Retrospective register-based studies do not require ethical approval in Denmark.

## Results

A total of 149 151 patients were alive after a first-time hospitalization for AF during 1997–2008. Of these, 102 591 (69%) were eligible for the study, according to the exclusion criteria explained previously (Figure 1). The mean follow-up time was 3.5 years ( $\pm 3.0$  SD). A detailed description of the baseline characteristics of the study population and distribution between all patients, patients on warfarin treatment, patients with at least one interruption period, and patients without treatment interruption is shown in Table 1.

### Warfarin therapy

Overall, 48 989 (48%) patients claimed a prescription of warfarin at a median of 6 days (25th–75th percentile, 1–51) after discharge (Table 1). The median age for patients receiving treatment was 71 years and these patients had a high prevalence of risk factors for thrombo-embolism with a mean CHADS<sub>2</sub> score of  $1.41 \pm 1.20$  SD. Males and younger patients were more likely to receive treatment than females and elderly patients. The median duration of warfarin treatment until first interruption was 202 days



**Figure 1** Study population. \*Exclusion criteria: cancer, liver disease, no warfarin treatment, outcome event during the period after hospital discharge before warfarin initiation, and other anticoagulant treatment than warfarin.

(25th–75th percentile, 89–577 days). A total of 95 759 periods of warfarin treatment were identified. The combined incidence rate of thrombo-embolism or death during treatment was 6.9 [95% confidence interval (CI) 6.7–7.0] events per 100 patient-years.

### Warfarin treatment interruption

A total of 35 396 (72%) of the 48 989 warfarin-treated patients had at least one treatment interruption. Interruptions were less common among elderly patients (Table 1). Correspondingly, the mean CHADS<sub>2</sub> score was lower in the interruption group compared with the non-interruption group (1.34 vs. 1.56;  $P < 0.001$ ). In the 67 257 episodes of treatment interruption, the median duration of treatment interruption was 36 days (25th–75th percentile, 14–207) and the median number of interruption periods in individual patients was 1 (25th–75th percentile, 1–2).

### Combined endpoint of hospitalization with thrombo-embolism and all-cause death

During the entire observational period, there were 16 738 thrombo-embolic events or deaths.

Of these, 8255 (49%) thrombo-embolic events or deaths occurred during treatment interruption (Table 2). The overall incidence rate during interruption was 14.2 (95% CI 13.9–14.6) events per 100 patient-years. There was a clustering of events during the initial period after interruption with 2717 events during the first 90 days corresponding to an incidence rate of 31.6 (95% CI 30.4–32.8) events per 100 patient-years. The event rate levelled off after 180 days of treatment interruption (Table 2 and Figure 2,  $P < 0.001$  for comparison between time intervals). In a multivariable analysis comparing event rates in the first three 90-day intervals to the fourth interval (Days 271–360), the IRR was 2.5 (95% CI 2.3–2.8) for the combined endpoint of thrombo-embolism or death during the first 90 days of interruption (Table 2).

### Secondary and sensitivity analyses

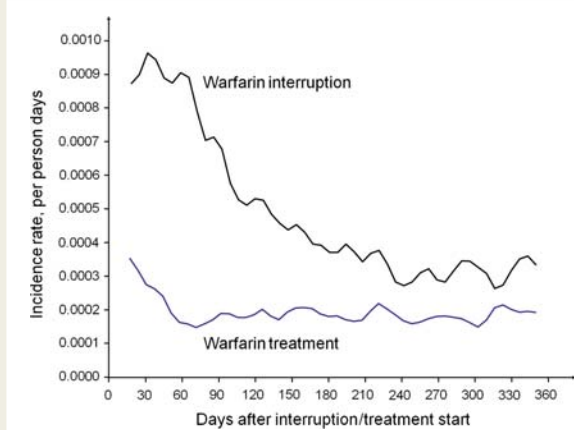
Table 3 shows the results of the secondary analyses. All subgroup analyses produced results similar to the primary result. A time shift of the analysis by 7, 14, and 30 days did not affect the results, indicating that the interruption date estimation is accurate.

**Table 2** Incidence and incidence rate ratio of the combined endpoint of thrombo-embolism or death and association with warfarin interruption

	No. of events	Observation time, years	Incidence rate, per 100 patient-years (95% CI)	IRR <sup>a</sup> (95% CI)
0–90 days after warfarin interruption	2717	8612	31.6 (30.4–32.8)	2.5 (2.3–2.8)
91–180 days after warfarin interruption	835	4725	17.7 (16.6–18.9)	1.5 (1.3–1.7)
181–270 days after warfarin interruption	500	4061	12.3 (11.3–13.4)	1.1 (0.9–1.2)
271–360 days after warfarin interruption	427	3654	11.4 (10.4–12.6)	1.0 (ref.)
0–360 days after warfarin interruption	4469	21 052	21.2 (20.6–21.9)	NA
Entire interruption period	8255	57 971	14.2 (13.9–14.6)	NA

NA, not applicable.

<sup>a</sup>Incidence rate ratio comparing Days 0–90 vs. 271–360 of interruption.



**Figure 2** Outcome events—instantaneous incidence rates of deaths or thrombo-embolisms during treatment and interruption of warfarin.

Of note, the comparison of event rates during treatment and interruption yielded a hazard ratio of 2.9 (95% CI 2.8–3.0) after interrupting treatment.

Some patients had several interruption periods, and to account for this, we calculated the risk during each individual's first interruption only. The corresponding IRR of 2.6 (95% CI 2.3–3.0) was consistent with the primary result.

Additionally, the increased event rate was consistent after exclusion of all-cause mortality, indicating that all-cause mortality was not the sole carrier of the primary result.

## Discussion

In the present study, we demonstrated a significantly increased risk of thrombo-embolic events or death from any cause among a nationwide cohort of patients with AF who interrupt warfarin treatment. The incidence rate of thrombo-embolism or death increased three-fold in the first 90 days after treatment interruption and gradually returned to a steady level after 180 days. The results were consistent among patient subgroups defined by age, gender, treatment duration, and the presence/absence of prior hospitalizations.

A large proportion of patients in the present study had at least one interruption of warfarin treatment, and to our knowledge, no previous studies have reported the number of interruptions in a warfarin-treated population. The interruption frequency in this study was higher than the frequency of warfarin cessation reported in different randomized trials where between 14 and 33% of patients discontinue treatment.<sup>15</sup> The present study did not distinguish between interruption and cessation which may have contributed to the increased interruption incidence in our study also underlined by the observation of a median interruption time of 36 days. Additionally, most participants in randomized clinical trials involving warfarin treatment are carefully selected and comprise motivated individuals with better compliance and adherence to warfarin.<sup>15</sup> The Atrial Fibrillation Follow-up Investigation of

**Table 3** Sensitivity analyses and model control

	No. of observations	IRR <sup>a</sup> (95% CI)
Specific subgroups		
Males	41 308	2.8 (2.4–3.2)
Females	25 949	2.2 (1.9–2.5)
Congestive heart failure	10 394	2.9 (2.4–3.6)
Age 75 or more	23 798	2.3 (2.1–2.7)
Diabetes	5 744	3.2 (2.3–4.6)
Previous ischaemic stroke	8 178	2.5 (1.9–3.2)
CHADS <sub>2</sub> score 0	19 228	2.3 (1.8–3.0)
CHADS <sub>2</sub> score 1	22 294	2.7 (2.2–3.3)
CHADS <sub>2</sub> score ≥2	25 735	2.5 (2.2–2.8)
No incident hospitalizations	20 437	1.9 (1.5–2.5)
No heparin/anti-platelet treatment	48 611	2.6 (2.3–3.0)
Model control		
First interruption	35 396	2.6 (2.3–3.0)
Warfarin treatment <180 days	33 879	2.3 (2.0–2.7)
Warfarin treatment ≥180 days	33 378	2.6 (2.3–3.0)
Analysis time shift +7 days	60 277	2.5 (2.4–2.7)
Analysis time shift +14 days	51 540	2.4 (2.2–2.7)
Analysis time shift +30 days	27 321	2.3 (2.2–2.5)
All-cause mortality excluded	67 257	1.5 (1.2–1.8)
Interruption vs. treatment as reference <sup>b</sup>	48 989	2.9 (2.8–3.0)
Interruption vs. treatment, only thrombo-embolisms <sup>b</sup>	48 989	2.1 (2.0–2.2)

<sup>a</sup>Incidence rate ratio comparing Days 0–90 vs. 271–360 of interruption in the specific subgroup.

<sup>b</sup>Multivariable Cox's regression, estimated as a hazard ratio.

Rhythm Management (AFFIRM) trial found that reasons for warfarin interruption were attainment of sinus rhythm (45%), bleeding complications (21%), surgical treatment (13%), physician refusal to continue warfarin treatment (12%), patient refusal (8%), and frailty/risk of falls (7%).<sup>16</sup> This illustrates that warfarin interruption can be medically warranted (for surgery and after cardioversion) or be due to patient factors (frailty, compliance, unwillingness). Although the patients in the AFFIRM trial were a selected group, it is likely that the patients in the present study have a similar distribution of reasons for interruption. The majority of thrombo-embolic events in the AFFIRM trial occurred during subtherapeutic INR and after warfarin cessation, regardless of reasons for cessation.<sup>16</sup>

At present, European and American treatment guidelines recommend that AF patients without mechanical valves can discontinue anticoagulant therapy 4 weeks after successful cardioversion and interrupt anticoagulant treatment for up to 1 week for surgical intervention.<sup>1–3,17</sup> Several recent studies have aimed to assess the risk associated with brief interruption of warfarin treatment for surgical treatment.<sup>18–22</sup> Garcia et al.<sup>23</sup> identified 1293 treatment interruptions due to minor surgery in 1024 patients but only seven events during the 30-day follow-up. No definitive conclusion on the risk of thrombo-embolism when interrupting warfarin treatment could be made due to the relatively few



events in the study. Most studies on thrombo-embolic events due to perioperative warfarin interruption have very short observation periods and are therefore not directly comparable to the present study.

It is debatable whether the increase in risk found in the present study is a true rebound effect due to pharmacological properties of warfarin or a 'catch-up' effect where the individuals' inherent thrombotic risk results in events as soon as the anticoagulation effect wears off. Various clinical studies have focused on a possible rebound effect upon cessation of warfarin treatment without producing consistent results.<sup>24–29</sup> However, several biochemical studies have documented a true rebound effect, where specifically clotting factor VII levels were shown to rise above normal levels after interruption of anticoagulant treatment.<sup>24,27,30–32</sup> The present study did not assess the changes in the coagulation system during warfarin interruption, but the above studies provide a possible explanation for the sharp increase in event rate during the first 90 days of interruption.

This leads us to conclude that interruption of warfarin treatment frequently occurs and that a sharp increase in incidence of thrombo-embolism or death after interruption of warfarin treatment is evident and may have serious clinical consequences.

## Limitations

There are several limitations to the study that need to be acknowledged. Due to the register-based nature of the study, it is impossible to explore the reasons for the individual patients' interruption of warfarin treatment. There may have been patients who interrupted treatment due to severe illness or bleeding episodes leading to their death shortly after interruption. Further, between the interruption and non-interruption groups, there were significant differences in the prevalence of co-morbidities associated with the risk of stroke (*Table 1*) which could have affected the results. The risk, however, was significant even when excluding all-cause death from the primary endpoint (*Table 3*), suggesting that there was a true increase in thrombo-embolic events shortly after interruption of warfarin treatment. Additionally, the results were independent of baseline CHADS<sub>2</sub> score as shown in *Table 3*, indicating that differences in co-morbidities had little or no impact on the results.

It is possible that the warfarin dosage estimations made in this study were inaccurate. Further, due to the uncertainty in the estimation of the exact interruption date, it is possible that an interruption occurred after an event (e.g. stroke) instead of before the event in some cases.

However, this was probably not the case since the method of recording the interruption periods by prescription analysis systematically underestimated the amount and length of interruptions because an interruption only was recorded when the individual patient had an estimated zero tablets left. In reality, patients often interrupt treatment while still having tablets in their possession yielding an underestimation as described. Additionally, the results were consistent when we time-shifted the analysis up to 30 days.

Some of the diagnoses used for baseline data had low accuracy.<sup>33</sup> However, outcome diagnoses have been validated

previously, e.g. ischaemic stroke had an excellent positive predictive value of 97%.<sup>34</sup>

Furthermore, the study was based on administrative registers that did not include clinical parameters correlated to outcome such as body mass index, smoking status, lipid levels, INR values, left ventricular ejection fraction, etc. and the results were prone to bias on this account. Additionally, there was no information on in-hospital bridging treatment with heparins; however, only a small number of patients were expected to have received such treatment due to exclusion patients with valvular AF. Finally, only patients hospitalized with AF have been included which could impede extrapolating the results to all patients with AF. However, data from the Copenhagen City Heart Study revealed that a majority of patients with AF were seen in hospital, indicating that the results may be generally applicable.<sup>35</sup>

The main strength of the study was the large nationwide cohort of unselected patients with AF. This study was the first to assess the problem of increased incidence of thrombo-embolism or death after warfarin interruption in a real-world setting with a broad and unspecific inclusion of all patients hospitalized with AF in a 12-year period. To our knowledge, this study is the first to examine warfarin interruption regardless of reason for interruption, thus providing longer follow-up and longer duration of interruption than studies focusing on interruption for surgical interventions only. The population was large and the analyses were statistically powerful. Even when analysed with caution, the results support an incentive for future testing in a prospective study to verify the results and elucidate the underlying mechanism. Additionally, the results stress the importance that clinicians consider the indication for warfarin interruption carefully in each patient and aim to minimize interruptions due to compliance issues.

## Conclusions

In an unselected nationwide population of patients with AF, almost three out of four patients on warfarin treatment had one or more periods of treatment interruption. Interruption of warfarin treatment was associated with a significantly increased short-term risk of thrombo-embolism or death during the first 90 days of interruption. The results were consistent across subgroups of patients.

This underlines the importance of careful and individual consideration of the balance between risk of thrombosis and bleeding before interrupting warfarin treatment.

## Supplementary material

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

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This study was conducted as part of J.R.'s PhD thesis while he was an employee at the Copenhagen University Hospital Gentofte, Denmark. No additional funding was received for the study.

**Conflict of interest:** none declared.

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