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Intracranial Hemorrhage and Subsequent Ischemic Stroke in Patients With Atrial Fibrillation

A Nationwide Cohort Study

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BACKGROUND: The risk of ischemic stroke/thromboembolic events after an intracranial hemorrhage (ICH) in patients with atrial fibrillation (AF) who are on warfarin treatment is poorly characterized. The aim of this study was to assess the association between the risk of ischemic stroke/thromboembolic events and ICH.

METHODS: Linkage of three Danish nationwide administrative registries in the period between 1999 and 2012 identified patients with AF on warfarin treatment. Event-rate ratios of stroke/thromboembolic events, major bleeding, and all-cause mortality stratified by ICH were calculated, and Cox proportional hazard models were used to compare event rates among ICH survivors. A matched OR was calculated for ICH occurrences within 0 to 3 months relative to the 3 to 6 months prior to a stroke/thromboembolic event. A rate ratio of claimed warfarin prescriptions in a 3-month period pre- and post-ICH was also calculated.

RESULTS: We studied 58,815 patients with AF (median age, 72.6 years; 60% men). When compared with the non-ICH group, the ICH group was at increased risk for stroke/systemic embolism/transient ischemic attack (TIA) (rate ratio, 3.67; 95% CI, 3.12-4.31) and mortality (rate ratio, 5.55; 95% CI, 5.20-5.92), but not for major bleeding (rate ratio, 1.06; 95% CI, 0.81-1.39). The matched OR of ICH occurrences prior to a stroke/systemic embolism/TIA was 4.33 (95% CI, 2.44-8.15). The rate ratio of claimed warfarin prescriptions post- and pre-ICH event was 0.28 (95% CI, 0.24-0.33).

CONCLUSIONS: In this large-scale study of patients with AF treated with warfarin, first-time ICH was associated with an increased rate of ischemic stroke/systemic embolism/TIA and mortality compared with the non-ICH group. There was a decrease in the warfarin-prescription purchase rate in the post-ICH period compared with pre-ICH, which may partly explain the excess risk.

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ABBREVIATIONS: AF = atrial fibrillation; CHA_2DS_2-VASc = cardiac failure or dysfunction, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled)-vascular disease, age 65 to 74 years, and sex category (female); ICD-10 = *International Classification of Diseases, 10th Revision*; ICH = intracranial hemorrhage; INR = international normalized ratio; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; TIA = transient ischemic attack; VKA = vitamin K antagonist

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Patients with atrial fibrillation (AF) have an increased risk for ischemic stroke, and stroke-prophylactic treatment with oral anticoagulants (OACs) is recommended if one stroke risk factor is present.[1] Treatment with antithrombotic agents such as the vitamin K antagonists (VKAs) (eg, warfarin) reduces stroke by 64% and all-cause mortality by 26%, when compared with placebo or a control.[2] However, patients on warfarin therapy are also at a higher risk of bleeding, the most severe being spontaneous intracranial hemorrhage (ICH). Indeed, anticoagulation-associated intracerebral hemorrhage has been reported to account for 20% of all ICH events.[3]

The anxiety of causing serious bleeding (particularly ICH) can lead physicians to withhold anticoagulants in some patients with AF, despite a greater benefit from OAC treatment (compared with no OAC or aspirin treatment) in terms of reduced risk of stroke.[4-6] More recently, the non-VKA OACs (NOACs, previously referred to as new or novel OACs[7]) have been shown to be associated with lower rates of ICH compared with VKAs, improving safety, in addition to their efficacy and convenience.[8-10] Nonetheless, a history of ICH was an exclusion criterion for patients included in recent trials of NOACs compared with VKAs.

In clinical practice, an ICH event necessitates temporary cessation of OAC therapy, requiring the physician to balance the risk of an additional bleeding event with the risk of a thromboembolic event in the absence of OAC treatment.[11] The preferred timing of OAC therapy resumption after an ICH event has been much debated,[12,13] and suggestions differ from 7 to 14 days to 30 weeks.[14-16] In practice, however, the timing of OAC therapy resumption is difficult, and attempts to err on the side of caution may lead to general undertreatment (or nontreatment), resulting in an increased risk for further fatal and disabling stroke among survivors of ICH.

The objective of this study was to investigate outcomes of ischemic stroke and thromboembolic events associated with ICH among patients with AF. We hypothesized that patients experiencing an ICH event would be at increased risk for thromboembolism, as reflected by a composite of ischemic stroke, systemic embolism, and transient ischemic attack (TIA), and by all-cause mortality. Further, we hypothesized that this increase in risk for thromboembolism among survivors of ICH would be accompanied by a decreased rate of warfarin-prescription purchase. We investigated these hypotheses in a large, nationwide cohort study.

Materials and Methods

Registry Data Sources and Study Population

All Danish residents are given a unique and permanent registration number at the time of birth or immigration. Nationwide registries enable retrieval of individual patient data on (1) discharge diagnosis classified by the *International Classification of Diseases, 10th Revision* (ICD-10) and admission and discharge dates (the Danish National Patient Registry); (2) dispensed prescriptions identified by the Anatomic Therapeutic Chemical classification code, date of purchase, package size and volume of the medication since 1994 (the Danish National Prescription Registry); and (3) information on sex, date of birth, emigration, and vital status (the Danish Civil Registration System).

By linking the three databases,[17-19] we established a cohort of patients with incident nonvalvular AF. Nonvalvular AF was defined as presence of ICD-10 diagnosis code I48, and baseline absence of mitral stenosis and mechanical heart valve (ICD-10 diagnosis codes: I05 and Z952-Z954). Specifically, we identified all patients discharged with a first-time hospital diagnosis (index date) of nonvalvular AF in the period January 1, 1999, to December 31, 2012. e-Appendix 1 gives detailed definitions on outcomes and concomitant pharmacotherapy. We excluded patients who died or experienced an ICH event (ICD-10 diagnosis codes: I60-I62, S063C, S064-S066, I690-I692) within the first 7 days after the index date. Patients who had claimed a prescription of heparin or low-molecular-weight heparin or non-VKAs 1 year prior to the index date were also excluded. We further restricted the cohort to patients who initiated warfarin treatment, defined as a warfarin prescription claim within the first 30 days after the index date.

Outcome Measures and Comorbidity

Patients were followed in the National Patient Registry from the index date (baseline) until the occurrence of the studied end point, emigration, end of study, or death, whichever came first. The primary end point was the composite of ischemic stroke/systemic embolism/TIA (ICD-10 diagnosis codes I63, I64, I74, G45). Secondary analyses were done on major bleeding, as well as all-cause mortality. The definition of major bleeding included acute posthemorrhagic anemia, hemothorax, conjunctival hemorrhage, retinal hemorrhage, vitreous hemorrhage, recurrent and persistent hematuria, menopausal and other perimenopausal disorders, hemorrhage from the respiratory passages, unspecified hematuria, and unclassified hemorrhage (ICD-10 diagnosis codes D62, J942, H113, H356, H431, N02, N95, R04, R31, R58).[20]

We imposed a dynamic stratification on the cohort by considering each patient's ICH status during follow-up. At the index date, all patients were ICH free. If a patient sustained an ICH, they would move irreversibly to the ICH group. Survivors of ICH were defined on the basis of the vital status from the Danish Civil Registration System (ie, no change in the vital status at the day of an ICH diagnosis).

The cardiovascular comorbidity and risk for stroke at baseline were assessed by the CHA_2DS_2-VASc (cardiac failure or dysfunction, hypertension, age $\geq$75 years [doubled], diabetes, stroke [doubled]-vascular disease, age 65-74 years, and sex category [female]) score, with higher scores indicating greater risk for stroke.[21] The CHA_2DS_2-VASc score has previously been applied in similar nationwide cohorts and is the preferred risk stratification tool for patients with AF, as recommended by the European Society of Cardiology.[22-25] We also calculated a (modified) HAS-BLED score (hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [$>$65 years], drugs [antiplatelet drugs or nonsteroidal antiinflammatory drugs]/alcohol excess concomitantly), but excluding labile international normalized ratio (INR) due to lack of data, for each patient to assess the risk of bleeding. Higher scores indicate greater risk of bleeding events.[23] Concomitant pharmacotherapy at baseline was defined as a prescription claim within 1 year prior to the index date.

Statistical Analysis

We performed three separate analyses. First, we compared the rate of stroke/systemic embolism/TIA, major bleeding, and all-cause mortality in the ICH group relative to the ICH-free group, defined according to the dynamic stratification. Second, we applied a case-crossover analysis among ischemic stroke/systemic embolism/TIA cases to describe the association between an ICH event and risk for ischemic stroke/systemic embolism/TIA. Third, we assessed among ICH survivors the rate of warfarin prescription purchases in a period before and after the ICH event.

Crude event rates of stroke/systemic embolism/TIA were calculated as the number of events divided by the total person-time within each of the dynamic ICH strata, and rates were compared using the Mantel-Haenzel rate-ratio method. This was done for 2 years of follow-up and using the entire follow-up period. Cumulative risk of stroke/systemic embolism/TIA as a function of time since ICH (taking into account competing risk for death[26]) was calculated to describe the absolute risk of stroke/systemic embolism/TIA in survivors of ICH. Events occurring within 7 days of the ICH event were excluded. To further investigate the outcomes for patients who sustained an ICH event, we performed a substudy to evaluate the presence of risk factors for ischemic stroke. This was done by using the Cox proportional hazards model to compare rates of stroke/systemic embolism/TIA in survivors of ICH on relative levels of (baseline) parameters in the CHA_2DS_2-VASc score. These analyses were adjusted for sex (binary), age (continuous), and year of inclusion (categorical); age adjustment was not applied when analyzing age 65 to 74 years and age $\geq$ 75 years.

We applied a case-crossover design to investigate the association between ICH and short-term risk for subsequent ischemic stroke/systemic embolism/TIA. The case-crossover is a case-only design that allows a patient to function as his or her own control subject by considering events in two separate time periods relative to the outcome of interest.[27,28] This self-controlled design controls for confounding by covariates that are (approximately) constant over the study period. We selected all incident cases of stroke/systemic embolism/TIA and ascertained occurrence of ICH in case periods and control periods, defined as 3 months prior to stroke/systemic embolism/TIA (case) and 6 to 3 months prior to stroke/systemic embolism/TIA (control period). A matched OR to assess the relative odds of an ICH event according to period was calculated using the McNemar test for matched pair's data. A sensitivity analysis assessing the definitions of the case and control periods was conducted by extending and reducing, respectively, the periods by 1 and 2 months. Further, a sensitivity analysis to assess the potential impact of seasonal variation was conducted by moving the control period to 9 to 6 months prior to the stroke/systemic embolism/TIA event.

Changes in exposure to warfarin following an ICH event were investigated by calculating the ratio of rates of warfarin purchase in a 3-month period immediately after and immediately before an event of ICH. The rates were calculated as the number of warfarin purchases divided by the person-time in the two 3-month periods.

A two-sided P value $<$ .05 was considered statistically significant. SAS 9.3 (SAS Institute Inc) and Stata/MP 13 (StataCorp LP) were used for the statistical analyses.

Results

A flowchart of the study is provided in Figure 1. In a cohort of 212,332 patients with incident nonvalvular AF, ascertained from January 1, 1999, to December 31, 2012, we identified 58,815 patients who satisfied the inclusion criteria. Of these patients, 1,639 (2.8%) had an incident ICH event, and 6,994 (11.9%) had a stroke/systemic embolism/TIA event, where the majority of this combined outcome was attributed to ischemic stroke (76.1%). The 30-day mortality rate of ICH was 44.2%. Median age of the study population was 72.6 years (interquartile range, 64.6-79.3 years), 60.0% were men, and 68.9% had a baseline CHA_2DS_2-VASc score $\geq$ 2 (Table 1).

Stroke/Systemic Embolism/TIA Relative to ICH

The rates of stroke/systemic embolism/TIA per 100 person-years based on the full follow-up period in the ICH and non-ICH groups were 9.59 and 2.62, respectively. This led to an increased rate ratio of 3.67 (95% CI, 3.12-4.31) (vs reference non-ICH) (Table 2). Excluding TIA events from the composite outcome did not alter the conclusion. The rate ratio for all-cause mortality was 5.55 (95% CI, 5.20-5.92), and for major bleeding events, 1.06 (95% CI, 0.81-1.39). The increased rate of stroke/systemic embolism/TIA and all-cause mortality, compared with patients without ICH, was more pronounced for 2 years of follow-up (Table 3).

The absolute risk of stroke/systemic embolism/TIA among survivors of ICH was markedly increased during the first 90 days after an ICH event (Fig 2). Hazard ratios for subsequent ischemic stroke/systemic embolism/TIA events in patients sustaining an ICH event were similar irrespective of selected baseline risk factors (based on the CHA_2DS_2-VASc score) at 2 years of follow-up (Fig 3).

A matched OR for occurrence of a recent ICH was calculated for all patients who had an event of stroke/systemic

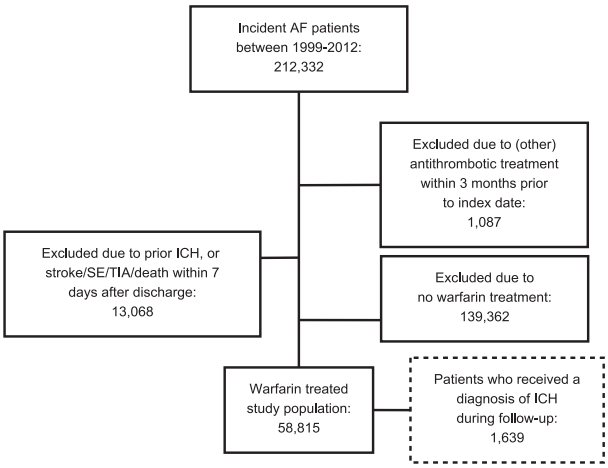

Figure 1 – *Flowchart of the study population. AF = atrial fibrillation; ICH = intracranial hemorrhage; SE = systemic embolism; TIA = transient ischemic attack.*

TABLE 1] Patient Baseline Characteristics by Status of ICH During Follow-up

Overall Study Population	Total Population	Free of ICH	ICH Group
Subjects, No.	58,815	57,176	1,639
Age, median (IQR), y	72.6 (64.6-79.3)	72.5 (64.5-79.3)	75.7 (68.9-80.7)
Male sex	35,225 (59.9)	34,286 (60.0)	957 (58.4)
Comorbidity			
Heart failure	5,573 (9.5)	5,427 (9.5)	146 (8.9)
Hypertension	13,777 (23.4)	13,631 (23.8)	409 (25.0)
Age 65-74 y	19,190 (32.6)	18,678 (32.7)	512 (31.2)
Age ≥ 75 y	24,255 (41.2)	23,385 (40.9)	869 (53.0)
Diabetes mellitus	7,102 (12.1)	6,918 (12.1)	184 (11.2)
Stroke	8,214 (14.0)	7,868 (13.8)	346 (21.1)
Vascular disease	9,358 (15.9)	9,116 (15.9)	242 (14.8)
Concomitant medication			
β-Blockers	18,524 (31.5)	18,021 (31.5)	503 (30.7)
Calcium channel blockers	15,245 (25.9)	14,787 (25.9)	458 (27.9)
ACEi/ARBs	20,766 (35.3)	20,220 (35.4)	546 (33.3)
Loop diuretics	13,028 (22.2)	12,674 (22.2)	354 (21.6)
Statin	13,426 (22.8)	13,118 (22.9)	308 (18.8)
NSAID	16,628 (28.3)	16,142 (28.2)	486 (29.7)
Digoxin	7,480 (12.7)	7,191 (12.6)	289 (17.6)
Amiodarone	311 (0.5)	307 (0.5)	4 (0.2)
Aspirin	21,729 (36.9)	21,037 (36.8)	692 (42.2)
Thienopyridines	1,517 (2.6)	1,489 (2.6)	28 (1.7)
CHA_2DS_2-VASc score			
0	5,830 (9.9)	5,742 (10.0)	88 (5.4)
1	12,464 (21.2)	12,134 (21.2)	330 (20.1)
2-9	40,521 (68.9)	39,300 (68.7)	1,221 (74.5)
HAS-BLED score			
0-2	46,828 (79.6)	45,556 (79.7)	1,272 (77.6)
≥ 3	11,987 (20.4)	11,620 (20.3)	367 (22.4)

Data given as No. (%) unless otherwise indicated. ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist; CHA_2DS_2-VASc = cardiac failure or dysfunction, hypertension, age ≥ 75 y (doubled), diabetes, stroke (doubled)-vascular disease, age 65 to 74 y, and sex category (female); HAS-BLED = hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 y), drugs (antiplatelet drugs or nonsteroidal antiinflammatory drugs)/alcohol excess concomitantly; ICH = intracranial hemorrhage; IQR = interquartile range; NSAID = nonsteroidal antiinflammatory drug.

embolism/TIA, to investigate the short-term risk of subsequent stroke/systemic embolism/TIA in patients who sustained an ICH event (Fig 4). Of 6,994 patients, 5,169 had sufficient history (> 6 months) to be included. Within this subgroup, 146 patients were identified as cases, which means they had an ICH event prior to an event of stroke/systemic embolism/TIA; 80 ICH events occurred within 6 months prior to the stroke/systemic embolism/TIA. During the case period (ie, 3 months prior to the stroke/systemic embolism/TIA), 65 patients had an ICH, while during the control period, 15 patients had an ICH.

The matched OR of having an ICH in the case vs the control period was 4.33 (95% CI, 2.44-8.18), which highlights the association of an increased risk for stroke/systemic embolism/TIA after an ICH event. A sensitivity analysis of prolonging and restricting the case and control periods did not qualitatively alter the results (Fig 4). Moving the control period relative to the case period to investigate the potential impact of seasonal variation reduced the number of subjects in the analysis but did not change the OR substantially (data not shown). A sensitivity analysis confining the end point of interest to "ischemic stroke" only or "ischemic

TABLE 2] Event Rates According to Status of ICH Using a Dynamic Stratification

Event	Person-y, No.	Events, No.	Event Rate/100 Person-y (95% CI)	Event Rate Ratio (95% CI)
Stroke/systemic embolism/TIA				
Non-ICH	261,681	6,843	2.62 (2.55-2.68)	Reference
ICH group	1,575	151	9.59 (8.18-11.25)	3.67 (3.12-4.31)
Major bleeding				
Non-ICH	263,667	6,130	2.32 (2.27-2.39)	Reference
ICH-group	2,114	52	2.46 (1.88-3.23)	1.06 (0.81-1.39)
All-cause mortality				
Non-ICH	281,927	20,010	7.10 (7.00-7.20)	Reference
ICH-group	2,404	946	39.36 (36.93-41.95)	5.55 (5.20-5.92)

TIA = transient ischemic attack. See Table 1 legend for expansion of other abbreviation.

stroke/systemic embolism" did not change our conclusions materially (data not shown).

Warfarin Treatment Relative to ICH

The subcohort of survivors of ICH was analyzed to assess exposure to warfarin treatment before and after an ICH event. The rate of claimed warfarin prescriptions was strongly and significantly reduced in 3 months after an ICH event compared with 3 months before (rate ratio, 0.28; 95% CI, 0.24-0.33). Similar effect size estimates were seen when restricting (rate ratio, 0.33; 95% CI, 0.29-0.38) or extending (rate ratio, 0.24; 95% CI 0.20-0.39) the periods by 1 month.

Discussion

Our principal findings were an increased rate of ischemic stroke and all-cause mortality in patients with AF who survived an ICH event compared with patients who had not experienced an ICH event. Second, among survivors of ICH, we observed a decrease in the warfarin-prescription purchase rate in the post-ICH period compared with pre-ICH period.

This register-based cohort study was undertaken to investigate the association between ICH and subsequent ischemic thrombotic events in patients with nonvalvular AF receiving warfarin treatment. The lack of controlled clinical trials assessing whether to reverse OACs and when to resume thromboprophylactic treatments poses a dilemma for clinicians: Having survived the acute phase, how does the increased risk for stroke/systemic embolism/TIA compare with the risk for recurrent ICH if OAC therapy is not restarted? Our study suggests that the risk for stroke/systemic embolism/TIA is, indeed, substantially increased, being up to a fivefold increase within the first 3 months after an ICH event. In the Swedish AF cohort study, Friberg et al[29] found that previous ICH was an independent predictor for

TABLE 3] Event Rates According to Status of ICH Using a Dynamic Stratification, Restricting the Cohort to 2 Years of Follow-up

Event	Person-y, No.	Events, No.	Event Rate per 100 Person-y (95% CI)	Event Rate Ratio per 100 Person-y (95% CI)
Stroke/systemic embolism/TIA				
Non-ICH	97,426	3,451	3.54 (3.43-3.66)	Reference
ICH group	241	46	19.29 (14.32-25.53)	5.40 (4.04-7.22)
Major bleeding				
Non-ICH	98,620	2,759	2.80 (2.70-2.90)	Reference
ICH group	297	15	5.04 (3.04-8.37)	1.80 (1.09-2.99)
All-cause mortality				
Non-ICH	101,099	6,701	6.63 (6.47-6.79)	Reference
ICH group	320	251	78.47 (69.34-88.81)	11.84 (10.44-13.42)

See Table 1 and 2 legends for expansion of abbreviations.

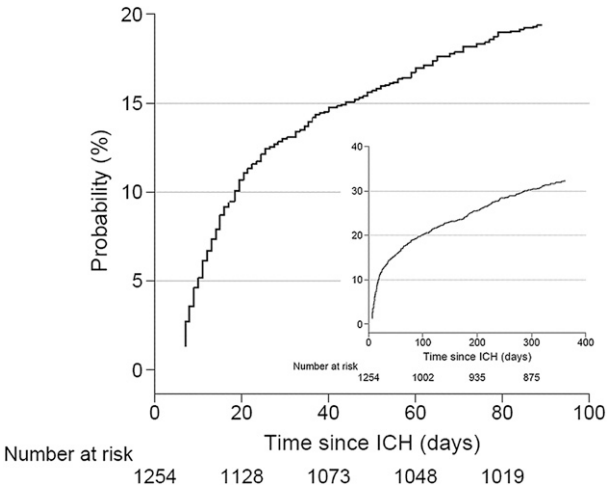

Figure 2 – *Absolute risk. Cumulative incidence of stroke/systemic embolism/TIA (taking into account the competing risk for death) in survivors of ICH using 3 mo and 1 y follow-up. Events occurring within first 7 d after the ICH event were excluded. See Figure 1 legend for expansion of abbreviations.*

subsequent ischemic stroke, reporting an adjusted hazard ratio of 1.49.

Our findings show a decreased rate of claims of warfarin prescriptions post-ICH, where the rate ratio of warfarin prescriptions was 0.33, which could indicate that only one-third of the patients restarted OAC treatment within the same time frame (3 months). A recent analysis by Qureshi et al[30] found that outcomes from thromboembolism were worse where OACs were discontinued following GI hemorrhage. In contrast, a decision to restart OAC therapy after an episode of major GI bleeding was associated with improved survival and decreased systemic embolism without increased risk of major GI bleeding recurrence after 7 days of interruption. It is important, however, to emphasize that the present analysis cannot be used to

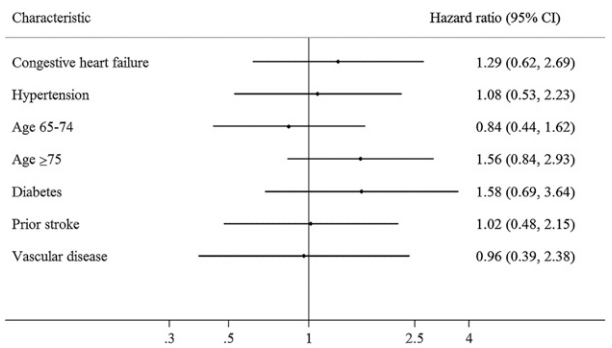

Figure 3 – *Hazard ratios for stroke/systemic embolism/TIA. Forest plot of adjusted hazard ratios for stroke/systemic embolism/TIA on selected levels of baseline risk factors in survivors of ICH, using 2 y of follow-up (46 events). Reference is to absence of the risk factor. See Figure 1 legend for expansion of abbreviations.*

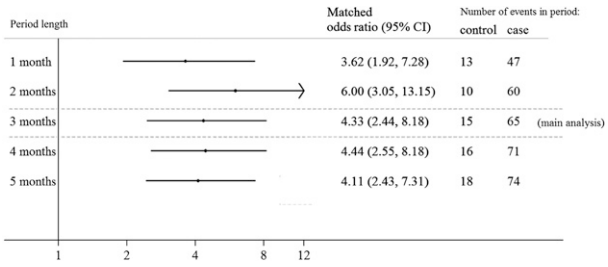

Figure 4 – *Case-crossover analysis of ICH events in control period (3 to 6 mo) and case period (0 to 3 mo) prior to an event of stroke/systemic embolism/TIA (main analysis marked between dashed lines). Sensitivity analysis was done by extending and restricting the control and case period (1 and 2 mo, and 4 and 5 mo, respectively). See Figure 1 legend for expansion of abbreviations.*

infer that the association between ICH and ischemic stroke is (causally) mediated by warfarin treatment. On the other hand, due to the lower risk of ICH among patients treated with the NOACs compared with warfarin,[10] it might be reasonable to consider these drugs instead of VKAs when considering a resumption of OACs. However, well-designed, clinically controlled trials investigating the optimal drug selection post-ICH are needed. Importantly, further investigation is needed to identify the cut of point in time when to restart warfarin. Indeed, one feasible approach could be done by using prospective registries of patients who sustain an ICH event.

Study Limitations

This observational study might be subject to ascertainment bias (ie, only hospital-diagnosed patients with AF are studied), and incompletely ascertained variables could lead to biased measures of associations. Also, the population registries lacked various important variables, which might have further elucidated associations. We did not have access to INR data, which are closely related to thromboembolic events as well as ICH events.[9,31] The ICH definition based on the registry data does not allow for analysis of the location and type of ICH, which could affect the outcome in survivors of ICH.[32] Indeed, patients with lobar hemorrhage or cerebral amyloid angiopathy remain at higher risk for further anticoagulant-related ICH recurrence than thromboembolic events, and current consensus suggests that such patients should be best managed without OACs.[14] In contrast, patients with deep hemispheric ICH and a baseline risk for ischemic stroke (eg, CHA_2DS_2-VASc score ≥ 5), may receive net benefit from restarting OAC therapy, especially if risk factors such as uncontrolled BP, labile INRs (as reflected by time in therapeutic range), and concomitant aspirin/nonsteroidal antiinflammatory

drug use in an anticoagulated patient are addressed.[14] Our lack of cerebral imaging data does not allow an assessment of ICH volume (which may be higher in warfarin users[33]), and is predictive of adverse outcomes.[34,35]

In conclusion, this nationwide cohort study clearly showed that an incident event of ICH was associated with a subsequent increased risk for ischemic stroke/systemic embolism/TIA and mortality but not major bleeding when compared with patients without ICH. This association may possibly be due to cessation of warfarin prescription in patients with AF, who are predisposed to an increased risk for stroke and thromboembolism.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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