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Outcomes Associated With Resuming Warfarin Treatment After Hemorrhagic Stroke or Traumatic Intracranial Hemorrhage in Patients With Atrial Fibrillation

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IMPORTANCE The increase in the risk for bleeding associated with antithrombotic therapy causes a dilemma in patients with atrial fibrillation (AF) who sustain an intracranial hemorrhage (ICH). A thrombotic risk is present; however, a risk for serious harm associated with resumption of anticoagulation therapy also exists.

OBJECTIVE To investigate the prognosis associated with resuming warfarin treatment stratified by the type of ICH (hemorrhagic stroke or traumatic ICH).

DESIGN, SETTING, AND PARTICIPANTS This nationwide observational cohort study included patients with AF who sustained an incident ICH event during warfarin treatment from January 1, 1998, through February 28, 2016. Follow-up was completed April 30, 2016. Resumption of warfarin treatment was evaluated after hospital discharge.

EXPOSURES No oral anticoagulant treatment or resumption of warfarin treatment, included as a time-dependent exposure.

MAIN OUTCOMES AND MEASURES One-year observed event rates per 100 person-years were calculated, and treatment strategies were compared using time-dependent Cox proportional hazards regression models with adjustment for age, sex, length of hospital stay, comorbidities, and concomitant medication use.

RESULTS A total of 2415 patients with AF in this cohort (1481 men [61.3%] and 934 women [38.7%]; mean [SD] age, 77.1 years [9.1 years]) sustained an ICH event. Of these events, 1325 were attributable to hemorrhagic stroke and 1090 were secondary to trauma. During the first year, 305 patients with a hemorrhagic stroke (23.0%) died, whereas 210 in the traumatic ICH group (19.3%) died. Among patients with hemorrhagic stroke, resuming warfarin therapy was associated with a lower rate of ischemic stroke or systemic embolism (SE) (adjusted hazard ratio [AHR], 0.49; 95% CI, 0.24-1.02) and an increased rate of recurrent ICH (AHR, 1.31; 95% CI, 0.68-2.50) compared with not resuming warfarin therapy, but these differences did not reach statistical significance. For patients with traumatic ICH, resuming warfarin therapy also was associated with a lower rate of ischemic stroke or SE (AHR, 0.40; 95% CI, 0.15-1.11); however, in contrast to patients with hemorrhagic stroke, therapy resumption was associated with a significantly lower rate of recurrent ICH (AHR, 0.45; 95% CI, 0.26-0.76). A reduction in mortality was associated with resuming warfarin therapy among patients with hemorrhagic stroke (AHR, 0.51; 95% CI, 0.37-0.71) and those with traumatic ICH (AHR, 0.35; 95% CI, 0.23-0.52).

CONCLUSIONS AND RELEVANCE Resumption of warfarin therapy after spontaneous hemorrhagic stroke in patients with AF was associated with a lower rate of ischemic events and a higher rate of recurrent ICH. Among patients with a traumatic ICH, a similar lower rate of ischemic events was found; however, a lower relative risk for recurrent ICH despite resuming warfarin treatment was also revealed.

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Supplemental content

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Treatment with oral anticoagulants (OACs) reduces the incidence of thromboembolic events and death among patients with atrial fibrillation (AF).[1] Thus, in contemporary guidelines,[2,3] anticoagulation is indicated for most patients with AF and at least 1 additional risk factor based on the CHA_2DS_2-VASc score (cardiac failure or dysfunction, hypertension, age 65-74 [1 point] or ≥75 years [2 points], diabetes, and stroke, transient ischemic attack or thromboembolism [2 points]-vascular disease, and sex category [female]). Given the close association of advanced age, AF, and subsequent increased risk for stroke, anticoagulation treatment is the mainstay of reducing the risk for cardioembolic stroke and all-cause mortality among these patients.[2,4] However, the treatment may come at the cost of an increased risk for bleeding, including bleeding in the brain, which is the most feared clinical situation in patients receiving antithrombotic therapy. In patients with AF who encounter a warfarin-associated intracranial hemorrhage (ICH), the risk for 30-day mortality approaches 50%.[5]

Despite evidence of benefit, warfarin treatment has been reported to be underused in such patients of advanced age.[6] This underuse may be related to a perceived risk for falls, but also an increase in the risk for ICH that has been shown to be associated with age.[7,8] Patients with AF who survive an ICH event are still at risk for thromboembolism, but this risk has to be balanced against the treatment-related risk for recurrent intracranial bleeding. This serious treatment conundrum has been investigated in previous studies,[9,10] which show a significant reduction in all-cause mortality among those who resume warfarin treatment. Nevertheless, evidence of benefit or harm from resuming warfarin treatment is scarce in this group of patients. We sought to investigate the prognosis in survivors of ICH with preexisting AF who receive warfarin treatment, stratified by whether or not warfarin treatment was resumed after the hospitalization and by the cause of the bleeding as a traumatic event, such as a fall or accident, or spontaneous ICH, such as hemorrhagic stroke.

Key Points

Question What is the prognosis associated with resuming oral anticoagulant treatment in patients with atrial fibrillation who sustain an intracranial hemorrhage?

Findings In this observational study of 2415 patients who experienced a traumatic intracranial hemorrhage or a hemorrhagic stroke, the associated risk of resuming oral anticoagulant therapy suggested a reduction in thromboembolism in both patient subgroups. Patients who experiences a hemorrhagic stroke had a higher rate of intracranial hemorrhage recurrence after treatment resumption, which was not present for patients who had sustained a traumatic intracranial hemorrhage.

Meaning Patients with atrial fibrillation who sustain a hemorrhagic stroke or traumatic intracranial hemorrhage have different prognoses, and recommendations for resuming oral anticoagulant treatment should consider this difference.

Methods

This observational cohort study using historical data was based on 3 Danish nationwide databases: (1) the Danish National Patient Register[11] (established in 1977), which includes admission and discharge dates and the discharge diagnoses for hospital admissions from the *International Classification of Diseases and Health Related Problems, Tenth Revision* (*ICD-10*); (2) the Danish National Prescription Registry,[12] which holds information on purchase date, Anatomical Therapeutic Chemical classification code, and package size for every prescription withdrawal since 1994; and (3) the Danish Civil Registration System,[13] which includes information on sex, date of birth, vital status and emigration status. Every resident in Denmark is assigned a unique identification number allowing linkage on an individual level between databases. No ethical approval or informed consent was obtained, because these are not mandated for registry studies in Denmark.

Study Population and Exposure

Persons with an incident diagnosis of AF from January 1, 1998, through February 28, 2016, were initially identified. All such patients with a subsequent ICH event underwent screening for inclusion based on primary and secondary diagnoses. For patients with a spontaneous hemorrhagic stroke defined by *ICD-10* codes, we included nontraumatic subarachnoid hemorrhage (code I60); nontraumatic intracerebral hemorrhage, including bleeding in hemisphere, brain stem, cerebellum, intraventricular, or multiple locations or unspecified bleeds (code I61); and nontraumatic subdural hemorrhage or nontraumatic extradural hemorrhage (code I62). For patients with a trauma-induced ICH defined by *ICD-10* codes we included focal traumatic intracranial bleeding (code SC063C), traumatic epidural hemorrhage (code SC064), traumatic subdural hemorrhage (code SC065), and traumatic subarachnoid hemorrhage (code SC065). Patients with a prior ICH or sequela from ICH (*ICD-10* codes I690-I692) were excluded. To investigate warfarin-associated ICH events, we required patients to be treated with warfarin as their anticoagulant; thus, patients who did not claim a prescription of warfarin 6 months before their index ICH event were excluded.

We used information from the National Prescription Registry to categorize patients into groups of warfarin exposure after hospital discharge. All patients were initially assigned to the no treatment group when discharged from the hospital. Patients who claimed a prescription for warfarin were assigned to the warfarin treatment group on the date of prescription claim, and their grouping remained unchanged throughout the follow-up period. Thus, treatment exposure to warfarin was considered as a time-dependent variable.

Comorbidities and Outcomes

Baseline information was acquired on the date of hospital discharge. Comorbidities were based on preceding hospital diagnoses until discharge after the incident ICH event. Prescription claims within the last year before baseline defined concomitant medications. The CHA_2DS_2-VASc score was calculated to assess cardiovascular comorbidity and the risk for stroke at baseline. We calculated the HAS-BLED score (hypertension, abnormal renal or liver function, stroke or thromboembolism, bleeding history, labile international normalized ratio [not included because of data unavailability], elderly [age >65 years], drug consumption/

alcohol excess [aspirin was not included owing to status of exposure]) for each patient to assess the bleeding risk. The eTable in the Supplement provides a detailed description of outcomes and concomitant medication. Owing to lack of clinically adjudicated ICH severity, the length of hospital stay (calculated as the date from the ICH event until the day of discharge) was used as a proxy of ICH severity; longer hospital stays reflected more complicated (and severe) conditions.

Patients were followed up in the National Patient Registry from 14 days after hospital discharge (index date) to ensure ascertained outcomes were not immediately related to the inclusion event. The primary study outcomes were (1) a composite outcome of ischemic stroke or systemic embolism (*ICD-10* codes I63, I64, and I74) and (2) recurrent ICH defined as a composite outcome of all types of bleeding in the brain (*ICD-10* codes I60, I61, I62, S063C, S064, S065, and S066). We also investigated a secondary outcome of all-cause mortality. To allow for a thorough prognostic evaluation, a principal outcome was defined as all stroke by a composite of ischemic stroke or intracerebral hemorrhage (*ICD-10* codes I61, I63, and I64). Because thromboembolism may be closely correlated with a terminal outcome and no postmortem data were available, an additional outcome analysis was performed using a composite outcome of ischemic stroke or systemic embolism (SE) and death. Given the severity of the studied outcomes, we only considered coded diagnoses as an outcome event if the patient was admitted to the hospital for at least 24 hours and the outcome was coded as the primary cause of hospital admission. Because of poor validity, emergency department–coded diagnoses were not included in this study.[14] The outcomes of ischemic stroke and ICH have previously been validated and found to be accurate for epidemiologic research.[15]

Statistical Analysis

We used time-to-event analysis to contrast the relative risk of an end point between groups, measuring time at risk from 14 days after hospital discharge until the relevant event; emigration; death; end of follow-up, defined as a maximum of 1 year; or the end of follow-up (April 30, 2016), whichever came first. Owing to lack of international normalized ratio values, we disregarded any treatment cessation; however, person-time was censored if patients initiated or shifted treatment to a non-vitamin K antagonist oral anticoagulation therapy (OAC). Exposure to warfarin treatment was regarded as a time-dependent variable with a single irreversible transition (0 for no treatment to 1 for OAC treatment). Crude 1-year incidence rates were calculated as the number of events divided by 100 person-years, where person-years were split in accordance with the time-dependent exposure variable. Adjusted Cox proportional hazards regression analyses were conducted to investigate relative risk between the treatment groups, with no warfarin treatment being the reference. The adjustment model included age (continuous, cubic spline), CHA_2DS_2-VASc score (continuous), HAS-BLED score (continuous), sex, previous thromboembolism, vascular disease, hypertension, diabetes, aspirin, β-blocker, nonsteroidal anti-inflammatory drugs, statins, and days in hospital from the index event (continuous, cubic spline). The adjustment model also included information on ischemic stroke or SE and recurrent ICH events occurring during the first 14 days after hospital discharge (binary) because such events could affect the choice of warfarin treatment before the observation time commenced.

To assess whether the analyses were confounded by indication (ie, selective prescribing due to complications of the index event and other comorbidities), we performed propensity-matched analyses in each stratum of hemorrhagic stroke and traumatic ICH. Specifically, we included the variables applied in the multivariable Cox proportional hazards regression model to calculate the propensity score of receiving OAC treatment or not. We attempted to match nonusers to users in a 2:1 ratio. Details on quality of matching are provided in the eMethods and eFigures 1 and 2 in the Supplement. Expert opinion suggests a maximum of 10 weeks before resuming warfarin treatment in patients with AF at high risk for stroke if no evidence suggests cerebral amyloid angiopathy.[16] Therefore, we imposed a 10-week period to allow sufficient time for warfarin treatment resumption in terms of time to claim a prescription before the observation time began. The treatment exposure groups were subsequently defined within this period and analyzed according to those who claimed a warfarin prescription (warfarin treatment group) and those who did not (no treatment group), with follow-up starting at week 10. To further elaborate on the consequences of the chosen landmark, we calculated the mean time to warfarin prescription claim (if any) from the day of hospital discharge to 3 months; this time was subsequently used as the landmark (ie, start of observation time) for the repeated analyses.

We used STATA/MP (version 14; StataCorp) and R software (version 3.1.1; https://www.r-project.org) for the statistical analysis and graphical illustrations. A 2-sided $P < .05$ was considered to be statistically significant.

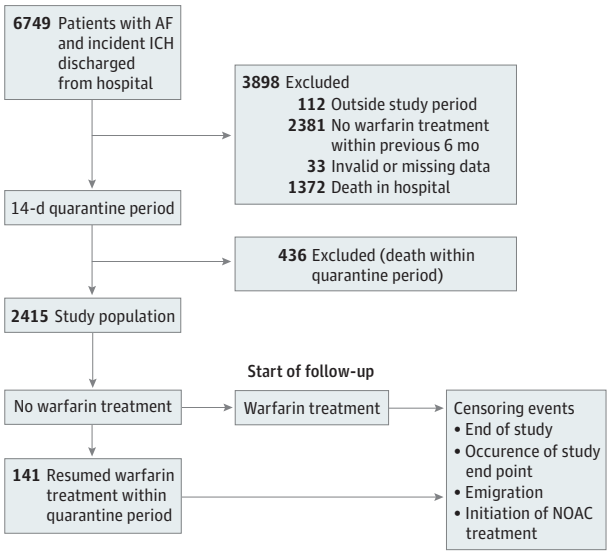
Results

A total of 6749 patients with incident ICH subsequent to their AF diagnosis were identified from January 1, 1998, through February 28, 2016; of patients who received prior warfarin treatment, 1372 died during hospital admission (**Figure 1**). In the cohort of patients discharged from the hospital, 436 died within 14 days. The study population consisted of 2415 patients with AF who received warfarin treatment at the first-time ICH event; of these, 1325 had a hemorrhagic stroke and 1090 had a traumatic ICH (**Table 1**). The mean (SD) age for the study population was 77.1 (9.1) years; 934 (38.7%) were women, and 1481 (61.3%) were men.

The most common comorbidities were hypertension (1552 [64.3%]) and heart failure or left ventricular dysfunction (708 [29.3%]). Among patients who presented with a hemorrhagic stroke, 550 (41.5%) had a prior thromboembolic event compared with 320 (29.4%) who presented with a traumatic ICH. The mean (SD) CHA_2DS_2-VASc score was 4.1 (1.7) for patients with a hemorrhagic stroke and 3.8 (1.7) for patients who sustained a traumatic ICH. The mean (SD) HAS-BLED score for all patients was 3.6 (1.1) and was similar for both subgroups. The hospital mean (SD) length of stay from the ICH event was higher for the hemorrhagic stroke cohort at 15.9 (18.4) vs 8.2 (12.0) days.

The cohort accrued a median follow-up period of 279 days. A total of 96 primary outcomes of ischemic stroke or SE and 139 recurrent intracranial bleeding episodes were observed. The

Figure 1. Flowchart of the Study Population



AF indicates atrial fibrillation; ICH, intracranial hemorrhage; and NOAC, non–vitamin K antagonist oral anticoagulant.

overall annualized all-cause mortality was high (514 events [25.4%]) and was higher among those who did not resume warfarin treatment (418 events [34.9%]) compared with those who did (96 events [15.5%]).

Prognosis for Patients With Hemorrhagic Stroke

The absolute number of events and event rates are presented in **Table 2**. The primary event of ischemic stroke or SE was observed in 69 patients, and intracranial bleeding was observed in 50. Patients who resumed warfarin therapy had a lower rate of ischemic stroke or SE (3.3 per 100 person-years) than did patients who did not resume treatment (8.9 per 100 person-years; adjusted hazard ratio [AHR], 0.49; 95% CI, 0.24-1.02) (**Figure 2**); however, statistical significance was not reached. For recurrent ICH, the rates were 5.8 per 100 person-years vs 5.3 per 100 person-years (AHR, 1.31; 95% CI, 0.68-2.50). The rates for the composite end point of all stroke (ischemic and hemorrhagic strokes) were 7.3 vs 12.1 per 100 person-years (AHR, 0.74; 95% CI, 0.44-1.27). For the secondary end point of all-cause mortality, the associated risk with resumption of warfarin therapy was an AHR of 0.51 (95% CI, 0.37-0.71).

Prognosis for Patients With Traumatic ICH

During the first year of follow-up, 27 patients experienced an ischemic stroke or SE, whereas 89 experienced a recurrent ICH almost solely driven by diagnoses of recurrent traumatic ICH (87 [97.8%]). Patients who resumed warfarin therapy had a lower rate of ischemic stroke or SE (2.1 per 100 person-years vs 4.1 per 100 person-year; AHR, 0.40; 95% CI, 0.15-1.11) (Figure 2), but the difference was not statistically significant. The adjusted relative risk for recurrent bleeding with resumption of warfarin treatment was 0.45 (95% CI, 0.26-0.76), and resumption of treatment was associated with a lower adjusted relative risk for all stroke (AHR, 0.36; 95% CI, 0.16-0.84) and death (AHR, 0.35; 95% CI, 0.23-0.52).

Table 1. Patient Characteristics[a]

Variable	Patient Group All (N = 2415)	Hemorrhagic Stroke (n = 1325)	Traumatic ICH (n = 1090)
Sex			
Female	934 (38.7)	574 (43.3)	360 (33.0)
Male	1481 (61.3)	751 (56.7)	730 (67.0)
Age, mean (SD), y	77.1 (9.1)	76.8 (9.2)	77.4 (9.0)
Age, y			
≥65	2163 (89.6)	1177 (88.8)	986 (90.4)
≥75	1533 (63.5)	820 (61.9)	713 (65.4)
Location of bleeding			
Intracerebral	1065 (44.1)	1042 (78.6)	23 (2.1)
Subdural	1111 (46.0)	149 (11.2)	962 (88.3)
Subarachnoid	239 (9.9)	134 (10.1)	105 (9.6)
Myocardial infarction	252 (10.4)	140 (10.6)	112 (10.3)
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.7)	4.1 (1.7)	3.8 (1.7)
HAS-BLED score, mean (SD)	3.6 (1.1)	3.7 (1.1)	3.6 (1.1)
Previous ischemic stroke/SE or TIA	870 (36.0)	550 (41.5)	320 (29.4)
Previous ischemic stroke	721 (29.9)	476 (35.9)	245 (22.5)
Heart failure or LVD	708 (29.3)	383 (28.9)	325 (29.8)
Vascular disease	458 (19.0)	244 (18.4)	214 (19.6)
Renal dysfunction	193 (8.0)	107 (8.1)	86 (7.9)
Hypertension	1552 (64.3)	850 (64.2)	702 (64.4)
Diabetes	442 (18.3)	234 (17.7)	208 (19.1)
Time since last OAC prescription claim, mean (SD), d	77.2 (62.7)	81.3 (62.8)	72.3 (62.2)
Medications used			
Aspirin	844 (34.9)	483 (36.4)	361 (33.1)
β-Blocker	1501 (62.2)	826 (62.3)	675 (61.9)
NSAID	465 (19.3)	247 (18.6)	218 (20.0)
Proton pump inhibitor	585 (24.2)	315 (23.8)	270 (24.8)
Statin	996 (41.2)	524 (39.5)	472 (43.3)
Phenprocoumon	117 (4.8)	73 (5.5)	44 (4.0)
Warfarin	2298 (95.2)	1252 (94.5)	1046 (96.0)
Cancer	424 (17.6)	225 (17.0)	199 (18.3)
Percutaneous coronary intervention	194 (8.0)	105 (7.9)	89 (8.2)
Coronary artery bypass surgery	160 (6.6)	85 (6.4)	75 (6.9)
In-hospital recurrent ICH before discharge	194 (8.0)	56 (4.2)	138 (12.7)
In-hospital stroke or SE before discharge	20 (0.8)	15 (1.1)	5 (0.5)
Length of hospital stay, mean (SD), d	12.4 (16.3)	15.9 (18.4)	8.2 (12.0)

Abbreviations: CHA_2DS_2-VASc, cardiac failure or dysfunction, hypertension, age 65-74 [1 point] or ≥75 y [2 points], diabetes, and stroke, transient ischemic attack or thromboembolism [2 points]–vascular disease, and sex category [female]; HAS-BLED, hypertension, abnormal renal or liver function, stroke or thromboembolism, bleeding history, labile international normalized ratio [not included because of data unavailability], elderly [age >65 y], drug consumption/alcohol excess [aspirin was not included owing to status of exposure]; ICH, intracranial hemorrhage; LVD, left ventricular dysfunction; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant; SE, systemic embolism; TIA, transient ischemic attack.

[a] Data are presented as number (percentage) unless otherwise indicated.

Sensitivity and Additional Analyses

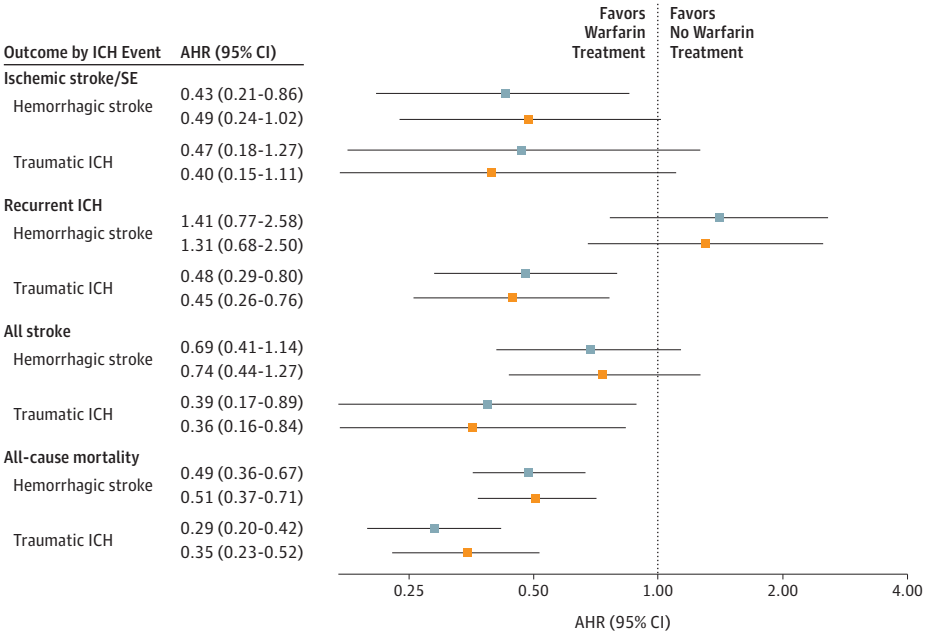
To investigate whether the main analyses were biased (eg, confounding by indication), 2 propensity-matched populations were constructed according to cause of ICH. For patients with

Table 2. Studied Outcomes During 1 Year of Follow-up

Outcome	Index ICH Event			
	Hemorrhagic Stroke		Traumatic ICH	
	No Warfarin Treatment Group	Warfarin Treatment Group	No Warfarin Treatment Group	Warfarin Treatment Group
Ischemic stroke/SE				
No. of events	60	9	20	7
Event rate per 100 person-years	8.9	3.3	4.1	2.2
Recurrent ICH				
No. of events	35	15	66	23
Event rate per 100 person-years	5.3	5.8	16.4	8.3
All stroke				
No. of events	78	19	31	10
Event rate per 100 person-years	12.1	7.3	6.6	3.1
All-cause mortality				
No. of events	250	55	169	41
Event rate per 100 person-years	35.5	19.6	34.0	12.1

Abbreviations: ICH, intracranial hemorrhage; SE, systemic embolism.

Figure 2. Forest Plots of Studied Outcomes and Associations With Resumption or No Resumption of Warfarin Treatment



No resumption was the reference condition. The analyses were stratified by index ICH event. Crude analyses are depicted by lines with blue boxes; lines with orange boxes for adjusted analyses. AHR indicates adjusted hazard ratio; ICH, intracranial hemorrhage; and SE, systemic embolism.

an index event of hemorrhagic stroke, the population was confined to 675 patients, including 331 with no warfarin treatment and 203 who resumed warfarin treatment within 10 weeks after hospital discharge. The propensity-matched HR for ischemic stroke or SE was 0.58 (95% CI, 0.33-0.99) for those who resumed warfarin treatment compared with no resumption as the reference. For recurrent ICH, the HR was 2.24 (95% CI, 1.10-4.58). Thus, resumption of warfarin treatment entailed a lower relative risk for ischemic events at the expense of an increased risk for recurrent ICH.

For patients with an index event of traumatic ICH, the propensity-matched population included 347 with no resumption of warfarin treatment and 203 who resumed warfarin treatment. The propensity-matched HRs were 0.60 (95% CI, 0.28-1.30) for ischemic stroke or SE and 1.05 (95% CI, 0.49-2.23) for recurrent ICH. In general, these results are in line with the main analyses; however, owing to the smaller population (due to matching criteria), the CIs were wide and may preclude statistically significant conclusions.

The choice of a 10-week period for allocation of treatment groups was additionally investigated, using the mean time to prescription claim within the first 3 months after hospital discharge (mean of 31 days); this sensitivity analysis did not materially affect the results. When the composite outcome of stroke or SE and death was examined, the AHRs with resumption of warfarin treatment for patients with prior hem-

orrhagic stroke was 0.62 (95% CI, 0.47-0.82) and with traumatic ICH was 0.37 (95% CI, 0.26-0.52). These associations were mainly driven by the outcome of all-cause mortality because this event occurred more than 5 times more frequently than thromboembolic events.

Discussion

In this observational cohort study of patients with AF who sustained an ICH while receiving warfarin treatment, our principal findings were 3-fold. First, patients with a first-time hemorrhagic stroke had a poor prognosis, but resumption of warfarin treatment was associated with a lower rate of ischemic stroke or SE, a higher rate of recurrent ICH, and significantly lower mortality. Second, patients with an incident traumatic ICH had a similarly poor prognosis and lower rate of ischemic stroke or SE with resumption of warfarin treatment but lower rates of recurrent ICH and mortality after resumption of warfarin treatment. Third, the relative risk for recurrent ICH associated with resumption of warfarin treatment was higher among patients with a hemorrhagic stroke than observed among patients with a traumatic ICH event in this cohort.

Patients with AF and a high thromboembolic risk who sustain an ICH (due to either cause) present a clinical dilemma and treatment conundrum. We found that patients presenting with an ICH carry a different prognosis in terms of associated outcomes from resuming warfarin treatment according to the cause of the bleeding. In a previous investigation of the prognosis of head trauma,[17] preinjury use of warfarin was associated with worse outcomes in comparison with no use of warfarin. For those receiving warfarin, regardless of cause, resumption of treatment resulted in a favorable prognosis in terms of a reduction in rates of ischemic and hemorrhagic stroke.[18] Although the finding of an attenuated risk for hemorrhagic stroke among patients resuming warfarin treatment could be attributable to some residual confounding, our study confirms prior observations by Albrecht et al[18] and extends the findings to a population of patients with AF. A very similar direction of associations can be observed with an adjusted odds ratio of 0.70 (95% CI, 0.52-0.95) vs an AHR of 0.45 (95% CI, 0.26-0.76).

In a cohort of patients with AF who shared risk factors for ischemic and hemorrhagic stroke, McGrath et al[19] found that none of these risk factors was associated with hemorrhagic stroke or ischemic stroke. They observed that age was a stronger predictor of ischemic stroke than hemorrhagic stroke, which indicates a more favorable risk profile if patients with AF are treated with warfarin according to guideline recommendations.[20,21] Whether these observations can be generalized to all patients with AF who sustain an ICH event remains to be fully investigated, but our results signal that these findings might apply to those who experience a traumatic ICH event. Ongoing prospective registries and randomized clinical trials will add to the current knowledge on whether to resume warfarin treatment after specific subtypes of ICH events.[22-24]

Limitations

The observational nature of the study should be considered when interpreting our results. The data are based on administrative databases primarily used for reimbursement, and thus not all clinically relevant and important variables were available. The result of a 50% reduction in mortality associated with resumption of warfarin treatment requires confirmation in other studies. Indeed, all-cause mortality associated with treatment exposure in observational studies requires careful consideration.[25] Nonetheless, some deaths in real-world observational studies could also be from undiagnosed (fatal) strokes because postmortem autopsy or cerebral imaging is not mandated.

We had no information on intensity of warfarin treatment and could not access the location and volume of the hematoma. These variables are crucial to capture the severity of the ICH event and could bias our analysis in terms of associations with resumption of OAC treatment (ie, residual confounding by indication bias). Clearly, spontaneous intracerebral hemorrhage is a heterogeneous disease ranging from macrovascular lesions to small vessel disease; we were unable to capture these variations, and thus our associations in relation to warfarin treatment effects may reflect these discrepancies in prognosis from the original bleeding event. Aside from OAC treatment, left atrial appendage closure may be an option for stroke prevention in this frail population; however, randomized clinical trials are warranted before this treatment alternative may be recommended.

Ascertainment on medication use and stratification to resumption of warfarin treatment was based on filled prescriptions. Thus, we risked including patients not receiving warfarin treatment at baseline because our inclusion criterion was chosen as a prescription claim within 180 days before the index event. In addition, we did not assess the proportion of days covered by warfarin treatment remaining from before the index event. This process may have misclassified some patients as not resuming warfarin treatment while they indeed did resume treatment before claiming a new prescription of warfarin. The propensity-matched analysis allowing 10 weeks to resume treatment did not lead to materially changed effect sizes, although we found marginal statistically significant results for patients sustaining a hemorrhagic stroke.

We did not have access to imaging data in this study; thus, the analyses did not include information on specific subtypes of ICH. In particular, information on small bleeds (obtained from imaging data) could have strengthened our analyses, because physicians treating stroke could be cautious about recommending resumption of warfarin treatment in patients with evidence of clinically important small bleeds.[26,27] We only considered primary coded diagnoses as events and required patients to be admitted to the hospital with a minimum stay of 24 hours. Although these criteria may not equate to the severity of the index diagnosis, they inform the adjustment model, ensuring that this information was not completely left out of the relative risk assessments.

Conclusions

Spontaneous hemorrhagic stroke and trauma-induced ICH confer different prognoses in patients with AF, and recommendations on resumption of warfarin treatment should consider this difference. Warfarin treatment resumption after a spontaneous hemorrhagic stroke event was associated with a lower rate for subsequent ischemic events, whereas the relative risk for recurrent ICH was increased; however, statistical uncertainty precludes firm conclusions of excess harm associated with treatment. Resumption of OAC therapy in patients with traumatic ICH was associated with a lower rate of ischemic events and a lower relative risk for recurrent ICH despite resumption of warfarin treatment. In both groups, warfarin resumption was associated with a lower risk for death within the first year after the event.

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Study concept and design: Nielsen, Larsen, Lip.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Nielsen, Skjøth.
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Editor's Note

The Tightrope of Resuming Anticoagulation Therapy After a Bleed

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In the absence of randomized clinical trial data to address complex treatment dilemmas when the therapeutic window of a therapy is narrow, the stakes are high, and the risk for harm is substantial, observational studies can help guide decision making. In the case of patients who have atrial fibrillation and an intracranial bleed while receiving anticoagulation therapy, whether one should resume that therapy is one such relatively common scenario. The risk for major bleeding associated with anticoagulation therapy varies from as low as 0.5% per year in low-morbidity populations to as high as 6% per year among patients with prior major bleeds. Given this incidence and the increasing prevalence of atrial fibrillation with an aging population, we can expect this dilemma to become even more common. In this issue of *JAMA Internal Medicine*, the observational study by Nielsen et al[1] suggests that resuming warfarin treatment results in a favorable trade-off. However, as with all observational studies, residual confounding may result. Specifically, healthier patients (defined by factors not captured in the multivariate analysis) may have been more likely to resume anticoagulation therapy. Thus, as one engages in a discussion of the risks and benefits of such a high-stakes decision, we think these data are helpful until randomized clinical trials can address the unbiased effects of resuming warfarin therapy. The observed mortality difference in this study is provocative and fills in the evidence gap while supporting the need for a definitive clinical trial.

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1. Nielsen PB, Larsen TB, Skjøth F, Lip GYH. Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation [published online February 20, 2017]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2016.9369