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Risk of Cerebrovascular Events in Intracerebral Hemorrhage Survivors With Atrial Fibrillation: A Nationwide Cohort Study

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BACKGROUND: In patients with intracerebral hemorrhage (ICH) and prevalent atrial fibrillation (AF), the optimal stroke prevention strategy is unclear. We sought to estimate the risk of cerebrovascular events among ICH survivors with AF.

METHODS: We used the Danish Stroke Registry to identify patients with incident ICH and prevalent AF between 2003 and 2018. Key inclusion/exclusion criteria of the PRESTIGE-AF (Prevention of Stroke in Intracerebral hemorrhage Survivors With Atrial Fibrillation) trial were applied. Cumulative incidence of recurrent ICH, cerebrovascular ischemic event, and all-cause death were investigated after one year.

RESULTS: A total of 1885 patients (median age 80.0 years; 47.6% females) were included in the study. We observed 191 cerebrovascular events and 650 all-cause deaths, and more cerebrovascular ischemic events (N=63) than recurrent ICH events (N=40). Risks of recurrent ICH, cerebrovascular ischemic event, and all-cause death were 1.5%, 3.2%, and 30.3%, respectively, among patients not exposed to OAC during follow-up. The cumulative incidences were 2.8% for recurrent ICH, 3.2% for cerebrovascular ischemic events, and 22.0% for all-cause death among patients initiating/resuming OAC during follow-up.

CONCLUSIONS: We observed a high risk of cerebrovascular ischemic events and a very high risk of all-cause death at one year after the incident ICH. The results of ongoing clinical trials are warranted to determine optimal stroke prevention treatment among ICH survivors with concomitant AF.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: anticoagulants ■ atrial fibrillation ■ epidemiology ■ hemorrhagic stroke ■ ischemic stroke

Atrial fibrillation (AF) is the most common sustained arrhythmia and substantially increases the risk of ischemic stroke.¹ Oral anticoagulant therapy (OAC) has a class Ia guideline recommendation in patients with AF with a CHA₂DS₂-VASc score ≥ 2 in males and CHA₂DS₂-VASc score ≥ 3 in females to prevent thromboembolic events.^{2,3} However, in patients with AF who have

suffered an intracerebral hemorrhage (ICH), the optimal stroke prevention strategy is debatable.^{2,3}

ICH is a devastating vascular event and the risk of recurrent ICH is high,^{4,5} but in patients with AF surviving an ICH, the risk of ischemic stroke is also high.⁶ A previous study found a higher risk of cerebrovascular ischemic events among patients with AF surviving an ICH than among

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ICH	intracerebral hemorrhage
IQR	interquartile range
NOAC	nonvitamin K antagonist oral anticoagulant
OAC	oral anticoagulant therapy
PRESTIGE-AF	Prevention of Stroke in Intracerebral Haemorrhage Survivors With Atrial Fibrillation

those without a prior ICH.⁶ No clear recommendations on the decision to initiate or resume antithrombotic treatment after an ICH in patients with AF exist.^{2,3} Consequently, clinicians around the globe have widely different preferences.^{7,8}

Several randomized controlled trials are currently investigating antithrombotic treatment options for stroke prevention in ICH survivors with concomitant AF.^{9–14} An ongoing European multinational randomized controlled trial, the PRESTIGE-AF (Prevention of Stroke in Intracerebral Haemorrhage Survivors With Atrial Fibrillation) trial is investigating stroke prevention strategies in patients with AF surviving an ICH.¹³ Patients are randomized to either a nonvitamin K antagonist oral anticoagulant (NOAC) or no anticoagulation. The results of the PRESTIGE-AF trial will provide important information about the optimal stroke prevention strategy in patients with AF and recent ICH.

To provide data from routine clinical practice on the risk of cerebrovascular events, we examined risk estimates for ischemic and hemorrhagic cerebrovascular events in a cohort of ICH survivors with AF mirroring the PRESTIGE-AF trial population. The cohort was stratified by levels of CHA₂DS₂-VASc score to reveal potential differential risk according to a widely used clinical risk scoring system in AF patients and supplemented with analyses accounting for stroke prevention treatment.

METHODS

This study was an observational cohort study describing the prognosis for patients with AF presenting with ICH at specialized stroke units in Danish hospitals from March 2003 through October 2018. The reporting of this study followed the STROBE checklist (see [Supplemental Material](#)).¹⁵

Data Availability

Data not published within this article cannot be shared because of Danish laws of data protection.

Data Sources

Data from 4 Danish nationwide registries was used: (1) The Danish Stroke Registry, which holds detailed quality data on stroke patients since 2003 including data on type of stroke,

stroke severity, smoking status, and alcohol consumption,¹⁶ (2) The Danish Civil Registration System, which holds information on sex, date of birth, vital, and emigration status of all persons living in Denmark (3) the National Prescription Registry which contains data on all prescriptions dispensed from Danish pharmacies, coded according to the Anatomic Therapeutic Chemical Classification System, and (4) the Danish National Patient Registry which has registered dates of hospital admissions and discharges, outpatient and emergency room contacts, and discharge diagnoses classified according to the 10th revision of the *International Classification of Diseases* for >99% of hospital admissions in Denmark. Data from the abovementioned registries were linked via a unique personal identification number, which is used across all Danish national registries.

Study Population and Design

The Danish Stroke Registry was used to identify a study population of patients presenting with incident ICH and prevalent AF between March 2003 to June 2018. The discharge date of the ICH event was defined as baseline (index date). Patients with a previous diagnosis of ICH from before the Danish Stroke Registry was established, and patients registered with thrombolysis treatment during admission were excluded. To resemble the expected trial population of the PRESTIGE-AF trial, key inclusion and exclusion criteria of the PRESTIGE-AF trial were applied. First, we identified patients with prevalent AF, or patients who received an AF diagnosis within 30 days after the inclusion event. This approach was selected to include patients with previously undiagnosed AF. To identify a population with a clear indication for OAC, patients with a CHA₂DS₂-VASc score ≥ 2 for males and CHA₂DS₂-VASc score ≥ 3 for females were considered for inclusion, as per the PRESTIGE-AF trial inclusion criteria. The CHA₂DS₂-VASc score was calculated based on points according to prevalent congestive heart failure (1 point), hypertension (1 point), diabetes (1 point), prior ischemic stroke/systemic embolism/transient ischemic attack (2 points), vascular disease (1 point), age 65 to 74 years (1 point), age ≥ 75 years (2 points), and female sex (1 point).¹⁷ Patients were excluded on the basis of age <18 years, the index ICH event occurred as a result of trauma, no brain imaging following the index ICH was available, had another indication for long-term anticoagulation (a diagnosis of venous thromboembolism within the last year or several diagnoses at earlier times), strong indication for antiplatelet therapy at baseline (acute myocardial infarction or any percutaneous coronary intervention within 12 months), prior left atrial appendage occlusion, or severe renal dysfunction requiring dialysis. Information on additional baseline comorbidities were obtained from the Danish Stroke Registry, the Danish National Patient Registry, and the Danish National Prescription Registry. Comorbidity was based on hospital discharge data using any primary or secondary record available up to and including baseline, excluding emergency room codes. Baseline medication use was ascertained from prescription claims within 180 days before the index event. Detailed information about the definition of inclusion and exclusion criteria, comorbidities, and medical therapies are provided in [Table S1](#).

Exposure to Oral Anticoagulant Treatment

At the incidence of an ICH event, cessation of OAC treatment is clinically mandated. However, patients may initiate/resume OAC during follow-up because of the risk of ischemic stroke

associated with AF. Redemption of a prescription of an oral anticoagulant drug (warfarin or a NOAC agent) was used to identify exposure groups of patients who initiate/resume OAC during follow-up. In the analytic strategy to describe risk of outcomes by treatment exposure groups, time at risk was split according to the initiation/resumption of OAC during follow-up. The timepoint for a change in status was defined by the date of a redemption of a prescription of an oral anticoagulant drug during follow-up. The risk of outcomes was subsequently calculated separately in patients followed from the incident ICH until the initiation/resumption of OAC, and in patients followed from the initiation/resumption of OAC and up to one year after the incident ICH.

Outcomes and Follow-Up

Information on outcomes was obtained from the Danish Stroke Registry. The outcomes of interest were recurrent ICH, cerebrovascular ischemic events (ischemic stroke, unspecified stroke, or transient ischemic attack), and all-cause death. The coding validity of these outcomes has previously been validated in a Danish setting with a positive predictive value of 90% in the Danish Stroke Registry.¹⁸ *International Classification of Diseases* codes used to define each outcome are provided in Table S1.

Statistical Methods

Baseline characteristics were described using means/medians and SD/interquartile range (IQR) for continuous variables and proportions for categorical variables. Patients were categorized according to their CHA₂DS₂-VASc score at baseline and stratified into 3 score categories (score 2–3, score 4–6, score >6).

Time-to-event analyses were used to investigate the risk of outcomes for the full study population and according to the CHA₂DS₂-VASc score categories. At-risk time was measured from the discharge date related to the index event (incident ICH) until the outcome of interest, emigration, death, end of follow-up (one year after index date), or end of study period (December 1, 2018), whichever came first. Risk estimates were calculated separately for each outcome of interest; thus, patients were followed until each outcome of interest separately in each analysis.

To present the risk of outcomes over time, we constructed cumulative incidence curves according to the CHA₂DS₂-VASc score categories, with death as a competing risk.¹⁹ In detail, we calculated absolute risk of outcomes after one year of follow-up using the Aalen-Johansen estimator to take competing risk of death into consideration.²⁰ To allow for additional clinical evaluation on the risk of cerebrovascular outcomes, we estimated the risk difference between an ischemic cerebrovascular event versus the risk of recurrent ICH. The risk differences within levels of the CHA₂DS₂-VASc were also calculated using the pseudo-value method to take into account competing risks of death.²¹

In a sensitivity analysis, the follow-up period for patients initiating/resuming OAC during follow-up were extended to one year after the initiation/resumption of OAC, and the analyses of the absolute risks of outcomes were repeated.

Statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC) and Stata version 16 software (StataCorp LP, College Station, TX).

Ethical Considerations

The Danish Health Data Agency provided the data for the study. The study was conducted in compliance with General Data Protection Regulation Article 30, recorded at Aalborg University Hospital and Aalborg University (project no. 2017-40). No ethical approval or patient consent are required for studies based on data from administrative Danish registries according to Danish laws.

RESULTS

Using the Danish Stroke Registry, we identified 2277 patients with incident ICH and concomitant AF between January 2003 and October 2018. After mirroring the expected PRESTIGE-AF trial population, a total of 1885 patients were included in our study (Figure 1). A total of 603 patients had a CHA₂DS₂-VASc score of 2 to 3, 866 patients had a CHA₂DS₂-VASc score of 4 to 6, and 416 patients had a CHA₂DS₂-VASc score of >6. Baseline patient characteristics for the full study population and according to the CHA₂DS₂-VASc score categories are summarized in Table 1. Patients were generally elderly (median age ranged between 78 and 83 years), and the percentage of females ranged between 29.9% and 71.2% in the 3 CHA₂DS₂-VASc score categories. The median Scandinavian Stroke Scale score was similar in the 3 CHA₂DS₂-VASc score categories, but the prevalence of cardiovascular risk factors was highest in the group of patients with a CHA₂DS₂-VASc score of >6. The most prevalent cardiovascular risk factors of the CHA₂DS₂-VASc score were hypertension and prior stroke/heart failure in the 3 CHA₂DS₂-VASc score categories.

Risk of Cerebrovascular Outcomes and All-Cause Death

At one year after the incident ICH, the overall number of outcome events were 841 in the study population; 40 recurrent ICH, 63 cerebrovascular ischemic events, and 650 all-cause deaths. Risks of cerebrovascular outcomes after one year were 2.2% for recurrent ICH and 3.4% for cerebrovascular ischemic events, and all-cause death was 34.8%. For the full study population, we observed a trend towards higher risk of all-cause death and recurrent ICH with increasing CHA₂DS₂-VASc score category at one year after the incident ICH, but for the outcomes of cerebrovascular ischemic events, the risks were largely similar across the categories (Figure 2). For the outcomes of all-cause death and recurrent ICH, the cumulative incidence curves demonstrated an apparent high risk immediately following the incident ICH event.

Stratified Analyses Based on OAC Initiation/Resumption

When analyzing outcomes during the follow-up period according to time-dependent status of initiation/

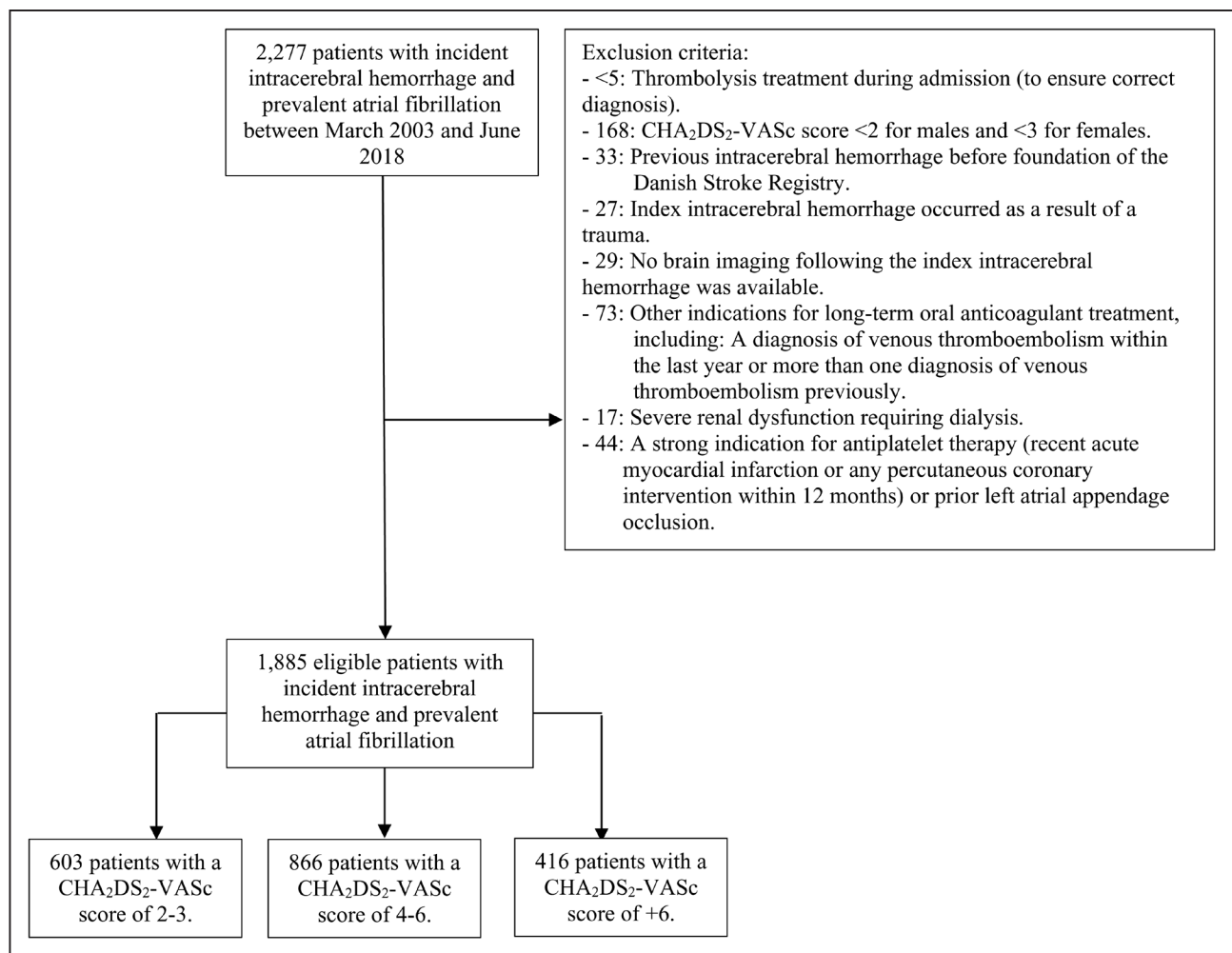


Figure 1. Flowchart of the study population.

All patients were aged ≥ 18 y.

resumption of OAC, 526 patients initiated/resumed OAC during the first year after ICH where 184 redeemed a warfarin prescription and 342 patients redeemed a NOAC prescription. The median time to initiation/resumption of OAC after the incident ICH was 5.3 months (IQR, 1.1–12.0).

For the subpopulation of patients not initiating/resuming OAC during follow-up, the median follow-up time after the incident ICH was 4.8 months (IQR, 1.1–12.0). We observed a 2.4% to 2.8% risk of cerebrovascular ischemic events, a 1.2% to 1.8% risk of recurrent ICH, and a 24.8% to 40.7% risk of all-cause death at one year after the incident ICH in this subpopulation (Table 2). The risk difference revealed a higher risk of cerebrovascular ischemic events, and most pronounced in the lowest score levels, risk difference 1.3 (–0.1 to 2.8), which indicated a higher risk for ischemic events than for recurrent ICH.

For the subpopulation of patients initiating/resuming OAC during follow-up, the median follow-up time was 9.2 months (IQR, 6.0–10.9) after initiation/resumption of OAC. A low number of cerebrovascular events was

observed in the follow-up period of this subpopulation: the risk of cerebrovascular ischemic events was 2.6% to 3.7%, and 2.2% to 3.6% risk of recurrent ICH, and a 12.7% to 28.6% risk of all-cause death at one year after the incident ICH in this subpopulation (Table 3). The risk difference among patients with a score level of 4 to 6 was 1.5 (–2.6 to 5.5), while the risk difference in the highest score group (>6 points) displayed higher risk for recurrent ICH, risk difference –1.2 (–6.2 to 3.7). However, these risk differences were based on few numbers of events and with wide CIs reflecting the uncertainty of the estimated risk difference.

Sensitivity Analyses

Baseline patient characteristics for the patients initiating/resuming OAC during follow-up are summarized in Table S2. In this subpopulation, median age was 78.0 years (IQR, 73.0–84.0), 63.3% were using OAC before the incident ICH, the median Scandinavian Stroke Scale score was 47.0 (IQR, 34.0–54.0), 34.4% had experienced a prior ischemic stroke, and 17.7%

Table 1. Baseline Patient Characteristics of Intracerebral Hemorrhage Survivors With Atrial Fibrillation

Characteristics, % (N)	All	CHA ₂ DS ₂ -VASc score 2–3	CHA ₂ DS ₂ -VASc score 4–6	CHA ₂ DS ₂ -VASc score >6
N	1885	603	866	416
Age, median (IQR)	80.0 (74.0–86.0)	78.0 (71.0–84.0)	80.0 (75.0–85.0)	83.0 (78.0–88.0)
≥65 y	94.6 (1,783)	89.2 (538)	96.0 (831)	99.5 (414)
≥75 y	74.6 (1,407)	62.7 (378)	76.0 (658)	89.2 (371)
Female sex	47.6 (898)	29.9 (180)	48.7 (422)	71.2 (296)
CHA ₂ DS ₂ -VASc score, median (IQR)	4.0 (3.0–5.0)	3.0 (2.0–3.0)	4.0 (4.0–5.0)	6.0 (6.0–7.0)
Scandinavian Stroke Scale score,* median (IQR)	42.0 (26.0–52.0)	40.0 (24.0–52.0)	42.0 (28.0–52.0)	43.0 (29.0–51.0)
Mild (58–44)	44.3 (835)	42.0 (253)	45.0 (390)	46.2 (192)
Moderate (26–43)	28.0 (527)	27.0 (163)	27.9 (242)	29.3 (122)
Severe (<26)	21.4 (403)	24.9 (150)	20.6 (178)	18.0 (75)
Missing	6.4 (120)	6.1 (37)	6.5 (56)	6.5 (27)
Surgical evacuation of intracerebral hemorrhage	2.8 (52)	3.5 (21)	2.7 (23)	1.9 (8)
Concurrent ischemic stroke on discharge date	9.1 (171)	3.0 (18)	10.7 (93)	14.4 (60)
Comorbidities				
Diabetes	18.0 (340)	7.1 (43)	17.0 (147)	36.1 (150)
Hypertension	75.5 (1,424)	58.5 (353)	78.8 (682)	93.5 (389)
Heart failure	27.7 (523)	10.8 (65)	28.1 (243)	51.7 (215)
Chronic kidney disease	6.9 (130)	4.3 (26)	7.2 (62)	10.1 (42)
Peripheral artery disease	17.1 (322)	7.5 (45)	15.0 (130)	35.3 (147)
Previous myocardial infarction	14.9 (280)	8.0 (48)	13.5 (117)	27.6 (115)
Chronic obstructive pulmonary disorder	13.2 (248)	10.8 (65)	12.9 (112)	17.1 (71)
Previous ischemic stroke	32.9 (621)	9.6 (58)	34.6 (300)	63.2 (263)
Previous major extracranial bleeding	15.4 (290)	15.4 (93)	15.1 (131)	15.9 (66)
Lifestyle				
Smoking				
Never	34.3 (646)	28.4 (171)	37.5 (325)	36.1 (150)
Former	27.2 (513)	27.9 (168)	26.7 (231)	27.4 (114)
Current	15.0 (283)	16.9 (102)	14.2 (123)	13.9 (58)
Missing	23.5 (443)	26.9 (162)	21.6 (187)	22.6 (94)
Alcohol intake†				
Recommended	73.1 (1,378)	67.3 (406)	76.0 (658)	75.5 (314)
Above recommended	7.6 (143)	10.6 (64)	6.7 (58)	5.0 (21)
Missing	19.3 (364)	22.1 (133)	17.3 (150)	19.5 (81)
Civil status				
Cohabitant	48.9 (921)	54.6 (329)	49.0 (424)	40.4 (168)
Alone	44.2 (833)	37.5 (226)	45.6 (395)	51.0 (212)
Other	3.3 (62)	3.6 (22)	2.4 (21)	4.6 (19)
Missing	3.7 (69)	4.3 (26)	3.0 (26)	4.1 (17)
Medication‡				
Statins	49.5 (934)	38.1 (230)	50.2 (435)	64.7 (269)
SSRI	13.5 (255)	10.9 (66)	13.0 (113)	18.3 (76)
Antithrombotic treatment				
None	18.7 (352)	26.2 (158)	17.0 (147)	11.3 (47)
Antiplatelet therapy alone	22.4 (423)	17.7 (107)	23.2 (201)	27.6 (115)
Oral anticoagulant therapy alone	44.4 (836)	43.8 (264)	45.7 (396)	42.3 (176)
Antiplatelet and oral anticoagulant therapy	14.5 (274)	12.3 (74)	14.1 (122)	18.8 (78)

Numbers are % (N) unless otherwise noted. ICH indicates intracerebral hemorrhage; IQR, interquartile range; and SSRI, selective serotonin reuptake inhibitor.

*Severity of the index ICH was graded by the Scandinavian Stroke Scale, which (among others) includes assessment of the patient's level of consciousness, eye movements, coordination ability, and ability to speak.⁴¹ The total of the score is a maximum of 58 and lower scores indicate more severe intracerebral hemorrhage events; categories of severity were defined as 58–44 mild; 43–26 moderate; and <26 severe.

†Recommended alcohol intake per week ≤7 for women and ≤14 for men.

‡Patients with a claimed prescription of the medication within 180 days before the incident intracerebral hemorrhage.

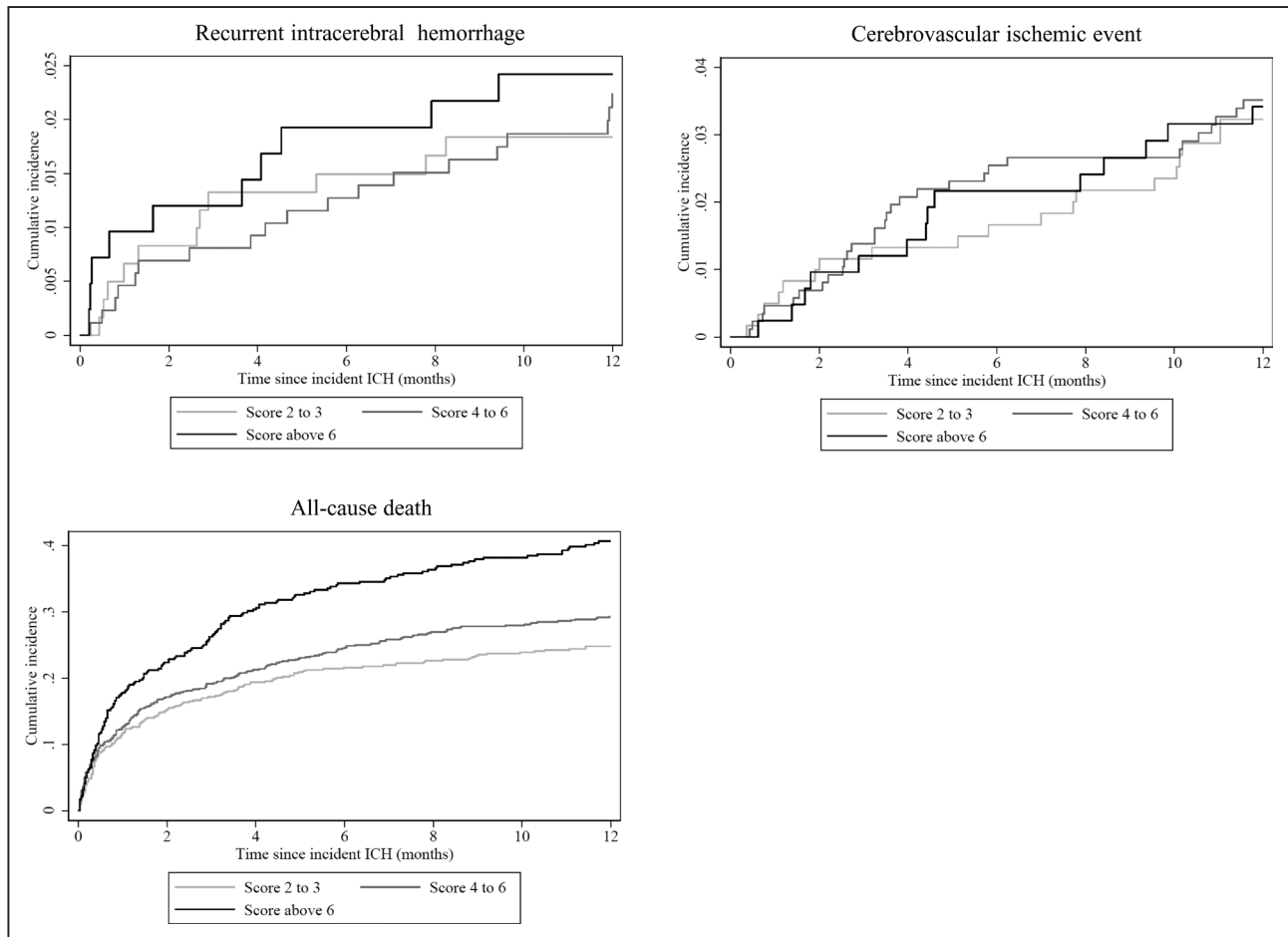


Figure 2. Cumulative incidence of recurrent intracerebral hemorrhage (ICH), cerebrovascular ischemic event, and all-cause death after 1 y of follow-up according to the baseline CHA₂DS₂-VASc score category.

had experienced a prior extracranial major bleeding. In the sensitivity analysis, where the follow-up period for patients initiating/resuming OAC during follow-up was extended to one year after the initiation/resumption of OAC, the median follow-up time was 12 months (IQR, 7.7–12.0). We observed marginally more events than in the main analysis of this subpopulation, as expected with longer follow-up time, yet most events occurred during the first months after OAC initiation/resumption (Table S3).

DISCUSSION

In this observational cohort study including a population of 1885 ICH survivors with concomitant AF mirroring the expected PRESTIGE-AF trial population, our main findings were (1) one year after the incident ICH, we observed a high risk of cerebrovascular events and a very high risk of all-cause death; (2) we observed more cerebrovascular ischemic events than recurrent ICH events; (3) for the full study population, we observed a

Table 2. Absolute Risk of Cerebrovascular Events and All-Cause Death After 1 Year of Follow-Up in the Subpopulation Not Initiating/Resuming Oral Anticoagulant Therapy During Follow-Up

Absolute risk after 1 y of follow-up	Recurrent intracerebral hemorrhage		Cerebrovascular ischemic event*		Estimated risk difference†	All-cause death	
	Events, n	Risk % (95% CI)	Events, n	Risk % (95% CI)		Events, n	Risk % (95% CI)
No OAC initiation during follow-up							
All (N=1884)	28	1.5 (1.0 to 2.2)	47	2.6 (1.9 to 3.4)	1.1 (0.1 to 2.0)	561	30.3 (28.3 to 32.5)
CHA ₂ DS ₂ -VASc score 2–3 (N=602)	7	1.2 (0.5 to 2.3)	14	2.4 (1.4 to 3.9)	1.3 (–0.1 to 2.8)	147	24.8 (21.5 to 28.5)
CHA ₂ DS ₂ -VASc score 4–6 (N=866)	15	1.8 (1.1 to 2.9)	23	2.8 (1.8 to 4.1)	1.0 (–0.1 to 2.3)	248	29.3 (26.3 to 32.5)
CHA ₂ DS ₂ -VASc score >6 (N=416)	6	1.4 (0.6 to 3.0)	10	2.5 (1.3 to 4.4)	1.0 (–0.1 to 3.0)	166	40.7 (36.1 to 45.6)

OAC indicates oral anticoagulant therapy.

*Composite of ischemic stroke, unspecified stroke, or transient ischemic attack.

†Cerebrovascular ischemic event was used as reference.

Table 3. Absolute Risk of Cerebrovascular Events and All-Cause Death After 1 Year of Follow-Up in the Subpopulation Initiating/Resuming Oral Anticoagulant Therapy During Follow-Up

Absolute risk after 1 y of follow-up	Recurrent intracerebral hemorrhage		Cerebrovascular ischemic event*		Estimated risk difference†	All-cause death	
	Events, n	Risk % (95% CI)	Events, n	Risk % (95% CI)	Risk % (95% CI)	Events, n	Risk % (95% CI)
OAC initiation during follow-up							
All (N=526)	12	2.8 (1.5 to 4.8)	13	3.2 (1.7 to 5.5)	0.4 (−2.1 to 2.9)	89	22.0 (17.3 to 27.8)
CHA ₂ DS ₂ -VASc score 2–3 (N=159)	<5	2.9 (1.0 to 6.9)	<5	2.9 (1.0 to 6.9)	0.1 (−4.0 to 4.2)	17	12.7 (8.0 to 19.9)
CHA ₂ DS ₂ -VASc score 4–6 (N=243)	<5	2.2 (0.7 to 5.3)	6	3.7 (1.4 to 7.8)	1.5 (−2.6 to 5.5)	50	28.6 (20.1 to 39.6)
CHA ₂ DS ₂ -VASc score >6 (N=124)	<5	3.6 (1.2 to 8.4)	<5	2.6 (0.7 to 7.0)	−1.1 (−6.2 to 3.7)	22	20.0 (13.6 to 29.0)

The exact number is masked because of individual level data protection if the event count is <5. OAC indicates oral anticoagulant therapy.

*Composite of ischemic stroke, unspecified stroke, or transient ischemic attack.

†Cerebrovascular ischemic event was used as reference.

trend towards higher risk of all-cause death and recurrent ICH with increasing CHA₂DS₂-VASc score category, but a similar risk across the categories for the other outcomes; (4) cerebrovascular outcomes were highest among those initiating/resuming OAC during follow-up, but with lower risk of all-cause death.

Several randomized controlled trials are currently investigating the optimal antithrombotic treatment strategy for stroke prevention in ICH survivors with concomitant AF^{9–14} and 2 of these trials have now been concluded and reported.^{22,23} Both trials were inconclusive and likely underpowered to detect a signal of benefit or harm from OAC treatment, and the trial investigators call for additional trial data to provide more robust evidence. Awaiting these results of ongoing trials become available, observational data such as the present on the risk of both ischemic and hemorrhagic cerebrovascular events in patient with AF surviving an ICH are important to provide additional scientific basis for the multidisciplinary expert consensus-decision approach on antithrombotic treatment that is presently recommended by guidelines.

Patients who experience an ICH and have concomitant AF are considered a very high-risk population, with a substantial risk of particularly death but also of both cerebrovascular ischemic events and recurrent ICH.^{4,6,24–28} In our large study population comprising high-quality stroke data,¹⁶ we observed a numerically higher number of cerebrovascular ischemic events than recurrent ICH events. In general, we observed a high overall risk of cerebrovascular events and a very high risk of all-cause death at one year after the incident ICH, which confirm previous findings.^{4,6,24–28} The absolute risk of a cerebrovascular ischemic event in the subpopulation not initiating/resuming OAC during follow-up exceeded the commonly accepted threshold for OAC to yield a net clinical benefit in the overall AF population.^{29,30} However, we also observed a high risk of recurrent ICH in the subpopulation of patients initiating/resuming OAC during follow-up, which is the most feared adverse event of OAC, and likely the main reason why OAC is not initiated/resumed in patients with AF surviving an ICH. Additionally, we estimated the risk difference between cerebrovascular ischemic events and recurrent ICH to be marginal, with largest risk difference

amounting to 1.3%. However, we emphasize that our aim of the study was solely to describe the risk of cerebrovascular events in patients with AF surviving an ICH, and the risks observed in the 2 subpopulations, therefore, cannot be interpreted as reflecting the effect of anticoagulation. The subpopulation of patients initiating/resuming OAC during follow-up (184 patients redeemed a prescription for warfarin and 342 patients redeemed a prescription a NOAC) is unlikely to be a random subset of the study population. These patients were slightly younger, but more often used OAC before the incident ICH, more often had a higher Scandinavian Stroke Scale score (eg, less severe ICH), and, generally, had more comorbidities including more often a history of ischemic stroke and extracranial major bleeding than the full study population. When estimating the risk difference between cerebrovascular ischemic events and recurrent ICH, we observed a risk difference of −1.2 (−6.2 to 3.7), which indicated that the risk of recurrent ICH exceeded that of cerebrovascular events. Importantly, this subpopulation included patients who have survived until the initiation/resumption of OAC, which is very likely to impact the observed risks as it constitutes a selected group of patients. Indeed, physicians may have been more inclined to provide OAC treatment after NOACs became available given the appealing safety profile as a class effect with low risk of ICH in comparison with warfarin.³¹

Few observational studies specifically designed to investigate the comparative effectiveness of initiation/resumption of OAC versus no OAC in patients with AF surviving an ICH exist.^{24–28} A meta-analysis of 7 observational studies including patients with AF surviving an ICH showed that use of OAC was associated with a lower risk of ischemic stroke and did not increase the rate of recurrent ICH.³² Additionally, the meta-analysis demonstrated that in patients not taking any antithrombotic agent, the rates of ischemic stroke were higher than the rates of recurrent ICH.³² However, the observational studies are inherently prone to confounding by indication, a notoriously stubborn bias,³³ and thus, have very limited capacity for guiding clinical practice on efficacy and safety on the use of OAC among ICH survivors with concomitant AF. In our descriptive study,

we also observed a higher risk of cerebrovascular ischemic events than recurrent ICH in the subpopulation of patients not initiating/resuming OAC, but we also observed a high risk of both recurrent ICH and cerebrovascular ischemic events in the subpopulation of patients initiating/resuming OAC during follow-up.

Since no randomized data exist, individual risk assessment by a multidisciplinary team is currently recommended to guide the decision of initiating/resuming OAC in AF patients surviving an ICH.³ Yet, the CHA₂DS₂-VASc score is the guideline-recommended tool to be used in the decision-making for prescribing life-long OAC in patients with AF. However, a previous study found a poor discriminative performance of the CHA₂DS₂-VASc score for cerebrovascular ischemic events in patients with AF surviving an ICH,³⁴ and another study did not find the CHA₂DS₂-VASc score predictive of recurrent ICH among patients with AF surviving an ICH.⁴ In contrast, another study observed a trend towards higher risk of ischemic stroke with increasing CHA₂DS₂-VASc score in patients with AF surviving an ICH.³⁵ We observed a trend towards higher risk of all-cause death and recurrent ICH with increasing CHA₂DS₂-VASc score category in the full study population but a similar risk across the categories for the outcome of cerebrovascular ischemic events. Thus, other risk stratification methods for guiding initiation/resumption of OAC in patients with AF surviving an ICH may be necessary.

Strengths and Limitations

We assessed the presence of the risk components of the CHA₂DS₂-VASc score at baseline, yet the stroke risk profile is not static. Given the advanced age and multiple comorbidities, the study population may change their risk profile during follow-up.³⁶ However, we chose a relatively short follow-up period to minimize the impact of this limitation.

Although antiplatelets do not provide optimal stroke prophylaxis in patients with AF, some evidence of benefit in terms of lower thromboembolic risk compared with no treatment may still persist.³⁷ Thus, use of antiplatelets could have affected the estimated risks in our study.

In the subpopulation of patients initiating/resuming OAC, we have no clear evidence of accurate timing of initiation or resumption of OAC, as we relied on the date for pharmacy dispensed medication. Our risk estimates were merely descriptive in these stratified analyses and cannot be compared with guide risk of the outcomes according to initiate/resume OAC treatment versus no treatment. Additionally, we did not have information on cerebral imaging features (given the association of ischemic stroke and re-bleeding with some imaging features³⁸), and did not have information on the international normalized ratio values or time in therapeutic range, and therefore, did not have information about the quality of

anticoagulation with a vitamin K antagonist. However, NOACs have gradually become the preferred oral anti-coagulant drug in patients with AF given the appealing safety profile.^{39,40}

Lastly, for the outcome of all-cause death, some deaths may be from unrecorded fatal strokes or ICH because not all outcomes are adjudicated and postmortem examinations are not mandated, hereby potentially underestimating the incidence of cerebrovascular events.

Conclusions

In this observational cohort study, we used the Danish Stroke Registry to identify a population of ICH survivors with concomitant AF mirroring the expected PRESTIGE-AF trial population. One year after the incident ICH, we observed a high risk of cerebrovascular ischemic events and a very high risk of all-cause death. We observed more cerebrovascular ischemic events than recurrent ICH events, with lower mortality among those restarting OAC. Prospective randomized trials such as the PRESTIGE-AF trial are warranted to determine optimal stroke prevention treatment among ICH survivors with concomitant AF.

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Disclosures

Dr Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Dr Larsen is a investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim. Speaker for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. No fees are received personally. Dr Nielsen received Speaking fees Daiichi-Sankyo, consulting fees from Bayer and Daiichi-Sankyo, and grant support from BMS/Pfizer and Daiichi-Sankyo. The other authors report no conflicts.

Supplemental Material

Tables S1–S3
PRESTIGE-AF Consortium Author List
STROBE Statement

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