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Association of Prior Antithrombotic Drug Use with 90-Day Mortality After Intracerebral Hemorrhage

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Purpose: To estimate the strength of association between use of antithrombotics (AT) drugs with survival after spontaneous intracerebral hemorrhage (s-ICH) comparing oral anticoagulant (OAC) or platelet antiaggregants (PA) with no AT use and in active comparator analyses OAC vs PA, direct oral anticoagulant (DOAC) vs vitamin K antagonist (VKA), and clopidogrel vs aspirin.

Patients and Methods: We identified patients ≥55 years with a first-ever s-ICH between 2015 and 2018 in Southern Denmark (population 1.2 million). From this population, patients who had used an AT at the time of ICH were identified and classified as OAC or PA vs no AT (reference group), and for active comparator analyses as OAC vs PA (reference group), DOAC vs VKA (reference group), or clopidogrel vs aspirin (reference group). We calculated adjusted relative risks (aRRs) and corresponding [95% confidence intervals] for 90-day all-cause mortality with adjustments for potential confounders.

Results: Among 1043 patients who had s-ICH, 206 had used an OAC, 270 a PA, and 428 had no AT use. The adjusted 90-day mortality was higher in OAC- (aRR 1.68 [1.39-2.02]) and PA-users (aRR 1.21 [1.03-1.42]), compared with no AT. Mortality was higher in OAC- (aRR 1.19 [1.05-1.36]) vs PA-users. In analyses by antithrombotic drug type, 88 used a DOAC, 136 a VKA, 111 clopidogrel, and 177 aspirin. Mortality was lower among DOAC- vs VKA-users (aRR 0.82 [0.68-0.99]), but similar between clopidogrel vs aspirin users (aRR 1.04 [0.87-1.24]).

Conclusion: In this unselected cohort from a geographically defined Danish population, 90-day mortality after s-ICH was higher in patients with prior use of an OAC compared with no AT use or patients using a PA. Mortality was slightly lower for patients using a DOAC than a VKA. Mortality was also higher in PA- vs no AT-users, but there were no differences in mortality between clopidogrel vs aspirin.

Keywords: stroke, intracerebral hemorrhage, stroke prevention, oral anticoagulants, platelet antiaggregants

Introduction

Intracerebral hemorrhage (ICH) is responsible for approximately half of all stroke-related deaths and for considerable disability among survivors.[1,2] The prognosis after ICH is related to factors such as initial hematoma volume and subsequent expansion, which might be worsened by the use of antithrombotic therapy (AT), ie, oral anticoagulants (OACs) and platelet antiaggregants (PAs).[3–7] In patients with spontaneous ICH (s-ICH), some studies suggest a similar short-term prognosis regardless of OAC type (ie, direct oral anticoagulant, DOAC vs vitamin K antagonist, VKA),[8–12]

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whereas others report smaller hematoma volumes[13] and lower mortality rates among DOAC users.[14–17] A meta-analysis of 8 studies[18–25] reported a higher risk of death within 3-months post-ICH in patients with prior PA use compared with no PA use,[7] but cautioned that the heterogeneity of these studies was high. Few studies provide 3-month mortality risk estimates for both OACs and PAs,[24,26,27] and data on specific PA types (eg, clopidogrel, are lacking).[7] Performing analyses by both AT class and type in the same unselected patient cohort with prospectively collected information on AT use could provide informative results and support meaningful comparisons of the risk estimates. We conducted this study to investigate 90-day all-cause mortality classified by prior AT use comparing (i) OAC vs no AT use, and PA vs no AT use, (ii) OAC vs PA, (iii) DOAC vs VKA, and (iv) clopidogrel vs aspirin in the same cohort. Our secondary objective was to provide data reflecting functional outcome (unaided gait) and radiological characteristics (ICH volume and hematoma expansion) in relation to pre-ICH AT use.

Materials and Methods

This retrospective cohort study was based on a combination of data abstracted from electronic health records (EHRs), data collected through systematic re-evaluation of brain scans, and registry data. This study complies with the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Setting and Data Sources

The study was conducted in the Region of Southern Denmark (RSD; population 1.2 million), which is representative of the population in Denmark with regards to demographic features, utilization of healthcare services, and patterns of medication usage.[28] Data on medication prescriptions were retrieved from the Danish National Prescription Registry.[29] Data on date of death were retrieved from the Civil Registration System.[30] The unique and permanent civil registration number provided to all Danish residents and recorded in all the registries used in this analysis enabled unambiguous data linkage.

Standard Protocol Approvals, Registration, and Patient Consent

The study was approved by the Region of Southern Denmark. Data were pseudonymized, and informed consent was waived.

Data Availability

Danish law prohibits the authors from sharing or granting access to the data used for this study.

Study Cohort

EHRs for all patients ≥55 years with a first-ever s-ICH (ie, not due to trauma, hemorrhagic transformation, sinus thrombosis, arteriovenous malformation, subarachnoid hemorrhage, or underlying tumor) admitted in 2015–2018 were identified and their first brain scan performed after ICH was re-evaluated masked to clinical data, including exposure to ATs (eMethods in the Supplement, eFigure 1).[31,32] We did not include patients <55 years because they are less likely to have s-ICH. Patients were classified as having no s-ICH after reevaluation of full EHRs or as having an isolated intraventricular hemorrhage after reevaluation of brain CTs were excluded.

Assessment of Antithrombotic Drug Use

As in previous studies,[33–35] exposure to medications, including ATs, was determined based on data from the Prescription Registry.[29] In Denmark, low-dose aspirin is the only PA available without prescription, but more than 90% is dispensed by prescription and is recorded in the Prescription Registry.[36] Based on the most recent AT prescription (for codes see eTable 1), exposure was classified into mutually exclusive time-periods: current use (prescription supply covered the index date (date of ICH onset)); recent use (prescription supply ended 1–30 days before the index date); past use (prescription supply ended 31–365 days before the index date); and no use (no recorded prescription before the index date or prescription supply ended >365-days before the index date).

PAs were classified as aspirin, clopidogrel, prasugrel, ticagrelor, or dipyridamole, whereas OACs were classified as VKAs (warfarin and phenprocoumon) or DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban).

Classification for Comparison by Antithrombotic Class

Based on the prescription information, patients were classified by AT class into current OAC use, current PA use (clopidogrel or aspirin), and no AT use. Comparisons were performed between OAC or PA vs no AT (reference) and in an active comparator analysis of OAC vs PA (reference). These classification groups were mutually exclusive. Patients with concurrent use of an OAC and PA were excluded from both analyses (Figure 1).

Classification for Comparison by Antithrombotic Type

Patients with current use of a DOAC, VKA, aspirin, or clopidogrel were used in active comparator analyses including those on more than one AT class (eg, patients taking a DOAC or a VKA in addition to an PA were included in the analyses; Figure 1).

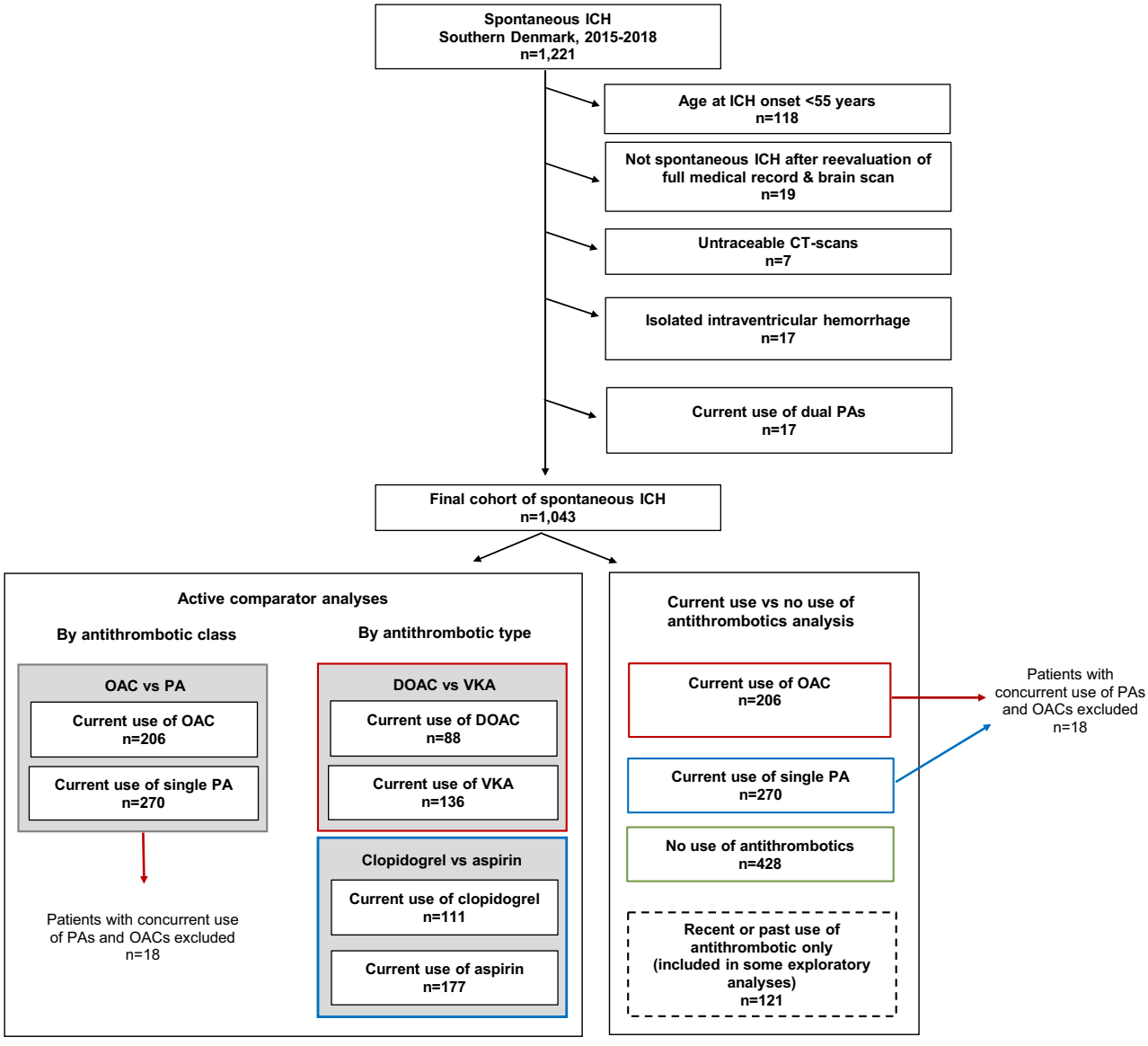

Figure 1 Study flow-chart.
Abbreviations: ICH, intracerebral hemorrhage; OAC, oral anticoagulant; PA, platelet antiaggregant; Rx, prescription.

Follow-Up and Outcome

Follow-up began from the day of the first-ever s-ICH and ended on the date of the outcome event, date or on day 90, whichever came first. The outcome was all-cause death.

Potential Confounders

Potential confounders included in the calculation of propensity scores included age (5-year bands), sex, smoking (current; former; non-smoker; missing values), alcohol use (weekly units: low [≤7 (women)/ ≤14 (men)]; high [>7 (women)/>14 (men)]; missing values), hypertension, diabetes, venous thromboembolism (VTE), atrial fibrillation (AF), prior ischemic stroke, prior myocardial infarction, congestive heart failure, peripheral artery disease, chronic kidney failure, prior gastrointestinal hemorrhage, disorders indicative of high alcohol intake and current medication use (separate variables for drugs with antihypertensive effects, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRI), and proton pump inhibitors (PPIs)). In addition, in analyses with DOAC/VKA, PA use was included as a weighted covariate, and vice-versa. In analyses of OAC/PA use vs no AT use and OAC use vs PA use, AF and VTE were not included as covariates as these conditions are strongly linked to OAC exposure. For further details, see eMethods and eTable 1 in the Supplement.

Statistical Analysis

Characteristics of the study cohort were summarized using descriptive statistics. The crude cumulative incidence of death post-ICH was derived based on Kaplan-Meyer analyses of the first 90-days of follow-up in groups defined by pre-ICH use by class (OAC/PA vs no AT; OAC vs PA) and type of antithrombotic (DOAC vs VKA, clopidogrel vs aspirin), respectively.

Binomial regression was used to calculate the relative risk (RR) and 95% confidence intervals (CIs) of 90-day survival after s-ICH, adjusted for age, sex, and additional potential confounders (as listed above) using propensity scores. For further details, see eMethods in the Supplement.

Supplementary Analyses

Several supplementary analyses were performed. Analyses by antithrombotic drug type were repeated after exclusion of patients who had a first CT scan performed more than 24-hours after the index ICH. DOAC vs VKA analyses were repeated after restriction to naive users only (ie, patients with a previous use of a VKA were excluded from DOAC group and vice-versa). DOAC vs VKA analyses were also repeated after classifying current VKA use as prior prescriptions with a supply covering the index date or up to 30-days before index date (corresponding to current or recent VKA use) and an INR>1.5[37] at time of admission. This additional rule for VKA was applied as the dose of this drug is INR-guided and highly individualized. We also repeated DOAC vs VKA analyses after excluding patients who received a reversal agent within 24 hours of hospitalization (numbers were too small to allow separate analyses of patients who did versus did not receive a reversal agent).

A 2-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using Stata SE software, version 18.0 (StataCorp LLC). Data were analyzed from November 6, 2023 to August 12, 2024.

Results

A cohort of 1,043 patients with s-ICH met inclusion/exclusion criteria (Figure 1).

Figure 2 depicts the crude cumulative incidence of all-cause death after ICH during 90 days by antithrombotic class and type.

After retrieval of medication data from the Prescription Registry and classification of AT use, we excluded patients who were taking dual PAs (n=17) (Figure 1).

Antithrombotic Class Comparisons

The comparison to no AT use (n=428; no AT-use; 50.2% men; mean age 72.5 [SD 9.7]) included patients with current OAC use (n=206; 55.3% men; mean age, 79.9 [SD 8.3] years) and current single PA use (n=270; 48.9% men; mean age 78.8 [9.4] years). Table 1 and eTables 2 and 3 summarize lifestyle, medical history, and comedication prescriptions, weighted data, and standardized difference of the means for OAC-group/PA-group vs no AT group. eTable 4 lists the data

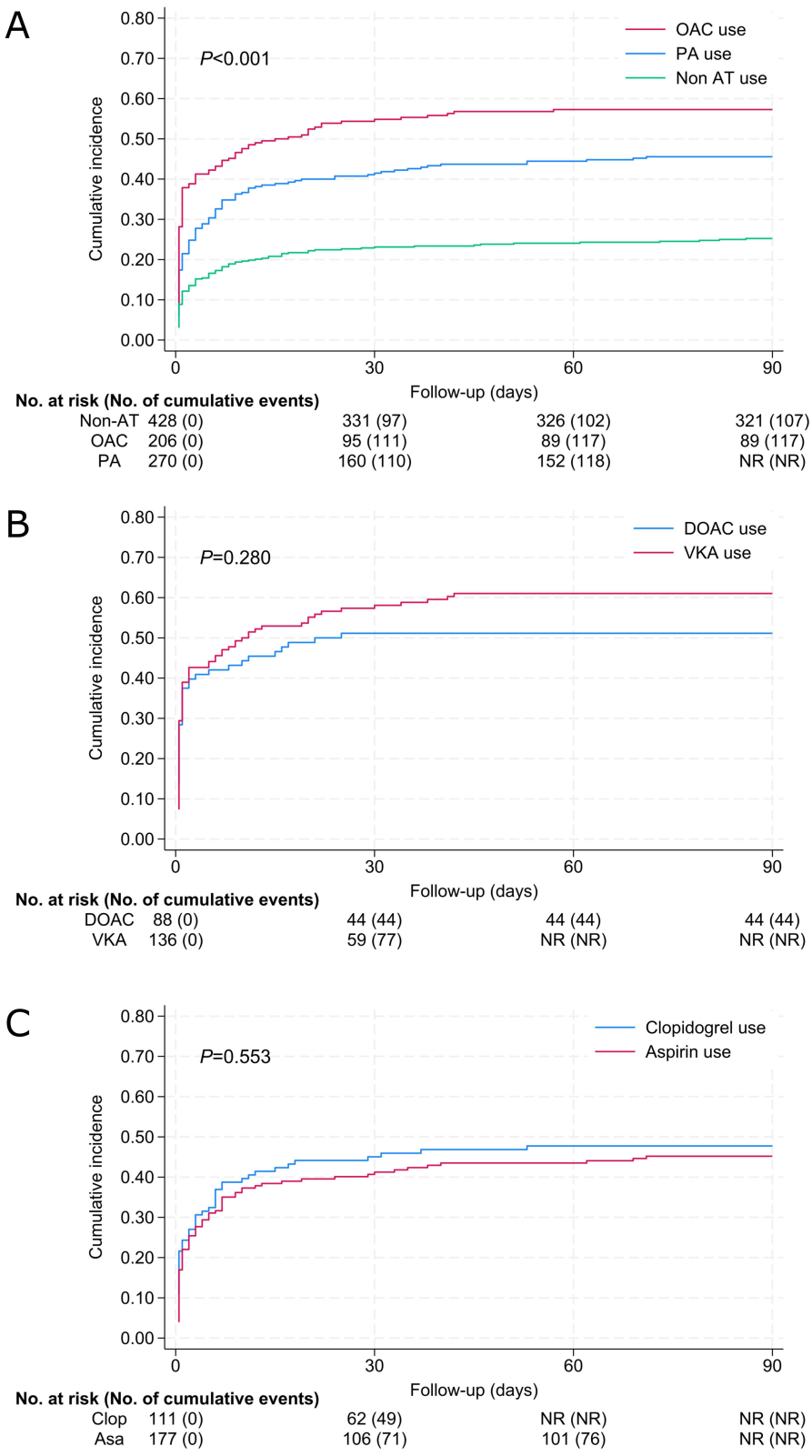

Figure 2 Crude cumulative incidence of all-cause death after ICH during 90 days of follow-up by class and type of prior antithrombotic use. Changes in number at risk/cumulative events <5 not reported (NR) to comply with cell suppression policy. (**A**) Comparison between antithrombotic classes. (**B**) Comparison between direct oral anticoagulants vs vitamin K antagonist. (**C**) Comparison between clopidogrel and aspirin.

Table 1 Baseline Characteristics of Patients with Intracerebral Hemorrhage by Class of Antithrombotic

Characteristic, No. (%) Unless Otherwise Stated	Current Oral Anticoagulant Use (DOAC or VKA)[a,b] (n=206)	Current Platelet Antiaggregant Use (Clopidogrel or Aspirin)[a,b] (n=270)	No Use of Any Antithrombotic[a] (n=428)
Age, mean (SD)	79.9 (8.3)	78.8 (9.4)	72.5 (9.7)
Sex			
Men	114 (55.3)	132 (48.9)	215 (50.2)
Women	92 (44.7)	138 (51.1)	213 (49.8)
Lifestyle data			
Smoker[c]			
Current	26 (12.6)	44 (16.3)	85 (19.9)
Former	68 (33.0)	79 (29.3)	109 (25.5)
Non-smoker	94 (45.6)	121 (44.8)	172 (40.2)
Missing values	18 (8.7)	26 (9.6)	62 (14.5)
Alcohol use[c], weekly units			
≤7 (women)/≤14 (men)	174 (84.5)	213 (78.9)	330 (77.1)
>7 (women)/ >14 (men)	15 (7.3)	24 (8.9)	55 (12.9)
Missing values	17 (8.3)	33 (12.2)	43 (10.0)
Medical history			
Hypertension[d,e]	182 (88.3)	226 (83.7)	253 (59.1)
Diabetes[d,e]	39 (18.9)	42 (15.6)	32 (7.5)
Prior ischemic stroke[d]	45 (21.8)	76 (28.1)	10 (2.3)
Prior myocardial infarction[d]	17 (8.3)	26 (9.6)	<5
Congestive heart failure[d]	38 (18.4)	15 (5.6)	8 (1.9)
Peripheral artery disease[d]	20 (9.7)	31 (11.5)	10 (2.3)
Chronic kidney failure[d]	14 (6.8)	7 (2.6)	8 (1.9)
Prior GIB[d]	27 (13.1)	30 (11.1)	30 (7.0)
Disorders indicative of high alcohol intake[d,e]	15 (7.3)	20 (7.4)	41 (9.6)
Comedication[e] – current use			
Antihypertensives	161 (78.2)	155 (57.4)	123 (28.7)
Statins	86 (41.7)	139 (51.5)	52 (12.1)
NSAIDs	12 (5.8)	16 (5.9)	35 (8.2)
SSRIs	26 (12.6)	44 (16.3)	24 (5.6)
PPIs	44 (21.4)	63 (23.3)	70 (16.4)

Notes: [a]Current use and no use defined in main text. [b]Patients with concurrent use of OACs and platelet antiaggregants were excluded from the analyses (n=18). [c]Information extracted from medical records (ICH admission record or, if not recorded there, most recent admission before ICH onset). [d]According to data from Danish National Patient Registry. [e]According to data from Danish National Prescription Registry.

Abbreviations: DOAC, direct oral anticoagulant; GIB, gastrointestinal bleed; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; PPI, proton pump inhibitor; VKA, vitamin K antagonist.

for the OAC vs PA-groups. Clinical and radiological data for patients at time of admission for ICH are listed in eTables 5 and 6. Hematomas were larger in OAC- (median 16 IQR [6–58] mL) and PA-treated groups (median 16 [IQR 4–54]), compared with the no AT group (median 12 IQR [4–29]). Hematomas ≥60 mL and intraventricular hemorrhage expansion were more frequent in both AT-treated groups compared with the no AT group (eTable 6). Do-not-resuscitate (DNR) orders recorded within the first 24-hours were also more common in the OAC group (age- and sex-adjusted OR (asOR) 2.12, 95% CI 1.44–3.11) and the PA-group (asOR 1.82 [95% CI 1.28–2.60]), compared with the no AT group (eTable 5). Patients from the OAC and PA-groups could less often walk unaided at discharge and more often died in-hospital compared with the no AT group (eTable 7). In adjusted analyses, the relative risk of death within 90-days was higher for the OAC group (aRR 1.68 [95% CI 1.39–2.02]) and for the PA group (aRR 1.21 [1.03–1.42]) compared

Table 2 Relative Risk of Death Within 90-Days of Intracerebral Hemorrhage in Patients on an Antithrombotic Drug

Comparison with no use of antithrombotics				
			Relative risk (95% CI) of death	
Current use[a] of antithrombotic	**No. at risk**	**No. of events**	**Age and sex adjusted**	**Standardized mortality ratio weighting adjusted[b]**
Oral anticoagulant[c] (DOAC or VKA)	206	118	1.88 (1.51–2.33)	1.68 (1.39–2.02)
Platelet antiaggregant[c] (aspirin or clopidogrel)	270	123	1.41 (1.18–1.68)	1.21 (1.03–1.42)
No prescription for any antithrombotic	428	108	1 (reference)	1 (reference)
Active comparator analyses				
			Relative risk (95% CI) of death	
Current use[a] of antithrombotic	**No. at risk**	**No. of events**	**Age and sex adjusted**	**Inverse probability weighting adjusted[d]**
Class of antithrombotic				
Oral anticoagulant[c] (DOAC or VKA)	206	118	1.31 (1.06–1.61)	1.19 (1.05–1.36)
Platelet antiaggregant[c] (aspirin or clopidogrel)	270	123	1 (reference)	1 (reference)
Type of antithrombotic				
Oral anticoagulant[c,e]				
DOAC	88	45	0.75 (0.55–1.03)	0.82 (0.68–0.99)
VKA	136	83	1 (reference)	1 (reference)
Platelet antiaggregant drug[c]				
Clopidogrel	111	53	1.06 (0.79–1.42)	1.04 (0.87–1.24)
Aspirin	177	80	1 (reference)	1 (reference)

Notes: [a]Current use defined in method section; patients with concurrent use of oral anticoagulant and platelet antiaggregant excluded (n=18). [b]Binomial regression adjusted for age, sex, smoking, alcohol use, hypertension, diabetes, prior ischemic stroke, prior myocardial infarction, congestive heart failure, peripheral artery disease, chronic kidney failure, gastrointestinal bleeds, disorders indicative of high alcohol intake and current use of medications (separate variables for: drugs with antihypertensive effects, statins, NSAIDs, SSRIs, PPIs and platelet antiaggregants). [c]Patients with concurrent use of oral anticoagulants and platelet antiaggregant excluded (n=18). [d]Binomial regression adjusted for age, sex, smoking, alcohol use, hypertension, diabetes, venous thromboembolism, atrial fibrillation, prior ischemic stroke, prior myocardial infarction, congestive heart failure, peripheral artery disease, chronic kidney failure, gastrointestinal bleeds, disorders indicative of high alcohol intake and current use of medications (separate variables for: drugs with antihypertensive effects, statins, NSAIDs, SSRIs, PPIs and platelet antiaggregants). [e]Patients with concurrent use of oral anticoagulant and platelet antiaggregant included (n=18).
Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

with the no AT group (Table 2). Mortality in the OAC group was higher than in the PA group (aRR 1.19 [95% CI 1.05–1.36]; Table 2).

Antithrombotic Type Comparisons

The comparisons by AT type included 88 patients on a DOAC (52.3% men; mean age 81.0 [SD 8.3] years), 136 on a VKA (59.6% men; mean age 78.6 [SD 8.4] years) and 111 on clopidogrel (55.0% men; mean age 79.1 [SD 9.7] years) vs 177 on aspirin (46.3% men; mean age 78.3 [SD 9.2] years) (Figure 1). eTable 8 (DOAC vs VKA) and eTable 9 (clopidogrel vs aspirin) depict baseline characteristics of patients included in AT type comparisons. Similar standardized means were observed after application of propensity weighting in the DOAC vs VKA (eTable 8) and the clopidogrel vs aspirin comparisons (eTable 9). Clinical characteristics at the time of admission (eTable 10) and brain CT findings (eTable 11) were similar for DOAC- vs VKA- and for clopidogrel- vs aspirin-treated patients, respectively. Functional outcomes were also similar between types of ATs (Table 3). In propensity score adjusted analyses, the relative risk of death within 90-days was lower for those on a DOAC vs a VKA (aRR 0.82 [95% CI 0.68–0.99]), but similar for clopidogrel vs aspirin (aRR 1.04 [0.87–1.24]) (Table 2).

Table 3 Preadmission Functional Level and Living Arrangement and Post Intracerebral Hemorrhage Functional Outcomes and Mortality by Prior Use of Direct Oral Anticoagulants Vs Vitamin K Antagonist (Reference) and Clopidogrel Vs Aspirin (Reference)

Outcome, No. (%)	Oral Anticoagulant, Current Use[a]			Platelet Antiaggregant, Current Use[a]		
	DOAC (n=88)	VKA (n=136)	Age and Sex Adj. Odds Ratio (95% CI)	Clopidogrel (n=111)	Aspirin (n=177)	Age and Sex Adj. Odds Ratio (95% CI)
Admitted from						
Own home	76 (86.4)	124 (91.2)	1 (reference)	96 (86.5)	157 (88.7)	1 (reference)
Retirement home (or similar arrangement)	12 (13.6)	12 (8.8)	1.19 (0.47–2.98)	15 (13.5)	20 (11.3)	1.15 (0.55–2.38)
Discharged to						
Pre-ICH living arrangement	22 (25.0)	24 (17.6)	1 (reference)	27 (24.3)	43 (24.3)	1 (reference)
Rehabilitation	15 (17.0)	27 (19.9)	0.72 (0.29–1.75)	26 (23.4)	45 (25.4)	0.95 (0.47–1.92)
Retirement home	14 (15.9)	14 (10.3)	1.24 (0.46–3.36)	14 (12.6)	23 (13.0)	0.87 (0.38–2.03)
Died during acute admission	37 (42.0)	71 (52.2)	0.58 (0.28–1.19)	44 (39.6)	66 (37.3)	1.07 (0.57–2.00)
Unaided gait pre-ICH[b]	79 (89.8)	128 (94.1)	0.56 (0.20–1.56)	101 (91.0)	166 (93.8)	0.73 (0.30–1.80)
Unaided gait post-ICH[b,c]						
At discharge from acute unit	19 (21.6)	29 (21.3)	0.95 (0.89–1.02)	27 (24.3)	47 (26.6)	0.97 (0.55–1.70)
At discharge from rehabilitation unit[d]	8 (9.1)	13 (9.6)	0.99 (0.74–1.33)	14 (12.6)	21 (11.9)	1.12 (0.53–2.34)
Mortality (in-hospital or after discharge)						
Day 1	25 (28.4)	40 (29.4)	1.01 (0.55–1.87)	24 (21.6)	30 (16.9)	1.35 (0.74–2.46)
Day 7	36 (40.9)	62 (45.6)	0.76 (0.43–1.33)	41 (36.9)	56 (31.6)	1.27 (0.77–2.10)
Day 90	45 (51.1)	83 (61.0)	0.56 (0.32–1.00)	53 (47.7)	80 (45.2)	1.10 (0.68–1.79)

Notes: [a]Patients with concurrent use of oral anticoagulant and platelet antiaggregants included (n=18). [b]Unaided by person, but the patient could be using cane, crutches, or Zimmer frame. [c]Only patients with unaided gait pre-ICH included. [d]Only patients referred to in-hospital rehabilitation and discharged within 90 days of ICH onset included.
Abbreviations: DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; VKA, vitamin K antagonist.

Supplementary Analyses

Supplementary analyses produced similar results in terms of the magnitude and direction of the risk estimates to the main analyses (eTables 12–15); however, except for the analysis restricted to patients scanned within 24-hours of ICH onset (eTable 12), there was no difference in 90-day mortality between DOAC- vs VKA-treated patients.

In a post-hoc analysis, change in hematoma volume from index scan to follow-up scan was analyzed (see eMethods in the Supplement). With growth defined as proportion with change >33% of index volume or ≥6mL increase in hematoma volume from baseline-to-follow-up scan, hematoma growth was more common in the OAC group compared to the PA or the no AT groups, albeit based on small numbers (eTable 16). In another post-hoc analysis which was stratified by DNR orders ≤24 hours after admission, post-ICH mortality only differed significantly for patients not given DNR orders for comparisons of OAC vs no AT (aRR 1.57 [1.22–2.02]) and OAC vs PA (aRR 1.39 [1.17–1.64]) (eTable 17).

Discussion

In this study of unselected patients with s-ICH from Southern Denmark, prior VKA use was associated with a higher 90-day mortality than either PA- or no AT-use. Post-ICH mortality was higher in PA than no AT users. Compared to no AT use, those with prior use of an OAC or a PA had larger hematoma volumes, more frequently presented with intraventricular hematoma extensions, and more frequently had DNR orders implemented after presentation, factors reported to be associated with a poorer prognosis.[38,39] In comparisons by AT type, patients on a DOAC had a lower 90-day mortality than those on a VKA. Post-ICH mortality for patients taking clopidogrel vs aspirin did not differ. Radiological characteristics were similar in patients on a DOAC vs VKA and clopidogrel vs aspirin.

Comparison to Previous Studies on Antithrombotic Class and Post-ICH Outcomes

With few exceptions,[40] most studies report that ICHs following OAC use is associated with a higher mortality than those following no AT use.[6,26,27,41] Our results on prior PA use vs no AT use are consistent with several previous studies,[26,27,42] including a recent meta-analysis.[7] We note that others report comparable outcomes between the two groups.[24,43,44]

Consistent with our findings, nationwide studies from Sweden[26] and Norway and Switzerland[17] found that prior OAC use was associated with higher 90-day mortality compared to no AT use. Similar to our findings, the Swedish study also reported a higher 90-day mortality with prior PA use, compared to no AT use (aRR 1.23 95% CI [1.14–1.33]).[26] We also found a higher risk of in-hospital death and a lower proportion of patients who were able to walk unaided at discharge in OAC- and PA-treated patients compared with no AT use. Other large registry-based studies focusing on in-hospital mortality after an ICH, however, reported similar case-fatality rates in patients with prior PA use vs no AT use.[6,43]

We included radiologic measures such as baseline hematoma volume and hematoma expansion in our study as we considered them of clinical interest and because of their association with post-ICH outcome.[45] Consistent with other studies,[5,7,41] we found that patients on an OAC or PA were more prone to having larger hematomas at baseline, compared to those not taking ATs. Despite similar clinical and radiological characteristics at presentation of patients with OAC use vs PA use, OAC users had a higher 90-day mortality. This may be explained by a higher propensity for hematoma expansion in patients on OACs,[3–5] as reflected in our supplementary analyses.

Comparison to Previous Studies on Antithrombotic Type and Post-ICH Outcomes

We found an approximately 20% lower risk of 90-day post-ICH mortality in patients who had used a DOAC compared with a VKA. Although the upper boundary for the confidence interval was close to unity, the point estimate of risk reduction was robust when subjected to various sensitivity analyses. This result is concordant with a large study from the US based on data from the Get With the Guidelines-Stroke registry which reported lower in-hospital mortality in patients with s-ICH with prior DOAC use, compared with prior VKA use,[16] as did a study based on pooled data from Norway and Switzerland.[17] Several observational studies[9,11,26,37,46] and 2 meta-analyses,[8,12] however, found no difference in mortality rates after ICH between patients with pre-ICH use of DOAC vs VKA. The reasons for these disparate results are not clear.

We did not find that DOAC users had better in-hospital outcomes (eg, unaided gait at discharge or lower in-hospital mortality) compared with those with VKA users, consistent with the results of one US study,[16] but not another.[8]

There is a gap in knowledge related to the relationship between prior aspirin compared to clopidogrel use and post-ICH mortality.[47] In our study, we found no differences in clinical or radiological characteristics at presentation, functional outcomes, or 90-day mortality rates between clopidogrel and aspirin users. This result is reassuring because clopidogrel is the recommended first choice for secondary prevention of stroke and TIA in Denmark.[48]

Strengths and Limitations

This study has several strengths. It is based on a regionwide cohort of unselected patients, which reduced the likelihood of selection bias. Full EHRs and brain CTs were evaluated for all patients, thereby ensuring the accurate diagnosis of s-ICH and enabling collection of key clinical and radiological information, data that was not available in previous studies based exclusively on registry data. We integrated the collected data with information on medication prescriptions from a Danish nationwide registry, thereby eliminating recall bias.

Potential study limitations need to be considered. Due to small numbers, we excluded patients with dual PA use. We did not have data on the exact timing of last AT intake prior to ICH onset, information that could be critical in correctly assessing outcomes in anticoagulant-associated s-ICH.[49] Use of prescription data rather than collecting data on patient reported drug use could have led to some degree of misclassification. With few exceptions,[37] studies on AT use and post-ICH mortality lack information on blood DOAC levels. This was also true of our study, as these tests were not routinely performed in the study period in this setting. INR-levels were available for patients on a VKA in our study. We note that use of INR-levels when determining VKA exposure had no major impact on the risk estimates of post s-ICH mortality for DOAC vs VKA compared to the main analyses in which only prescription data were used. We performed analyses stratified by DNR orders.[39] These results should be interpreted with caution, as the complex relationship of DNR orders and post-ICH mortality is likely influenced by both patient and treating physician characteristics and may not be adequately addressed by stratification. Our study lacked detailed data on functional outcome after ICH, which is of major interest to survivors of this devastating disorder.[27,41] Our secondary outcome on the ability to walk 3-months after an ICH was based on hospital medical records and therefore liable to some degree of underestimation of recovery;[50] also, our choice of a 3-month window may be too short to assess outcomes after ICH.[50,51] Finally, as the Danish population is primarily of European ancestry, the results may not be generalizable to other populations.

Conclusion

In this unselected cohort of patients with s-ICH, prior OAC use was associated with poor short-term prognosis compared to prior PA use or no AT use. Patients with prior PA use had a higher mortality after ICH than patients with no AT use, but there were no differences in mortality for clopidogrel vs aspirin. Prior DOAC use was associated with lower post s-ICH mortality than VKA use.

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