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Intracerebral haemorrhage in patients taking different types of oral anticoagulants: a pooled individual patient data analysis from two national stroke registries

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ABSTRACT

Background We investigated outcomes in patients with intracerebral haemorrhage (ICH) according to prior anticoagulation treatment with Vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs) or no anticoagulation.

Methods This is an individual patient data study combining two prospective national stroke registries from Switzerland and Norway (2013–2019). We included all consecutive patients with ICH from both registries. The main outcomes were favourable functional outcome (modified Rankin Scale 0–2) and mortality at 3 months.

Results Among 11 349 patients with ICH (mean age 73.6 years; 47.6% women), 1491 (13.1%) were taking VKAs and 1205 (10.6%) DOACs (95.2% factor Xa inhibitors). The median percentage of patients on prior anticoagulation was 23.7 (IQR 22.6–25.1) with VKAs decreasing (from 18.3% to 7.6%) and DOACs increasing (from 3.0% to 18.0%) over time. Prior VKA therapy (n=209 (22.3%); adjusted ORs (aOR), 0.64; 95% CI, 0.49 to 0.84) and prior DOAC therapy (n=184 (25.7%); aOR, 0.64; 95% CI, 0.47 to 0.87) were independently associated with lower odds of favourable outcome compared with patients without anticoagulation (n=2037 (38.8%)). Prior VKA therapy (n=720 (49.4%); aOR, 1.71; 95% CI, 1.41 to 2.08) and prior DOAC therapy (n=460 (39.7%); aOR, 1.28; 95% CI, 1.02 to 1.60) were independently associated with higher odds of mortality compared with patients without anticoagulation (n=2512 (30.2%)).

Conclusions The spectrum of anticoagulation-associated ICH changed over time. Compared with patients without prior anticoagulation, prior VKA treatment and prior DOAC treatment were independently associated with lower odds of favourable outcome and higher odds of mortality at 3 months. Specific reversal agents unavailable during the study period might improve outcomes of DOAC-associated ICH in the future.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Direct oral anticoagulants (DOACs) largely replaced Vitamin K antagonists (VKAs) for the treatment of various thromboembolic conditions. Knowledge about the clinical importance of DOAC-associated intracerebral haemorrhage (ICH) is scarce and restricted to small studies from tertiary hospitals.

WHAT THIS STUDY ADDS

⇒ Our large observational study including more than 11 000 patients with ICH combining national registry data from Switzerland and Norway found that DOAC-associated ICH increased over time largely replacing VKA-associated ICH with both types of ICH having poorer functional outcome and higher mortality at 3 months compared with patients without prior anticoagulation having an ICH.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND POLICY

⇒ Our study helps to focus research priorities on improving treatment options for patients with DOAC-ICH, as specific reversal agents for these anticoagulants were not available during the study period.

INTRODUCTION

Intracerebral haemorrhage (ICH) is the most devastating form of stroke with high mortality

and morbidity.[1] Prior anticoagulation is a complicating factor associated with larger baseline haematoma volume, more frequent secondary expansion, poorer functional outcome and higher mortality.[2] Most of the evidence is based on patients on Vitamin K antagonist (VKA) therapy prior to ICH onset. Direct oral anticoagulants (DOACs) — the direct thrombin inhibitors[3] (dabigatran) and the factor Xa inhibitors[4] (apixaban, edoxaban and rivaroxaban) have emerged as mainstay of anticoagulant therapy. They have been available in Switzerland and Norway since 2011 for treatment and prophylaxis. Current knowledge about the influence of prior DOAC therapy on ICH is mainly based on an indirect comparison of patients on VKAs with patients on DOACs.[5–7] Data from a US-based registry study found higher in-hospital mortality in patients on prior DOAC and prior VKA therapy compared with patients without prior anticoagulation but data on long-term outcomes and temporal trends are lacking.[6 8]

We aimed to determine the frequency of anticoagulation-associated ICH overall and according to the type of anticoagulant (VKAs or DOACs) and to assess the association of prior anticoagulation as compared with patients without anticoagulation (no OACs) with favourable functional outcome and mortality at 3 months in a large cohort study including individual patient data from two prospective national stroke registries from Switzerland and Norway.

METHODS

Study design and participants

This is an individual patient data analysis from the Swiss Stroke Registry (SSR) and Norwegian Stroke Registry (NSR). Both are compulsory prospective national stroke registries designed for quality control and research in stroke management. Since 2013 (NSR) and 2014 (SSR), all consecutive patients with any stroke (ischemic stroke and non-traumatic ICH) admitted to a stroke centre or unit (certified according to national criteria and in line with those of the European Stroke Organisation)[9] in the two countries have been enrolled and prospectively followed-up at 3 months. For the present analysis, we included all patients aged ≥18 years with imaging-proven non-traumatic ICH enrolled in one of the participating stroke registries from January 2013 (NSR) and January 2014 (SSR), until December 2019 (NSR and SSR). We excluded patients with missing data on prior anticoagulation therapy and secondary aetiologies (ie, tumour, arteriovenous malformation, cerebral venous thrombosis, primary subdural, subarachnoidal or epidural haemorrhage).

Baseline characteristics

Local investigators at the participating SSR and NSR hospitals recorded standardised and prespecified variables using electronic case report forms. In Norway, data are registered on paper forms at the hospitals by trained physicians and nurses, who then enter data into the NSR by use of a web-based form. The NSR has previously been shown to provide a correct, complete and valuable source of data for epidemiological, clinical and healthcare studies.[10] The collection of data has been described previously and part of the dataset has been used in prior research.[11 12] The respective web-based and encoded databases were hosted by the Clinical Trials Unit Basel (Switzerland) and St. Olav's University Hospital, Trondheim (Norway). For this analysis, we used the following variables: demographic characteristics (age, sex, country), risk factors (diabetes, atrial fibrillation (AF)), concomitant medications (antiplatelet agents, antihypertensive and lipid-lowering drugs), medical history (history of prior ischaemic stroke, ICH and coronary heart disease/prior myocardial infarction), pre-stroke disability (measured using the modified Rankin Scale (mRS)), clinical presentation on admission (measured using the National Institute of Health Stroke Scale (NIHSS) and level of consciousness (LOC)), treating hospital level (local stroke unit, ie, monitored high-dependency unit for stroke patients but without local neurosurgery department, vs stroke centre, ie, fully equipped tertiary level of care hospital including neurosurgery) and local management (treatment at high-dependency stroke unit/intermediate care (IMC)/intensive care unit (ICU) vs general ward). We applied a plausibility check and set data items as missing if they were implausible.

Three-month follow-up

At 3 months, all patients enrolled in the registries received standardised follow-up assessments by local investigators for functional outcome (using the mRS). All follow-up checks were performed by mRS-certified stroke physicians or research staff during clinical visits, or by structured telephone interviews.

Prior anticoagulation therapy

We assigned patients according to anticoagulant treatment prior to ICH onset into one of the following groups: (1) VKAs (patients taking VKA (eg, phenprocoumon, acenocoumarol, warfarin) prior to onset), (2) DOACs (patients taking any of the following: apixaban, edoxaban, rivaroxaban or dabigatran prior to onset) and (3) no OACs (patients taking neither VKAs nor DOACs prior to onset; patients may be on antiplatelet therapy or low-dose heparins). Prior anticoagulation in both registries was regarded as ongoing, therapeutic anticoagulation. There was no pre-specified time-window or compliance check but patients who had stopped prescribed anticoagulation therapy were regarded as not-anticoagulated.

Outcomes

For this analysis, the following outcomes were defined: (1) frequency of anticoagulation-associated ICH overall and according to the type of anticoagulant (VKAs or DOACs), (2) favourable functional outcome (defined as mRS 0–2) and (3) mortality at 3 months.

Statistical analysis

The statistical analysis was planned by BMS, EF, OMR, MBr and DJS and was performed by BMS and MBr using Stata V.16.1 (StataCorp). We presented absolute and proportional frequency of prior anticoagulation therapy according to different types of anticoagulants (VKAs and DOACs) among patients with ICH. We presented counts (no.) and percentages (%) for categorical and ordinal variables and used the mean (SD) for normally distributed, continuous variables and median (IQR) for non-normally distributed variables. We compared baseline characteristics among groups using the chi-square test for categorical variables and the analysis of variance or Kruskal-Wallis test for continuous and ordinal variables. Observed differences for all analyses were considered significant if p<0.05.

We used univariable, multivariable mixed-effects regression models (for NIHSS) and inverse probability weighting (IPW) with multiple imputation (imputing missing baseline variables with 100 imputed datasets using chained equations; a detailed overview of missing values and those used for multiple imputation can be found in online supplemental table 1) to analyse the association between prior anticoagulation therapy, baseline stroke severity (NIHSS and LOC on admission), favourable functional outcome and mortality at 3 months. Prior anticoagulation (VKAs and DOACs) was included as an independent variable, with no anticoagulation (no OACs) as the reference group. The multivariable regression models and IPW were adjusted for predefined literature-based confounders at baseline.[6 8 12] Hospitals (ie, participating stroke centres or units in the SSR and NSR) were handled in the models as a random effect. We calculated adjusted ORs (aOR) with corresponding 95% CIs.

To assess the association between prior anticoagulation therapy and baseline stroke severity, we performed a quantile (NIHSS) or binary multiple (LOC) regression model. To analyse the association between prior anticoagulation therapy and favourable functional outcome and mortality at 3 months, we performed IPW. As there was a discrepancy for some hospitals in reporting mortality and functional outcome, we limited the analysis for functional outcome to hospitals with at least 70% availability of mRS at 3 months to reduce bias. All multivariable analyses and IPW were adjusted for the following predefined variables: demographic characteristics (age, sex, country), risk factors (diabetes, AF), concomitant medications (antiplatelet agents, antihypertensives and lipid-lowering drugs), medical history (history of prior ischaemic stroke, ICH and coronary heart disease/prior myocardial infarction), pre-stroke disability (pre-mRS), clinical presentation on admission (NIHSS and LOC), treating hospital level (stroke centre or stroke unit) and local management (treatment at high-dependency unit or other department).

We performed post-hoc sensitivity analysis using ordinal shift analysis instead of dichotomised mRS at 3 months.

Further, we repeated the multivariable regression models and the IPW analysis on stroke severity on admission (NIHSS and LOC) and outcomes (favourable functional outcome and mortality at 3 months) comparing the DOAC group to the VKA group only. Prior DOACs therapy was included as an independent variable, with VKA therapy as the reference group.

RESULTS

Baseline characteristics

Overall, 11 734 patients with non-traumatic ICH were enrolled in the SSR and NSR from 76 different hospitals between January 2013 and December 2019. Of these, 11 349 (96.7%) patients had available information on prior anticoagulation therapy and were included in the final study population (figure 1). The mean age was 73.6 (SD, 13.4) years, 47.6% were women, 1491 (13.1%) patients were taking VKAs and 1205 (10.6%) were taking DOACs (95.2% factor Xa inhibitors). Median NIHSS on admission was 7 (IQR, 2–15) and 3886 (34.8%) patients had decreased LOC; 4739 (41.8%) patients were hospitalised at a stroke centre (ie, fully equipped tertiary level of care hospital including neurosurgery) and overall 7767 (68.7%) were treated at a high-dependency unit in their respective hospital.

Compared with patients not treated with anticoagulants, patients on prior VKA or DOAC therapy were older (mean difference was 7.8 years for both VKAs and DOACs, p<0.001), had more risk factors (diabetes, AF), more concomitant medications (antiplatelets, antihypertensives and lipid-lowering drugs), more often a history of ischaemic stroke, previous ICH and coronary heart disease/prior myocardial infarction, a higher pre-stroke disability (pre-mRS) and were less often treated at a high-dependency unit.

Baseline characteristics of all patients and according to prior anticoagulation therapy are displayed in table 1.

Prior anticoagulation therapy

While the frequency of prior anticoagulation therapy was stable during the study period with median percentage of 23.7 (IQR, 22.6–25.1), the spectrum changed with decreasing rates of VKAs (from 18.3% in 2013 to 7.6% in 2019; p<0.001) and increasing rates of DOACs (from 3.0% in 2013 to 18.0% in 2019; p<0.001) (figure 2). The results per country were comparable (online supplemental figure 1).

Stroke severity

Information on NIHSS and LOC was available in 7994 (70.4%) and 11 155 (98.3%) patients, respectively. Patients on VKAs or DOACs had a higher stroke severity score (median NIHSS were 8 (IQR, 3–17) for VKA and 7 (IQR, 3–15) for DOAC) and more often a decreased LOC (40.2% for VKA and 37.0% for DOAC) than patients with no anticoagulation (median NIHSS were 7 (IQR 2–15), p<0.001 compared with VKAs and p<0.05 compared with

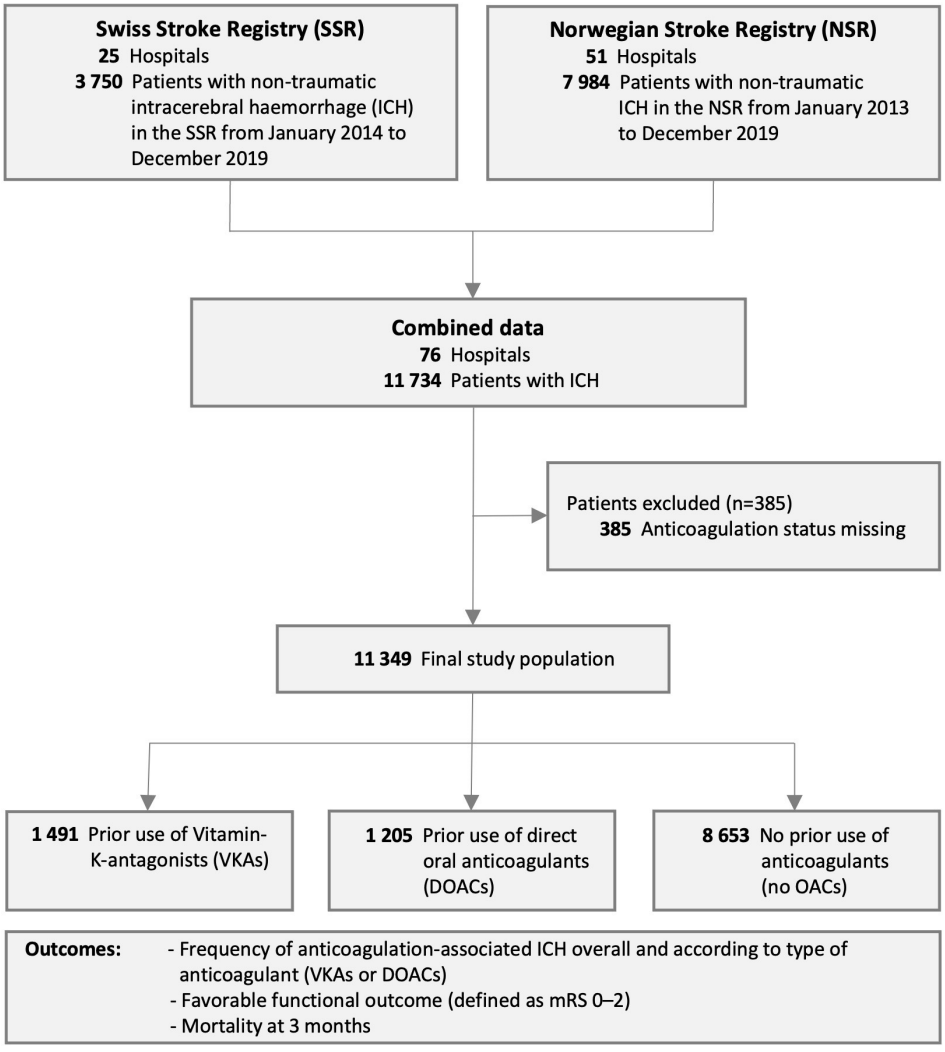

Figure 1 Study patient flowchart. mRS, modified Rankin Scale.

DOACs; decreased LOC 33.6%, p<0.001 compared with VKAs and p<0.05 compared with DOACs).

After adjusting for confounders, there was no significant association neither for NIHSS (β, 0.30; 95% CI, −0.41 to 1.00 for VKA and β, 0.06; 95% CI, −0.72 to 0.83 for DOAC) nor decreased LOC (aOR, 1.02; 95% CI, 0.86 to 1.22 for VKA and aOR, 0.91; 95% CI, 0.75 to 1.09 for DOAC) compared with patients without prior anticoagulation. Results of the quantile and binary logistic regression are displayed in table 2.

Three-month functional outcome and mortality

Information on functional outcome and mortality at 3 months was available in 8646 (76.2%) and 10 939 (96.4%) patients, respectively. There was no difference in the availability of functional outcome between the three groups (p=0.071). Compared with no OACs, information on mortality was more frequently available in patients on prior VKAs (p=0.004) but not DOACs (p=0.867). Patients with missing information on functional outcome at 3 months (n=2703) were younger, more often from the NSR, less often on prior anticoagulation and antiplatelet therapy, had a lower prevalence of AF, a lower prevalence of prior antihypertensive therapy, more favourable clinical presentation on admission (ie, lower NIHSS, higher LOC) and were less often treated at a stroke centre (table 3).

After limiting the analysis for functional outcome to hospitals with at least 70% availability of mRS at 3 months, 49 out of 76 hospitals (64%) were included (n=6903). At 3 months, 209 (22.3%) patients with VKAs, 184 (25.7%) with DOACs and 2037 (38.8%) with no anticoagulation had a favourable functional outcome (figure 3). Results per country were largely similar (online supplemental figure 2). After adjusting for confounders, prior VKA therapy (aOR, 0.64; 95% CI, 0.49 to 0.84) and prior DOAC therapy (aOR, 0.64; 95% CI, 0.47 to 0.87) were independently associated with lower odds of favourable outcome compared with patients without anticoagulation.

In the post-hoc sensitivity analysis using ordinal shift analysis instead of dichotomised mRS at 3 months, prior VKA treatment and DOAC treatment (both compared with no anticoagulation) were associated with poorer

Table 1 Baseline characteristics

Characteristic	Total (n=11 349)	VKAs (n=1491)	DOACs (n=1205)	No OACs (n=8653)	P value*
Demographics					
Age (years), mean (SD)	73.6 (13.4)	79.6 (8.9)	79.6 (8.7)	71.8 (14.0)	<0.001
Female, no. (%)	5403 (47.6)	595 (39.9)	557 (46.2)	4251 (49.2)	<0.001
Country, no. (%)					0.002
Norway	7849 (69.2)	1083 (72.6)	852 (70.7)	5914 (68.3)	
Switzerland	3500 (30.8)	408 (27.4)	353 (29.3)	2739 (31.7)	
Risk factors, no. (%)					<0.001
Diabetes	1604 (14.7)	305 (21.1)	221 (19.0)	1078 (13.0)	
Atrial fibrillation	2719 (24.7)	1084 (74.0)	938 (79.9)	697 (8.3)	
Concomitant medication, no. (%)					<0.001
Antiplatelets					
None	7545 (68.3)	1184 (83.0)	1017 (87.0)	5344 (63.3)	
Single	3060 (27.7)	218 (15.3)	140 (12.0)	2702 (32.0)	
Dual	430 (3.9)	23 (1.6)	11 (0.9)	396 (4.7)	
Triple	7 (0.1)	2 (0.1)	1 (0.1)	4 (0.0)	
Antihypertensives	3779 (48.1)	673 (68.2)	650 (71.1)	2456 (41.2)	
Lipid-lowering drugs	2653 (31.9)	489 (43.2)	388 (43.0)	1776 (28.3)	
DOAC type, no. (%)					<0.001
None	10 144 (90.9)	1491 (100.0)		8653 (100.0)	
Apixaban	455 (4.1)		455 (44.7)		
Edoxaban	12 (0.1)		12 (1.2)		
Rivaroxaban	503 (4.5)		503 (49.4)		
Dabigatran	49 (0.4)		49 (4.8)		
Medical history, no. (%)					<0.001
History of ischaemic stroke	1672 (15.1)	348 (23.7)	281 (23.9)	1043 (12.3)	
History of ICH	1136 (10.2)	83 (5.7)	88 (7.5)	965 (11.4)	
History of coronary heart disease/ myocardial infarction	1073 (13.0)	262 (23.5)	147 (16.2)	664 (10.7)	
Pre-stroke disability					
Pre-mRS, no. (%)					<0.001
No symptoms at all (mRS 0)	4023 (50.9)	457 (42.4)	320 (38.2)	3246 (54.2)	
No significant disability (mRS 1)	1348 (17.1)	217 (20.1)	161 (19.2)	970 (16.2)	
Slight disability (mRS 2)	1066 (13.5)	175 (16.2)	154 (18.4)	737 (12.3)	
Moderate disability (mRS 3)	908 (11.5)	150 (13.9)	114 (13.6)	644 (10.8)	
Moderately severe disability (mRS 4)	459 (5.8)	64 (5.9)	76 (9.1)	319 (5.3)	
Severe disability (mRS 5)	102 (1.3)	15 (1.4)	13 (1.6)	74 (1.2)	
Clinical presentation on admission					

Continued

Table 1 Continued

Characteristic	Total (n=11 349)	VKAs (n=1491)	DOACs (n=1205)	No OACs (n=8653)	P value*
NIHSS on admission, median (IQR)	7.0 (2.0–15.0)	8.0 (3.0–17.0)	7.0 (3.0–15.0)	7.0 (2.0–15.0)	<0.001
Level of consciousness at admission, no. (%)					<0.001
Alert†	7269 (65.2)	882 (59.8)	752 (63.0)	5635 (66.4)	
Drowsy‡	2364 (21.2)	331 (22.4)	294 (24.6)	1739 (20.5)	
Comatose§	1522 (13.6)	263 (17.8)	147 (12.3)	1112 (13.1)	
Treating hospital level, no. (%)					
Treatment at stroke center¶	4739 (41.8)	610 (40.9)	464 (38.5)	3665 (42.4)	0.031
Local management, no. (%)					
Treatment at high-dependency unit**	7767 (68.7)	859 (57.7)	745 (62.4)	6163 (71.4)	<0.001

*Univariate comparison between no OACs, VKAs and DOACs.
†GCS 13–15 (SSR) or patient is drowsy, responds by light stimulation (NSR).
‡GCS 9–12 (SSR) or patient is drowsy, reacts only with vigorous repetitive stimulation (NSR).
§GCS 3–8 (SSR) or patient does not respond, or just with non-targeted movement (NSR).
¶Fully equipped tertiary level of care hospital including neurosurgery.
**High-dependency stroke unit/IMC/ICU.
DOACs, direct oral anticoagulants; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; ICU, intensive care unit; IMC, intermediate care; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NSR, Norwegian Stroke Registry; OACs, oral anticoagulants; SSR, Swiss Stroke Registry; VKAs, Vitamin K antagonists.

functional outcome (higher mRS) at 3 months (aOR, 1.67; 95% CI, 1.31 to 2.12 for VKAs and aOR, 1.49; 95% CI, 1.18 to 1.88 for DOACs).

At 3 months, 720 (49.4%) patients with VKAs, 460 (39.7%) with DOACs and 2512 (30.2%) patients with no anticoagulation had died. After adjusting for confounders, prior VKA therapy (aOR, 1.71; 95% CI, 1.41 to 2.08) and prior DOAC therapy (aOR, 1.28; 95% CI, 1.02 to 1.60) were independently associated with higher odds of mortality compared with patients without anticoagulation. Results of the multivariable logistic regressions and IPW are displayed in table 2.

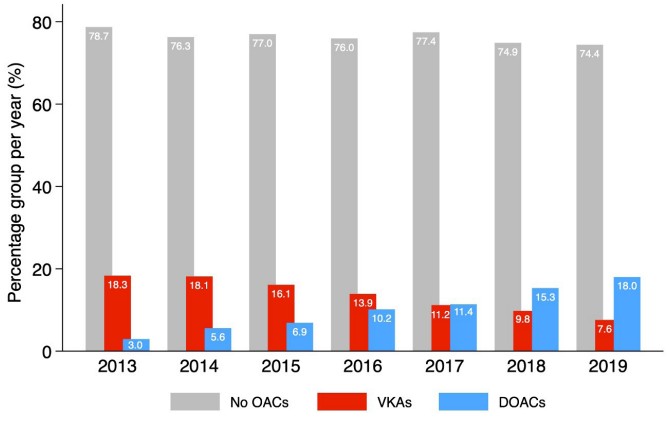

Figure 2 Frequency of prior anticoagulation therapy as compared with no prior anticoagulation in patients with intracerebral haemorrhage from 2013 to 2019. Combined data from Switzerland and Norway (n=11 349). The median percentage of patients on prior anticoagulation during the study period was 23.7% (IQR, 22.6–25.1) with VKAs decreasing and DOACs increasing. DOACs, direct oral anticoagulants; OACs, oral anticoagulants; VKAs, Vitamin K antagonists.

Comparison of DOACs to VKAs only

In the analysis comparing DOACs to VKAs only, we found consistent results to the main analysis with no difference in NIHSS (β, −0.24; 95% CI, −1.01 to 0.53 for DOACs) and similar odds for decreased LOC (aOR, 0.99; 95% CI, 0.75 to 1.31 for DOACs;) on admission and favourable functional outcome at 3 months (aOR, 1.00; 95% CI, 0.67 to 1.49 for DOACs).

However, prior DOAC therapy was associated with lower odds of mortality (aOR, 0.75; 95% CI, 0.57 to 0.99 for DOACs) compared with patients on prior VKA therapy.

DISCUSSION

This large international study comprising data from two prospective national stroke registries including 11 349 patients with non-traumatic ICH revealed the following main findings: First, one out of four patients with non-traumatic ICH was on prior anticoagulation therapy and the percentage remained stable during the 7 years study period. Second, the spectrum of prior anticoagulation changed dramatically from VKAs to DOACs during the

Table 2 Main outcomes according to prior anticoagulation therapy among patients with non-traumatic intracerebral haemorrhage

Outcome	VKAs	DOACs	No OACs	P Value*
Stroke severity on admission				
NIHSS, median (IQR)	8.0 (3.0–17.0) (n=999)	7.0 (3.0–15.0) (n=844)	7.0 (2.0–15.0) (n=6150)	<0.001
β (95% CI)††† (n=7993)	0.30 (–0.41 to 1.00)	0.06 (–0.72 to 0.83)	1 (Reference)	
Decreased LOC‡, no./ total no. (%)	594/1476 (40.2)	441/1139 (37.0)	2851/8486 (33.6)	<0.001
aOR (95% CI)§‡‡ (n=11 155)	1.15 (0.94–1.41)	1.15 (0.92–1.45)	1 (Reference)	
Functional outcome at 3 months				
mRS 0–2, no./total no. (%)	209/938 (22.3)	184/716 (25.7)	2037/5249 (38.8)	<0.001
aOR (95% CI)¶‡‡ (n=6903)**	0.64 (0.49 to 0.84)	0.64 (0.47 to 0.87)	1 (Reference)	
mRS, median (IQR)	6 (3–6)	4 (2–6)	3 (2–6)	<0.001
aOR (95% CI)¶§§ (n=6903)**	1.67 (1.31 to 2.12)	1.49 (1.18 to 1.88)	1 (Reference)	
Mortality at 3 months				
Mortality, no./total no. (%)	720/1457 (49.4)	460/1158 (39.7)	2512/8324 (30.2)	<0.001
aOR (95% CI)¶‡‡ (n=10 939)	1.71 (1.41 to 2.08)	1.28 (1.02 to 1.60)	1 (Reference)	

*Univariate comparison between no OACs, VKAs and DOACs.
†Multivariable mixed-effects analysis using MI adjusted for demographic characteristics (age, sex, country), risk factors (diabetes, atrial fibrillation), concomitant medications (antiplatelet agents, antihypertensives and lipid-lowering drugs), medical history (history of prior ischaemic stroke, ICH and coronary heart disease/prior myocardial infarction), pre-stroke disability (pre-mRS), clinical presentation on admission (LOC), treating hospital level (stroke centre or stroke unit) and local management (treatment at high-dependency unit).
‡Decreased LOC defined as LOC drowsy or comatose.
§IPW using MI adjusted for demographic characteristics (age, sex, country), risk factors (diabetes, atrial fibrillation), concomitant medications (antiplatelet agents, antihypertensives and lipid-lowering drugs), medical history (history of prior ischaemic stroke, ICH and coronary heart disease/prior myocardial infarction), pre-stroke disability (pre-mRS), clinical presentation on admission (NIHSS), treating hospital level (stroke centre or stroke unit) and local management (treatment at high-dependency unit).
¶IPW using MI adjusted for demographic characteristics (age, sex, country), risk factors (diabetes, atrial fibrillation), concomitant medications (antiplatelet agents, antihypertensives and lipid-lowering drugs), medical history (history of prior ischaemic stroke, ICH and coronary heart disease/prior myocardial infarction), pre-stroke disability (pre-mRS), clinical presentation on admission (NIHSS, LOC), treating hospital level (stroke centre or stroke unit) and local management (treatment at high-dependency unit).
**Analysis limited to sites with ≥70% availability of mRS at 3 months.
††Quantile regression.
‡‡Binary logistic regression.
§§Ordinal logistic regression.
aOR, adjusted OR; DOACs, direct oral anticoagulants; ICH, intracerebral haemorrhage; IPW, inverse probability weighting; LOC, level of consciousness; MI, multiple imputation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OACs, oral anticoagulants; VKAs, Vitamin K antagonists.

study period. Third, compared with patients with ICH without prior anticoagulation, neither prior VKA nor prior DOAC therapy was associated with higher stroke severity on admission. Fourth, compared with patients without prior anticoagulation, prior VKA treatment and prior DOAC treatment were independently associated with lower odds of favourable outcome and higher mortality at 3 months.

In our study, 24% of patients with ICH were on prior anticoagulant therapy. This percentage is significantly higher than reported from a recent national stroke registry study from Sweden (17%)[13] and a US-based registry study (13%).[6] Differences with data from the USA are potentially related to healthcare system differences with the availability of a universal, insurance-based healthcare for all citizens of Switzerland and Norway making access to oral anticoagulation treatment easy and affordable. Expanding on this, we found that over a period of 7 years (2013–2019), the frequency of anticoagulation-associated ICH was overall stable but with a clear shift from VKA to DOAC-associated ICH. This finding was independently observed in Switzerland and Norway. The overall proportion of DOAC-associated ICH (10.6%) in our study was much higher than in the USA (3.5%).[6] This difference is likely explained by differences in healthcare systems and access to DOACs.

Patients on prior VKAs or DOACs were older, had more comorbidities and were more often pre-stroke dependent

Table 3 Comparison of baseline characteristics of patients with available versus missing functional outcome at 3 months

Characteristic	mRS available (n=8646)	mRS missing (n=2703)	P value*
Demographics			
Age (years), mean (SD)	73.8 (13.1)	72.9 (14.1)	<0.001
Female, no. (%)	4123 (47.7)	1280 (47.4)	0.81
Country, no. (%)			<0.001
Norway	5737 (66.4)	2112 (78.1)	
Switzerland	2909 (33.6)	591 (21.9)	
Risk factors, no. (%)			
Diabetes	1247 (15.0)	357 (13.7)	0.12
Atrial fibrillation	2116 (25.1)	603 (23.2)	0.045
Concomitant medication, no. (%)			
Antiplatelets	2705 (32.3)	792 (29.8)	0.017
Antiplatelets			0.059
None	5678 (67.7)	1867 (70.2)	
Single	2371 (28.3)	689 (25.9)	
Dual	330 (3.9)	100 (3.8)	
Triple	4 (0.0)	3 (0.1)	
Antihypertensives	2896 (48.9)	883 (45.6)	0.011
Lipid-lowering drugs	1987 (32.4)	666 (30.6)	0.12
OACs, no. (%)	2098 (24.3)	598 (22.1)	0.022
OAC status, no. (%)			0.071
No OACs	6548 (75.7)	2105 (77.9)	
VKAs	1163 (13.5)	328 (12.1)	
DOACs	935 (10.8)	270 (10.0)	
DOAC type, no. (%)			0.015
None	7711 (90.5)	2433 (92.2)	
Apixaban	349 (4.1)	106 (4.0)	
Edoxaban	8 (0.1)	4 (0.2)	
Rivaroxaban	413 (4.8)	90 (3.4)	
Dabigatran	43 (0.5)	6 (0.2)	
Medical history, no. (%)			
History of ischaemic stroke	1273 (15.0)	399 (15.3)	0.71
History of ICH	869 (10.2)	267 (10.2)	0.99
History of coronary heart disease/myocardial infarction	792 (13.3)	281 (12.5)	0.34
Pre-admission mRS, no. (%)			0.17
No symptoms at all	2930 (50.1)	1093 (53.0)	
No significant disability	1019 (17.4)	329 (16.0)	
Slight disability	814 (13.9)	252 (12.2)	
Moderate disability	667 (11.4)	241 (11.7)	
Moderately severe disability	339 (5.8)	120 (5.8)	
Severe disability	75 (1.3)	27 (1.3)	
Clinical presentation on admission			
NIHSS on admission, median (IQR)	7.0 (2.0–16.0)	6.0 (2.0–13.0)	<0.001
Level of consciousness at admission, no. (%)			<0.001
Alert†	5444 (64.1)	1825 (68.7)	
Drowsy‡	1766 (20.8)	598 (22.5)	

Continued

Table 3 Continued

Characteristic	mRS available (n=8646)	mRS missing (n=2703)	P value*
Comatose§	1289 (15.2)	233 (8.8)	
Treating hospital level, no. (%)			
Treatment at stroke center¶	4043 (46.8)	696 (25.7)	<0.001
Local management, no. (%)			0.17
Treatment at high-dependency unit**	5948 (69.0)	1819 (67.6)	

*Univariate comparison between available mRS and missing mRS.
†GCS 13–15 (SSR) or patient is drowsy, responds by light stimulation (NSR).
‡GCS 9–12 (SSR) or patient is drowsy, reacts only with vigorous repetitive stimulation (NSR).
§GCS 3–8 (SSR) or patient does not respond, or just with non-targeted movement (NSR).
¶Fully equipped tertiary level of care hospital including neurosurgery.
**High-dependency stroke unit/IMC/ICU.
DOACs, direct oral anticoagulants; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; ICU, intensive care unit; IMC, intermediate care; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NSR, Norwegian Stroke Registry; OACs, oral anticoagulants; SSR, Swiss Stroke Registry; VKAs, Vitamin K antagonists.

compared with patients without prior anticoagulation. This is in line with previous studies, reporting a higher risk profile at ICH onset among patients with prior anticoagulation therapy.[6 8 13] Our study is the first to report pre-ICH disability status.[6 14] We found no difference in stroke severity on admission between the three groups, which is in line with prior findings[6] but in contrast to data from the US-based registry[8] and national stroke registry from Sweden.[13] However, neither of the studies adjusted for confounders. Further, we found no difference in stroke severity on admission comparing DOAC to VKA-associated ICH only, a finding in contrast to a prior study.[15]

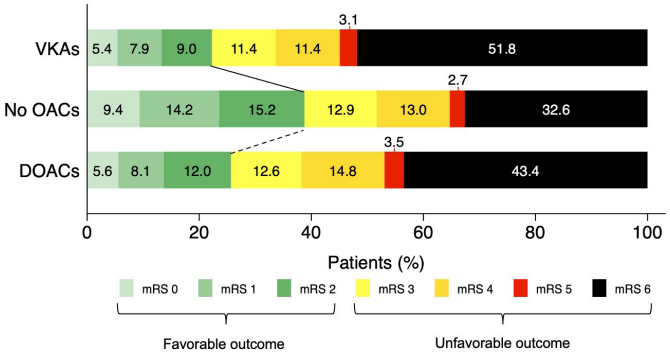

Figure 3 Functional outcome at 3 months using modified Rankin Scale (mRS) according to prior anticoagulation therapy as compared with no prior anticoagulation in patients with intracerebral haemorrhage. Combined data from Switzerland and Norway. Figure includes only sites with ≥70% availability of mRS at 3 months (49 hospitals; n=6903). Overall, prior VKA therapy (aOR, 0.64; 95% CI, 0.49 to 0.84; indicated by the continuous line) and prior DOAC therapy (aOR, 0.64; 95% CI, 0.47 to 0.87; indicated by the dashed line) were independently associated with lower odds of favourable outcome compared with patients without anticoagulation. DOACs, direct oral anticoagulants; OACs, oral anticoagulants; VKAs, Vitamin K antagonists.

Our study is the largest study reporting 3-month functional outcome in patients with ICH according to prior anticoagulation therapy. It overcomes limitations of prior studies either comparing only patients on anticoagulants (ie, VKA vs DOAC) without a reference group of non-anticoagulated patients,[5 7 15–17] limiting outcomes to hospital discharge[6] or lacking to differentiate between VKA and DOAC.[13] We found that prior VKA and prior DOAC therapy were associated with lower odds of favourable outcome compared to no prior anticoagulation, a finding in contrast to prior results.[6 8] In line with previous studies,[7 15 17] comparing DOAC to VKA-associated ICH only, we found no difference in functional outcome at 3 months.

Overall, favourable functional outcome across all three groups (mRS 0–2 at 3 months: 22.3% in VKAs, 25.7% in DOACs and 38.8% in no OACs) was better than in the national stroke registry study from Sweden[13] (mRS 0–2 at 3 months: 15.7% in OACs and 27.7% in no antithrombotics) and US-based registry study[8] (mRS 0–2 at discharge: 9.0% in VKAs, 10.8% in factor Xa inhibitors and 15.3% in no OACs). A potential explanation is a broad access to certificated stroke centres and treatment at high-dependency units in our study (41.8% and 68.7%) and thus access to high-level of acute management of ICH.

Our study is the largest contemporary study reporting mortality rates at 3 months for patients with ICH according to prior anticoagulant therapy. A recent meta-analysis consistently found increased rates of mortality in patients with VKA-associated ICH but data on DOAC-associated ICH were lacking.[2] We found that both VKA and DOAC-associated ICH were associated with higher mortality at 3 months compared to no prior anticoagulation. For DOAC-associated ICH, prior studies were restricted to in-hospital mortality[6 8] or lacked comparison with non-anticoagulated patients.[5 17] This is in line with the US-based registry study[6 8] reported hospital-discharge outcomes.

Comparing DOAC to VKA-associated ICH only, we found that prior DOAC therapy was related with lower mortality at 3 months compared with prior VKA therapy. This is in contrast to two previous studies[5 17] which found no difference. Our results are in contrast to mortality outcomes of patients suffering ICH during the pivotal phase-3 randomised controlled trials on DOACs, where no mortality difference with VKA-associated ICH was found.[18–21] Although outcomes of incident ICH occurring in patients randomised to VKA or DOAC minimise confounding, it is unclear how selection bias and acute management influenced outcomes of the aforementioned randomised controlled trials. Treatment of patients who had ICH on experimental anticoagulants (ie, DOACs in phase 3 trials before market approval) is likely to be very different from treatment of ICH in patients with DOAC in our study, which was conducted 5–10 years after market approval with guidelines and treatment experience for this type of ICH. In addition, general management of ICH (ie, blood pressure control[22]) has changed significantly since the time of the phase 3 trials.

During the study period, the specific reversal agent for factor Xa inhibitor-associated ICH, andexanet alfa, was neither available in Switzerland nor Norway. Treatment with prothrombin complex concentrate for VKA-associated ICH was standard of care in both countries and was recommended for DOAC-associated ICH by guidelines. Outcomes of factor Xa inhibitor-associated ICH may improve in the future with specific reversal agents proved to be superior to current non-specific treatment options (NCT03661528).

Worth noting is that even with almost a doubled total daily dose sale of OAC in Norway during the period of the study of 72.31%[23] there has been no increase in number or proportion of OAC-associated ICH.

Strengths and limitations

Our study has several strengths. First, it comprises a binational dataset including 76 hospitals and over 11 000 patients overcoming limitations from previous smaller studies. This is an argument for generalisability in Western (European) countries and healthcare settings. Second, the overall dataset was large and data were collected prospectively using pre-defined variables and follow-ups. This decreases the risk of bias. Third, we included patients without prior anticoagulation therapy as reference group which allows nuanced analysis of outcomes. Fourth, we report 3-month outcome data rather than hospital discharge outcomes, which is more appropriate in patients with ICH. Fifth, our study has a high rate of follow-up completeness with high quality and predefined outcomes. Sixth, we corrected for potential hospital-specific differences using a random effects model and pre-ICH mRS, which is a significant strength compared with prior reports lacking this variable.[6 14] Finally, the large number of cases and the universal healthcare insurances in Switzerland and Norway are strong arguments for an 'unselected' population compared with prior studies conducted in selective healthcare settings with limited access to hospital healthcare for deprived patient groups.

This study has several limitations. First, although data collection was prospective, the analysis was retrospective. Second, due to the limitations of large, national stroke registries, information on haematoma characteristics, indication of antithrombotic therapy and details of treatment was not available and might have confounded the differential effect on outcomes. Third, some co-variables included in the multivariable analysis had a significant amount of missing values. We tried to overcome this limitation by using multiple imputation. Although a few variables had >20% of missing values, these were missing at random and previous research found that in this scenario, multiple imputations is likely to reduce the bias.[24] Fourth, although the overall follow-up rate was good, some patients had missing outcomes. However, the rate of missing 3-month mRS in our study (23.8%) was significantly lower compared with prior studies (eg, 43.7% missing mRS)[6] and the rate of missing information on mortality was minimal. Therefore we refrained from using multiple imputation to impute outcomes. Given a favourable risk profile in patients with missing outcomes, it is possible that we underestimate functional independence at 3 months. Fifth, our study provided data from two Western countries with highly developed universal healthcare systems. While the proportion of ICH might be lower compared with low-income countries due to higher levels of awareness and control of hypertension,[1] the risk of anticoagulation-associated ICH is much higher in high-income countries due to ageing population with broad access to antithrombotic therapy for atrial fibrillation, which was the predominate risk factor in our study. Therefore, a generalisation of our findings to the global population and other settings may be limited.

CONCLUSIONS

In conclusion, our study shows that the landscape of anticoagulation-associated ICH changed dramatically during the last years with DOAC-associated ICH largely replacing VKA-associated ICH. However, compared with patients without prior anticoagulation, both prior VKA and DOAC treatment were independently associated with lower odds of favourable outcome and higher mortality at 3 months. Given that the majority of patients in our study used factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) and the specific reversal agent andexanet alfa was not available during the study period, future research needs to focus on specific reversal treatments (ie, andexanet alfa), which have superior hemostatic efficacy. Future research is also needed to determine the individual contribution of anticoagulant activity of DOACs measured with calibrated coagulation assays, haematoma volume and secondary expansion on outcomes to further refine our knowledge on DOAC-associated ICH.

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Contributors BMS, EF, OMR, MBr and DJS designed to current analysis. MK, PM, CC, FM, NP, SR, JN, EC, TK, GK, MBo, SS, M-LM, SW, WJZ, MS, BR, MA, STE, LB and UF made significant contributions to the concept and designed the Swiss Stroke Registry. LB and MK are the coordinators of the Swiss Stroke Registry. ESK, KTL, TBW and OMR made significant contributions to the concept and design of the Norwegian Stroke Registy. BMS, EF, MBG, MBo, AAP, JK, BV and TRM made significant contributions to acquisition and analysis of the data. BMS, MBr and DJS performed the statistical analysis. BMS, EF, OMR and DJS wrote the first version of the manuscript. BMS and DJS drafted the figures. DJS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests MBo: personal fees from AstraZeneca, a company that produces Andexanet alfa (a specific reversal agent for factor Xa-inhibitor-associated ICH, discussed in this study). SW: consultancy fees from Bayer, a company that produces Rivaroxaban (a DOAC discussed in this study). BV: personal fees from Pfizer AG/Bristol-Myers Squibb SA and Bayer AG, producesr of Apixaban and Rivaroxaban, two drugs discussed in this study. DJS: grants from Alexion/AstraZeneca, producer of andexanet alfa discussed in this study. Personal fees from Bayer, producer of Rivaroxaban, discussed in this study. Consultancy fees from VarmX (producer of VarmX, a compound under development for the treatment of FXaI-associated bleeding). All other authors have nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ethics committee in Bern, Switzerland (Project-ID 2019-00689) and Regional Committees for Medical and Health Research Ethics in Norway (Project-ID 2015/2373). Patients were enrolled as part of national stroke registries. Patients were informed about the use of their data for research and had the possibility to opt out.

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