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Original article

Anticoagulation resumption after intracranial hemorrhage in patients treated with VKA and DOACs

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ABSTRACT

Background: Intracranial hemorrhage (ICH) is associated with severe prognosis and recurrent risk. This impacts on the decision to resume anticoagulation in atrial fibrillation (AF) or venous thromboembolism (VTE) patients. Purpose of our study is to evaluate the incidence rate of recurrent ICH in patients with AF or VTE resuming anticoagulation after a first ICH episode.

Methods: We report data of two cohorts of AF or VTE after a first ICH. The Vitamin K antagonist (VKA) cohort (166 patients) derives from CHIRONE Study, the direct oral anticoagulant (DOAC) cohort (178 patients) derives from START2-Register

Results: The clinical characteristics of the two cohort are similar with the exception of more prevalence of history of previous stroke/TIA in DOAC patients with respect to VKA ($p = 0.02$) and serum creatinine levels > 1.5 mg/dL in VKA patients with respect to DOAC($p = 0.0001$). The index ICH was spontaneous in 66.4% and in 33.7% among DOAC and VKAs cohort respectively ($p = 0.0001$). During follow-up, 14 recurrent ICH were recorded; 9 (rate 2.5 × 100 patient-years) in VKA and 5 (rate 1.3 × 100 patient-years) in DOAC (Relative Risk 1.9; 95% CI 0.6–7.4; $p = 0.2$). The univariate logistic regression analysis showed that patients with recurrent ICH were more frequently males, hypertensive, with a history of previous Stroke/TIA and older than patients without recurrence. VKA patients showed a higher risk of recurrence with respect to DOAC patients (OR 1.9;95% CI 0.7–6.7).

Conclusions: A trend toward fewer ICH recurrences was detected among DOACs patients in comparison to the previously reported rate of patients on warfarin.

1. Introduction

Intracranial hemorrhage (ICH) is associated with high mortality and severe functional outcome [1]. ICH is frequently associated to antithrombotic treatment and carries a substantial risk of recurrence. This risk impacts on the decision to resume anticoagulation in patients with atrial fibrillation (AF) or venous thromboembolism (VTE).

The aging of the population in the Western countries causes a

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growing number of patients suffering from AF or VTE, conditions that require long-term anticoagulation. The proposed tools for the stratification of bleeding risk are insufficient to reliably estimate the absolute bleeding rates, [2] and no specific bleeding stratification model has been implemented for ICH. Moreover, risk factors for ischemic stroke are also risk factors for ICH, and the definition of '*shared risk factors*' have been proposed for age, hypertension, diabetes, renal failure, and previous stroke [3] that are associated with both conditions.

When ICH occurs, there is no solid evidence to drive the decision on whether anticoagulation should be resumed or not and the timing for resumption [4,5]. Available evidence only originates from observational studies, which included patients treated with vitamin K antagonists (VKAs) or antiplatelet drugs [6–13]. Presently, few data are available on patients treated with direct oral anticoagulants (DOACs) [14] and indicate a slight reduction in the risk of recurrent ICH, without reaching statistical significance. The lower risk of ICH in patients treated with DOACs compared to that of patients treated with warfarin has been consistently demonstrated in all the registrative studies, both in AF [15]and in VTE patients [16]. Therefore, the role of DOACs in patients who have suffered from ICH appeared widely promising to achieve lower ICH recurrent rates, although no direct evidence of this lower risk of recurrence exists.

The purpose of our study was to evaluate the incidence rate of recurrent ICH in a cohort of patients with AF or VTE who survived after a first episode of ICH and resumed anticoagulation with DOACs. We compared this cohort with a previously described cohort of patients [17] with AF or VTE who started anticoagulation with VKAs after a first episode of ICH.

2. Methods

In the present study we report data of two cohorts of patients who started anticoagulant treatment for atrial AF or VTE after the occurrence of a first ICH. The first cohort is derived from the previously published CHIRONE Study and includes AF and VTE patients on treatment with VKA (VKA cohort), the second cohort was obtained from the START2-Register and includes AF and VTE patients on treatment with DOAC (DOAC cohort).

The Cerebral Haemorrhage in Patients Restarting Oral Anticoagulant Therapy (CHIRONE) Study has been previously published [17]. The study included 267 patients who survived a first ICH and who were on VKA treatment, whatever the clinical indication for the therapy. The study was conducted in 27 Centers affiliated with the Italian Federation of Anticoagulation Clinics. In the CHIRONE Study 90 patients (33.7%) were on warfarin because carriers of prosthetic heart valves, 121 patients (45.3%) for AF, 45 patients (16.8%) for VTE, and 11 patients (4.2%) for other reasons. In this study only the 166 patients of the cohort of the CHIRONE study anticoagulated for AF and VTE were included.

AS previously described, the START2-Register is an observational, multicenter, prospective cohort study that includes patients aged > 18 years, who start anticoagulation therapy, whatever the clinical indication for the therapy, the drug and dosage used [18].

All participating centers are asked to consecutively include patients who start anticoagulant treatment, for any indication and with any available drug. Baseline patient's clinical features are recorded by participants on web based case report forms, detailed methods for enrollment in the study has been previously published [18]. The registry has been approved on October 2011 (N = 142/2010/0/0ss) by the Ethical Committee of the Institution of the Coordinating Member (AziendaOspedaliero-Universitaria, Policlinico S. Orsola-Malpighi, Bologna, Italy), and by all Ethical Committees of participating centers. All patients gave their written informed consent before enrollment. The study is registered in Clinical Trials gov Identifier: NCT02219984; it is ongoing and actively recruiting.

Here we present the results of the cohort of patients included in the START2 Register who started DOAC treatment for AF or for VTE after the occurrence of a first ICH. The patients of this cohort were enrolled in 15 Centres participating in the Registry, 9 of them participated also to the enrollment of the CHIRONE Study. For the purpose of the present analysis, data were collected from July 2013, when dabigatran was firstly marketed in Italy, to July 2019.

For both cohorts the decision about starting anticoagulation after ICH was the responsibility of the referring physician, on the basis of the thromboembolic risk estimate. To evaluate neurologic sequelae of the first ICH episode, modified Rankin Scale (mRS) score was assessed for each patient in both cohorts when anticoagulation was started after index ICH.

The follow-up started when an anticoagulant drug was resumed after the first episode of ICH and ended when a patient stopped being monitored by the Center, or at the occurrence of a recurrent ICH or death. Major bleedings (MB) different from ICH were defined as recommended by the International Society on Thrombosis and Haemostasis [19].

The major endpoint of the study was recurrent ICH during anticoagulant treatment.

2.1. Statistical analysis

Continuous variables are expressed as median with interquartile range (IQR). Categorical variables are expressed as frequencies and percentages. The number of bleeding events was expressed as percentage (with 95% confidence intervals [CI]) and incidence rate, calculated as the number of events per 100 patient/years of observation. Chi-squared test was used to compare proportions. Univariate analysis was used to explore the association among risk factors and recurrent ICH. P value < 0.05 was considered statistically significant. The SPSS software for Windows, version 25 (SPSS Inc.) and Stata, version 14 statistical software package (Stata Corp. College Station, Texas USA) were used for data processing. Anonymized study data can be made available to qualified investigators by contacting the first author

3. Results

We reported data of 344 survivors from ICH included in two cohorts. VKA cohort included 166 patients on oral anticoagulant treatment with warfarin for AF or VTE with a history of previous ICH. DOAC cohort included 178 patients who started oral anticoagulant treatment with one of the four available DOACs for AF or VTE after the occurrence of an episode of ICH. In particular, 48.3% of DOAC patients were treated with apixaban, 25.3% with rivaroxaban, 20.2% with dabigatran and 6.2% with edoxaban; 127 patients (71.3%) received the reduced dosage of the prescribed drug.

Clinical characteristics of patients are reported in Table 1. The two cohorts of patients had a similar median age (76.7 and 76.6 years) and similar gender distribution (males 61.8% and 60.8%, respectively). Similarly, several co-morbidities were equally represented in the two groups. The severity of the neurologic sequelae after the index event, performed by using the mRS, showed that about 60% of patients in the two cohorts had no symptoms or no significant disability (mRS 5 0–1), and patients with more severe neurological sequelae were equally represented in the two cohorts. Instead, the prevalence of history of previous stroke/TIA was 23.6% among DOAC patients and 16.3% in VKA patients. On the contrary, the prevalence of renal insufficiency (serum creatinine >1.5 mg/dL) was 6.7% among DOAC patients and 25.9% among VKA patients.

The index ICH was spontaneous in 66.4% of cases among DOAC cohort and in 33.7% of cases among VKAs cohort. The site of the ICH was similar between the two cohorts (Table 2).

During follow-up, 14 recurrent ICH were recorded; 9 of them (rate 2.5 × 100 patient-years) among AVK patients and 5 (rate 1.3 × 100 patient-years) among DOAC patients. In the VKA cohort, 6 and 3

Table 1
Characteristic of patients enrolled in the two cohort.

	VKA cohort	DOAC cohort	p
N, (%)	166	178	
Males	101 (60.8)	110 (61.8)	
Median age (IQR), years	76.7 (10.0;95.0)	76.6 (70.8;82.0)	
Età > 75 years	99 (59.6)	103 (58.2)	
Follow-up (years)	362	390	
Median follow-up years (range)	1.6 (0.1–10.1)	1.9 (0.1–7.2)	
Indication for OA			
AF	121 (72.9)	123 (69.9)	
VTE	45 (27.1)	53 (30.1)	
Co-morbidities			
Hypertension	135 (81.3)	149 (83.7)	
Diabetes Mellitus	35 (21.2)	34 (19.1)	
Heart failure	21 (13.2)	37 (20.8)	0.04
Previous stroke/TIA	28 (16.3)	42 (23.6)	0.02
Creatinine > 1.5 mg/dl	37 (25.9)	12 (6.7)	0.0001
e-GFR < 30 mL/min	14 (18.4)	7 (3.9)	0.0001
CAD/PAD	33 (21.6)	26 (14.6)	
Cancer	6 (3.7)	9 (5.0)	
Antipletelet therapy	18 (10.8)	20 (11.2)	

VKA = vitamin K antagonist; DOAC = direct oral anticoagulant; TIA = transient ischemic attack.
CAD = coronary artery disease; PAD = peripheral artery disease.

Table 2
Characteristics of index event.

	VKA cohort n, (%)	DOAC cohort n, (%)
Type of index ICH	*163/166*	*152/178*
Spontaneous	55 (33.7)	101 (66.4)*
Traumatic	108 (66.3)	51 (33.6)
Localization	*163/166*	*134/178*
Subdural hematoma	80 (49.1)	46 (34.3)
Subarachnoid	26 (16.0)	18 (13.4)
Intraparenchimal lobar	42 (25.8)	33 (24.6)
Intraparenchimal tipical	15 (9.2)	37 (27.6)
Intraparenchimal all	57 (35.0)	70 (39.3)
Modified Rankin score after the event	*166*	*144/178*
4	12 (7.2)	14 (9.7)
3	14 (8.5)	16 (11.1)
2	34 (20.6)	30 (20.8)
0–1	105 (63.6)	84 (58.4)
Treatment of the cerebral bleeding		
Surgical	19 (11.4)	33 (18.5)
Medical	147 (88.6)	145 (81.5)
Type of drug at the index event		
VKAs	152 (91.6)	77 (43.3)
DOACs	–	18 (10.1)
Antiplatelet	–	11 (6.2)
None	14 (8.4)	39 (21.9)
Unknown	–	33 (18.5)
Type of drug during follow-up		
Apixaban	–	86 (48.3)
Dabigatran	–	36 (20.2)
Edoxaban	–	11 (6.2)
Rivaroxaban	–	45 (25.3)
Warfarin (Target INR 2.5)	166	–
Reduced dosage		
All	–	127 (71.3)
Apixaban	–	63 (73.3)
Dabigatran	–	33 (91.7)
Edoxaban	–	8 (72.7)
Rivaroxaban	–	23 (51.1)

ICH = intracranial hemorrhage; VKA = vitamin K antagonist; DOAC = direct oral anticoagulant.
* $p = 0.001$.

recurrent ICH occurred in patients whose index ICH was spontaneous or post-traumatic, respectively (Table 3). In DOAC cohort, all the recurrent ICH were recorded in patients with spontaneous index ICH. However, the recurrent rate was not statistically different between the two cohorts (Relative Risk 1.9; 95% CI 0.6–7.4; $p = 0.2$). Three out of the five patients who had recurrence in the DOAC cohort were on treatment with full dose DOAC.

Table 3
Characteristics of ICH recurrences.

	VKA cohort	DOAC cohort
Recurrent ICH (rate x100 pt-yrs)	9 (2.47)	5 (1.3)
Males, n (%)	7 (77.8)	3 (60.0)
Median Age (range) years	74 (56–85)	76.7 (60–89)
Indication for OA		
AF	6	4
VTE	3	1
Median Time from First ICH, years (range)	3.5 (0.1–32.5)	2.9 (2.5–4.3)
Type of first ICH		
Spontaneous	6 (66%)	5 (100%)
Site of recurrent ICH		
Intraparenchimal	3	2
Subdural hematoma	3	1
Subarachnoid	2	0
Unknown	1	2
Modified Rankin score after recurrent ICH		
5	3	1
4	1	0
3	0	1
2	2	1
1–0	3	2
Fatal events (rate x100 pt-yrs)	3 (0.82)	1 (0.26)
Type of AO drug		
Apixaban	–	3
Dabigatran	–	0
Edoxaban	–	0
Rivaroxaban	–	2
Warfarin	9	–
Death, n(%)	23 (13.8)	21 (11.8)

ICH = intracranial hemorrhage; OA = oral anticoagulation.

DOAC patients showed 8 major bleedings not cerebral (5 gastrointestinal) (rate 3.4 × 100 patient-years), instead no other major bleeding events occurred among VKA patients.

Overall mortality was 13.8% in VKA cohort and 11.8% in DOAC cohort (Table 3)

To evaluate the risk factors associated with recurrent ICH, a univariate logistic regression analysis was performed including both cohorts (Table 4). Patients with recurrent ICH were more frequently males, hypertensive, with a history of previous Stroke/TIA and older

Table 4
Risk factors associated with recurrent ICH calculated in the whole population: univariate analysis.

	Patients without recurrence	Patienst with recurrence	OR	95% CI	p
N	330	14			
Male sex, N(%)	201 (60.9)	10 (71.4)	1.6	0.5–5.2	0.4
Patients with Age >75 y	192 (58.4)	10 (71.4)	1.8	0.5–5.8	0.3
Previous Stroke or TIA	66 (22.1)	4 (28.6)	1.4	0.4–4.6	0.6
Spontaneous ICH	147 (48.8)	9 (64.3)	1.9	0.6–5.7	0.3
Hypertension	271 (82.1)	13 (92.9)	2.6	0.3–20.9	0.3
Diabetes Mellitus	68 (21.1)	1 (7.7)	0.3	0.04–2.5	0.3
Heart Failure	57 (18.0)	1 (7.7)	0.4	0.05–3.0	0.4
CAD/PAD	56 (18.3)	3(23.1)	1.3	0.4–5.0	0.7
Active cancer	5 (1.5)	1 (7.7)	1.7	0.5–5.6	0.4
Serum creatinine > 1.5	47 (15.2)	2 (16.7)	1.1	0.2–5.2	0.9
Clearance < 30 mL/min	20 (8.2)	1(7.7)	1.6	0.2–13.7	0.7
DOAC treatment	173(52.4)	5(35.7)	1.9	0.7–6.0	0.2

ICH = intracranial hemorrhage; CAD = coronary artery disease; PAD = peripheral artery disease.

than patients without recurrence. However, none of these differences reached statistical significance. Patients treated with VKA showed a higher risk of recurrence with respect to patients treated with DOAC (OR 1.9)(95% CI 0.7–6.7; $p = 0.2$).

4. Discussion

In this study we report data of AF and VTE patients survived to a first episode of ICH who started or resume an anticoagulant drug after the hemorrhagic event. In particular, two cohorts of patients have been described, the first treated with VKA (in part previously described in the CHIRONE Study) and the second with DOACs. The main finding of our study is the lower rate of recurrent ICH among patients on DOACs with respect to patients on VKAs.To date only one study have been published reporting data on ICH recurrence in patients treated with DOACs [14]. However, this study was conducted on administrative data and no information were available on the quality of VKA treatment. Our findings are in agreement with the results of this study, confirming a comparable reduction of ICH recurrent risk.

The favorable safety profile of DOACs is well supported by clinical evidence and by guidelines for the treatment of both patients with AF [20] and VTE [21]. The lower risk of ICH in patients on treatment with DOACs compared to that of patients treated with warfarin has been widely demonstrated in all the registrative studies, both in AF [15] and in VTE patients [16]. Therefore, the role of DOACs in these patients appeared widely promising, even in the absence of direct evidence.

The resumption of anticoagulation is a frequent clinical challenge in routine practice and information on the risk of recurrence with and without antithrombotic treatment is still a controversial issue. Several studies reported data on the risk of recurrence during anticoagulant treatment [6–13].

In our study, the main difference between the two cohorts was the higher rate of spontaneous index ICH among DOAC patients in comparison to VKA patients. The present is an observational study and the decision about starting anticoagulation after ICH was the responsibility of the referring physician, on the basis of the thromboembolic and bleeding risk estimate. In our study, the index ICH event was spontaneous in more than 60% of patients in the DOAC cohort, in comparison to only 30% of the VKA cohort. The fear of ICH recurrence is higher in spontaneous ICH in comparison to patients who suffered from post-traumatic hemorrhage. Our findings could be related to a higher confidence of physicians on a lower cerebral bleeding risk of DOACs, leading to more frequent prescription of these in patients suffering from spontaneous ICH, nevertheless the scant information available. It should be noted that 9/15 (60%) Centres participating in the DOAC cohort have already participated to CHIRONE Study.

4.1. Limitations and strength

This study has a significant limitation due to the observational design, leading to the selection of patients enrolled. Our patients were all survivors of a first ICH for whom the decision to start anticoagulation after ICH was taken. Therefore, no information on patients judged to be at very high bleeding risk or treated with antiplatelet drugs were recorded, and probably patients with severe neurologic sequelae were not included in the study. As a matter of fact, our patients had low mRS scores in more than 60% of cases, and only few patients had severe neurologic impairment. The second limitation is due to the low number of recurrent ICH recorded in our study. However, patients who restarted anticoagulation after ICH are rare and few data are available on this matter.

The strength of our study is the prospective and multicenter design, with long follow-up. Moreover, no patients were lost to follow-up. The follow-up started at the beginning of anticoagulation and periodic clinical evaluation have been performed. The information related to the acute phase of the index ICH have been derived from neurological hospital records and reported in the case report form at the beginning of follow-up by the physician of the center.

4.2. Conclusion

In conclusion, a trend toward fewer ICH recurrences was detected among patients who resumed anticoagulation with DOACs after intracranial hemorrhage in comparison to the previously reported rate of patients treated with warfarin. The results of ongoing randomized clinical trials will provide more reliable data on this issue.

Ethics approval

Institutional Review Boards of the participating centres.

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

List of participating centers

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CRediT authorship contribution statement

Daniela Poli: Conceptualization, Formal analysis, Writing - original draft. **Emilia Antonucci:** Formal analysis, Writing - original draft. **Elisa Vignini:** Data curation. **Lucia Martinese:** Data curation. **Sophie Testa:** Data curation. **Paolo Simioni:** Data curation. **Vittorio Pengo:** Writing - review & editing. **Pasquale Pignatelli:** Data curation. **Anna Falanga:** Data curation. **Lucilla Masciocco:** Data curation. **Doris Barcellona:** Data curation. **Antonio Ciampa:** Data curation. **Paolo Chiarugi:** Data curation. **Carmelo Paparo:** Data curation. **Walter Ageno:** Writing - review & editing. **Gualtiero Palareti:** Writing - review & editing.

Declaration of Competing Interest

None declared

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