Spontaneous Intracranial Hemorrhage and Oral Anticoagulation: A Retrospective Study

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Abstract

Background: Canadian data on intracranial hemorrhage (ICH) associated with oral anticoagulation is limited.
Objectives: Primary study outcomes were baseline hematoma volumes and in-hospital mortality in patients with ICH associated with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs). Secondary outcomes included the use of four-factor prothrombin complex concentrate (4f-PCC).
Methods: Retrospective cohort study of patients with ICH associated with oral anticoagulation in three tertiary care hospitals in Montreal, Canada, between 2011 and 2018.
Results: Twenty-nine patients were receiving DOACs and 114 patients were under VKAs. Median baseline hematoma volumes were similar, 14.8 ml [5.7–42.8] in the DOAC group and 15.6 ml [5.9–38.1] in the VKA group ($p = 0.91$). In-hospital mortality rate was 34.5% in the DOAC group and 48.2% in the VKA group ($p = 0.26$). Only 17 patients (58.6%) in the DOAC group received 4f-PCC.
Conclusion: Our study did not demonstrate significant differences in outcomes of ICH associated with DOACs versus VKAs. Management approaches were variable.

Résumé

Contexte: Il existe peu de données canadiennes sur l'hémorragie intracrânienne (HIC) associée à la prise d'anticoagulants par voie orale.

Objectifs: Les critères d'évaluation principaux de l'étude sont le volume initial de l'hématome et la mortalité à l'hôpital chez des patients présentant une HIC associée à la prise d'anticoagulants oraux directs (AOD) par rapport à la prise d'antagonistes de la vitamine K (AVK). Les critères d'évaluation secondaires comprennent l'utilisation d'un concentré de complexe prothrombique à quatre facteurs (4f-PCC pour *four-factor prothrombin complex concentrate*).
Méthodologie: Étude de cohorte rétrospective portant sur des patients présentant une HIC associée à la prise d'anticoagulants oraux dans trois hôpitaux de soins tertiaires de Montréal (Canada) entre 2011 et 2018.
Résultats: Au total, 29 patients prenaient des AOD et 114 des AVK. Les volumes médians des hématomes au départ sont semblables, soit de 14,8 ml (de 5,7 à 42,8) dans le groupe des AOD et de 15,6 ml (de 5,9 à 38,1) dans le groupe des AVK ($p = 0,91$). Le taux de mortalité à l'hôpital est de 34,5 % pour le groupe des AOD et de 48,2 % pour celui des AVK ($p = 0,26$). Seuls 17 patients (58,6 %) du groupe des AOD ont reçu le 4f-PCC.
Conclusion: Notre étude ne montre aucune différence importante dans les résultats concernant l'HIC associée à la prise d'AOD par rapport à la prise d'AVK. Les méthodes de prise en charge sont variables.

Keywords: Intracranial hemorrhage; cerebral hemorrhage; warfarin; antithrombins, factor Xa inhibitors

Introduction

Intracranial hemorrhage (ICH) constitutes a rare but feared complication of oral anticoagulation. A recent meta-analysis confirmed worsened ICH outcomes in anticoagulated patients noting higher hematoma volumes (mean difference of 9,66 ml), increased risk of hematoma expansion (OR 2.96), and higher in-hospital mortality rate (32.8% versus 22.4%) in patients with intracerebral hemorrhage associated with the use of vitamin K antagonists (VKAs).[1]

Direct oral anticoagulants (DOACs) are now the preferred agents for the treatment of venous thromboembolism (VTE) and stroke prevention in atrial fibrillation (AF).[2,3] These agents offer similar efficacy and improved safety compared to VKAs.[4,5] In a meta-analysis evaluating four randomized controlled trials (RCTs), DOACs were associated with a 50% lower risk of ICH than VKAs in patients anticoagulated for AF. The reported incidence of ICH ranged from 0.1% to 0.2% in patients under DOACs and from 0.3% to 0.6% in patients receiving VKAs.[5] Emerging data from animal models and small observational studies suggest more favorable radiological presentations while data from two large observational studies suggest better neurological outcomes and lower mortality in patients with ICH associated with DOACs compared to VKAs.[6–10]

Blood pressure control and restoration of hemostasis are the cornerstones of the management of ICH. With observational data supporting its use, four-factor prothrombin complex concentrate (4f-PCC) was recommended by expert guidelines for restoration of hemostasis in patients with ICH associated with DOACs.[11] Idarucizumab, a specific reversal agent for dabigatran, was approved in Canada in 2016 while andexanet alfa has been approved for reversal of rivaroxaban and apixaban in the United States since 2018 but is not yet available in Canada.[12,13] Current guidelines provide limited guidance on the preference of either 4f-PCC or specific reversal agents for the restoration of hemostasis in patients with ICH.[14,15]

Data from stroke registries suggest a decreasing mortality rate associated with ICH over the years in Canada and an increasing need for inpatient and outpatient support.[16–18] Canadian data on ICH associated with oral anticoagulation is limited. Oral anticoagulation was associated with increased in-hospital mortality and one-year mortality in a cohort of patients with ICH from Ontario.[19] Therefore, with a growing number of patients requiring oral anticoagulation and increasing use of DOACs, along with possible incomplete knowledge of clinicians, our goal was to describe the clinical experience with oral anticoagulant-associated ICH.[20,21] More specifically, we aimed to compare radiological and clinical outcomes and management strategies of spontaneous ICH associated with DOACs versus VKAs, as observed in the first years following commercialization of DOACs in Canada.

Methods

Study design

We conducted a retrospective longitudinal cohort study in three tertiary care hospitals in Montreal, Canada: Centre

Hospitalier de l'Université de Montréal (CHUM), McGill University Health Center (MUHC) and Hôpital du Sacré-Coeur de Montréal (HSCM) between January 1st, 2011 and June 30th, 2018. The research protocol received multicenter approval from the ethics committee of CHUM and was authorized by the local ethics boards in the other sites. Individual informed consent was deemed not necessary and approval was given to carry out the research on denominalized medical files. Study data were collected and managed using REDCap electronic data capture tools.[22,23]

Population

Patients were retrospectively identified using the World Health Organization International Classification of Diseases (ICD-10) diagnosis codes for a spontaneous ICH and an anticoagulant treatment (D68.3, Z92.1, Y44.2, T45.5).[24] Patients 18 years old and older, treated with a DOAC (apixaban, dabigatran, edoxaban or rivaroxaban) or a VKA (warfarin or acenocoumarol) for VTE or AF with a spontaneous ICH (intraparenchymal, intraventricular or subarachnoid hemorrhage) were included. Patients were excluded if they had either (1) a traumatic cause of the ICH, (2) a subdural hematoma, (3) an epidural hematoma, (4) a hemorrhagic transformation of an ischemic stroke, (5) a mechanical valve, (6) a previous ICH under VKA, or if there was a (7) classification error or (8) missing documents. In addition, we opted to exclude patients with mechanical heart valves as DOACs are not approved for use in this indication, and the target international normalized ratio (INR) with warfarin is usually higher in these patients.

Outcome Measures

Primary outcome measures included: baseline hematoma volumes (ml) for patients with intraparenchymal hemorrhage (IPH), combined baseline hemorrhage volumes (mL) for patients with IPH and intraventricular hemorrhage (IVH) and in-hospital mortality.

Secondary outcome measures included: significant hematoma expansion (defined as either absolute or relative IPH expansion of ≥ 6 ml or ≥ 33% respectively or IVH progression of ≥ 1 ml on the first available follow-up scan),[25,26] modified Rankin Scale (mRS) score at discharge (range 0 [no symptoms] to 6 [death]), survival at 3 months and one year and use and dose of 4f-PCC if administered.

Imaging Interpretation and Clinical Data Collection

ICH was diagnosed with non-contrast computed tomography (NCCT). NCCT images from 2 out of 3 centers (blinded for review) were available for analysis (CHUM and HSCM). The volume of IPH and associated IVH, if applicable, were quantified by manual segmentation using the 3-D Slicer Software version 4.10 (slicer.org).[27] Subarachnoid hemorrhage (SAH) was not segmented, given its low prevalence and inherent technical difficulties associated with accurate segmentation. Segmentations were performed by a medical student (T.C.) and a radiology resident (M.D.A), with all cases subsequently reviewed by a board-certified neuroradiologist with 7 years of experience (L.L.G). We decided not to restrict the time interval between the first available and follow-up computed tomography to 72 hours, as recently recommended, to capture the largest possible number of patients.[25]

Clinical data were obtained from medical records review. Three trained investigators (A.A., J.S.D. and A.R.) collected data using a previously pilot-tested (10% of cases) collection form. A sample of 30% of patients' data collection forms were reviewed for completeness by senior investigators (A.B., Z.T.).

Data Analysis

Descriptive statistics were calculated for all variables as pre-specified. Continuous variables are presented as means with standard deviations (SD) or medians with interquartile range (IQR) as appropriate. Categorical variables are presented as percentages. Comparisons of hemorrhage volumes (as continuous variables) were performed using the Mann-Whitney U and Fisher exact tests for dichotomous classes of expansion. Mortality risk was evaluated through unadjusted odds ratios (ORs). A sensitivity analysis excluding patients with CrCl < 30 mL/min was planned to reduce confounding by indication for the mortality analysis. Overall distribution difference of mRS score was assessed using the χ^2 statistic. No adjustment for missing data was performed. Statistical analyses were performed by independent statisticians from the CITADEL team at CHUM and by the authors using R v4.03 (including the epiR and irr libraries).

Results

Baseline Characteristics

A total of 431 patients were screened for inclusion, of whom 143 patients were included in the study; 114 on VKAs and 29 on DOACs (14 on apixaban, 12 on rivaroxaban and 3 on dabigatran) (Figure 1). One hundred and fifteen (80.4%) patients had IPH, 23 (16.1%) had isolated SAH, and 5 (3.5%)

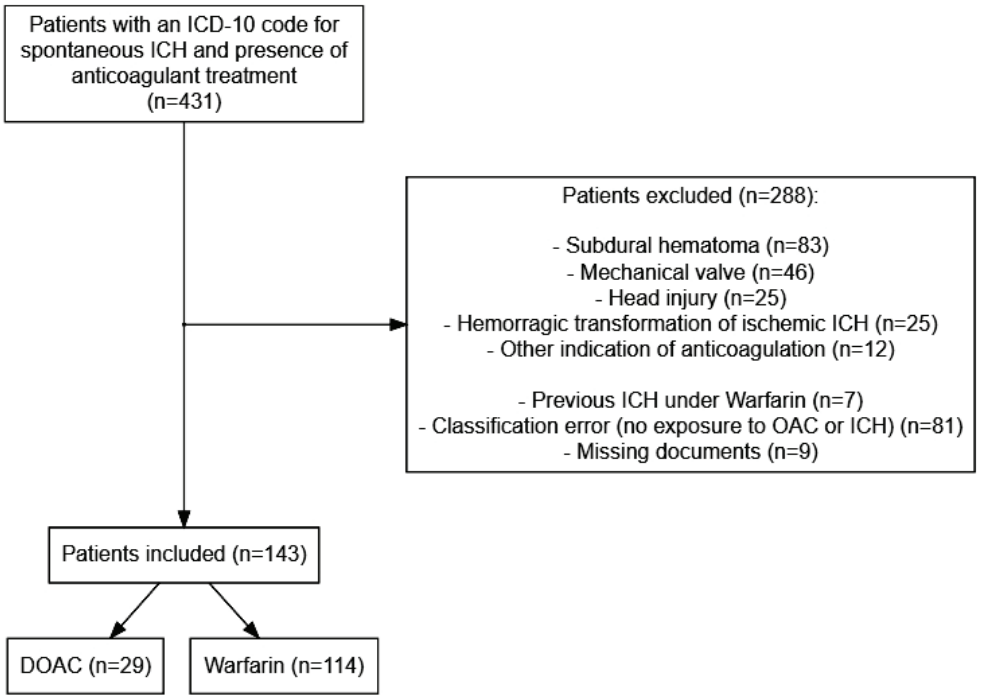

Figure 1. Patient enrollment.

had isolated IVH. Among the patients with IPH, 93 (80.9%) received VKAs and 22 (19,1%) received DOACs. The characteristics of the patients are shown in Table 1. Patients were more frequently male (60.8%) and slightly younger in the DOAC group compared to the VKA group (mean [SD] age, 73.6 [10.7] years versus 76.8 [10.8] years, respectively). The majority of patients were treated for AF (87.4%). Patients in the DOAC group seemed to present fewer comorbidities. There were also fewer patients with concomitant antiplatelet treatment in the DOAC group (17.2%) than in the VKA group (27.2%).

Initial Hematoma Size and Hematoma Expansion

Imaging data of 83 of 115 patients with IPH was available for analysis, 15 receiving DOACs and 68 receiving VKAs. The radiological analyses were performed on this subgroup of patients. Fifty-seven patients had a follow-up CT (including 10 receiving DOACs and 47 receiving VKAs). Median baseline hematoma volumes were similar but more extreme values of initial hematoma volumes and expansion were observed in the VKA group (Table 2, Figures 2, 3, 4, and 5). The proportion of patients with significant hematoma expansion was 40% in both groups (Table 2, Figure 3). Eighteen patients had delayed presentations > 24 hours after time last seen normal (4 in the DOAC group, 14 in the VKA group, range from 27 to 358 hours). The relation between IPH volume and the time interval between the first and follow-up CTs is depicted in Figure 4.

Prognosis and Mortality

The unadjusted in-hospital mortality rate was 34.5% in the DOAC group and 48.2% in the VKA group (unadjusted OR 0.51, 95% CI 0.20–1.19). Results from the planned sensitivity analysis excluding patients with CrCl < 30 mL/min were similar (OR 0.76, 95% confidence interval 0.27–1.96). Six patients (20.7%) in the DOAC group were classified as having functional independence at discharge (mRS score 0–2) versus 12 patients (10.5%) in the VKA group ($p = 0.25$) (Table 3, Figure 6). Overall mRS score distribution difference between groups was not statistically different (χ^2 of 3.73, $p = 0.71$). There was no difference in survival at 3 months and 1 year (Table 3). The overall mortality rate was 51% at 3 months.

Management

4f-PCC was administered in 17 patients (58.6%) receiving DOACs and 102 patients (89.5%) receiving VKAs, along with vitamin K. No reversal agent was administered in 11 patients (37.9%) receiving DOACs versus 5 patients (4.4%) receiving VKAs. 4f-PCC doses administered varied, the distribution of 4f-PCC doses is shown in Table 4. No patient received a specific reversal agent for DOACs (idarucizumab

Table 1. Demographic and Clinical Characteristics of Patients

	Total (N = 143)	VKA (n = 114)	DOAC (n = 29)
Age, years (mean [SD])	76.2 (10.7)	76.8 (10.8)	73.6 (10.2)
Male (no. [%])	87 (60.8)	67 (58.8)	20 (69.0)
Weight, kg (mean [SD])	79.6 (18.6)	79.4 (18.2)	80.4 (20.2)
Indication for anticoagulation			
Atrial fibrillation (no. [%])	125 (87.4)	99 (86.8)	26 (89.7)
CHADS2 score (mean [SD])	2.4 (1.2)	2.5 (1.1)	1.8 (1.2)
CHADS2 score 0 (no. %)	2 (1.6)	0 (0.0)	2 (7.7)
CHADS2 score 1 (no. %)	21 (16.8)	12 (12.1)	9 (34.6)
CHADS2 score 2 (no. %)	52 (41.6)	44 (44.4)	8 (30.8)
CHADS2 score 3 (no. %)	26 (20.8)	22 (22.2)	4 (15.4)
CHADS2 score 4 (no. %)	18 (14.4)	16 (16.2)	2 (7.7)
CHADS2 score 5 (no. %)	6 (4.8)	5 (5.1)	1 (3.8)
CHADS2 score 6 (no. %)	0 (0)	0 (0)	0 (0)
CHA2DS2-VASc score (mean [SD])	4.2 (1.5)	4.4 (1.3)	3.4 (1.6)
Pulmonary embolism or deep vein thrombosis (no. [%])	17 (11.9)	14 (12.3)	3 (10.3)
Comorbidities			
History of stroke or TIA (no. [%])	34 (23.8)	29 (25.4)	5 (17.2)
Hypertension (no. [%])	120 (83.9)	98 (86.0)	22 (75.9)
Diabetes (no. [%])	50 (35.0)	40 (35.1)	10 (34.5)
CrCl, mL/min (Cockcroft-Gault) (median [IQR])	76.8 [52.3–92.4]	74.4 [50.4–87.3]	84.5 [71.7–98.7]
Concomitant antiplatelet use (no. [%])	36 (25.2)	31 (27.2)	5 (17.2)
Single antiplatelet therapy (no. [%])	32 (22.4)	28 (24.6)	4 (13.8)
Dual antiplatelet therapy (no. [%])	4 (2.8)	3 (2.6)	1 (3.4)

Table 2. Radiological Intraparenchymal Hematoma (IPH) and Associated Intraventricular Hemorrhage (IVH) Presentation and Outcomes

All patients	VKA (n = 68)	DOAC (n = 15)	p-value
Baseline IPH volume, ml (median [IQR])	15.6 [5.9–38.1]	14.8 [5.7–42.8]	0.91
Baseline IPH and IVH combined volume, ml (median [IQR])	21.0 [8.7–52.9]	22.9 [7.2–48.0]	0.94
Patients with available CT follow-up	**VKA (n = 47)**	**DOAC (n = 10)**	
Time interval from symptom onset to baseline head CT, hours (median [IQR])	3.8 [1.6–17.5]	7.8 [1.9–23.5]	0.54
Time interval from baseline CT to follow-up CT, hours (median [IQR])	19.8 [13.7–39.2]	15.5 [9.6–19.4]	0.24
Absolute IPH expansion, mL (median [IQR])	0.9 [–0.1–9.1]	1.5 [–0.5–16.5]	0.91
Relative IPH expansion, % (median [IQR])	15.2 [–4.0–82.9]	38.0 [–6.6–86.9]	0.94
Absolute IVH expansion, mL (median [IQR])	1.8 [0.0–3.1]	0.2 [–11.0–9.6]	0.84
Relative IVH expansion, % (median [IQR])	14.7 [0.5–46.5]	7.1 [–27.1–118.3]	0.95
Patients with hematoma expansion (IPH alone), (no. %)	15 (31.9)	4 (40.0)	0.72
Patients with hematoma expansion (combined ICH and IVH), (no. %)	19 (40.4)	4 (40.0)	1.00
Patients with new IVH on follow-up CT, (%)	6 (12.8)	1 (10.0)	1.00

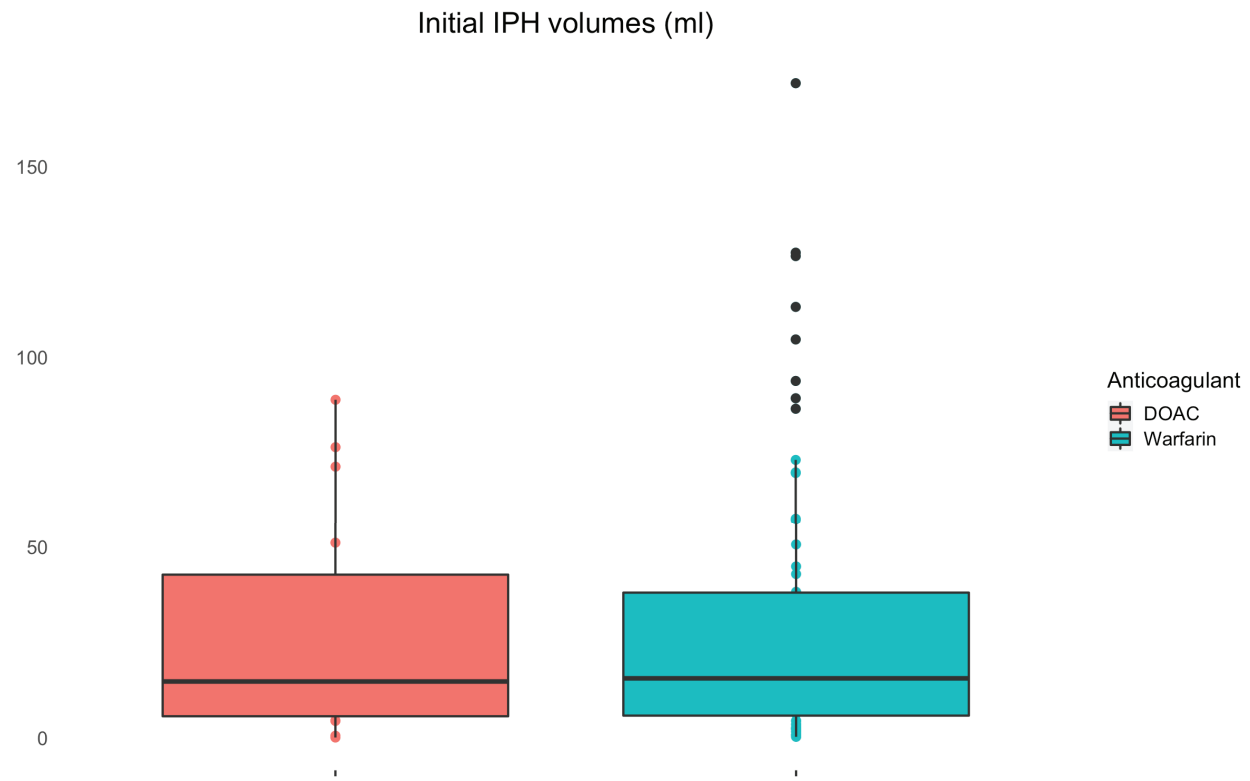

Figure 2. Baseline hematoma volumes.

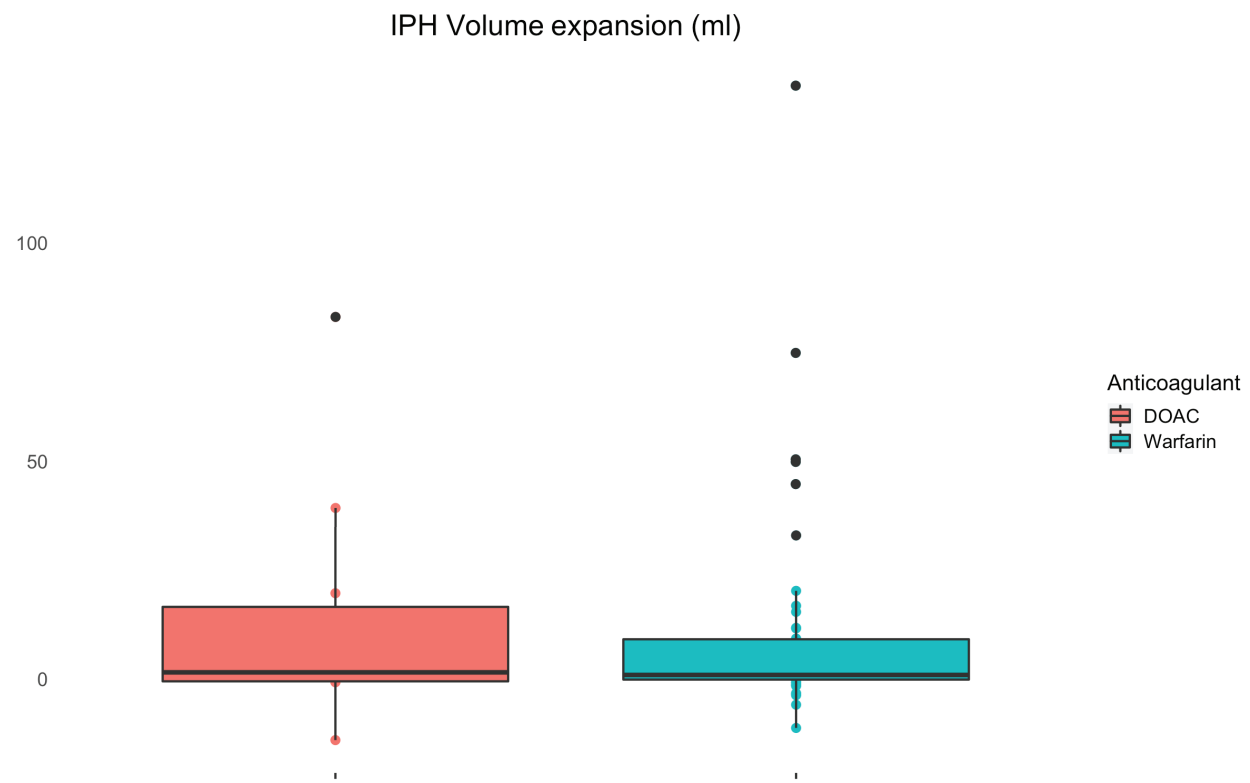

Figure 3. Hematoma expansion.

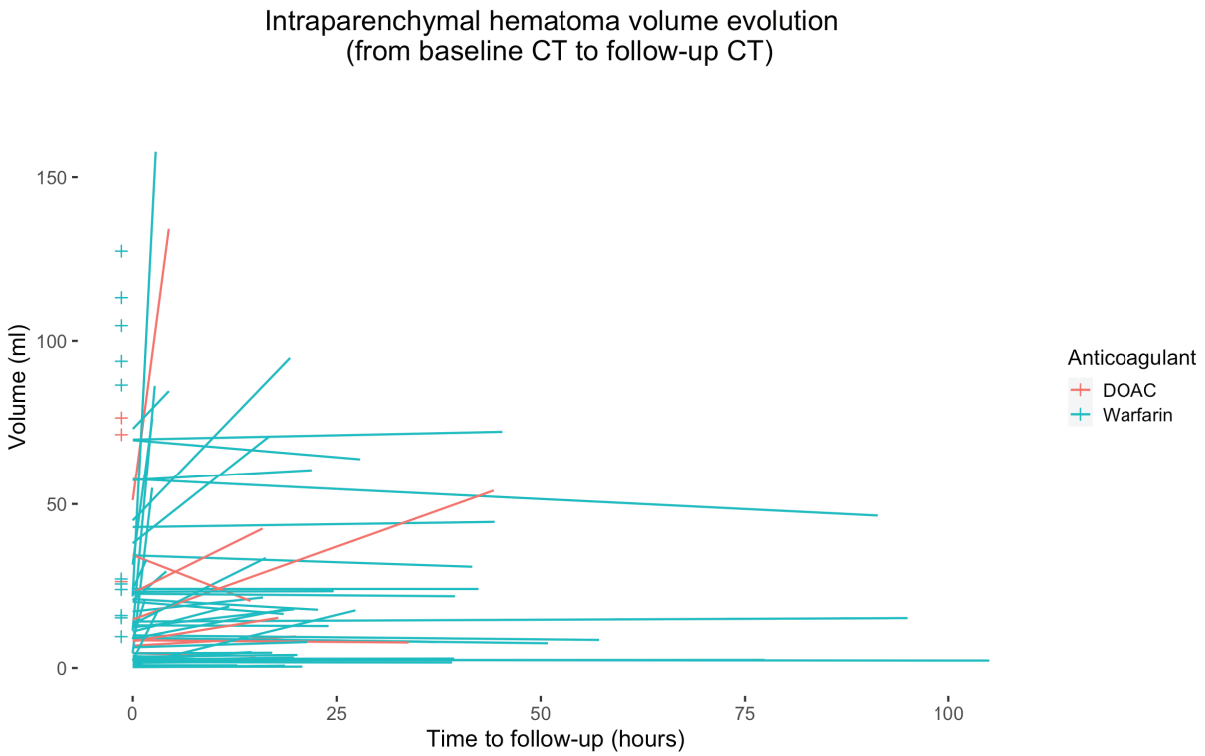

Figure 4. Time course of intraparenchymal hematoma volume for each patient between the baseline (t = 0) and follow-up CTs. Patients with mortality before follow-up CT have baseline IPH volumes indicated with a plus sign to the left of t = 0.

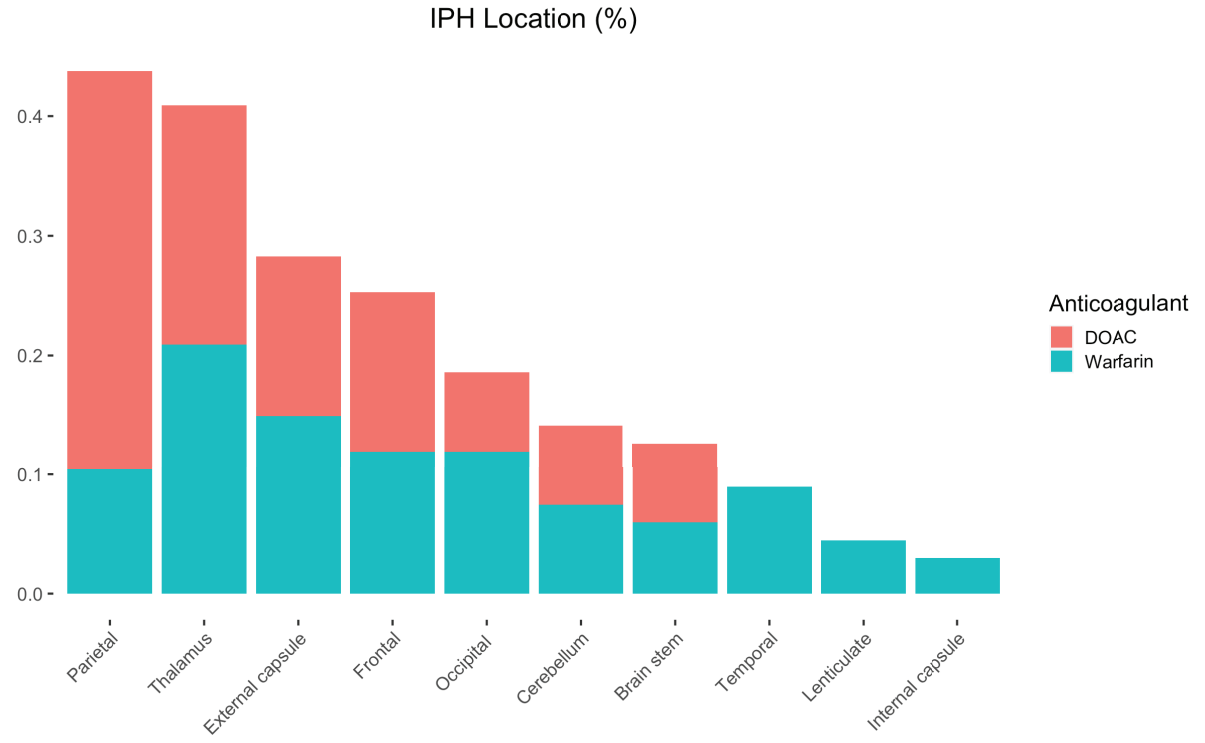

Figure 5. Location of hematomas according to the type of anticoagulation.

Table 3. Clinical Presentation and Outcomes

	Total (N = 143)	VKA (n = 114)	DOAC (n = 29)	p value
Initial Glasgow coma scale score (mean [SD])	12.9 (3.2)	12.8 (3.3)	13.1 (3.1)	0.72
In-hospital mortality (no. [%])	65 (45.5)	55 (48.2)	10 (34.5)	0.26
Functional independence at discharge mRS 0-2 (no. [%])	18 (12.6)	12 (10.5)	6 (20.7)	0.25
Survival at 90 days (no. [%])	70 (49.0)	56 (49.1)	14 (48.3)	1.00
Survival at one year (no. [%])	62 (43.4)	50 (43.9)	12 (41.4)	0.98

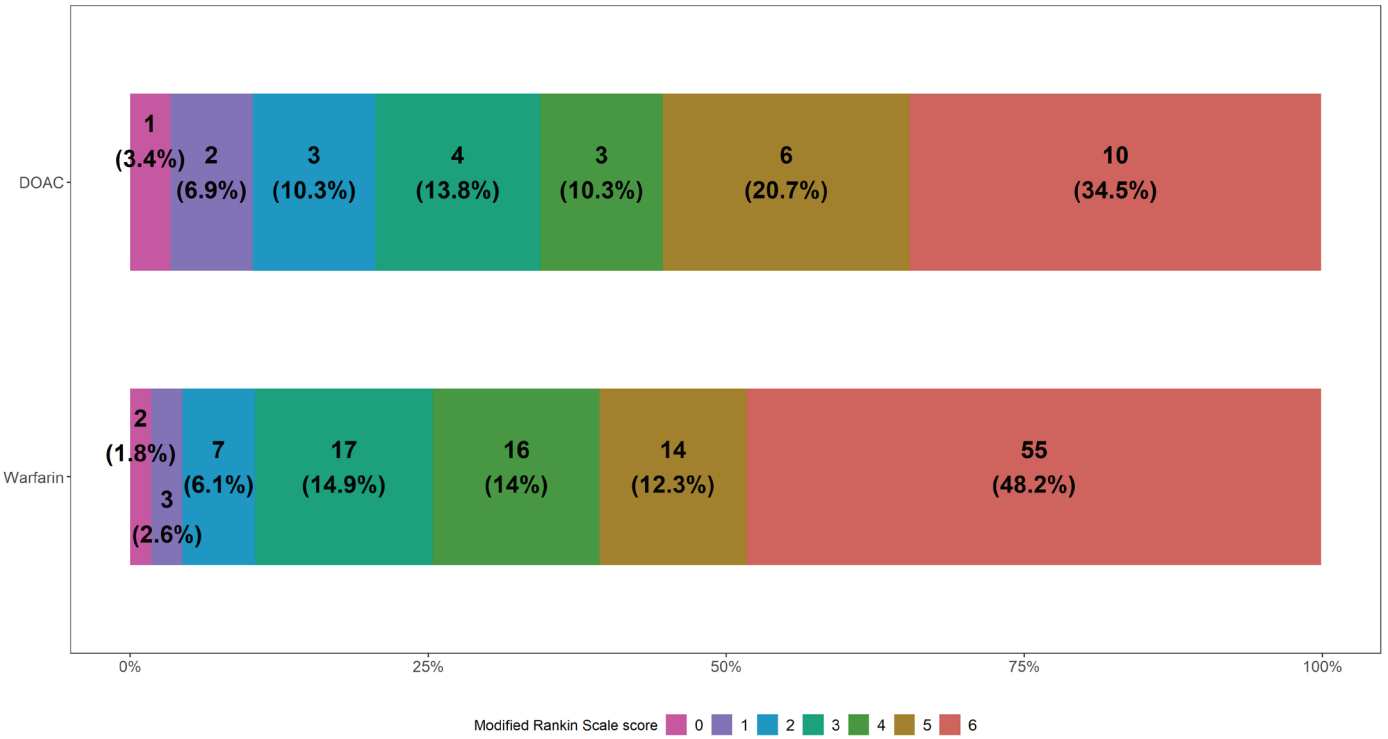

Figure 6. Modified Rankin Scale score at discharge.

or andexanet alfa), as they were unavailable in our centers. Fresh frozen plasma and platelets were administered in some cases (Table 4). A total of 17 patients had their oral anticoagulation resumed during their hospital stay. Eight patients on VKAs at the time of ICH were restarted on a VKA despite having normal renal function.

Discussion

Interpretation of Findings

Our study provides data on radiological and clinical outcomes and management strategies in patients with spontaneous ICH associated with oral anticoagulation in a Canadian setting. We did not demonstrate a significant difference in radiological and clinical outcomes between patients with spontaneous ICH under DOACs versus VKAs. We observed variable approaches to restore hemostasis, especially in patients treated with DOACs.

Comparison to Previous Studies

In our retrospective cohort, no significant difference was observed between DOAC and VKA-related baseline hematoma volumes (IPH alone and combined IPH/IVH). However, more extreme IPH volumes were found in the VKA group. Despite heterogeneity in prior studies, DOACs appear to be associated with lower baseline IPH volumes as summarized by recent meta-analyses.[7,8,28–30] Median IPH volumes in our study were in the range of previous descriptions.[8] No study to date has demonstrated a significant difference in hematoma expansion, consistent with our results.[7,8,30–32]

Table 4. Restoration of Hemostasis

	Total (N = 143)	VKA (n = 114)	DOAC (n = 29)
INR at admission (mean [SD])	-	3.0 (2.5)	-
INR category at admission[†]	-	-	-
Subtherapeutic (< 2) (no. [%])	-	18 (16.2)	-
Therapeutic (2–3) (no. [%])	-	55 (49.5)	-
Supratherapeutic (> 3) (no. [%])	-	38 (34.2)	-
Agents used for restoration of hemostasis	-	-	-
4f-PCC (no. [%])	119 (83.2)	102 (89.5)	17 (58.6)
4f-PCC dose range	-	-	-
0–15UI/kg (no. [%])	-	23 (20.2)	3 (10.3)
15–30UI/kg (no. [%])	-	38 (33.3)	7 (24.1)
30–45UI/kg (no. [%])	-	5 (4.4)	2 (6.9)
45–60UI/kg (no. [%])	-	1 (0.9)	1 (3.4)
4f-PCC >60UI/kg (no. [%])	-	(0)	1 (3.4)
Missing (no. [%])	-	35 (30.7)	3 (10.3)
Vitamin K (no. [%])	108 (75.5)	103 (90.4)	5 (17.2)
Fresh frozen plasma (no. [%])	16 (11.2)	15 (13.2)	1 (3.4)
Platelets (no. [%])	14 (9.8)	9 (7.9)	5 (17.2)
No reversal agent (no. [%])	16 (11.2)	5 (4.4)	11 (37.9)

[†] 3 missing

We found no statistically significant differences in mortality and functional outcomes between the groups. However, as shown in other studies, we observed a favorable outcome trend for the DOAC group (Figure 6). In two large recent cohort studies, in-hospital mortality was lower and functional outcomes were better in patients with ICH associated with DOACs than VKAs.[9,10] In-hospital mortality in our study was higher than in other cohorts of patients with oral anticoagulation-related ICH[1,9,10,33] but similar to in-hospital mortality noted in another Canadian cohort (43.6% in-hospital mortality rate versus 45.5% in our study).[19]

As expected, we noted uneven use of 4f-PCC for restoration of hemostasis in patients anticoagulated with DOACs in the first few years following approval. Many patients on DOACs did not receive 4f-PCC and the doses administered varied. Observational data and expert consensus recommendations support the use of 4f-PCC to restore hemostasis in patients with ICH associated with DOACs.[11,14,15] The most recent Canadian hemorrhagic stroke guidelines recommend that, if available, idarucizumab should be used in patients under dabigatran. Otherwise, 4f-PCC (50UI/kg) is recommended in patients presenting with ICH associated with DOACs.[15] Andexanet alfa is not yet available in Canada. Transfusion of platelets is generally not recommended yet remains controversial in certain situations.[15,34] Finally, DOACs would now be considered a safer alternative in patients with ICH associated with VKAs.[35]

Strengths and Limitations

Our multicenter study provides real-world data on radiological and clinical outcomes and management strategies of ICH in anticoagulated patients in the first years following commercialization of DOACs in Canada. We evaluated radiological data carefully. We used manual segmentations to precisely quantify hematoma volumes as opposed to the ABC/2 formula, the most widely used volume calculation method in previous studies. The ABC/2 formula has been shown to overestimate hematoma volume compared to volumetric analyses, especially in anticoagulation.[31,36] We also included IVH volumes to refine the hematoma expansion evaluation, as recently recommended.[25,26] Finally, we evaluated management approaches for the restoration of hemostasis thoroughly to provide insight to clinicians regarding practice.

Our study is limited by a small sample size, especially for the DOAC group, likely because of the period when DOAC use was adopted. This could explain why we did not

observe significant differences in outcomes noted in other studies. Other confounders and biases could also explain the discrepancy between our results and prior studies. For example, referral bias may explain that patients with less severe presentations were not referred and thus not captured by our study examining tertiary centers. Without a formal registry and access to information in primary and secondary centers in our network, it is difficult to draw definitive conclusions.

Clinical implications

ICH remains a severe complication of oral anticoagulation with a high burden of morbidity and mortality. Our results further reinforce that management should be standardized and based on the best available evidence to contribute to improved patient outcomes.[33]

Research implications

Our initial results could help plan future studies on ICH associated with oral anticoagulation, encourage the development of registries, and promote recent recommendations for research on this topic.[37] RCT data will help clarify the role of 4f-PCC and specific reversal agents in patients with ICH receiving DOACs.[38] Development and commercialization of new specific reversal agents are also likely.

Conclusion

ICH in anticoagulated patients remains a dreaded complication. Our study did not demonstrate a statistically significant difference in radiological and clinical outcomes of patients on VKAs or DOACs. We observed variable management approaches, especially in patients treated with DOACs, highlighting the need for further research and consensus on the most appropriate management strategies. As such, the role of specific reversal agents in managing ICH in patients under DOACs will likely be better defined in the coming years. Further research is critical to develop standardized approaches to management and contribute to improved patient outcomes.

Statement of Authorship

All authors meet criteria for authorship as per the ICJME recommendations.

A.B. and Z.T.: conception and design of study, acquisition of clinical data, analysis and interpretation of data, original draft preparation

M.D.A. and L.L.G.: conception and design of study, acquisition of radiological data, analysis and interpretation of data, original draft preparation

A.A., J.S.D. and A.R.: design of study, acquisition of clinical data, analysis and interpretation of data

T.C.: design of study, acquisition of radiological data, analysis and interpretation of data

A.H., D.W., M.P., M.L.: design of study, analysis and interpretation of data

All authors were involved in the revision and editing of the manuscript and have read and approved the final version of the manuscript before submission.

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Conflict of interest

M.D.A., A.A., J.S.D., A.R., T.C., A.H., and M.P. declare that they have no conflict of interest.

A.B. has received an educational grant from Sanofi, has participated in an advisory board for Valeo Pharma and has received an unrestricted research grant from Pfizer and the Faculté de Pharmacie at the Université de Montréal for the conduct of this study.

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M.L. has received speaker fees from Bayer; has participated in industry-funded trials from Idorsia; has served on advisory boards for Servier and JAMP/Orimed Pharma; and has received in-kind and financial support for investigator-initiated grants from Leo Pharma, and Fujimori Kogyo. M.L. was supported by the FRQS Junior 1 Research Scholarship (33048); and is a Canada Research Chair in Platelets as biomarkers and vectors.

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Ethics Approval

The research adhered to ethical guidelines. The research protocol received multicenter approval by the ethics committee of CHUM and was authorized by the local ethics boards in the other sites. Individual informed consent was deemed unnecessary and the ethics boards approved the research team to carry out the research on denominalized medical files.

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References

1. Seiffge DJ, Goeldlin MB, Tatlisumak T, et al. Meta-analysis of haematoma volumes, haematoma expansion and mortality in intracerebral haemorrhage associated with oral anticoagulant use. J Neurol 2019;266:3126–35. https://doi.org/10.1007/s00415-019-09536-1
2. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4:4693–738. https://doi.org/10.1182/bloodadvances.2020001830
3. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the management of atrial fibrillation. Can J Cardiol 2020;36:1847–948. https://doi.org/10.1016/j.cjca.2020.09.001
4. Gomez-Outes A, Terleira-Fernandez AI, Lecumberri R, Suarez-Gea ML, Vargas-Castrillon E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res 2014;134:774–82. https://doi.org/10.1016/j.thromres.2014.06.020
5. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. Lancet 2014;383:955–62. https://doi.org/10.1016/S0140-6736(13)62343-0
6. Foerch C, Lo EH, van Leyen K, Lauer A, Schaefer JH. Intracerebral hemorrhage formation under direct oral anticoagulants. Stroke 2019;50:1034–42. https://doi.org/10.1161/STROKEAHA.118.023722
7. Ahmed A, Ahmed R, Ali SS, et al. Intracerebral hemorrhage outcomes in patients using direct oral anticoagulants versus vitamin K antagonists: a meta-analysis. Clin Neurol Neurosurg 2020;198:106146. https://doi.org/10.1016/j.clineuro.2020.106146
8. DiRisio AC, Harary M, Muskens IS, et al. Outcomes of intraparenchymal hemorrhage after direct oral anticoagulant or vitamin K antagonist therapy: A systematic review and meta-analysis. J Clin Neurosci 2019;62:188–94. https://doi.org/10.1016/j.jocn.2018.11.032
9. Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non-vitamin K antagonists vs vitamin K antagonist oral anticoagulants with in-hospital mortality. JAMA 2018;319:463–73. https://doi.org/10.1001/jama.2017.21917
10. Xian Y, Zhang S, Inohara T, et al. Clinical characteristics and outcomes associated with oral anticoagulant use among patients hospitalized with intracerebral hemorrhage. JAMA Netw Open 2021;4:e2037438. https://doi.org/10.1001/jamanetworkopen.2020.37438
11. Frontera JA, Lewin JJ, Rabinstein AA, et al. Guidelines for reversal of antithrombotics in intracranial hemorrhage. A statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016;24:6–46 https://doi.org/10.1007/s12028-015-0222-x
12. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - Full cohort analysis. N Engl J Med 2017;377:431–41. https://doi.org/10.1056/NEJMoa1707278
13. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019;380:1326–35. https://doi.org/10.1056/NEJMoa1814051
14. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report from the American College of Cardiology solution set oversight committee. J Am Coll Cardiol 2020;76:594–622. https://doi.org/10.1016/j.jacc.2020.04.053
15. Shoamanesh A, Lindsay MP, Castellucci et al. Canadian stroke best practice recommendations: Management of spontaneous intracerebral hemorrhage 7th Edition update 2020. Int J Stroke 2021;16:321–41. https://doi.org/10.1177/1747493020968424

16. Kamal N, Lindsay MP, Côté R, Fang J, Kapral MK, Hill MD. Ten-year trends in stroke admissions and outcomes in Canada. Can J Neurol Sci 2015;42:168–75. https://doi.org/10.1017/cjn.2015.20
17. Pham TM, Thanh NX, Wasylak T, et al. Average lifespan shortened due to stroke in Canada A nationwide descriptive study from 1990 to 2015. Stroke 2021;52:573–81. https://doi.org/10.1161/STROKEAHA.120.032028
18. Yu AYX, Fang J, Porter J, Austin PC, Smith EE, Kapral MK. Hospital-based cohort study to determine the association between home-time and disability after stroke by age, sex, stroke type and study year in Canada. BMJ Open 2019;9:e031379. https://doi.org/10.1136/bmjopen-2019-031379
19. Fernando SM, Qureshi D, Talarico R, et al. Intracerebral hemorrhage incidence, mortality, and association with anticoagulant use. Stroke 2021;52:1673–81. https://doi.org/10.1161/STROKEAHA.120.032550
20. Weitz JI, Semchuk W, Turpie AGG, et al. Trends in prescribing oral anticoagulants in Canada 2008–2014. Clin Ther 2015;37:2506–14. https://doi.org/10.1016/j.clinthera.2015.09.008
21. Piran S, Schulman S, Salib M, Delaney J, Panju M, Pai M. Direct Oral Anticoagulants in the Real World: Insights into Canadian Health Care Providers' Understanding of Medication Dosing and Use. Can Journ Gen Int Med 2017;12:23–7.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81. https://doi.org/10.1016/j.jbi.2008.08.010
23. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software partners. J Biomed Inform 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208
24. World Health Organization. (2004). ICD-10: international statistical classification of diseases and related health problems: tenth revision, 2nd ed. World Health Organization. https://apps.who.int/iris/handle/10665/42980
25. Morotti, A., Boulouis G, Dowlatshahi D, et al. Standards for detecting, interpreting, and reporting noncontrast computed tomographic markers of intracerebral hemorrhage expansion. Ann Neurol 2019; 86: 480–92. https://doi.org/10.1002/ana.25563
26. Yogendrakumar V., Ramsay T, Fergusson DA, et al. Redefining hematoma expansion with the inclusion of intraventricular hemorrhage growth. Stroke 2020; 51:1120–7. https://doi.org/10.1161/STROKEAHA.119.027451
27. Fedorov A., Beichel R., Kalpathy-Cramer J., et al. 3D Slicer as an image computing platform for the quantitative imaging network. Magn Reson Imaging. 2012;30:1323–41. https://doi.org/10.1016/j.mri.2012.05.001
28. Wilson D, Seiffge DJ, Traenka C, et al. Outcome of intracerebral hemorrhage associated with different oral anticoagulants. Neurology 2017;88:1693–700. https://doi.org/10.1212/WNL.0000000000003886
29. Tsivgoulis G, Lioutas VA, Varelas P, et al. Direct oral anticoagulant vs vitamin K antagonist-related nontraumatic intracerebral hemorrhage. Neurology 2017;89:11422–51. https://doi.org/10.1212/WNL.0000000000004362
30. Tsivgoulis G, Wilson D, Katsanos AH, et al. Neuroimaging and clinical outcomes of oral anticoagulant-associated intracerebral hemorrhage. Ann Neurol 2018;84:694–704. https://doi.org/10.1002/ana.25342
31. Melmed KR, Lyden P, Gellada N, Moheet A. Intracerebral hemorrhagic expansion occurs in patients using non-vitamin K antagonist oral anticoagulants comparable with patients using warfarin. J Stroke Cerebrovasc Dis 2017;26:1874–82. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.04.025
32. Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral hemorrhage: a systematic review and meta-analysis of individual patient data. Lancet Neurol 2018;17:885–94. https://doi.org/10.1016/S1474-4422(18)30253-9
33. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulation reversal, blood pressure levels, and anticoagulation resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA 2015;313:824–36. https://doi.org/10.1001/jama.2015.0846
34. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral hemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet 2016;387:2605–13. https://doi.org/10.1016/S0140-6736(16)30392-0
35. Tsai CT, Liao JN, Chiang CE, et al. Association of ischemic stroke, major bleeding, and other adverse events with warfarin use vs non-vitamin K antagonist oral anticoagulant use in patients with atrial fibrillation with a history of intracranial hemorrhage. JAMA Netw Open 2020;3:e206424. https://doi.org/10.1001/jamanetworkopen.2020.6424
36. Huttner HB, Steiner T, Hartmann M, et al. Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke 2006;37:404–8. https://doi.org/10.1161/01.STR.0000198806.67472.5c
37. Concha M, Cohen AT. Recommendations for research assessing outcomes for patients with anticoagulant-related intracerebral bleeds. Stroke 2021;52:1520–6. https://doi.org/10.1161/STROKEAHA.120.031730
38. National Library of Medicine (U.S.) (2018 Sept 7). Trial of andexanet in ICH patients receiving an oral FXa inhibitor. Identifier NCT03661528, https://clinicaltrials.gov/ct2/show/NCT03661528