Multinational cohort study of intracranial hemorrhage in patients with brain metastases receiving anticoagulation

Spontaneous intracranial hemorrhage (ICH) represents a common complication in patients with brain metastases.[1,2] As cardiovascular complications, including venous thromboembolism (VTE), are prevalent in cancer patients, many patients with brain metastases have an indication for therapeutic anticoagulation. The incidence rate of ICH with anticoagulation is approximately 15% in patients with metastatic brain cancer.[2] Although anticoagulation increases the risk of any bleeding event, prior cohort studies suggest that the risk of ICH in patients with brain metastases is similar with or without anticoagulation.[1,2,3] While two small retrospective cohort studies suggest safety of direct oral anticoagulants (DOAC) compared to low-molecular-weight heparin (LMWH) in this population,[4,5] due to the limited sample sizes and wide Confidence Intervals (CI) of point estimates, the ICH profile of DOAC *versus* LWMH in patients with metastatic brain tumors remains uncertain. Data are also lacking regarding risk factors for ICH and clinical and radiological presentation of ICH, as well as outcomes following ICH including recurrent thrombosis and recurrent hemorrhage after re-initiation of anticoagulation. To address these knowledge gaps, we conducted a multinational cohort study to compare rates of hemorrhage among patients with brain metastases treated with DOAC or LMWH and evaluate outcomes including mortality, recurrent thrombosis, and hemorrhage.

The Anticoagulation in Brain Cancer (ABC) Study was a retrospective cohort study involving 12 academic and non-academic hospitals in Canada, Israel, Mexico, Switzerland, the Netherlands, and the United States. The study protocol was approved by local medical ethics committees. Informed consent was waived and the study was conducted in line with local regulations. We screened the records of all patients in the hemato-oncology or medical oncology departments at the study centers between January 1st, 2014 and January 1st, 2022 for eligibility. The study included adult patients with systemic solid cancer and brain metastases confirmed through pathology and imaging, respectively. Eligibility criteria were active cancer, defined as newly diagnosed or undergoing treatment, and therapeutic anticoagulation (both full dose and indicated dose reductions prescribed with therapeutic intent) with either DOAC or LMWH. Patients with ICH before the initiation of anticoagulation and those lacking any follow-up data were excluded. Repeat brain imaging during follow-up was not a prerequisite for inclusion. Study index was defined as the first day of concurrent anticoagulation and brain metastases diagnosis, and patients were followed for 12 months. An additional 90-day follow-up was conducted for patients who experienced anticoagulation-related ICH to evaluate management and outcomes. The primary outcome was spontaneous ICH confirmed by central adjudication of radiographic imaging. The cumulative incidence of any ICH, major ICH, overt ICH (i.e., any ICH excluding hemosiderin deposits and/or trace/unmeasurable ICH), VTE or stroke/systemic arterial thromboembolism over 12 months with corresponding 95% CI was calculated, and was compared between anticoagulation groups with anticoagulation as a fixed variable for ICH. Hazard Ratios (HR) with corresponding 95% CI for any ICH and major ICH were calculated using a Cox proportional hazards model, with anticoagulation as time-dependent variable, and death and loss to follow-up as competing risks (Fine and Gray model).

A total of 505 patients were included in the study: 202 patients received DOAC and 303 received LMWH (Table 1). Lung and breast cancer were the most common primary tumors, with similar distributions between the two groups. VTE was the most frequent indication for anticoagulation, although atrial fibrillation was more common in the DOAC group. DOAC-treated patients often had brain metastases diagnosed while on chronic anticoagulation (median 278.5 days of anticoagulation before diagnosis), compared to a median of 131 days for the LMWH group. The median follow-up duration was 209 days in the DOAC group and 173 days in the LMWH group. Loss to follow-up occurred in 13.4% of DOAC patients and 12.5% of LMWH patients.

The 12-month cumulative incidence of spontaneous ICH was 11.1% (95% CI: 7.1-16.2) in the DOAC group (N=21) and 8.6% (95% CI: 5.6-12.4) in the LMWH group (N=23), yielding a HR of 1.08 (95% CI: 0.56-2.08) when anticoagulation was treated as a time-dependent variable (Figure 1). After adjustment for age, sex, cancer type, and high-bleeding-risk cancer treatments, the HR for ICH was 0.84 (95% CI: 0.41-1.70). For major ICH, the cumulative 12-month incidence was 1.7% (95% CI: 0.5-4.7) in the DOAC group and 2.7% (95% CI: 1.2-5.3) in the LMWH group, with an adjusted HR of 0.56 (95% CI: 0.14-2.24). The incidence of overt ICH was also similar: 8.5% (95% CI: 5.1-13.1) in DOAC-treated patients and 7.4% (95% CI: 4.6-10.9) in LMWH-treated patients, with a HR of 1.19 (95% CI: 0.62-2.29).

Mortality rates were high in both groups; 94 of 202 patients (46.5%) in the DOAC group and 154 of 303 patients (50.8%) in the LMWH group had died by the end of 12 months of follow-up. Three DOAC-treated patients (1.5%) and 2 LMWH-treated patients (0.7%) experienced an ICH leading to death within 24 hours. The 12-month incidence of VTE was 5.3% (95% CI: 2.6-9.4) in DOAC-treated patients and 5.5% (95% CI: 3.6-8.0) in the LMWH group. The 12-month incidence of arterial thrombosis was 1.6% (95%

Table 1. Patient characteristics stratified for type of anticoagulation.

Baseline variable	DOAC, N (%) Total=202	LMWH, N (%) Total=303
Age in years, median (IQR)	65 (56-72)	63 (55-70)
Female sex	93 (46.0)	168 (55.5)
Cancer type		
Breast	23 (11.4)	30 (9.9)
Colon	5 (2.5)	9 (3.0)
Lung	122 (60.4)	197 (65.0)
Melanoma	8 (4.0)	12 (4.0)
Renal cell cancer	11 (5.5)	13 (4.3)
Esophageal cancer	10 (5.0)	8 (2.6)
Other[1]	23 (11.4)	34 (11.2)
Cancer status		
New diagnosis	53 (2.2)	81 (26.7)
Relapsed	24 (11.9)	25 (8.3)
Refractory	125 (61.9)	197 (72.9)
Cranial radiotherapy		
Stereotactic radiosurgery	69 (34.2)	83 (27.4)
Whole brain radiotherapy	71 (35.2)	79 (26.1)
None	62 (30.7)	139 (45.9)
Recent history of neurosurgery[2]	20 (9.9)	54 (17.8)
Medical anticancer treatment[3]	158 (78.2)	221 (72.9)
Treatment with increased bleeding risk		
Afatinib	5 (2.5)	0
Axitinib	2 (1.0)	2 (0.7)
Bevacizumab	10 (5.0)	16 (5.3)
Pazopanib	1 (0.5)	2 (0.7)
Sunitinib	2 (1.0)	5 (1.7)
Indication for anticoagulation		
Venous thromboembolism	139 (68.8)	265 (87.5)
Atrial fibrillation	55 (27.2)	8 (2.6)
Both	4 (2.0)	21 (6.9)
Anticoagulation dose		
Prophylactic	5 (2.5)	3 (1.0)
Intermediate (LMWH only)	-	12 (4.0)
Therapeutic	193 (95.5)	288 (95.1)
Dose-adjusted (DOAC only)	4 (2.0)	-
Anticoagulation/brain cancer timing		
Anticoagulation prior to brain metastases	116 (57.4)	69 (22.8)
Brain cancer prior to anticoagulation start	79 (39.1)	223 (73.6)
Simultaneous	3 (1.5)	11 (3.6)
Comorbidities		
Hypertension	80 (39.6)	112 (37.0)
Chronic kidney disease[4]	17 (8.4)	11 (3.6)
Prior ischemic stroke/TIA	9 (4.5)	12 (4.0)
Concomitant aspirin therapy	20 (9.9)	34 (11.2)
History of anticoagulation-associated ICH[5]	0 (0.0)	4 (1.3)
Bleeding disorder[6]	1 (0.5)	1 (0.3)
Grade 3-4 thrombocytopenia[7]	25 (12.4)	30 (9.9)

[1]Other cancer types included carcinoma of unknown primary (N=8), ovarian (N=6), cervical (N=3), endometrial (N=3), diffuse large B-cell lymphoma (N=3), clear cell sarcoma (N=1), Ewing sarcoma (N=1), follicular lymphoma (N=1), germinal center lymphoma (N=1), germ cell tumor (N=2), oropharyngeal (N=1), trachea (N=1), neurofibrosarcoma (N=1), chondrosarcoma (N=1), osteosarcoma (N=1), pancreatic (N=1), prostate (7), parotid (N=1), sarcoma not otherwise specified (N=3), tonsil (N=1), stomach (N=1), thymic (N=3), urothelial (N=2). [2]Included brain biopsies and other neurosurgical procedures. Lumbar punctures and spinal anesthesia were not considered neurosurgical procedures. Recent was defined as <1 month prior to study index. [3]Defined as any type of anticancer medication at any time from study index until intracranial hemorrhage (ICH) or end of follow-up. [4]Defined as a glomerular filtration rate <60 mL/min/1.73m^2. [5]Defined as a history of ICH while on anticoagulation, occurring prior to brain cancer diagnosis. [6]Defined as any congenital or acquired bleeding disorder. [7]Defined as a platelet count <50x10^9/L, at any time from study index until ICH or end of follow-up. DOAC: direct oral anticoagulant; IQR: interquartile range; LMWH: low-molecular-weight heparin; N: number; TIA: transient ischemic attack.

CI: 0.4-4.2) and 2.5% (95% CI: 1.0-5.2), respectively. The clinical presentation of ICH events was comparable between the DOAC and LMWH groups, with approximately half of the patients (12/22 [55%] and 10/20 [50%], respectively) presenting without any clinical emergency (Figure 2). The clinical course of ICH, classified according to our predefined criteria (Figure 2), demonstrated an uneventful immediate course in most patients, whether treated with DOAC (82%) or LMWH (95%). Radiological review showed that most ICH events were overt (73% in the DOAC group and 65% in the LMWH group) and primarily intra-tumoral (86% and 85%, respectively) (*Online Supplementary Table S1*). Following ICH, anticoagulation was continued in 19 of 42 patients (45%). In 7 (37%) of the 19 patients continuing anticoagulation immediately, the ICH was characterized by presence of hemosiderin residues only (indicative of remote prior bleeding). Approximately one-third of the patients who initially discontinued anticoagulation resumed it within 90 days (*Online Supplementary Table S2*). Recurrent ICH occurred in only one patient (2.4%) within 90 days post-ICH, while the cumulative incidence of VTE during this period was 19.1% (95% CI: 8.8-32.2), with no arterial thromboembolic events observed. Exploratory multivariable analyses identified several potential risk factors for ICH. The use of anticancer medication, a history of anticoagulant-associated ICH prior to the diagnosis of brain cancer, the presence of a concomitant bleeding disorder, concurrent use of aspirin, and primary tumor sites of melanoma or renal cell carcinoma were found to be significantly associated with ICH, albeit with notably wide corresponding CI (*Online Supplementary Table S3*).

The ABC Study represents the largest cohort to date evaluating ICH risk in patients with brain metastases treated with DOAC or LMWH. The study found no significant difference in ICH risk between the two anticoagulation groups, even after adjusting for confounders. These findings are consistent with previous studies[2,4,5] and a recent meta-analysis that included data from the ABC study, which found no significant difference in ICH risk between DOAC and LMWH use in patients with metastatic brain cancer (relative risk 1.05, 95% CI: 0.71-1.56).[6] In the ABC study, radiological and clinical outcomes were comparable between groups. Notably, patients presenting with hemosiderin residues continued anticoagulation without recurrent ICH, suggesting that such findings may not contraindicate therapeutic anticoagulation. This is consistent with prior studies showing low recurrent ICH rates in patients with minor bleeds who resumed anticoagulation.[7] The high incidence of VTE post-ICH underscores the thrombotic risk in this population. More VTE events were observed in patients who resumed anticoagulation post ICH, which likely reflects confounding by indication, given the high baseline thrombotic risk in these patients. The observed association between aspirin use and increased ICH risk warrants further investigation, particularly in the light of contrasting data from a recent cohort study that found no increased ICH risk with antiplatelet therapy.[8] We acknowledge the potential for residual confounding and the selection of patients with lower bleeding risk for DOAC treatment. The heterogeneity in patient characteristics, inherent to the retrospective study design, and loss to follow-up numbers are clear limitations. The current study lacks power to exclude increased risk of ICH with DOAC compared to LMWH, as funding restrictions did not permit the time it would take to reach the calculated sample size. Furthermore, we acknowledge that data on ICH presentation and course are limited by the low number of

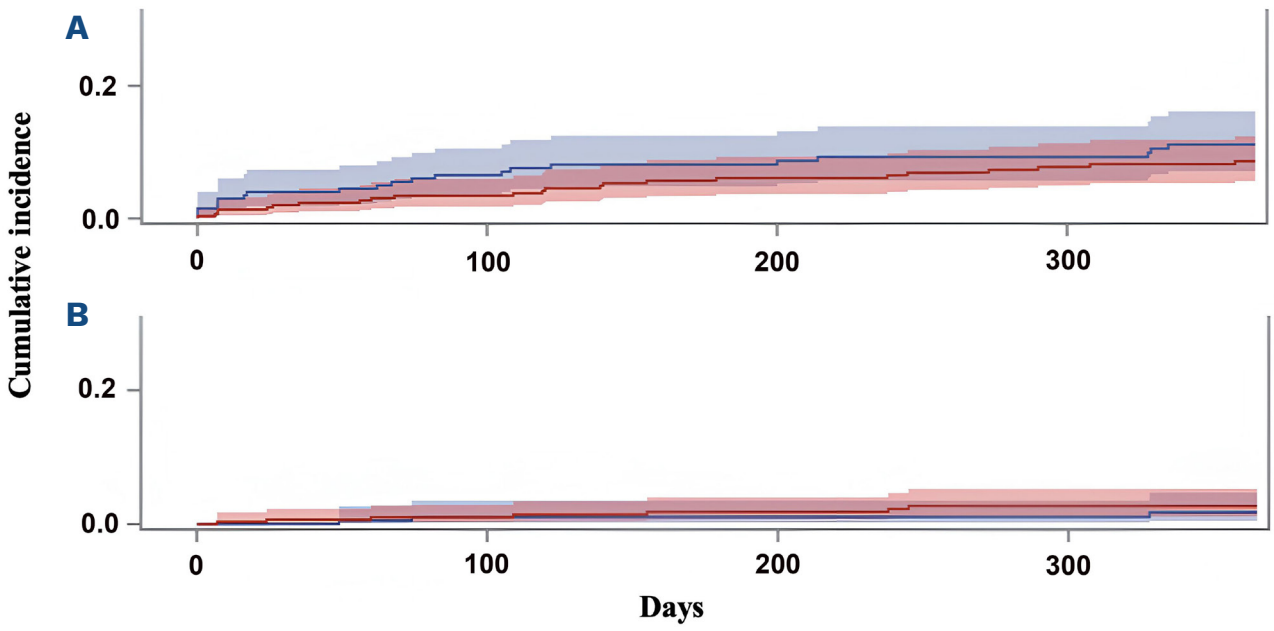

Figure 1. 12-month cumulative incidence of intracranial hemorrhage. Cumulative incidence of any intracranial hemorrhage (ICH) (A), major ICH (B) with direct oral anticoagulant DOAC (blue curve) or low-molecular-weight heparin (LMWH) (red curve) treatment. The shaded areas represent the 95% Confidence Interval. Major ICH was defined as volume ≥10 mL OR surgical intervention OR clinical symptoms, focal neurologic deficits or cognitive changes. Overt ICH was defined as any ICH excluding hemosiderin deposits and/or trace/unmeasurable ICH (indicative of prior intra/extra-tumoral hemorrhage).

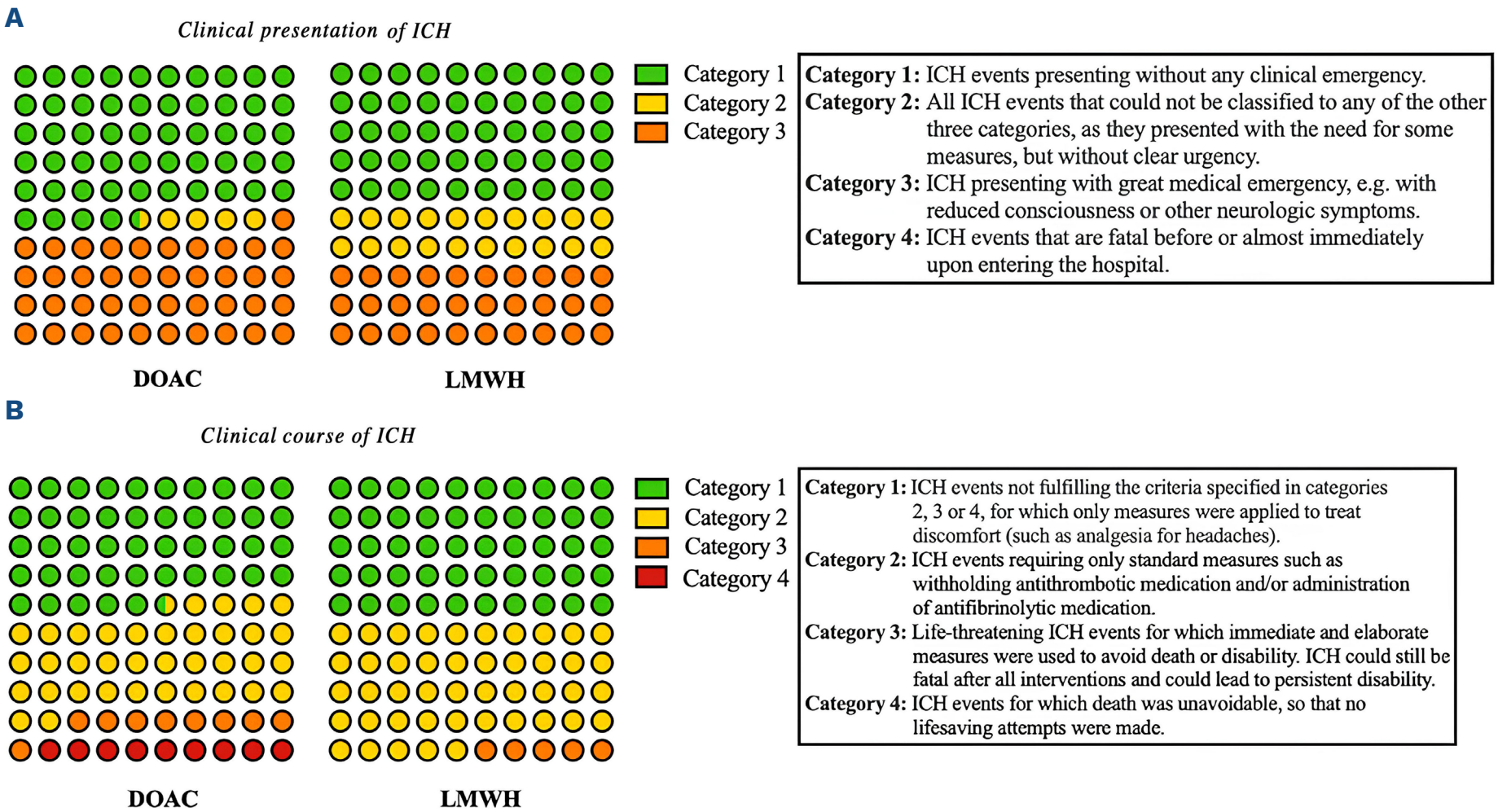

Figure 2. Clinical presentation and course of any anticoagulation-associated intracranial hemorrhage. Severity of hemorrhage by percentage of patients at clinical presentation (A) and clinical course (B) of any spontaneous intracranial hemorrhage (ICH) in patients experiencing ICH while on direct oral anticoagulant (DOAC) (N=22) compared to those on low-molecular-weight heparin (LMWH) (N=20). Clinical severity of ICH was assessed using pre-specified criteria.[9] None of the patients presented with an ICH event of category 4.

events, precluding definitive conclusions. Strengths include the analysis of anticoagulation type as a time-dependent variable, the use of a strict ICH definition, and showing radiological outcomes in the context of clinical parameters, such as presentation, course and management of ICH.

In conclusion, our study indicates similar ICH profiles with LMWH and DOAC in patients with brain metastases. The variability in clinical presentation and course of ICH suggests that a subset of patients may safely continue anticoagulation after ICH. Validation of the identified clinical predictors of ICH, using standardized reporting and classification of ICH, is needed to support clinical decision-making in this setting.

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Contributions

ENH, HRB, JIZ, GS and ALe, participated in all aspects of the study and authored the manuscript. SR and LFB performed radiologic review of imaging in the respective centers. HRB, GS and SM adjudicated clinical presentation and course of all bleeding events. All authors interpreted data, reviewed drafts, and approved the final draft of the manuscript.

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Data-sharing statement

For original data, please contact leadera@mskcc.org

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