RESEARCH ARTICLE

Intracranial Hemorrhage With Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin in Brain Tumors

A Review and Meta-Analysis

Thiago Oscar Goulart,[1] Chen Wang,[1] Kenshiro Fuse,[1] Daniela Zambrano,[1,2] Yasir Bukhari,[1,3] and John Y. Rhee[4,5]

Correspondence
Dr. Rhee
john_rhee@dfci.harvard.edu

Neurology® 2025;105:e214140. doi:10.1212/WNL.0000000000214140

MORE ONLINE

Supplementary Material

Abstract

Background and Objectives

Patients with brain tumors face an increased risk of arterial and venous thromboembolic events. However, owing to risk of intracranial hemorrhage (ICH), clinician practice patterns vary on preference for anticoagulation treatment. This meta-analysis evaluates the safety of direct oral anticoagulants (DOACs) vs low-molecular-weight heparin (LMWH) on the development of ICH in patients with brain tumor.

Methods

We searched MEDLINE, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (January 2010–June 2025) for randomized-controlled trials or cohort studies enrolling adults (age ≥18 years) with primary or metastatic brain tumors receiving therapeutic DOACs (apixaban, rivaroxaban, edoxaban, betrixaban, and dabigatran) vs LMWH (enoxaparin, dalteparin, nadroparin, and tinzaparin). Studies limited to prophylactic dosing or non–brain tumor patients were excluded. Pooled risk ratios (RRs) with 95% CIs were calculated using a restricted random-effects model. Heterogeneity (I^2) and bias were evaluated, with prespecified subgroups (tumor type, follow-up duration, and study quality) and sensitivity analyses. The study protocol was registered on PROSPERO (CRD42025635334).

Results

Among 762 publications identified, 10 retrospective cohort studies (1,572 patients: 645 DOAC, 895 LMWH) were included. Patients' mean or median age ranged 60.4–67 years (DOAC) vs 53–64 years (LMWH), with follow-up durations ranging from 3 to 12 months. Patients with primary or metastatic brain tumors receiving DOACs had a statistically significantly lower risk of any ICH compared with LMWH (RR = 0.50, 95% CI 0.29–0.87; $p = 0.01$, $I^2 = 49.50\%$). Reduction was more pronounced in 3 studies with three-month follow-up (RR = 0.23, 95% CI 0.09–0.57; $p < 0.01$, $I^2 < 0.01\%$). Stratified analyses showed reduced ICH risk with DOACs in primary brain tumors (5 studies, RR = 0.20, 95% CI 0.08–0.54; $p < 0.01$, $I^2 < 0.01\%$) but not in metastatic brain tumors (5 studies, RR = 0.86, 95% CI 0.44–1.68; $p = 0.66$, $I^2 = 36.04\%$). Leave-one-out analyses confirmed robustness, and cumulative meta-analysis demonstrated stable estimates with narrowing CIs. Egger ($p = 0.19$) and Begg ($p = 0.59$) tests showed no statistical evidence of publication bias.

Discussion

In the current meta-analysis, DOACs were associated with significantly lower ICH risk than LMWH in patients with anticoagulated brain tumor, particularly those with primary brain tumors. Findings support DOACs as a safe anticoagulant in arterial and venous thromboembolism. Given observational designs with inherent confounding, findings warrant cautious interpretation.

[1]Harvard T.H. Chan School of Public Health, Boston, MA; [2]The Robert Larner, M.D. College of Medicine, University of Vermont, Burlington, VT; [3]Faculty of Medicine, King Abdul Aziz University, Jeddah, Saudi Arabia; [4]Center for Neuro-oncology, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA; and [5]Division of Adult Palliative Care, Department of Supportive Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA.

Glossary

ATE = arterial thromboembolism; **CENTRAL** = Cochrane Central Register of Controlled Trials; **DOAC** = direct oral anticoagulant; **GBM** = glioblastoma multiforme; **GRADE** = Grading of Recommendations, Assessment, Development, and Evaluation; **ICH** = intracranial hemorrhage; **LMWH** = low-molecular-weight heparin; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCT** = randomized-controlled trial; **RR** = risk ratio; **TF** = issue factor; **VTE** = venous thromboembolism.

Introduction

Patients with cancer experience high risk of both arterial and venous thromboembolic events,[1] which may be due to a prothrombotic state characterized by inflammation and elevated levels of cytokines, including interleukin 6, 8, and 10.[2,3] In addition, cancer-associated thrombosis risk is increased due to impaired fibrinolysis, abnormal activation of the coagulation cascade through tissue factors (TFs), tumor-driven angiogenesis, and treatment-related factors that increase hypercoagulability, including chemotherapy, radiation, and surgery.[4-6] Thrombotic risk varies by cancer type and stage, but, overall, patients with active malignancy have a seven-fold increased risk of deep vein thrombosis and approximately double the risk of stroke compared with the general population.[6,7]

Patients with brain tumors are at higher risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE) compared with those with other malignancies.[8,9] Risk is particularly elevated for VTE, affecting up to 30% of patients with high-grade glioma and 20% of those with brain metastases and primary CNS lymphoma.[8] This heightened thrombotic risk is largely driven by factors such as overexpression of TF and prolonged immobility. Moreover, the clinical consequences are severe for thrombotic events in patients with brain tumor, associated with increased morbidity and poor prognosis.[8,9] Studies have shown that patients with malignant glioma who develop VTE have a 30% higher risk of death within 2 years.[10] However, the challenge of managing thromboembolism in this population is compounded by the elevated risk of intracranial hemorrhage (ICH).[8,9]

In recent years, direct oral anticoagulants (DOACs), particularly factor Xa inhibitors, have gained preference over traditional anticoagulants due to their safety profile, limited drug interactions, ease of administration, and the lack of need for routine monitoring or dose adjustments.[7,11] Despite the fact that approximately 20% of patients with malignant brain tumors develop DVTs during the disease course, these patients have typically been excluded from randomized controlled trials (RCTs) due to concerns about increased risk of ICH. As a result, low-molecular-weight heparin (LMWH) remains the preferred treatment for this condition.[12,13] It is important that the mortality associated with both arterial and venous thrombosis is higher in this population.[14] Therefore, identifying the most effective and safest treatment strategies for thromboembolic complications in patients with cancer is critical. There has been a more recent growing body of research examining the safety and efficacy of these agents in patients with primary and metastatic brain tumors, with small scale trials suggesting the possibility of using DOACs as a safe alternative.[15]

Thus, the aim of this study was to evaluate the safety of DOACs compared with LMWHs in patients with primary or metastatic CNS tumors in developing ICH. We performed a systematic review and meta-analysis, looking at ICH outcomes in patients with a diagnosis of primary or metastatic brain tumor who received either DOAC or LMWH to treat arterial or VTE.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This systematic review and meta-analysis protocol was registered in PROSPERO (registration number: CRD42025635334) and conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] This work drew on data from published studies and did not involve enrolment of new participants or collection of primary data; therefore, neither institutional review board or ethics committee approval was required; no informed consent or authorization for data disclosure was necessary.

Data Sources

We conducted a systematic search of MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant studies, including articles and abstracts, published between January 1, 2010, and June 18, 2025. This timeframe was chosen to coincide with the approval of the first DOAC, dabigatran, in 2010.[17] The search strategy incorporated controlled terms, such as MeSH and Emtree, and free-text keywords related to "brain tumors" and "anticoagulants." Boolean operators, including "AND" and "OR," were used to combine search terms. Detailed search strings for each database are provided in eTable 1.

The searches were conducted independently by multiple reviewers (T.G., K.F., and C.W. for MEDLINE; D.Z. and Y.B. for Embase; C.W. and D.Z. for Web of Science; and T.G. and K.F. for Cochrane CENTRAL). Reference lists of included studies and relevant systematic reviews were manually reviewed to identify additional eligible studies. The searches were rerun before the final analysis to ensure the inclusion of

the most recent publications. Only articles and abstracts published in English were included, with preprints or ongoing trials excluded from consideration.

Study Selection

Eligible study designs included RCTs or cohort studies if they met the criteria of including adults older than 18 years with primary or metastatic brain tumors requiring therapeutic anticoagulation for indications such as atrial fibrillation, stroke, VTE, or cancer-associated thrombosis. The intervention involved the use of DOACs, including apixaban, rivaroxaban, edoxaban, betrixaban, or dabigatran. Comparators were LMWHs including enoxaparin, dalteparin, nadroparin, or tinzaparin. The primary outcome of interest was the incidence of any (major or minor) ICH. ICH was recorded based on the incidence reported in each included study, without imposing uniform diagnostic criteria. Definitions generally reflected any radiologically confirmed bleeding—whether symptomatic or asymptomatic—as determined by the study authors. Detailed definitions of ICH for each included study are listed in eTable 2.

Studies were excluded if they were nonhuman, single-arm studies, placebo-controlled trials comparing anticoagulation with no anticoagulation, or studies involving prophylactic anticoagulation doses. Studies that enrolled patients with cancers other than brain tumors were also excluded. Titles and abstracts were screened independently by 2 reviewers (T.G. and C.W.) using prespecified inclusion and exclusion criteria. Full-text articles of potentially eligible studies were reviewed by 5 reviewers (T.G., K.F., C.W., D.Z., and Y.B.). Any disagreements during screening or selection were resolved through group discussion with the final reviewer (J.Y.R.). The management and coordination of reviewers were facilitated using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), available at covidence.org.

Data Extraction

The current systematic review and meta-analysis were conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines.[18] Data were extracted independently by 5 reviewers (T.G., K.F., C.W., D.Z., and Y.B.), using a structured data extraction form. All extracted data were cross verified by at least 1 other team member, and discrepancies were resolved through group discussion. The extracted information included study characteristics (study design, first author, year of publication, type of brain tumor studied, country, and follow-up duration), participant demographics (mean age, tumor type, and anticoagulation indications), intervention and comparator details (type and duration of anticoagulation), and outcome of any ICH. Measures of effect were cumulative incidence of outcomes in the DOAC and LMWH groups. When primary outcome data were not directly reported, individual patient data were reconstructed from Kaplan-Meier curves using the MD Anderson online too.[19,20] Data extraction and management were performed using Covidence and Excel spreadsheets.

Quality Assessment

The quality for cohort studies was assessed using the U.S. Preventive Services Task Force grading system, which evaluates evidence quality as good, fair, or poor based on the directness, study design, generalizability of results, and sufficiency in assessing health outcomes.[21] Studies with insufficient data to assess bias, such as abstracts, were marked accordingly. Risk of bias assessments were performed independently by 2 reviewers (K.F. and C.W.) and verified by a third reviewer (T.G.). Disagreements were resolved through discussion or arbitration by other reviewers (D.Z. and Y.B.). Certainty of evidence presented in this meta-analysis was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and GRADEpro Guideline Development Tool.[22,23]

Data Synthesis

A restricted random-effects meta-analysis was performed to calculate pooled risk ratios (RR) with 95% CIs for the primary outcome of any ICH. Interstudy statistical heterogeneity was assessed using the I^2 statistic, with thresholds of 0%–25% indicating low heterogeneity, 26%–50% moderate, 51%–75% substantial, and greater than 75% as high heterogeneity. Funnel plots and Egger and Begg tests were used to evaluate publication bias.

Subgroup analyses were performed by (1) study quality: studies were categorized as good or fair vs poor or insufficient data (such as abstracts) because study quality, including the completeness of data reporting, is well known to impact results; (2) brain tumor type: separate analyses were conducted for primary vs metastatic brain tumors due to differences in risk of ICH; and (3) follow-up duration: studies with data for 3 months of follow-up were analyzed separately because this is the most common time frame for many clinical indications, particularly for anticoagulation studies.

Sensitivity analyses included leave-one-out meta-analyses to assess the influence of individual studies, cumulative meta-analyses by ascending year to evaluate trends over time, and fixed-effects models to ensure consistent results for the overall effect. All analyses were conducted using the StataCorp. 2023, Stata Statistical Software: Release 18, College Station, TX: StataCorp LLC. Statistical significance was set at a 2-sided p value <0.05.

Data Availability

Data presented in this study are included in the main text, its supplementary materials, or in the source publications' texts and appendices. The data used for the present meta-analysis are provided in the supplementary material (eTables 3–6).

Results

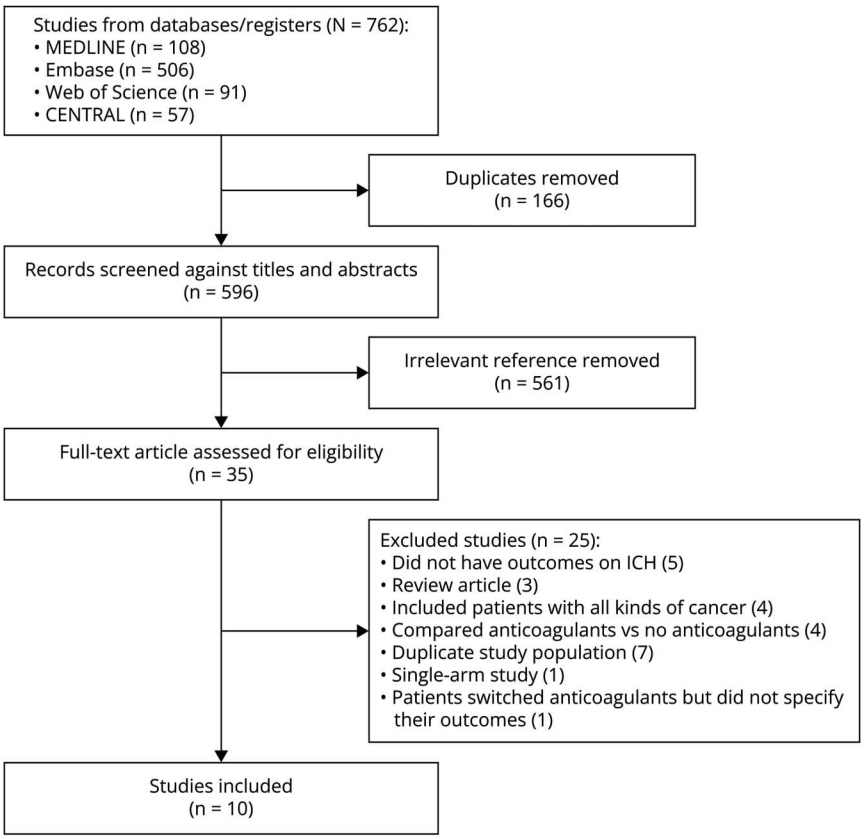
The systematic search identified 762 publications of which 35 underwent full-text screening. The final analysis consisted of 10 retrospective cohort studies, which met the inclusion criteria.[24-33] The study selection process and reasons for

exclusion are detailed in the PRISMA diagram (Figure 1). Among the 10 studies included, 6 evaluated both primary and metastatic brain tumors,[28-33] 2 focused exclusively on primary brain tumors (glioblastoma multiforme [GBM]),[26,27] and 2 focused on metastatic brain tumors[24,25] (Table 1). GBM was the most prevalent primary tumor type (61%–100%), while lung cancer was the most common source of metastatic brain tumors (39%–71%). DOACs, primarily rivaroxaban and apixaban, were used in 68%–100% of cases, and enoxaparin was the most common LMWH (62%–100%). The primary indications for anticoagulation were VTE and atrial fibrillation. Based on the US Preventive Services Task Force grading system,[21] 8 studies provided fair-quality evidence,[24-27,30-33] and 2 were classified as poor-quality studies or studies with insufficient data due to abstract-only formats.[28,29] Eight studies were conducted in the United States,[26-33] and 2 were multinational.[24,25]

Comparisons were derived from all studies involving a total of 1,572 participants, 645 in the DOAC group and 895 in the LMWH group. From the available data, the mean or median age of patients ranged 60.4–67 years in the DOAC group and 53–64 years in the LMWH group. The follow-up duration was primarily 6 or 12 months (Table 1). A total of 46 ICH events (7.1%) occurred in the DOAC group, compared with 141 ICH events (16.0%) in the LMWH group across all studies at their longest follow-up. The main analysis showed a lower risk of any ICH among those allocated to DOAC compared with LMWH (RR = 0.50, 95% CI 0.29–0.87; $p = 0.01$, $I^2 = 49.50\%$) (Figure 2). Sensitivity analyses confirmed the robustness of main results, with leave-one-out analysis showing no dependence on any single study (eFigure 1). Cumulative meta-analysis demonstrated consistent effect sizes and improved precision over the years (eFigure 2). Fixed-effects models also yielded consistent results (RR = 0.54, 95% CI 0.38–0.75; $p < 0.01$, $I^2 = 55.13\%$) (eFigure 3). Egger ($p = 0.19$) and Begg ($p = 0.59$) tests showed no statistical evidence of publication bias, while visual inspection of funnel plots suggested asymmetry due to the absence of small studies (Figure 3). Pooled data from 3 studies with 3-month follow-up interim results showed a further reduced risk of ICH with DOACs (RR = 0.23, 95% CI 0.09–0.57; $p < 0.01$, $I^2 < 0.00\%$) (eFigure 4).[30,31,33]

Stratified analysis of primary brain tumors from 5 of the 10 studies showed a significantly lower risk of any ICH with DOACs compared with LMWH (RR = 0.20, 95% CI 0.08–0.54; $p < 0.01$, $I^2 < 0.01\%$) (Figure 4A).[26,27,30-32] However, no significant difference in any ICH risk was observed for metastatic brain tumors from 5 of the 10 studies

Figure 1 PRISMA Diagram of the Selection Process of the Studies Included in the Present Systematic Review and Meta-analysis



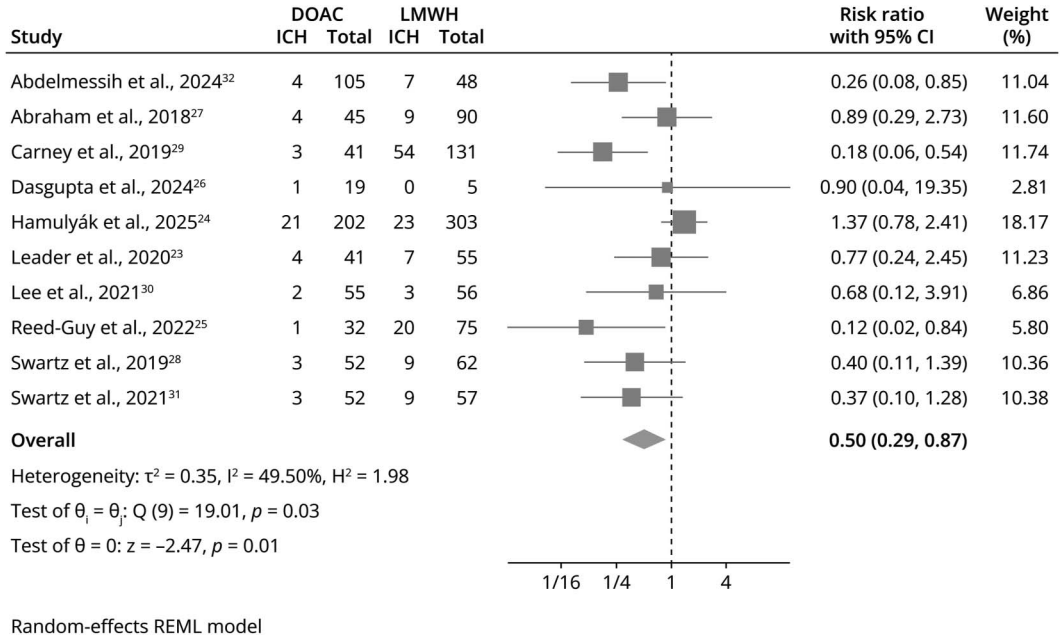
Studies were published between January 1, 2010, and June 18, 2025. n = number.

Table 1 Characteristics of Included Studies Contributing Data to the Pooled Analysis of Any Intracranial Hemorrhage (ICH) Risk, Comparing Direct Oral Anticoagulant (DOAC) With Low-Molecular-Weight Heparin (LMWH) in Patients With Brain Tumors Requiring Therapeutic Anticoagulation

Author y	BT type	n (PT and/or MT)	Overall PT type (n, %)	Overall primary site of MT (n, %)[a]	Intervention (type, n)	Comparator (type, n)	Indication for AC DOAC vs LMWH	Mean age (y)	Length of AC (DOAC vs LMWH)	Follow-up period	Location (Country)
Dasgupta 2024	PT	24 (PT 24 MT 0)	GBM	N/A	DOACs 19 Rivaroxaban 7 Apixaban 12	LMWH 5 Enoxaparin 5	Any indication	61 (63 vs 53)	96.4 d (128.3 vs 41.6)	N/A	The United States
Reed-Guy 2022	PT	121 (PT 121 MT 0)	GBM	N/A	DOACs 33 Apixaban 28 Rivaroxaban 4 Edoxaban 1	LMWH 88 Enoxaparin 88	VTE	60 (60.5 vs 60.1)	6 mo	6 mo	The United States
Carney 2019	PT and MT	172 (PT 105 MT 67)	Glioma 53 (79%) Others 14 (21%)	Lung 57 (54%) Breast 13 (12%) RCC 12 (11%) Others 23 (22%)	DOACs 41 Apixaban 20 Rivaroxaban 16 Dabigatran 5	LMWH 131 Enoxaparin 88	Any indication	61.5 (61.1 vs 61.6)	[PT] (14 mo vs 5 mo) [MT] (4 mo vs 3 mo)	12 mo	The United States
Abdelmessih 2024	PT and MT	153 (PT 136 MT 17)	GBM 83 (61%) Anaplastic astrocytoma 21 (15%) Glioma 13 (10%) Others 19 (142.6%)	Lung 12 (71%) Others 5 (29%)	DOACs 105 Apixaban 62 Rivaroxaban 30 Dabigatran 12 Edoxaban 1	LMWH 48 Enoxaparin 48	VTE AF	65 (67 vs 59.5) median	2.3 mo vs 2.1 mo	24+ mo	The United States
Hamulyák 2025	MT	505 (PT 0 MT 505)	N/A	Lung 319 (63.2%) Breast 53 (10.5%) RCC 24 (4.8%) Esophageal/ colon 32 (6.3%) Melanoma 20 (4.0%) Others 57 (11.3%)	DOACs 202 types N/A	LMWH 303 Types N/A	VTE AF	65 vs 63 (median)	278.5 vs 131 d (before MT diagnosis) 209 vs 173 d (after MT diagnosis)	12 mo	Multinational
Lee 2021	PT and MT	111 (PT 26 MT 85)	Glioma 15 (58%) Others 11 (42%)	Lung 33 (39%) Breast 18 (21%) Genitourinary 8 (9%) Others 26 (30%)	DOACs 55 Rivaroxaban 38 Apixaban 13 Edoxaban 3 Dabigatran 1	LMWH 56 Enoxaparin 56	VTE (DVT and/or PE)	62.3 (62.9 vs 61.8)	6.1 mo vs 4.4 mo	6 mo	The United States
Leader 2020	MT	96 (PT 0 MT 96)	N/A	Lung 54 (56%) Esophageal 11 (11%) Breast 9 (9%) Others 22 (23%)	DOACs 41 Rivaroxaban 17 Apixaban 11 Edoxaban 8 Dabigatran 5	LMWH 55 Enoxaparin 34 Nadroparin 15 Tinzaparin 6	VTE or AF (including prophylaxis)	66 vs 64 (median)	N/A	12 mo	Israel and the Netherlands
Swartz 2019	PT and MT	130 (PT 109 MT 21)	110 Types N/A	21 Types N/A	DOACs 52 types N/A	LMWH 62 types N/A	N/A	N/A	N/A	N/A	The United States
Swartz 2021	PT and MT	125 (PT 104 MT 21)	GBM 63 (61%) PCNSL 19 (18%) Glioma 15 (14%) Meningioma 7 (6%)	Lung 11 (52%) Breast 5 (24%) RCC 2 (10%) Others 3 (14%)	DOACs 52 Rivaroxaban 40 Apixaban 11 Dabigatran 1	LMWH 57 types N/A	VTE or AF or hypercoagulable state	63	6 mo	N/A	The United States
Abraham 2018	PT and MT	135 (PT 65 MT 70)	65 types N/A	70 types N/A	DOACs 45 types N/A	LMWH 90 types N/A	VTE or AF	60.4 vs 59.7	N/A	N/A	The United States

Abbreviations: AC = anticoagulation; AF = atrial fibrillation; BT = brain tumor; DOAC = direct oral anticoagulation; DVT = deep venous thrombosis; GBM = glioblastoma multiforme; ICH = intracranial hemorrhage; LMWH = low-molecular-weight heparin; MT = metastatic brain tumor; N/A = not available; n = number; *p* = *p* value; PCNSL = primary CNS lymphoma; PE = pulmonary embolism; PT = primary brain tumor; RCC = renal cell carcinoma; VTE = venous thromboembolism; mo = month; d = day.
[a] Detailed breakdown of the primary site is listed in eTable 2 in the Supplementary material.

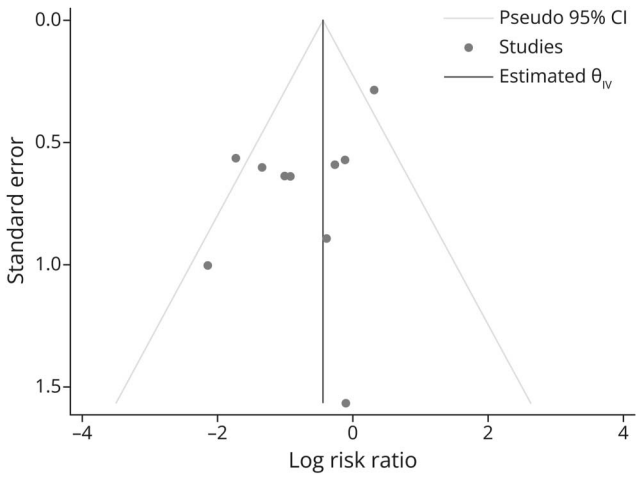
Figure 2 Forest Plot Showing Risk Ratio (RR) From Restricted Random-Effects (REML) Model of Any Intracranial Hemorrhage (ICH) Comparing Direct Oral Anticoagulation (DOAC) With Low-Molecular-Weight Heparin (LMWH) in Patients With Brain Tumors



The squares represent individual study estimates with 95% CIs; the diamond indicates the pooled RR. Heterogeneity metrics and statistical tests are provided (τ^2, variance of true effects; I^2, proportion of variability due to heterogeneity; H^2: ratio of total variability to expected sampling variability).

(RR = 0.86, 95% CI 0.44–1.68; p = 0.66, I^2 = 36.04%) (Figure 4B).[24,25,30-32] Subgroup analysis by study quality showed a pooled RR of 0.46 (95% CI 0.24–0.91; p = 0.03, I^2 = 56.16%) for 8 fair-quality studies (excluding the 2 abstracts).[24-27,30-33] Two studies (abstracts) with insufficient data yielded a pooled RR of 0.62 (95% CI 0.27–1.43; p = 0.26, I^2 < 0.01%) (eFigure 5).[28,29] Grade assessment of the presented results is shown in eTable 7.

Figure 3 Funnel Plot Assessing Publication Bias in the Meta-Analysis of Any Intracranial Hemorrhage (ICH) Risk Comparing Direct Oral Anticoagulation (DOAC) With Low-Molecular-Weight Heparin (LMWH) in Patients With Brain Tumor



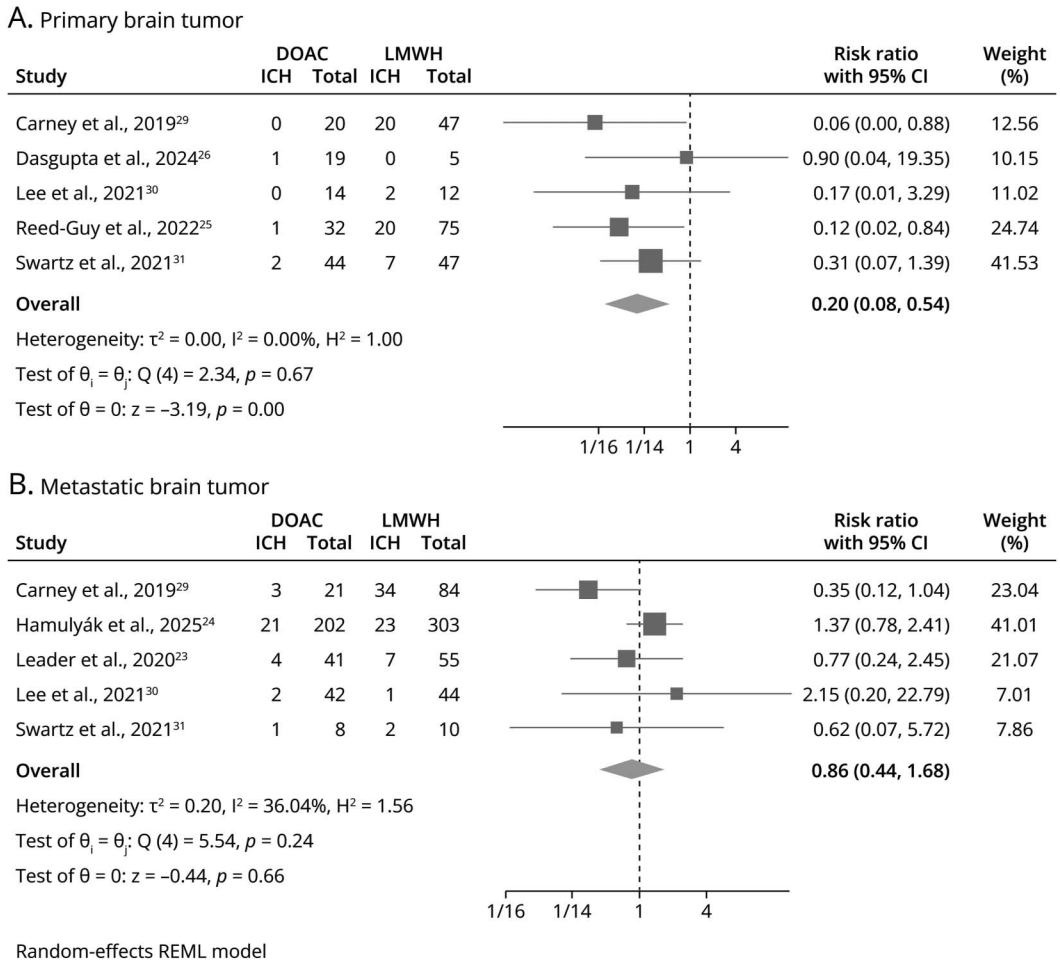
Each dot represents an individual study, plotted against its standard error and log risk ratio. The central line indicates the overall estimated effect size, and the lines on the side represent pseudo 95% CIs. Studies plotted toward the top of the graph have the lowest standard errors (i.e., largest sample sizes), while those toward the bottom have higher standard errors.

Discussion

In this meta-analysis, we found a lower risk of any ICH with DOACs compared with LMWH in patients with brain tumors (RR = 0.50, 95% CI 0.29–0.87; p = 0.01, I^2 = 49.50%). The pooled analysis revealed that DOACs were associated with a statistically significantly lower risk of any ICH among patients with overall brain tumors, with stratified analysis showing the effect limited to primary brain tumors, suggesting a favorable safety profile in this high-risk population.

Previous meta-analyses have examined anticoagulation and ICH risk in patients with brain tumors,[34-36] but with different patient populations and a more limited sample size. A recent meta-analysis[36] also examined risk of ICH with DOACs vs LMWH in patients with brain tumors. Seven of our 10 studies overlapped; 3 studies included by this meta-analysis[36] were excluded from our analysis due to not satisfying our inclusion criteria: one article[37] compared anticoagulated vs non-anticoagulated patients; another article[38] focused on post-operative patients, where perioperative hemorrhage could be a confounding risk; another article[39] included patients receiving prophylactic rather than therapeutic anticoagulation. In addition, we incorporated 3 studies published after the

Figure 4 Forest Plot Showing Risk Ratio (RR) From Restricted Random-Effects (REML) Model of Any Intracranial Hemorrhage (ICH) Comparing Direct Oral Anticoagulation (DOAC) With Low-Molecular-Weight Heparin (LMWH) in Patients With Primary Brain Tumors (A) and Metastatic Brain Tumors (B)



The squares represent individual study estimates with 95% CIs; the diamond indicates the pooled RR. Heterogeneity metrics and statistical tests are provided (τ^2, variance of true effects; I^2, proportion of variability due to heterogeneity; H^2: ratio of total variability to expected sampling variability).

recent meta-analysis,[25,27,33] increasing our analytical power to detect a reduction in ICH risk. Overall, this meta-analysis[36] found no significant difference in any ICH (RR = 0.65, 95% CI 0.36–1.17; p = 0.15), likely reflecting differences in inclusion criteria. By focusing on therapeutic-dose anticoagulation, tumor-specific ICH endpoints, and prespecified subgroup analyses, our review reduced heterogeneity and delivered a more specific assessment of anticoagulant safety in this high-risk population.

The reduced risk of any ICH with DOACs may reflect more targeted mechanisms of action on coagulation pathways, inhibiting directly factor Xa or thrombin, whereas LMWHs have broader effects on coagulation cascade, inhibiting multiple targets.[40] The findings of the current meta-analysis were particularly critical because individuals with brain tumors were already predisposed to ICH due to tumor-related factors, such as vascular disruption and peritumoral inflammation, but also had a higher risk of venous or ATE events.[12,14] The ability to lower this risk without compromising anticoagulant efficacy was an important clinical advantage. It is important that our meta-analysis included only studies assessing treatment doses of DOACs and LMWHs, excluding prophylactic doses. Although this exclusion limited the generalizability to prophylactic anticoagulation, the study's clinical relevance was reinforced by addressing the critical decision-making challenge of full-dose anticoagulation in patients with brain tumor. These findings offered robust evidence supporting the safety of treatment doses in this high-risk population. In addition, our subgroup analysis focused on studies with available three-month follow-up data (eFigure 4), a clinically common observed period for anticoagulation indications, demonstrated that DOACs were safer than LMWHs. However, this analysis included only 3 studies, warranting a cautious interpretation of the findings.

The tumor-specific analyses revealed distinct differences between primary and metastatic brain tumors (Figure 4).

Patients with primary brain tumors showed a significantly lower risk of any ICH with DOACs, accompanied by lower heterogeneity among studies. This finding aligned with previous meta-analyses[35,36] and likely reflected unique tumor-related mechanisms in primary brain tumors, such as localized vascular disruption and inflammatory changes.[31,33] By contrast, the reduction in any ICH risk was less pronounced and not statistically significant in metastatic brain tumors.[10] Notably, Hamulyák et al. (2025)[25] contributed 41% of weight in the metastatic subgroup analysis due to larger sample size, heavily influencing the pooled estimate (Figure 4B). The heterogeneity observed in metastatic brain tumor studies may arise from variability in tumor origins and treatment protocols (detailed primary site of metastatic tumor is listed in Table 1 and eTable 2). In addition, studies had shown risk of ICH varied across different subtypes of metastatic brain tumors, with certain tumors such as metastatic melanoma, renal cell carcinoma, and choriocarcinoma, exhibiting a much higher hemorrhagic risk,[41] that could also contribute to the heterogeneity observed in the included studies on metastatic brain tumors. These findings underscored the importance of stratifying patients by tumor type to optimize anticoagulation strategies, motivating future studies to adopt this tailored approach.

Our subgroup analyses showed that risk reduction associated with DOACs was consistent across the 8 higher-quality studies, with pooled analysis of the fair-quality data demonstrating a more pronounced reduction in any ICH risk (RR 0.46, 95% CI 0.24–0.91; $p = 0.03$, $I^2 = 56.16\%$) (eFigure 5). By contrast, analysis of the 2 studies with insufficient data or abstract-only publications failed to show significant results (RR 0.62, 95% CI 0.27–1.43; $p = 0.26$, $I^2 < 0.01\%$). These findings underscored the critical role of rigorous study design and comprehensive data reporting in accurately and precisely assessing ICH risks. Including studies with limited data may have biased the overall estimate slightly toward the null. However, given our reliance on nonrandomized studies with variable methodologic quality and risk of bias, the GRADE assessment rated the main result certainty as low (eTable 7). Future research would benefit from large, well-designed RCTs with ICH as a primary endpoint and prespecified subgroup analyses by tumor type, individual risk factors, and primary disease group in metastatic brain tumors.

Although the findings were compelling, several limitations should be acknowledged. First, there was moderate heterogeneity ($I^2 = 49.50\%$) in the overall analysis, which indicated variability among the included 10 studies. The heterogeneity may be attributed to differences in the study quality, study populations, and methodologies of the included studies. However, it is important to note that prior similar meta-analyses also reported moderate heterogeneity.[34-36] Despite the heterogeneity, the findings consistently supported the use of DOACs as a safer anticoagulant option for patients with brain tumors at risk for ICH. Second, there were inherent limitations to the meta-analyses based on the information available. For example, (1) not all included studies differentiated outcomes between primary and metastatic brain tumors or among specific tumor subtypes, reducing the number of studies available for tumor-specific stratification; (2) there was variability in the specific DOACs, and dosing regimens were not uniformly addressed, potentially influencing outcome heterogeneity; and (3) the articles that met inclusion criteria were observational studies, which were subjected to bias such as confounding and selection bias. However, we made all efforts to conduct a rigorous quality review and sensitivity analyses to confirm our results. In addition, we included 2 abstracts, which may have incomplete data reporting; however, we made efforts to obtain supplementary information from abstract authors to address missing data and performed a sensitivity analysis excluding abstracts, yielding results consistent with our primary findings. Finally, the studies that were included in this study had a 6-to-12 month follow-up; therefore, it was difficult to extrapolate ICH risk beyond 1 year. Nevertheless, the findings had important practice implications for high-grade primary brain tumors where life expectancy may be limited.

In conclusion, this meta-analysis suggested that DOACs were associated with a statistically significantly lower risk of ICH compared with LMWH in patients with brain tumors, particularly in those with primary brain tumors. Increased DOAC use may lower ICH risk in this population and, given the ease of administration over LMWH, could also improve quality of life. Future research should prioritize RCTs with consistent ICH definitions, detailed characterization of anticoagulant regimens, and stratified analyses by clinical context. Overall, our results offer clinically relevant evidence supporting DOAC safety in this high-risk population.

Author Contributions

T.O. Goulart: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Wang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. K. Fuse: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D. Zambrano: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. Y. Bukhari: major role in the acquisition of data. J.Y. Rhee: drafting/revision of the manuscript for content, including medical writing for content.

Study Funding

The authors report no targeted funding.

Disclosure

J.Y. Rhee was partially funded through the American Academy of Neurology Clinical Research Training Scholarship. The

other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® March 3, 2025. Accepted in final form July 21, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Rebecca Burch, MD.

References

1. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293(6):715-722. doi:10.1001/jama.293.6.715
2. Zhang Y, Zhang Z, Wei R, et al. IL (Interleukin)-6 contributes to deep vein thrombosis and is negatively regulated by miR-338-5p. *Arterioscler Thromb Vasc Biol.* 2020;40(2):323-334. doi:10.1161/ATVBAHA.119.313137
3. Reitter EM, Ay C, Kaider A, et al. Interleukin levels and their potential association with venous thromboembolism and survival in cancer patients. *Clin Exp Immunol.* 2014;177(1):253-260. doi:10.1111/cei.12308
4. Koizume S, Miyagi Y. Tissue factor in cancer-associated thromboembolism: possible mechanisms and clinical applications. *Br J Cancer.* 2022;127(12):2099-2107. doi:10.1038/s41416-022-01968-3
5. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med.* 2000;160(6):809-815. doi:10.1001/archinte.160.6.809
6. Zaorsky NG, Zhang Y, Tchelebi LT, Mackley HB, Chinchilli VM, Zacharia BE. Stroke among cancer patients. *Nat Commun.* 2019;10(1):5172. doi:10.1038/s41467-019-13120-6
7. 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(19):4693-4738. doi:10.1182/bloodadvances.2020001830
8. Jo JT, Schiff D, Perry JR. Thrombosis in brain tumors. *Semin Thromb Hemost.* 2014;40(3):325-331. doi:10.1055/s-0034-1370791
9. Wang J, Kim YD, Kim CH. Incidence and risk of various types of arterial thromboembolism in patients with cancer. *Mayo Clin Proc.* 2021;96(3):592-600. doi:10.1016/j.mayocp.2020.05.045
10. Semrad TJ, O'Donnell R, Wun T, et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. *J Neurosurg.* 2007;106(4):601-608. doi:10.3171/jns.2007.106.4.601
11. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American college of cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation.* 2019;140(2):e125-e151. doi:10.1161/CIR.0000000000000665
12. Riedl J, Ay C. Venous thromboembolism in brain tumors: risk factors, molecular mechanisms, and clinical challenges. *Semin Thromb Hemost.* 2019;45(4):334-341. doi:10.1055/s-0039-1688493
13. Gerber DE, Grossman SA, Streiff MB. Management of venous thromboembolism in patients with primary and metastatic brain tumors. *J Clin Oncol.* 2006;24(8):1310-1318. doi:10.1200/JCO.2005.04.6656
14. Sørensen HT, Pedersen L, van Es N, Büller HR, Horváth-Puhó E. Impact of venous thromboembolism on the mortality in patients with cancer: a population-based cohort study. *Lancet Reg Health Eur.* 2023;34:100739. doi:10.1016/j.lanepe.2023.100739
15. Riaz IB, Fuentes H, Deng Y, et al. Comparative effectiveness of anticoagulants in patients with cancer-associated thrombosis. *JAMA Netw Open.* 2023;6(7):e2325283. doi:10.1001/jamanetworkopen.2023.25283
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. doi:10.1136/bmj.n71
17. Direct Oral Anticoagulant Use. A Practical Guide to Common Clinical Challenges. *J Am Heart Assoc.* 2020;9(13):e017559. doi:10.1161/JAHA.120.017559
18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA.* 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008
19. Accessed December 14, 2024. biostatistics.mdanderson.org/shinyapps/IPDfromKM/
20. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published kaplan-meier survival curves. *BMC Med Res Methodol.* 2021;21(1):111. doi:10.1186/s12874-021-01308-8
21. *The Guide to Clinical Preventive Services 2014.* Agency for Healthcare Research and Quality (US); 2014.
22. In: Schünemann H, Brożek J, Guyatt G, Oxman A, eds. The GRADE Working Group; 2013. Available from guidelinedevelopment.org/handbook.*GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*
23. GRADEpro Guideline Development Tool [Software]. *Mcmaster University and Evidence Prime*; 2025. Available from gradepro.org.
24. Leader A, Hamulyák EN, Carney BJ, et al. Intracranial hemorrhage with direct oral anticoagulants in patients with brain metastases. *Blood Adv.* 2020;4(24):6291-6297. doi:doi:10.1182/bloodadvances.2020003238
25. Hamulyák EN, Wang TF, Kreuziger LB, et al. Multinational cohort study of intracranial hemorrhage in patients with brain metastases receiving anticoagulation. *Haematologica.* 2025;110(6):1417-1421. doi:10.3324/haematol.2024.286973
26. Reed-Guy L, Desai AS, Phillips RE, et al. Risk of intracranial hemorrhage with direct oral anticoagulants vs low molecular weight heparin in glioblastoma: a retrospective cohort study. *Neuro-Oncol.* 2022;24(12):2172-2179. doi:10.1093/neuonc/noac125
27. Dasgupta P, Rousseau JF. Clinical and molecular determinants of bleeding-related adverse outcomes in high-grade glioma. *J Neurooncol.* 2024;166(3):569-574. doi:10.1007/s11060-024-04574-w
28. Abraham RSIV, Millard TA, Palkimas S, Wages NA, Maitland HS. Bleeding risk of low-molecular weight heparin Vs direct oral anticoagulant in patients with intracranial tumors. *Blood.* 2018;132(Supplement 1):2524. doi:10.1182/blood-2018-99-113949
29. Swartz A, Drappatz J. Safety of doacs in patients with CNS malignancies. *Blood.* 2019;134(Supplement_1):1160. doi:10.1182/blood-2019-125161
30. Carney BJ, Uhlmann EJ, Puligandla M, et al. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. *J Thromb Haemost.* 2019;17(1):72-76. doi:10.1111/jth.14336
31. Lee A, Oley F, Lo M, et al. Direct oral anticoagulants or low-molecular-weight heparins for venous thromboembolism in patients with brain tumors. *Thromb Res.* 2021;208:148-155. doi:10.1016/j.thromres.2021.10.023
32. Swartz AW, Drappatz J. Safety of direct oral anticoagulants in central nervous system malignancies. *Oncologist.* 2021;26(5):427-432. doi:10.1002/onco.13698
33. Abdelmessih E, Ahuja T, Wo S, et al. Anticoagulant prescribing patterns in patients with primary central nervous system malignancies and secondary metastases. *J Thromb Thrombolysis.* 2024;57(3):418-427. doi:10.1007/s11239-023-02936-1
34. Giustozzi M, Proietti G, Becattini C, Roila F, Agnelli G, Mandalà M. ICH in primary or metastatic brain cancer patients with or without anticoagulant treatment: a systematic review and meta-analysis. *Blood Adv.* 2022;6(16):4873-4883. doi:10.1182/bloodadvances.2022008086
35. Yang J, He Z, Li M, Hong T, Ouyang T. Risk of intracranial hemorrhage with direct oral anticoagulation versus low molecular weight heparin in the treatment of brain tumor-associated venous thromboembolism: a meta-analysis. *J stroke Cerebrovasc Dis.* 2023;32(8):107243. doi:10.1016/j.jstrokecerebrovasdis.2023.107243
36. Iyengar V, Agrawal S, Chiasakul T, et al. Comparison of direct oral anticoagulants versus low-molecular-weight heparin in primary and metastatic brain cancers: a meta-analysis and systematic review. *J Thromb Haemost.* 2024;22(2):423-429. doi:10.1016/j.jtha.2023.10.011
37. Kewan TZ, Rahman S, Covut F, et al. Risk of intracerebral hemorrhage with and without anticoagulation in patients with brain metastasis: the Cleveland clinic experience. *Blood.* 2019;134(Supplement_1):3683. doi:10.1182/blood-2019-131758
38. Dubinski D, Won SY, Voss M, et al. Direct oral anticoagulants vs. low-molecular-weight heparin for pulmonary embolism in patients with glioblastoma. *Neurosurg Rev.* 2022;45(1):451-457. doi:10.1007/s10143-021-01539-9
39. Burth S, Ohmann M, Kronsteiner D, et al. Prophylactic anticoagulation in patients with glioblastoma or brain metastases and atrial fibrillation: an increased risk for intracranial hemorrhage? *J Neurooncol.* 2021;152(3):483-490. doi:10.1007/s11060-021-03716-8
40. Heestermans M, Poenou G, Hamzeh-Cognasse H, Cognasse F, Bertoletti L. Anticoagulants: a short history, their mechanism of action, pharmacology, and indications. *Cells* 2022;11(20):3214. doi:10.3390/cells11203214
41. Donato J, Campigotto F, Uhlmann EJ, et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. *Blood.* 2015;126(4):494-499. doi:10.1182/blood-2015-02-626788