Neuro-Oncology
24(3), 455–464, 2022 | https://doi.org/10.1093/neuonc/noab198 | Advance Access date 12 August 2021

Management of venous thromboembolism in high-grade glioma: Does low molecular weight heparin increase intracranial bleeding risk?

Jasmin Jo, Joseph Donahue, Guneet Sarai, Gina Petroni, and David Schiff

Department of Internal Medicine, Division of Hematology and Oncology, East Carolina University/Vidant Medical Center, Greenville, North Carolina, USA (J.J.); Department of Radiology, University of Virginia, Charlottesville, Virginia, USA (J.D.); Department of Primary Care and Population Health, Virginia Commonwealth University, Richmond, Virginia, USA (G.S.); Department of Public Health Sciences, Division of Biostatistics, University of Virginia, Charlottesville, Virginia, USA (G.P.); Department of Neurology, Division of Neuro-Oncology, University of Virginia, Charlottesville, Virginia, USA (D.S.)

Corresponding Author: David Schiff, MD, University of Virginia Neuro-Oncology Center, Box 800432, Charlottesville, VA 22908-0432, USA (ds4jd@virginia.edu).

Abstract

Background. Venous thromboembolism (VTE) occurs in up to 30% of patients with high-grade glioma (HGG). Concern for increased risk of intracranial hemorrhage (ICH) with therapeutic anticoagulation (AC) complicates VTE treatment. Some retrospective studies have reported an increased risk of ICH associated with therapeutic AC; however, effective alternatives to AC are lacking. The aim of our study is to assess the risk of ICH in HGG patients with VTE on low molecular weight heparin (LMWH).

Methods. We performed a retrospective matched cohort study of HGG patients from January 2005 to August 2016. Blinded review of neuroimaging for ICH was performed. For analysis of the primary endpoint, estimates of cumulative incidence (CI) of ICH were calculated using competing risk analysis with death as competing risk; significance testing was performed using the Gray's test. Median survival was estimated using the Kaplan-Meier method.

Results. Two hundred twenty patients were included, 88 (40%) with VTE treated with LMWH, 22 (10%) with VTE, not on AC, and 110 (50%) without VTE. A total of 43 measurable ICH was recorded: 19 (26%) in LMWH, 3 (14%) in VTE not on AC, and 21 (19%) in non-VTE cohort. No significant difference was observed in the 1-year CI of ICH in the LMWH cohort and non-AC with VTE group (17% vs 9%; Gray's test, $P = .36$). Among patients without VTE, the 1-year CI of ICH was 13%. Median survival was similar among all 3 cohorts.

Conclusions. Our data suggest that therapeutic LMWH is not associated with substantially increased risk of ICH in HGG patients.

Key Points

- The risk of intracranial hemorrhage in patients with primary brain tumor influences venous thromboembolism treatment.
- In this matched cohort study, low molecular weight heparin did not significantly increase the risk of intracranial hemorrhage in high-grade glioma patients.

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), occurs in up to 20%-30% of patients with high-grade glioma (HCG).[1–4] It often occurs within 6 months after first surgery; however, the risk continues throughout the course of the disease.[2,3] HGGs are highly vascular tumors that occasionally hemorrhage spontaneously, and concerns for increased risk of intracranial hemorrhage (ICH) with therapeutic

Importance of the Study

Due to the paucity of evidence in the treatment of venous thromboembolism (VTE) in high-grade glioma (HGG) patients, there remains uncertainty in the treatment approach, especially in balancing the risks and benefits of administering therapeutic anticoagulation (AC) in this patient population. Some recent retrospective studies have reported a higher risk of intracranial hemorrhage (ICH) in patients who received AC compared to patients who did not. Our study addressed this important concern of increased risk of ICH in HGG patients receiving therapeutic low molecular weight heparin (LMWH), and our data demonstrated no significant difference in the risk of ICH among patients with VTE who received and did not receive therapeutic AC. Similarly, AC did not increase the risk of symptomatic ICH compared to that in HGG patients without VTE not receiving AC. Our findings provide some reassurance in the safety in initiating the necessary VTE treatment in HGG patients. However, due to the conflicting results from recent studies, our study also underscores the desirability of a prospective study to determine the association of ICH and LMWH therapy.

anticoagulation (AC) complicate VTE treatment. While inferior vena cava filters are sometimes employed, data suggest these have a much higher failure and complication rates in neuro-oncology patients.[5,6] The risk of ICH further complicates the treatment of VTE in patients with recurrent glioblastoma (GBM) receiving bevacizumab. Current evidence demonstrates an increased risk of ICH with AC during bevacizumab treatment in HGG patients, although most of these events are asymptomatic, and uncontrolled case series suggest the risk-to-benefit ratio favors AC treatment.[7–10]

There are currently no established guidelines on the treatment of VTE in HGG patients. Direct oral anticoagulants (DOACs) such as dabigatran, an activated factor II inhibitor, and rivaroxaban, apixaban, and edoxaban, which are activated factor X inhibitors, are potentially a more convenient option than subcutaneous low molecular weight heparin (LMWH) given the possible lifetime administration of AC treatment in HGG patients. While data on safety and effectiveness of DOACs in cancer-associated VTE have been recently established, their role in glioma-associated VTE remains to be determined.[11–14] Recent treatment guidelines for cancer-associated VTE recommended LMWH for initial treatment; for patients who do not have high risk of gastrointestinal or genitourinary bleeding, DOAC can also be used.[15,16] For primary brain tumor patients, AC should also be offered, although no strong recommendations were made regarding the choice of agent.[15,16] Thus, LMWH is generally the recommended first-line VTE therapy in HGG.

ICH is historically reported to occur in 2% of patients with HGG on AC, comparable to the incidence of symptomatic ICH in those who are not on AC therapy.[17] In the CLOT trial, LMWH was shown to be more effective than warfarin in reducing the risk of recurrent thromboembolism in patients with cancer and acute VTE without increasing the risk of major or any bleeding. ICH was reported in 1 of the 14 patients with primary brain tumor who received dalteparin. However, this study was not designed to assess the risk of ICH.[18] Recently, retrospective studies reported up to a 7-fold increased risk of ICH in association with administration of therapeutic AC in patients with HGG.[19–22] Moreover, HGG patients who received enoxaparin were more than 3 times more likely to develop major ICH than those who were not treated with AC.[19] These findings raise further concern in initiation of the necessary VTE treatment in HGG patients. Consequently, we performed a retrospective matched cohort study to assess the risk of ICH in HGG patients on therapeutic LMWH for VTE treatment at the University of Virginia.

Materials and Methods

Study Design

This study was approved by the University of Virginia Institutional Review Board. Eligible patients were screened from the University of Virginia Neuro-Oncology database from January 1, 2005 to August 1, 2016, and data were collected from electronic health records. Included patients satisfied all the following criteria: age ≥18 years old; histologic diagnosis of 2016 WHO grade III anaplastic astrocytoma, oligodendroglioma, oligoastrocytoma or WHO grade IV GBM following biopsy or resection; VTE diagnosis; and patients with available radiologic study reports and images. Patients with brain tumors other than HGG, on other anticoagulants aside from LMWH, and those with no follow-up radiologic studies after initiation of LMWH were excluded from the study. A 1:1 retrospective match cohort study was performed. Cases or "LMWH" cohort were identified on the basis of HGG diagnosis, VTE, and prescription for enoxaparin or dalteparin. Patients who developed VTE but were not treated with AC were grouped under "non-AC with VTE." The control "non-VTE" group are patients not diagnosed with VTE and not on therapeutic AC. The matched controls were based upon age (±5 years), HGG diagnosis (GBM or anaplastic glioma), extent of resection, and sex chosen at random from 688 controls conditional satisfying the matching criteria for each case with VTE. All radiology reports were reviewed for documentation of ICH. A blinded board-certified neuroradiologist reviewed the images to confirm the presence and calculate the volume of ICH.

Assessment of Intracranial Hemorrhage

Segmentation of ICH was performed by a single board-certified neuroradiologist utilizing the lesion segmentation tools available with Carestream Vue PACS Client (Carestream Health, Inc., Version 12.1.5.0440, Rochester, NY, USA). Manual segmentation correction was performed on a per slice basis in cases of automated segmentation error. Intracranial hemorrhage was evaluated on either axial non-contrast CT head (section thickness, 2.5 mm) or multisequence MRI brain examinations, as available. Intracranial hemorrhage volume and location (ie, parenchymal, subarachnoid, subdural) were specified. Modified Fisher Scale was recorded when acute subarachnoid hemorrhage was present. Surgical cavities and cysts were not included in the lesion measurements. In cases of multiple foci of hemorrhage, individual lesion volumes were measured and summed. ICH was categorized into 3 groups with volumes 0-29 cm^3, 30-60 cm^3, and >61 cm^3, based on evidence of a more favorable 30-day mortality rate in patients with less than 30 cm^3 and higher Glasgow Coma Scale (GCS) compared to patients with ICH volume of greater than 30 cm^3 and low GCS.[23]

Statistical Analysis

The primary objective of the study was to determine the risk of ICH in patients with HGG on LMWH for treatment of VTE. Demographic results were summarized using frequency counts for categorical variables presented as percentages; and mean for continuous variables. For the purpose of comparing the risk of ICH, patients with VTE on LMWH were compared to those with VTE who were not treated with AC. This was performed to maintain a homogenous comparison of patient population in terms of VTE diagnosis as well as having similar time points of event (ie, from the time of VTE diagnosis to event) in computing for cumulative risk for developing ICH. In comparison, the cumulative incidence (CI) of ICH for patients without VTE cohort was measured from the time of HGG diagnosis until death or last known follow-up. For analysis of the primary end point, estimates of CI of ICH were calculated using competing risk analysis with death as competing risk; significance testing was performed using the Gray's test. Median survival was estimated using the Kaplan-Meier method.

Results

A total of 220 patients (120 men, 100 women) were included in the study, 88 (40%) in the LMWH group, 22 (10%) in non-AC with VTE group, and 110 (50%) in non-VTE group (Table 1). Of the 22 patients in the non-AC with VTE group, 15 patients were treated with IVC filter due to contraindication for AC such as bleeding and thrombocytopenia, 3 patients were enrolled to hospice, 1 patient was treated with aspirin, 1 did not receive DVT treatment due to rectal bleeding, 1 elected not to receive AC, and 1 was diagnosed prior to HGG diagnosis and had completed AC treatment. Two hundred four (93%) patients were diagnosed with GBM and 16 (7%) with anaplastic glioma. A total of 103 (47%) of the total population had IDH testing, of whom only 9 (9%) patients harbored IDH mutations. All 3 groups were similar in distribution in terms of mean age at presentation, gender, fraction of patients who underwent subtotal and gross total resection, and treatment with radiation therapy (RT) plus concomitant and adjuvant temozolomide. The percentages of patients who underwent biopsy and patients who received bevacizumab were higher in the LMWH group. No patients in the non-AC with VTE cohort harbored IDH mutation. The median time from initial HGG diagnosis to development of VTE was 3.3 months and 5.1 months in the LMWH group and non-AC with VTE group, respectively. There was no significant difference in the median survival between the 3 cohorts, ranging 1.3-1.5 years from the time of diagnosis or first surgery. Likewise, there was no significant survival difference among patients with VTE on LWMH (0.8 years, 95% CI: 0.5-1.0 years) and those not on AC (0.7 years, 95% CI: 0.2-1.2 years) after VTE diagnosis (Figure 2a and b).

Intracranial Hemorrhage Frequency and Characteristics

A total of 43 ICH was recorded: 19 (26%) in LMWH group, 3 (14%) in non-AC with VTE group, and 21 (19%) in patients without VTE (Table 2). Patients who had intratumoral or intracavitary petechial hemorrhage evident only on susceptibility-weighted imaging (SWI) MR sequences were not considered to have ICH. Intratumoral hemorrhage was the most common location of ICH seen among all 3 cohorts; subdural and subarachnoid hemorrhage were reported only in patients who received LMWH, while 2 patients who did not develop VTE had ICH in multiple locations. The majority of ICHs in both LWMH and non-VTE groups were <30 cm^3 (79% and 81%, respectively); both LMWH and non-VTE groups also had comparable incidence of ICH bleed between 30 and 60 cm^3 volume (16% and 14%, respectively). One patient each in the LMWH and non-VTE group developed ICH volume of >60 cm^3, while none was reported in the "non-AC with VTE" cohort. Twelve (63%) in LMWH group, 1 (33%) in non-AC with VTE group, and 13 (62%) in non-VTE group developed symptoms from ICH. The median time for VTE diagnosis to development of ICH was 8.8 weeks in LMWH and 3.7 weeks in non-AC with VTE group.

Three (16%) patients on LMWH required surgical intervention: 1 patient presented with herniation syndrome due to ICH with volume of >60 cm^3, the second patient experienced worsening neurological deficit from ICH into recurrent tumor with volume of <30 cm^3, and the third patient developed worsening hemiplegia from a subdural hemorrhage. One patient in the "non-VTE" group underwent surgery for evacuation of bleed in the recurrent tumor with a blood volume of 23.7 cm^3; while 4 patients in this cohort developed intratumoral hemorrhage at initial presentation and underwent nonurgent surgery primarily for resection of the tumor. One patient receiving LMWH developed encephalopathy and died due to ICH

Table 1 Demographic Data of Patients

Factors	LMWH Group, n = 88 (40%)	Non-AC With VTE Group, n = 22 (10%)	Non-VTE Group, n = 110 (50%)
Mean age at presentation, years (range)	58 (21-84)	61 (41-85)	59 (21-85)
Male gender	51 (58%)	12 (55%)	57 (52%)
Diagnosis			
Glioblastoma	80 (91%)	21 (95%)	103 (94%)
Anaplastic glioma	8 (9%)	1 (5%)	7 (6%)
IDH			
Mutated	3 (3%)	0 (0%)	6 (6%)
Wild type	45 (51%)	7 (32%)	41 (38%)
Not assessed	40 (47%)	15 (68%)	62 (57%)
Extent of resection			
Biopsy	28 (32%)	5 (23%)	30 (27%)
Subtotal resection	42 (48%)	14 (64%)	60 (55%)
Gross total resection	18 (20%)	3 (14%)	20 (18%)
Treatment			
RT and temozolomide	78 (89%)	20 (91%)	96 (87%)
Bevacizumab	45 (51%)	8 (36%)	45 (41%)
Development of intracranial hemorrhage	19 (26%)	3 (14%)	21 (19%)
Median time from HGG diagnosis to development of VTE in months	3.3	5.1	NA
Median time from VTE diagnosis to development of ICH in weeks	8.8	3.7	NA
Median survival from time of surgery in years (95% CI)	1.5 (1.2-1.7)	1.3 (0.8-1.8)	1.5 (1.2-1.8)
Median survival from time of VTE diagnosis in years (95% CI)	0.8 (0.5-1.0)	0.7 (0.2-1.2)	NA

Abbreviations: AC, anticoagulation; CI, confidence interval; ICH, intracranial hemorrhage; LMWH, low molecular weight heparin; NA, not applicable; RT, radiation therapy; VTE, venous thromboembolism.

Table 2 Patients With Intracranial Hemorrhage

	LMWH Group, n = 19	Non-AC With VTE Group, n = 3	Non-VTE Group, n = 21
Intracranial hemorrhage location			
Intratumoral	16 (84%)	3 (100%)	17 (81%)
Extratumoral	1 (5%)	0	2 (10%)
SDH or SAH	2 (11%)	0	0
Intratumoral/SDH/SAH	0	0	2 (10%)
Bleed volume			
0-29 cm^3	15 (79%)	1 (33%)	17 (81%)
30-60 cm^3	3 (16%)	2 (67%)	3 (14%)
>60 cm^3	1 (5%)	0	1 (5%)
Surgical intervention	3 (16%)	0	5 (24%)

Abbreviations: AC, anticoagulation; LMWH, low molecular weight heparin; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; VTE, venous thromboembolism.

with bleed volume of 36 cm^3.There were 2 ICH-related deaths in the "non-VTE" group due to intratumoral ICH: 1 patient who became comatose (volume 57.6 cm^3) and another who developed seizures and encephalopathy (volume 48 cm^3). All 3 patients did not undergo any aggressive management and were enrolled into hospice. Statistical comparison to determine a significant difference in the incidence of major ICH (volume >30 cm^3 and/or surgical intervention) was not performed due to the small number of events.

Cumulative Incidence of Intracranial Hemorrhage

There was no significant difference in the risk of ICH in patients with VTE receiving LMWH compared to patients with VTE without therapeutic AC (Figure 1a).The CI of ICH at 1 year was 17% (95% CI, 0.10-0.26) in LMWH group vs 9% (95% CI, 0.01-0.26) in non-AC with VTE patients (Gray's test, $P = .36$). As shown in Figure 1a, the risk of ICH remained parallel between the 2 groups on longer observation with 5-year CI of 22% (95% CI, 0.14-0.31) for LMWH group and 14% (95% CI, 0.03-0.32) for non-AC with VTE group. Among patients without VTE, the CI of ICH at 1 year was 13% (95% CI, 0.07-0.20) and 19% (95% CI, 0.12-0.28) at 5 years (Figure 1b). Statistical comparison of CI of ICH between patients with VTE with and without LWMH vs patients without VTE was not performed due to different time points of events (time of VTE and LMWH initiation vs time of HGG diagnosis).There were a similar percentage of death and loss to follow-up in all 3 groups. Please refer to Table 3 for summary of CI.

Discussion

Recurrent VTE occurs in almost a third of patients with GBM who have had a prior VTE event, particularly in patients who are not on long-term therapeutic AC and those with second primary malignancies prior to diagnosis of GBM.[24] The administration of lifelong therapeutic AC has been associated with a reduced risk of recurrent VTE.[3,24] Thus, it is imperative to understand the risks and benefits of treating VTE with anticoagulants in HGG patients.

Contrary to recent studies, our results do not suggest a substantially higher risk of ICH in HGG patients receiving therapeutic LMWH.[19,20,22] We found no statistically significant difference in the 1-year and 5-year CI of ICH between LMWH group and non-AC with VTE cohort (1-year CI: 17% vs 9%; 5-year CI: 22% vs 14%, respectively). The risk of ICH in patients who received LMWH begins to rise, albeit not significantly, within the first year of VTE diagnosis and initiation of AC (Figure 1a). After this time period, the risk of ICH in both groups plateaued throughout the course of HGG disease. Similarly, Mantia et al[19] did not find a significant difference in the 1-year CI of any and measurable ICH in HGG patients who received LMWH for VTE in comparison to patients who did not develop VTE. GBM patients with atrial fibrillation (AF) who received therapeutic AC to prevent stroke likewise did not significantly develop a higher ICH rate compared to the matched GBM patients without AF and to patients without GBM but on AC for AF (10.2% vs 12.2% vs 8%, respectively; $P = .076$).[25] In contrast to our findings, Khoury et al[20] and Al Megren et al[22] (Table 4) reported significantly higher incidence of ICH among patients with VTE who received therapeutic AC (16%) compared to those who were not on AC (<3%). Both studies utilized incidence rate to estimate the risk of ICH. However, neither of these studies accounted for death as competing risk with the ICH as an endpoint in this study population, for which a competing risk analysis rather than incidence rate is the recommended statistical approach to estimate the primary endpoint and avoid overestimation of ICH risk, as did Mantia et al[19,26] and our studies. However, in contrast to the patient population included in the study by Mantia et al[19] where both arms differed in the baseline risk factor of having VTE (VTE on AC group vs non-VTE group), our study compared the cumulative risk of ICH among patients who developed VTE and received therapeutic LMWH to patients who developed VTE but were not anticoagulated.

We reported a total of 43 (20%) ICH and 1-year CI of 17%, considerably lower than the 61 (46%) total number of ICH and 1-year CI of 28.1% reported by Mantia et al[19] and 1-year CI of 36.8% reported by Carney et al[27] (Table 4). This may result from our exclusion of SWI-only trace or petechial hemorrhage, as compared to both Mantia et al and Carney et al where patients with trace (too small to be measured or less than 1 mL volume) were included in the ICH incidence. Major ICH was reported in 8 out of 47 patients treated with LMWH in the study by Carney et al.[27] Mantia et al reported

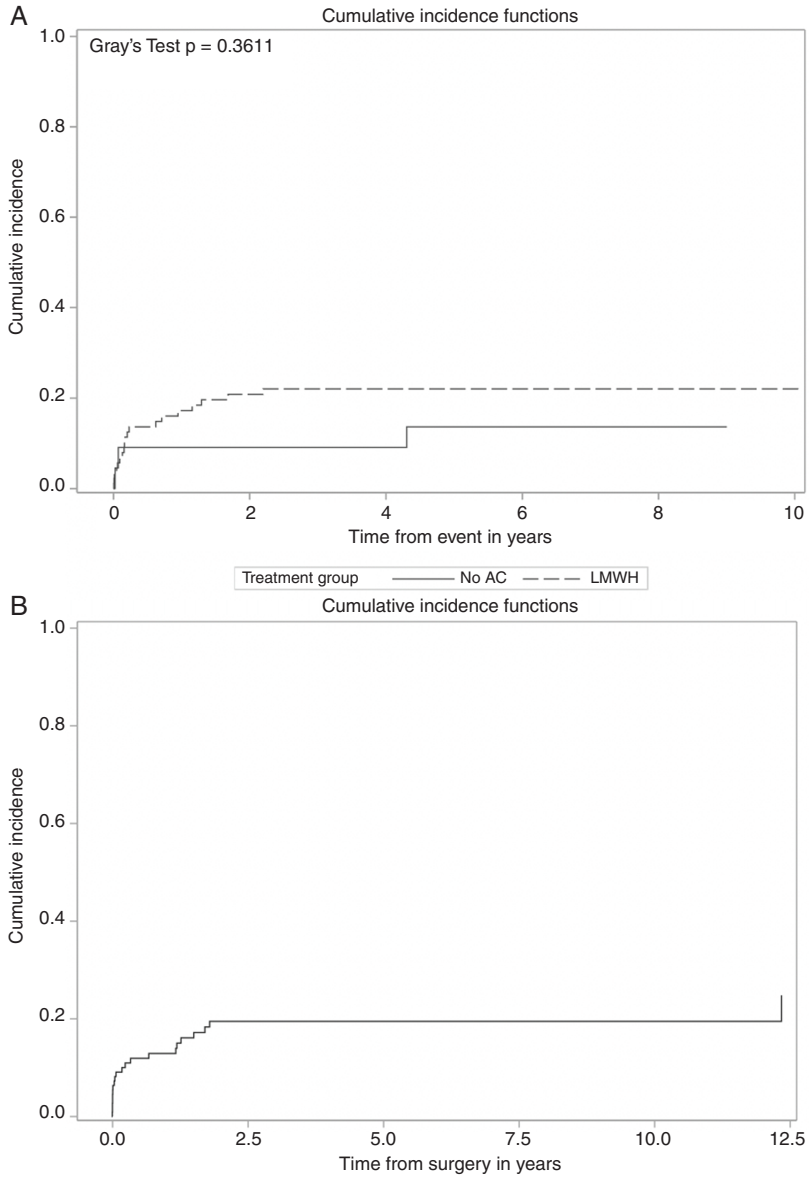

Fig. 1 (a) Cumulative incidence of ICH in patients who developed VTE treated with LMWH vs those not treated with anticoagulation. (b) Cumulative incidence of ICH in patients who did not develop VTE. Abbreviations: ICH, intracranial hemorrhage; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

a 3-fold increased risk of major ICH at 1 year.[19] However, the number of patients with major ICH out of the 61 total ICH recorded was not reported. In both aforementioned studies, major ICH was defined as any hemorrhage ≥10 mL, requiring surgical intervention, or associated with clinical symptoms. In our study, computation of statistical significance and postulating a valid conclusion on the association of LMWH with major ICH was not performed due to the small number of patients who developed more than 30 cm^3 ICH and those requiring surgical intervention.

Similar to findings in other recent retrospective studies,[19,22] the overall survival from the time of diagnosis was not significantly different among patients who received AC, those who developed VTE but did not receive therapeutic AC, and patients who did not develop VTE (Figure 2a and b). VTE has historically been reported to be associated with a 30% increased risk of death within 2 years.[1,2] However, a large prospective multicenter study reported the absence of any VTE-related mortality in 107 HGG patients.[3]This could be due to the heightened suspicion for VTE and timely treatment among experienced neuro-oncologists in the institutions included in the cited study. In contrast, Khoury et al reported a longer post-VTE diagnosis survival and overall survival in patients who received therapeutic AC for VTE than in those who did not receive AC.[20] However, as the authors noted, several clinical factors may have played a role in the decision not to administer AC and could have had an indirect effect on patient survival.

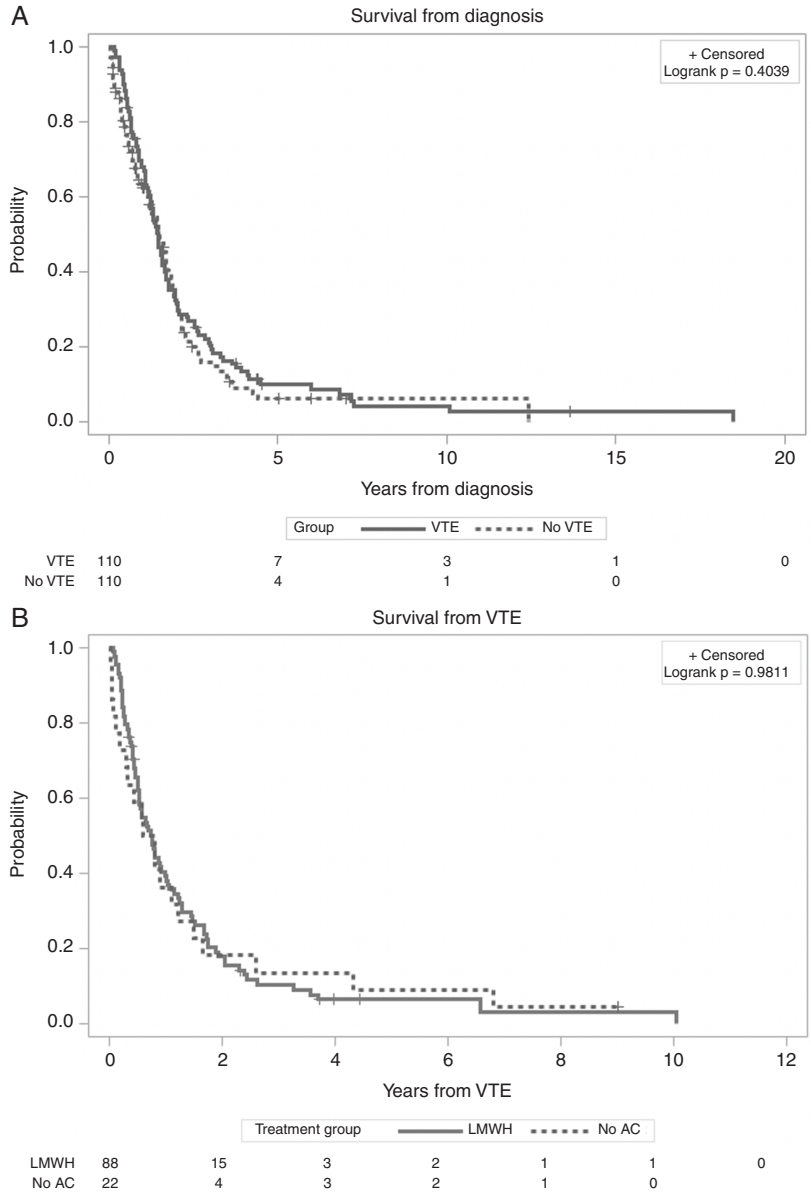

Fig. 2 (a) Median survival of all patients from the time of first HGG surgery. (b) Median survival of patients with VTE from the time of VTE diagnosis. Abbreviations: HGG, high-grade glioma; VTE, venous thromboembolism.

Table 3 Summary of Cumulative Incidence of Intracranial Hemorrhage

Patient Cohorts	0.5-yr Cumulative Incidence	1-yr Cumulative Incidence	5-yr Cumulative Incidence
LMWH	14% (95% CI, 0.07-0.22)	17% (95% CI, 0.10-0.26)	22% (95% CI, 0.14-0.31)
Non-AC with VTE group	9% (95% CI, 0.01-0.26)	9% (95% CI, 0.01-0.26)	14% (95% CI, 0.03-0.32)
Non-VTE group	12% (95% CI, 0.07-0.19)	13% (95% CI, 0.07-0.20)	19% (95% CI, 0.12-0.28)

Abbreviations: AC, anticoagulation; CI, confidence interval; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

Table 4 Comparison of ICH Risk With Recent Retrospective Studies

Author/year	Population	Population Categories			ICH			P Value
		VTE on AC	VTE Not on AC	Non-VTE	VTE on AC	VTE Not on AC	Non-VTE	
Khoury et al/2016	GBM n = 173	97 (56%)	76 (44%)	–	Incidence = 15 (15.5%)	Incidence = 2 (2.6%)	–	.005
Mantia et al/2017	HGG n = 133	50 (38%)	–	83 (62%)	1-yr CI = 28.1%	–	1-yr CI = 13.6%	.37
Al Megren et al/2017	Glioma n = 152	70 (46%)	6 (4%)	76 (50%)	Incidence = 11 (15.7%)	Incidence = 2 (2.4%)		.011
Carney et al/2019	Glioma n = 67	47 (70%)[a]	–	–	1-yr CI = 36.8%	–	–	–
Current study	HGG n = 220	88 (40%)	22 (10%)	110 (50%)	1-yr CI = 17%	1-yr CI = 9%	1-yr CI = 13%	.36[b]

Abbreviations: 1-yr CI, cumulative incidence at 1 year; AC, anticoagulation; HGG, high-grade glioma; ICH, intracranial hemorrhage; VTE, venous thromboembolism.
[a]Patients treated with enoxaparin only; patients treated with direct oral anticoagulant in this study were not reported in this table.
[b]Gray's test between VTE on AC group vs VTE not on AC group.

Despite its retrospective nature, our study has several strengths. In an effort to minimize selection bias in a retrospective cohort study, we compared all patients with VTE who were exposed and unexposed to LWMH and assessed the outcome, which differs from the statistical approaches performed in the other recent retrospective studies, as discussed above.[19,20,22] We also only included patients with measurable, clinically relevant ICH in the computation of the CI of ICH, which prevents the overestimation of ICH risk associated with LMWH treatment.

Our study has several limitations. Although our study had a larger patient population than the recent studies, the small number of ICH events precluded further subgroup analysis to determine a significant difference among patients who received LMWH vs patients who were not treated with AC. We also did not assess the role of other independent risk factors such as hypertension, thrombocytopenia, concurrent use of antiplatelet medications, and treatment with bevacizumab, which could potentially influence the decision to anticoagulate as well as increase the risk of ICH. The PANWARDS (platelet, albumin, no congestive heart failure, warfarin, age, race, diastolic blood pressure, stroke) risk score predicted major ICH in a retrospective cohort study of glioma but was not associated with ICH risk in patients with brain metastases.[19,28]

Prospective study of the risk of AC in HGG patients is extremely challenging. The PRODIGE trial, a randomized controlled study of dalteparin thromboprophylaxis, revealed no significant reduction in VTE and a trend toward more ICH complications.[29] Unfortunately, recruitment was lower than anticipated and the study was closed as a result of expiration of the study drug. The failure to detect a statistical significance may have been due to reduced statistical power from low accrual. This study underscores the challenges in performing a phase III randomized prospective study in this patient population. Short of performing a randomized study, a larger prospective observational study is fundamental to determine the efficacy and safety of therapeutic AC in HGG patients. There is evidence correlating IDH mutational status and the risk of VTE in glioma patients, with a 3-fold higher VTE risk in those who lack IDH mutation.[4] Future studies assessing primary thromboprophylaxis in IDH-wildtype glioma-only patients may provide more understanding on the role and safety of AC in glioma patients. Another important question in the treatment of VTE in primary brain tumors is the safety and efficacy of DOAC. The SELECT-D trial, which randomly assigned 406 patients with systemic cancer to receive either dalteparin or rivaroxaban, provides evidence that rivaroxaban is an effective alternative for LMWH in the treatment of VTE with relatively low risk of major bleeding.[11] There was no ICH reported on all patients, although this trial only included 3 patients with brain tumors. The ADAM-VTE trial found that apixaban, compared to dalteparin, for VTE treatment in patients with systemic cancer, was associated with a low bleeding risk, similar to those without cancer, and lower recurrence rates. In this study, only 8 patients with primary brain tumor out of 300 patients were included.[12] Edoxaban was compared to dalteparin in 1050 patients with active cancer, of which only 74 patients had primary or brain metastases.[14] While VTE recurrence was lower in the edoxaban group, the rate of major bleeding, mostly

gastrointestinal bleeding predominantly occurring in patients with primary gastrointestinal tumors, was higher in the edoxaban group. Due to the limited efficacy and safety data, prospective studies using DOACs in VTE treatment focused on glioma patients are also needed.

Conclusion

VTE is a common complication among patients with HGG and appropriate treatment is essential. Unfortunately, there are currently no prospective studies investigating the safety and efficacy of therapeutic LMWH in HGG patients. Contrary to some recent retrospective studies, our results demonstrated a slight, but not significant increased risk of ICH in HGG patients who received LMWH for VTE treatment compared to those who were not treated with AC. Our results offer reassurance that therapeutic LMWH can be utilized for VTE treatment in this population with acceptable safety. However, we recommend caution when initiating therapeutic AC in HGG patients such as a screening non-contrast head CT due to the potential serious ICH complication.[30] A prospective observational study with a larger number of patients is imperative to determine the role and safety of therapeutic AC, including the novel oral anticoagulants in the treatment of VTE in HGG patients.

Keywords

glioblastoma | high-grade glioma | intracranial hemorrhage | low molecular weight heparin | venous thromboembolism

Funding

No funding was reported.

Conflict of interest statement. The authors report no conflicts of interest relevant to the manuscript.

Authorship statement. Substantial contributions to conception and design: D.S. and J.J. Acquisition of data: J.J., G.S., and J.D. Analysis and interpretation of data: G.P., J.J., and D.S. Drafted the manuscript for important intellectual content: J.J. Revised the manuscript for important intellectual content: D.S., J.D., G.S., and G.P. Approved the final version to be published: J.J., J.D., G.S., G.P., and D.S.

References

1. 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.
2. Jenkins EO, Schiff D, Mackman N, Key NS. Venous thromboembolism in malignant gliomas. *J Thromb Haemost.* 2010;8(2):221–227.
3. Streiff MB, Ye X, Kickler TS, et al. A prospective multicenter study of venous thromboembolism in patients with newly-diagnosed high-grade glioma: hazard rate and risk factors. *J Neurooncol.* 2015;124(2):299–305.
4. Diaz M, Jo J, Smolkin M, Ratcliffe SJ, Schiff D. Risk of venous thromboembolism in grade II-IV gliomas as a function of molecular subtype. *Neurology.* 2021;96(7):e1063–e1069.
5. Levin JM, Schiff D, Loeffler JS, Fine HA, Black PM, Wen PY. Complications of therapy for venous thromboembolic disease in patients with brain tumors. *Neurology.* 1993;43(6):1111–1114.
6. Cavaliere R, Schiff D. Fatal pulmonary embolism despite an inferior vena cava filter in glioblastoma multiforme. *Neurocrit Care.* 2005;3(3):249–250.
7. Jo JT, Schiff D, Perry JR. Thrombosis in brain tumors. *Semin Thromb Hemost.* 2014;40(3):325–331.
8. Norden AD, Bartolomeo J, Tanaka S, et al. Safety of concurrent bevacizumab therapy and anticoagulation in glioma patients. *J Neurooncol.* 2012;106(1):121–125.
9. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27(28):4733–4740.
10. Nghiemphu PL, Green RM, Pope WB, Lai A, Cloughesy TF. Safety of anticoagulation use and bevacizumab in patients with glioma. *Neuro Oncol.* 2008;10(3):355–360.
11. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol.* 2018;36(20):2017–2023.
12. McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. *J Thromb Haemost.* 2020;18(2):411–421.
13. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med.* 2020;382(17):1599–1607.
14. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018;378(7):615–624.
15. Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol.* 2019;20(10):e566–e581.
16. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol.* 2020;38(5):496–520.
17. Ruff RL, Posner JB. Incidence and treatment of peripheral venous thrombosis in patients with glioma. *Ann Neurol.* 1983;13(3):334–336.
18. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349(2):146–153.
19. Mantia C, Uhlmann EJ, Puligandla M, Weber GM, Neuberg D, Zwicker JI. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin. *Blood.* 2017;129(25):3379–3385.
20. Khoury MN, Missios S, Edwin N, et al. Intracranial hemorrhage in setting of glioblastoma with venous thromboembolism. *Neurooncol Pract.* 2016;3(2):87–96.
21. Zwicker J, Leaf R, Carrier M. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. *J Thromb Haemost.* 2016;14:1736–1740.
22. Al Megren M, De Wit C, Al Qahtani M, Le Gal G, Carrier M. Management of venous thromboembolism in patients with glioma. *Thromb Res.* 2017;156:105–108.

23. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1991;24(7):987–993.
24. Edwin NC, Khoury MN, Sohal D, McCrae KR, Ahluwalia MS, Khorana AA. Recurrent venous thromboembolism in glioblastoma. *Thromb Res*. 2016;137:184–188.
25. 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.
26. Campigotto F, Neuberg D, Zwicker JI. Biased estimation of thrombosis rates in cancer studies using the method of Kaplan and Meier. *J Thromb Haemost*. 2015;10(7):1449–1451.
27. 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.
28. 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.
29. Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost*. 2010;8(9):1959–1965.
30. 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.