ARTICLE

Risk of Venous Thromboembolism in Grade II–IV Gliomas as a Function of Molecular Subtype

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Neurology® 2021;96:e1063-e1069. doi:10.1212/WNL.0000000000011414

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Abstract

Objective

To determine the incidence of venous thromboembolism (VTE) in lower-grade gliomas (LGGs, WHO grades II–III) and to stratify the risk of VTE by molecular subtype in gliomas grade II–IV, we performed a retrospective review of a large cohort of patients with glioma.

Methods

We performed a retrospective analysis of a cohort of 635 adult patients with glioma with molecular testing seen at the University of Virginia with a diagnosis of diffuse glioma established from January 2005 to August 2017. Estimates of cumulative incidence of VTE were calculated with death as competing risk; significance was determined using the Fine and Gray model.

Results

Of 256 patients with LGG, 81 were isocitrate dehydrogenase (IDH) wild-type; 113 IDH mutant, 1p/19q codeleted; and 62 IDH mutant, 1p/19q intact. With a median follow-up of 17.9 months, the overall cumulative incidence of VTE was 8.2% for grade II (147 patients), 9.2% for grade III (109 patients), and 30.5% for grade IV (334 patients). In grade II–IV patients, absence of an IDH mutation was associated with a threefold increase in VTE risk when compared to IDH-mutant patients (hazard ratio 3.06, 95% confidence interval 2.03–4.64). In patients with glioblastoma, there was no difference in VTE incidence according to O6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status.

Conclusion

Patients with LGG have a higher VTE risk compared to the general population, which is decreased, but not eliminated, in the presence of an IDH mutation. *MGMT* promoter methylation in glioblastoma does not affect the incidence of VTE.

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Glossary

CI = confidence interval; **CVST** = cerebral venous sinus thrombosis; **DVT** = deep venous thrombosis; **EGFR** = epidermal growth factor receptor; **GBM** = glioblastoma; **HR** = hazard ratio; **IDH** = isocitrate dehydrogenase; **LGG** = lower-grade glioma; **PE** = pulmonary embolus; **SHR** = subdistribution hazard ratio; **TF** = tissue factor; **VTE** = venous thromboembolism.

Venous thromboembolism (VTE) is a known complication of glioblastoma (GBM, grade IV of the WHO classification), with an estimated incidence of 20%–30% over the course of the disease, and an association with a 30% increase in the risk of death within 2 years.[1,2] However, the incidence of VTE in lower-grade gliomas (LGGs, WHO grades II and III) is not clearly established. Multiple risk factors have been associated with increased risk of VTE, including some that are applicable to thromboembolic risk in general (such as prior history of VTE or postoperative immobility) and others that are specific for gliomas (e.g., tumor size >5 cm or subtotal resection).[3] In recent years, the classification of gliomas has shifted from a purely histologic perspective to a molecular paradigm, as reflected by the 2016 WHO classification of CNS tumors, and there has been interest in correlating the new molecular subtypes with different clinical characteristics. It has been suggested that isocitrate dehydrogenase (IDH) mutation status dramatically affects the incidence of VTE in patients with glioma,[4,5] but the influence of other cornerstone molecular alterations such as 1p/19q codeletion has not been well-characterized. In this study, we aimed to determine the incidence of VTE in a large cohort of patients with LGGs and to explore the differences in risk of VTE according to several molecular characteristics, including 1p/19q codeletion in patients with LGG, O6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation in patients with GBM, and IDH mutation in patients of all grades.

Methods

Patient Selection and Molecular Data

The Neuro-Oncology database, a prospectively collected database at University of Virginia that includes details of VTE events due to our group's longstanding interest in this complication in brain tumors, was screened for patients 18 years or older with a pathologic diagnosis of glioma grade II–IV obtained from January 2008 to June 2017. All patients for whom information regarding status of IDH mutation, 1p/19q codeletion, or *MGMT* promoter methylation was available were included in our data set. A few patients had their original diagnosis prior to 2008, but were included in our cohort by having a second or third surgery within the established dates. For all patients, the date of initial diagnosis was considered to be the date of the first surgery of any kind that established a pathologic diagnosis of glioma. Molecular information was obtained through review of pathology slides by neuropathologists at University of Virginia in all but 15 patients, for whom only local data were available. As is standard clinical practice at our institution, IDH mutational status was initially determined using immunohistochemistry testing for IDH1 R132H mutant protein, followed by genetic sequencing of *IDH1* and *IDH2* through PCR, in some cases with negative immunohistochemistry; immunohistochemistry-negative cases in patients older than 55 years were assigned IDHwt without routine further testing, per WHO guidelines. 1p/19q codeletion status was established through fluorescence in situ hybridization.

Outcome Measures

Medical charts were reviewed and information regarding age, sex, duration of follow-up, histologic diagnosis, pathologically confirmed progression, and VTE occurrence was collected. VTE was defined as an event of deep venous thrombosis (DVT), pulmonary embolus (PE), or cerebral venous sinus thrombosis (CVST), identified by radiologic studies and occurring any time after the date of histologic diagnosis of glioma. There were several patients with an initial diagnosis of LGG who over time had progression to GBM, confirmed through a pathologic sample; given that one of our specific objectives was to determine the incidence of VTE in LGG as it compares to GBM, episodes of VTE that occurred after progression to GBM in these patients were not counted. For patients with multiple VTE events throughout the follow-up period, only the first VTE was included.

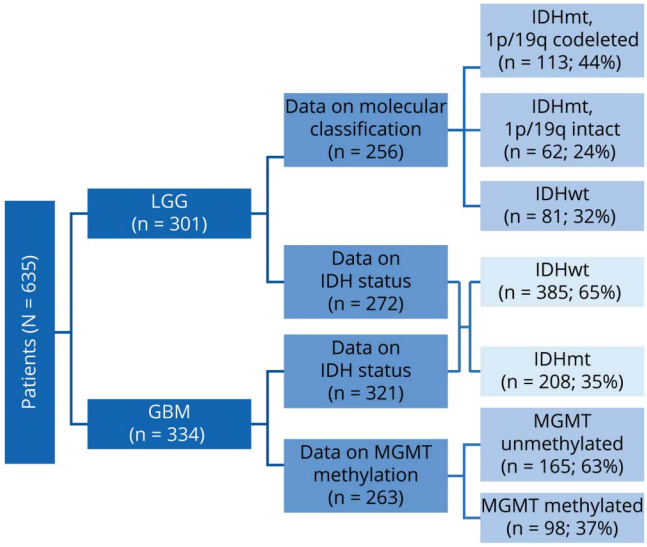
Statistical Analysis

VTE incidence was calculated at 6 months and 1 and 2 years postdiagnosis overall, by grade, IDH mutation status, 1p/19q codeletion status, and *MGMT* promoter methylation status. The primary outcome was time to first VTE after pathologic diagnosis of glioma, with death as a competing event. Competing-risks regressions were performed, as these provide a more accurate estimate of the risk of an outcome over time for patients with short life expectancy than traditional survival analyses, while controlling for different lengths of follow-up given the disparity in prognosis in our patient groups (LGG vs GBM). Specifically, Fine and Gray models were used to compare differences in time to first VTE between grade, IDH mutation status, 1p/19q codeletion status, and *MGMT* promoter methylation status. Pairwise comparisons between categories were adjusted for multiple comparisons using a Sidak-Holm adjustment. Analyses were conducted using StataSE 15.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval from an ethical standards committee to conduct this study was received. Institutional waiver of informed consent

Figure 1 Patient Groups



GBM = glioblastoma; IDH = isocitrate dehydrogenase; LGG = lower-grade glioma.

was obtained due to minimal patient risk associated with participation in the study.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

Patient Demographics and Clinical Characteristics

A total of 635 patient charts were reviewed, of which 301 were patients with LGG and 334 were patients with GBM. Among patients with LGG, there were 256 patients whose charts contained enough information to be classified into one of the following molecular groups based on the WHO 2016 classification[6]: IDH mutant (IDHmt) and 1p/19q codeleted (113 patients, 44%), IDHmt and 1p/19q intact (62 patients, 24%), and IDH wild-type (IDHwt, 81 patients, 32%). IDHmt patients with no information on 1p/19q codeletion but evidence of ATRX loss were included in the 1p/19q-intact group, as these genetic alterations are generally exclusive. A separate analysis was performed dividing the 593 patients of grades II–IV with information on IDH mutation status into 2 groups, IDHwt (385 patients, 65%) and IDHmt (208 patients, 35%). Finally, patients with GBM were divided according to their *MGMT* status (263 patients with available data, 165 [63%] methylated and 98 [37%] unmethylated) (figure 1).

Table 1 summarizes the characteristics of our patients, including the 256 patients with LGG fully classified according to their molecular characteristics and all 334 patients with GBM. As expected, median age increased with tumor grade (42.7 years in grade II vs 50 in grade III and 61.3 in grade IV, $p < 0.001$), and there was a higher percentage of IDHwt tumors in higher tumor grades (23.8% in grade II vs 42.2% in grade III and 91.3% in grade IV). Overall median follow-up was 17.9 months, but lower tumor grades were associated with a lengthier follow-up period (median 66 months for grade II vs 19.1 for grade III and 11.1 for grade IV). Episodes of VTE and other competing events (including death, censoring, and for patients with LGG, progression to grade IV) also occurred considerably later in the follow-up period in lower tumor grades (median time to first event 64.2 months in grade II vs 17.1 in grade III and 6.7 in grade IV, $p < 0.001$).

VTE Cumulative Incidence

During the length of follow-up, a total of 12/147 patients (8.2%) from the grade II group had a VTE event, compared to 10/109 patients (9.2%) in the grade III group and 103/334 patients (30.8%) in grade IV. Most of these patients did not have hemiparesis (1/12 patients, or 8.3%, in the grade II group, and 2/10 patients, or 20%, in the grade III group). Although the median time to an event was very prolonged in grade II patients, the majority of VTE episodes (8/12) occurred within the first 24 months of follow-up, being particularly frequent in the first 6 months after diagnosis (6/12). Of the total of 125 events of VTE in patients of all grades, 27 (21.6%) occurred in the postoperative period (first 30 days after surgery; mean time from surgery to VTE 12.5 days for this group). This proportion was only slightly higher in the LGG group (6/22 events [27.2%] in the postoperative period) than in the GBM group (21/103 events [20.4%]).

Among patients with GBM, cumulative incidence of VTE was very similar in patients with or without *MGMT* promoter methylation (overall cumulative incidence 52/165 [30.8%] for unmethylated patients vs 32/98 [32.7%] for methylated patients). Although it was not part of our original objectives, we also had information on increased epidermal growth factor receptor (EGFR) expression by immunohistochemistry available for 92 of our patients, most of them (73) in the GBM group. Increased EGFR expression was present in 62 patients of all grades, of whom 15 had a VTE (24.2%), compared to 8/30 (26.7%) in patients without overexpression.

When comparing based on IDH mutation status for patients of all grades, VTE occurred more frequently in IDHwt patients (overall cumulative incidence 102/385 patients, 26.5%), but there were infrequent cases of VTE among the IDHmt group (18/208 patients, 8.7%), most of which (13/18) were patients with LGG (table 2). The majority of events consisted of DVT, PE, or both, and there were only 2 instances of CVST in the entire dataset, both occurring in IDHwt, *MGMT*-promoter-methylated patients with GBM.

Competing-Risks Regression

The competing-risks regression for time to VTE in patients of all grades demonstrated that lack of IDH mutation was associated with a threefold increase in VTE risk when compared to IDHmt patients (hazard ratio [HR] 3.06, 95% confidence interval [CI] 2.03–4.64, $p < 0.001$) (figure 2). After adjusting for age, tumor

Table 1 Patient Characteristics

Characteristics	Grade II (n = 147)	Grade III (n = 109)	Grade IV (n = 334)
Age, y	42.7 (32.4–53.2)	50.0 (35.2–59.6)	61.3 (52.6–70.4)
Race			
White	130 (88.4)	103 (94.5)	303 (90.7)
Black	11 (7.5)	2 (1.8)	23 (6.9)
Hispanic	3 (2)	2 (1.8)	4 (1.2)
Asian	1 (0.7)	0 (0)	4 (1.2)
Native American	0 (0)	2 (1.8)	0 (0)
Sex			
Female	75 (51)	50 (45.9)	140 (41.9)
Male	72 (49)	59 (54.1)	194 (58.1)
Molecular type			
IDHwt	35 (23.8)	46 (42.2)	305 (91.3)[a]
IDHmt, 1p/19q-codeleted	71 (48.3)	42 (38.5)	IDHmt: 16 (4.8)[a]
IDHmt, 1p/19q-intact	41 (27.9)	21 (19.3)	
Hemiparesis			
Present	9 (6.1)	15 (13.8)	65 (19.5)
Absent	138 (93.9)	94 (86.2)	269 (80.5)
Months of follow-up	66 (27.8–112.1)	19.1 (5.2–51.8)	11.1 (4.2–22.4)
Months to first event[b]	64.2 (21.7–109.5)	17.1 (4.8–47.9)	6.7 (2.6–18.2)

Values are n (%) or median (interquartile range).
[a] For 13 patients with glioblastoma (3.9%), information on IDH status was not available.
[b] An event was defined as venous thromboembolism, censoring, death or, for patients with lower-grade glioma, progression to grade IV.

grade, and presence or absence of hemiparesis, the risk of VTE was still over double for patients without an IDH mutation (HR 2.11, 95% CI 1.17–3.79, $p = 0.013$). This same type of analysis in the LGG group demonstrated a higher risk of VTE in IDHwt patients compared to both IDHmt, 1p/19-codeleted and IDHmt, 1p/19q-intact patients, but this result did not reach statistical significance (IDHwt vs IDHmt, 1p/19q-codeleted, subdistribution HR [SHR] 1.67, 95% CI 0.59–4.72, $p = 0.56$; IDHwt vs IDHmt, 1p/19q-intact, SHR 1.87, 95% CI 0.54–6.53, $p = 0.55$) (figure 3). Adjusting for age and hemiparesis yielded similar results (IDHwt vs IDHmt, 1p/19q-codeleted, SHR 1.42, 95% CI 0.46–4.40, $p = 0.84$; IDHwt vs IDHmt, 1p/19q-intact, SHR 1.34, 95% CI 0.43–4.19, $p = 0.90$). There was no difference in the risk of VTE for patients with GBM according to *MGMT* promoter methylation (for methylated vs unmethylated, HR 0.99, 95% CI 0.64–1.54, $p = 0.97$).

Discussion

In recent years, classification of gliomas has shifted from a purely histologic perspective to the current system based on molecular profiling, upon which grade II and III gliomas have emerged as a more similar disease entity than they were previously considered, in turn separate from GBMs on account of their different molecular characteristics.[7] However, most studies looking at VTE incidence in gliomas occurred prior to this paradigm change, and while some of them included gliomas of all grades or, more commonly, what has classically been referred to as high-grade gliomas (grades III and IV), the number of grade II and III patients was overall too small to establish solid conclusions,[8–13] or they were not analyzed separately from GBMs.[14–16] Only one large series analyzing gliomas of all grades included sufficient numbers of grade III patients to determine their risk of VTE, finding a cumulative 2-year incidence of VTE of 6.8% in 843 patients with anaplastic astrocytoma and 7.8% in 192 patients with anaplastic oligodendroglioma.[1] However, the data for this study were extracted from a statewide database containing information from dozens of different institutions; since at the time of that analysis classification into different tumor categories was based exclusively on histology rather than molecular characteristics, the heterogeneous backgrounds of the diagnosing pathologists may have affected the accuracy of the

Table 2 Cumulative Incidence of Venous Thromboembolism (VTE), n (%)

Group	6 mo	12 mo	24 mo	Overall
Grade II (n = 147)	6 (4.1)	7 (4.8)	8 (5.4)	12 (8.2)
IDHwt (n = 35)	2 (5.7)	2 (5.7)	3 (8.6)	4 (11.4)
IDHmt, 1p/19q-codeleted (n = 71)	4 (5.6)	5 (7)	5 (7)	6 (8.4)
IDHmt, 1p/19q-intact (n = 41)	0 (0)	0 (0)	0 (0)	2 (4.9)
Grade III (n = 109)	5 (4.6)	8 (7.3)	10 (9.2)	10 (9.2)
IDHwt (n = 46)	3 (7.1)	5 (10.9)	5 (10.9)	5 (10.9)
IDHmt, 1p/19q-codeleted (n = 42)	1 (2.4)	2 (4.8)	4 (9.5)	4 (9.5)
IDHmt, 1p/19q-intact (n = 21)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)
Grade IV (n = 334):	77 (23.1)	89 (26.6)	97 (29.0)	103 (30.8)
***MGMT* unmethylated (n = 165)[a]**	39 (23.6)	46 (27.9)	50 (30.3)	52 (31.5)
***MGMT* methylated (n = 98)[a]**	23 (23.5)	26 (26.5)	30 (30.6)	32 (32.7)
IDHwt (n = 304)[b]	69 (22.7)	81 (26.6)	89 (29.3)	93 (30.6)
IDHmt (n = 17)[b]	3 (17.6)	3 (17.6)	3 (17.6)	4 (23.5)
All grades, IDHmt (n = 208)	10 (4.8)[c]	12 (5.8)[c]	14 (6.7)[c]	18 (8.7)[c]
All grades, IDHwt (n = 385)[d]	74 (19.2)	88 (22.9)	97 (25.2)	102 (26.5)

[a] Information on *MGMT* promoter methylation status was only available for 263 of the patients with glioblastoma.
[b] Information on IDH mutation was only available for 321 of the patients with glioblastoma.
[c] There was one event of VTE in a grade III patient with known IDH mutation but unknown 1p/19q codeletion status, who was therefore not included in the 109 grade III patients that were used to estimate VTE incidences according to molecular subgroup (upper half of the table), but was included as an IDHmt patient when analyzing patients of all grades together (bottom half of the table).
[d] IDHwt status was determined by immunohistochemistry alone in a majority of patients with glioblastoma (247/304), and by immunohistochemistry followed by PCR sequencing (as detailed in Methods) for 45/81 patients with lower-grade glioma.

results.[17] Moreover, a recent review of thousands of patients with glioma from a nationwide cancer database demonstrated that, based on 1p/19q codeletion status alone, up to 8.8% of histologically diagnosed astrocytomas and over 20% of histologically diagnosed oligodendrogliomas were historically misclassified according to the current WHO 2016 criteria, underscoring the importance of relying on molecular data to correctly interpret study results in patients with LGG.[18]

Our study, which examines large numbers of grade II and III disease, shows that the risk of VTE extends well beyond the postoperative period and is similar for both grades at 6 months (4.1% in grade II and 4.6% in grade III), then decelerates slightly for grade II at the 12- and 24-month mark before becoming again similar at the end of the follow-up period (8.2% for grade II and 9.2% in grade III). Although the incidence of VTE in LGG in our study was lower than for patients with GBM, the numbers still represent a major increase in the risk of VTE when compared to the general population, in which epidemiologic studies estimate VTE incidence at less than 0.2% per year.[19] This finding suggests that gliomas in general and not only GBMs are associated with a state of hypercoagulability.

Several studies have recently investigated the relationship between *IDH1* mutation status and VTE incidence in gliomas of all grades. The largest of these looked at 2 separate cohorts totaling 317 patients with glioma (of which 79 were grade II and III), and found a striking 0% incidence of VTE in the 76 patients who had an IDH mutation, compared to 27% in IDHwt patients.[4] Two subsequent articles reported similar results (1 with only 1 VTE in 42 IDHmt patients, occurring in

Figure 2 Competing Risks Regression for Venous Thromboembolism Incidence in Patients of All Grades According to IDH Mutation

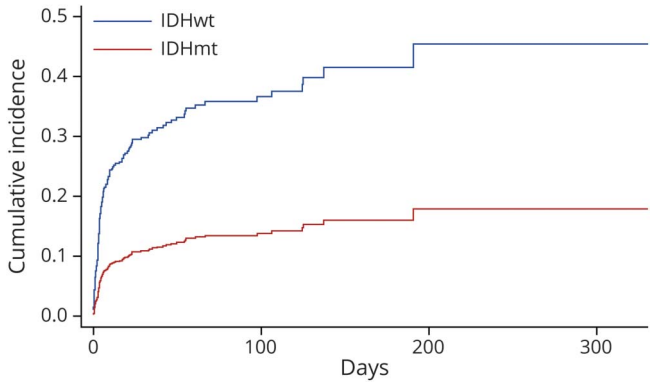
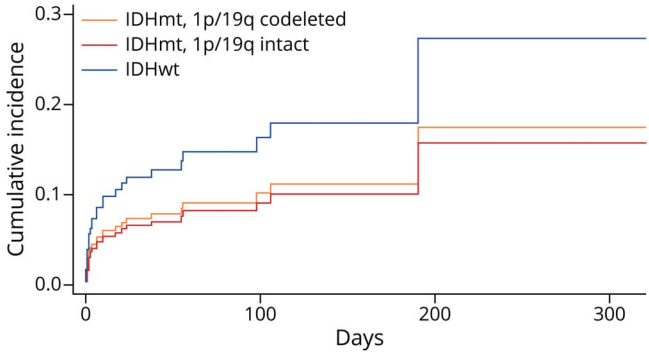


Figure 3 Competing Risks Regression for Venous Thromboembolism Incidence in Patients With Lower-Grade Glioma According to Molecular Type



a patient with a previous history of thrombosis,[5] and another one with 1 VTE in 27 IDHmt patients[20]). *IDH1* mutation in gliomas has been associated with hypermethylation and downregulation of *F3*, which in turn decreases the expression of procoagulant tissue factor (TF); this reduction in TF has been linked not only with an inhibition of coagulation,[4] but also with a decline in tumor proliferation and invasion, which may partially explain the lower level of malignancy seen in IDHmt gliomas.[21] D-2-hydroxyglutarate, the direct metabolite of mutant IDH, has been shown to inhibit platelet aggregation, although it is unclear if the levels of this substance are high enough in peripheral serum to have a distant effect on coagulation.[4] Our data confirm that IDH mutation status substantially affects the risk of VTE, with a threefold increase in VTE in IDHwt compared to IDHmt; this heightened risk persists when adjusting for known risk factors for VTE that tend to be disproportionately more frequent in IDHwt patients, including older age, higher tumor grade, and presence of hemiparesis. However, in contrast to previous studies, we did find a considerable number of VTE events in IDHmt patients, with 10/208 cases (4.8%) in the first 6 months, and 18 (8.7%) overall. Our larger number of patients (208 IDHmt patients) may partially explain this discrepancy. We identified our patients from a research database that specifically aimed to record VTE events, which may have increased our ability to capture those events that occurred outside our institution (5 out of 18 VTE episodes in IDHmt patients were not diagnosed at our center).

On the other hand, our results indicate that other routinely tested molecular alterations such as *MGMT* promoter methylation and EGFR overexpression have no influence in the risk of VTE. This is concordant with a recent retrospective study showing no difference in VTE risk according to *MGMT* promoter methylation status in patients with GBM.[22] Although *EGFR* amplification and mutation has been associated with an upregulation in tissue factor expression and an in vitro procoagulant effect,[23–25] our sample suggests that this may not translate into a heightened systemic hypercoagulability in clinical practice.

This study is a large single-center study of thromboembolic complications in patients with grade II and III gliomas. Weaknesses include its retrospective nature; data were collected from a retrospective database spanning several years and included patients diagnosed at other institutions, which limits the amount of clinical and molecular information available for some patients; for example, not all of our patients with LGG underwent genetic sequencing for rare noncanonical mutations in *IDH1* and *IDH2*, and subsequently some of those patients may have been misclassified as IDHwt. Strengths include the large number of patients and long follow-up time. Although our results do not fully overlap with other studies looking at the risk of VTE in IDHmt patients, they do add to the evidence that this mutation is linked with a decreased risk of systemic thrombosis.

Given the high risk of VTE in patients with glioma and its associated morbidity, there has been interest in determining whether long-term prophylaxis could be beneficial. Whereas a few recent randomized clinical trials have demonstrated a possible benefit in the use of direct oral anticoagulants as primary prophylaxis in select high-risk ambulatory cancer patients,[26–28] the applicability of these data to brain tumor patients in general is unclear. The only randomized trial that analyzed this issue in grade III and IV patients showed a reduction in VTE incidence in patients receiving low-molecular-weight heparin compared to placebo, accompanied by an increased risk of intracranial hemorrhage in these patients, neither of which was statistically significant.[29] Based on the results of our group and others demonstrating that IDH mutation is associated with a considerably lower VTE risk, a future trial that includes only IDHwt patients could provide more insight into a subpopulation with a favorable benefit–risk ratio from long-term VTE prophylaxis.

Patients with LGG have an increased risk of VTE compared to the general population that is decreased, but not eliminated, in the presence of an IDH mutation. Prospective trials analyzing anticoagulant use for primary prophylaxis specifically in IDHwt gliomas could help clarify the best management for these patients.

Study Funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 25, 2020. Accepted in final form October 12, 2020.

Appendix Authors

Name	Location	Contribution
Maria Diaz, MD	University of Virginia, Charlottesville	Major role in the acquisition of data, drafted the manuscript for intellectual content
Jasmin Jo, MD	University of Virginia, Charlottesville	Major role in the acquisition of data, revised the manuscript for intellectual content
Mark Smolkin, MS	University of Virginia, Charlottesville	Analyzed the data, revised the manuscript for intellectual content
Sarah J. Ratcliffe, PhD	University of Virginia, Charlottesville	Analyzed the data, revised the manuscript for intellectual content
David Schiff, MD	University of Virginia, Charlottesville	Designed and conceptualized study, revised the manuscript for intellectual content

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