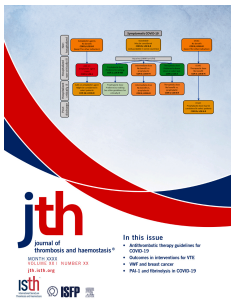

Antiplatelet medications and intracranial hemorrhage in patients with primary brain tumors

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Original Article:

Antiplatelet medications and intracranial hemorrhage in patients with primary brain tumors

Running title: Antiplatelet Medications in Primary Brain Tumors

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Essentials:

- Intracranial hemorrhage (ICH) occurs commonly in patients with primary brain tumors
- The role of antiplatelet agents in this setting has not been previously assessed
- Antiplatelet medications were not associated with an increased risk of ICH in patients with primary brain tumors
- In a glioblastoma subgroup, the use of antiplatelet medications did not increase the risk of ICH

Abstract

Background

Spontaneous intracranial hemorrhage (ICH) is a frequent and severe consequence of primary brain tumors. The safety of antiplatelet medications in this patient population is undefined.

Objective

The primary objective was to determine whether antiplatelet medications are associated with an increased risk of ICH in patients with primary brain tumors.

Patients/Methods

We performed a matched, retrospective cohort study of patients with the diagnosis of primary brain tumor treated at our institution between 2010 and 2021. Radiographic images of all potential ICH events underwent blinded review. The primary end point of the study was the cumulative incidence of ICH at 1 year after tumor diagnosis.

Results and Conclusions

A total of 387 patients with primary brain tumors were included in the study population (130 exposed to antiplatelet agents, 257 not exposed). The most common malignancy was glioblastoma (n=256, 66.1%). Among the intervention cohort, 119 patients received aspirin monotherapy. The cumulative incidence of any ICH at 1 year was 11.0% (95% confidence interval [CI], 5.3 - 16.6) in those receiving antiplatelet medications and 13.0% (95% CI, 8.5 – 17.6) in those not receiving antiplatelet medications (Gray test p = 0.6). The cumulative incidence of major ICH was similar between the cohorts (3.3% in antiplatelet cohort vs 2.9% in control cohort, p = 1.0). This study did not observe an increased incidence of ICH in patients with primary brain tumors exposed to antiplatelet medications.

Key words: Brain Tumors; Intracranial Hemorrhage; Glioblastoma; Anticoagulation, Aspirin

Introduction

Spontaneous intracranial hemorrhage (ICH) frequently complicates the clinical course of patients with primary brain tumors [1–3]. Among these tumors, higher grade gliomas and the highly vascular glioblastoma appear particularly prone to hemorrhage [4,5]. ICH can represent a devastating neurologic event in cancer patients and portends high morbidity and mortality. Previous studies have identified 30-day mortality rates as high as 50% and significant impaired functional status among survivors [6,7].

Antiplatelet medications, including aspirin and P2Y12 inhibitors, are often prescribed in patients with malignancy due to concomitant cardiovascular or cerebrovascular indications [8]. Though commonly regarded as safe and available for over-the-counter use, aspirin has been associated with an increased risk of hemorrhagic adverse events [9–11]. The impact of these agents on the risk of ICH in patients without brain tumors is uncertain [12–14]. There are limited data exploring antiplatelet medication and brain tumor-associated ICH [15]. Although the risk of ICH associated with antiplatelet agents was not increased in patients with brain metastases, whether this translates to patients with primary brain tumors is not known [16]. Accordingly, the risk of ICH is significantly higher among patients with primary brain tumors receiving therapeutic anticoagulation but not in the setting of secondary brain metastases [15].

To address whether antiplatelet agents influence the risk of ICH among patients with primary brain tumors, we investigated the incidence of ICH in patients with primary brain tumors on anti-platelet therapies compared to a matched cohort of patients without.

Methods

Study design

We conducted a retrospective matched cohort study at Beth Israel Deaconess Medical Center (BIDMC). The study was approved by the Institutional Review Board. Patients with a diagnosis of primary brain tumor treated at our institution between 2010 and 2021 were identified through

the BIDMC tumor registry. Patients with metastatic brain disease or with < 2 intracranial radiologic studies in the electronic medical record were excluded. Using both manual chart review and an electronic query tool, we extracted clinical variables including demographic information, medications exposures, comorbid conditions, and specific tumor location. Patients were included until patient death, date of last known contact (i.e. date of discharge to hospice), or date of final intracranial imaging study if death or hospice information was not available. Exposure to anticoagulation was defined as occurring within the 30 days prior to tumor diagnosis up to death or other censoring date. Information regarding cancer-directed therapies including systemic therapy, neurosurgery, involved field radiation, and stereotactic brain radiation were extracted manually from patient chart review.

The intervention group was defined by documented exposure to antiplatelet medications within 30 days prior to brain tumor diagnosis. Antiplatelet agents included aspirin and P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor). Each patient from the intervention cohort was matched with a control not exposed to antiplatelet agent using a "round-robin" scoring algorithm that ranked controls according to age, year of diagnosis, sex, anticoagulation exposure (either therapeutic or prophylactic), and tumor diagnosis [16,17]. Each patient from the intervention group was matched with one control and, if available, a second control.

Intracranial hemorrhage

Manual chart review was performed of all intracranial imaging reports including magnetic resonance imaging (MRI) and computed tomography (CT) scans to identify potential bleeding events. Information surrounding these events including patient symptomatology and subsequent clinical management were collected from the electronic medical record if a report indicated bleeding. We excluded any bleed that occurred within 4 weeks following neurosurgical intervention or that was attributable to stereotactic radiosurgery, which was determined by radiologic report describing hemorrhage or blood products in the irradiated field co-occurring with post-radiation changes. Radiologic images of each potential hemorrhage event were then reviewed by a neuro-radiologist with certificate of added qualification and 10 years' experience

and two trained research assistants blinded to the study cohort allocation to generate a consensus read confirming the presence or absence of bleed, calculate hemorrhage volume, and identify the type of bleeding event. Bleed size was calculated using the one-half ABC method [18]. ICH was classified as trace (< 1 cm^3), measurable (1 – 10 cm^3), or major (> 10 cm^3 or associated with clinical symptoms) [19].

Statistical analysis

The primary end point of the study was the cumulative incidence of ICH after initial tumor diagnosis. The initial sample size estimates were based on prior observed frequencies of ICH among patients with primary brain tumors receiving anticoagulation [17,20]. Accordingly, with an anticipated rate of ICH of 28% in the antiplatelet cohort and 14% in the control cohort, the target sample size was approximately 400 with a 1:2 sample size ratio (two-sided α of 0.05% and power of 0.80). The cumulative incidence of hemorrhage was compared across cohorts using the Gray test with death as a competing risk [22]. The Fine-Gray model was utilized to identify risk factor for ICH events in a competing risk analysis and report associated hazard ratios for covariables. A Kaplan-Meier analysis was used to estimate overall survival (OS) and compared using the log-rank test across the treatment and control cohorts. Statistical significance was defined as a P value < 0.05 across all analyses.

Results

Patient characteristics

The study population included 387 total patients with primary brain tumors. Of these patients, 130 were exposed to antiplatelet medications and 257 were not. The median age of patients at diagnosis was 66 years, and 47.8% of the cohort were female (n=185). As shown in Table 1, glioma represented the most common category of malignancy (n=319, 82.4%), and glioblastoma specifically comprised 66.1% of all study patients (n=256). The median number of intracranial imaging studies was seven across both study and control cohorts. The primary tumor was in a

supratentorial location for 86.6% of the cohort (n=355), and the remaining 13.4% were infratentorial (n=32). There were a higher proportion of patients with cardiovascular disease on the anti-platelet cohort (Table 1).

Within the intervention group, 119 patients (91.5%) were exposed to aspirin monotherapy, and 10 patients (7.7%) received dual antiplatelet therapy with aspirin and clopidogrel. One patient (0.8%) received clopidogrel monotherapy. Among the study cohort, the median time between primary tumor diagnosis and initiation of antiplatelet therapy was 18 days. A total of 60 patients (15.5%) across the study population received therapeutic anticoagulation. The number of patients on anticoagulants were: 29 (48.3%) enoxaparin, 8 (13.3%) warfarin, 5 (8.3%) apixaban, 2 (3.3%) heparin, 1 (1.7%) rivaroxaban and 15 (25%) received multiple anticoagulant agents during the study period.

Antiplatelet agents and ICH

The cumulative incidence of any ICH at 1 year was 11.0% (95% confidence interval [CI], 5.3 - 16.6) in those receiving antiplatelet medications compared with 13.0% (95% CI, 8.5 – 17.6) in those not receiving antiplatelet medications (P = 0.6, Gray test; Figure 1A). The cumulative incidence of major ICH at 1 year was 3.3% (95% CI, 0.1 – 6.5) in the intervention cohort compared to 2.9% (95% CI, 0.6 – 5.1) in the control cohort (P = 1, Gray test; Figure 1B).

There was not a significant difference in the volumes of ICH measured between those exposed and not exposed to antiplatelet medications (P = 0.28; Figure 2). Two of ten ICH (20.0%) were larger volume ($\geq$ 10 cm^3) in the antiplatelet group and 3 of 23 (13.0%) in the control group. A majority of the bleeding events were intraparenchymal (n=36, 65.5%) followed by subdural (n=12, 21.8%). Thirteen of the ICH events were associated with symptoms (Table 2). Five ICH events could not be categorized given that they were only captured on MRI images and the one-half ABC method is only validated for CT scans [18]. These bleeding events were excluded from Table 2. Bleeding events attributable to stereotactic radiosurgery or occurring in the four-week

period following neurosurgical intervention were excluded *a priori* (79 ICH in the antiplatelet-exposed cohort and 81 in the non-exposed cohort).

Clinical predictors for ICH

A univariate analysis to identify variables predictive of measure or major ICH found no significant predictive value of age at diagnosis, hypertension, exposure to neurosurgery, or tumor location (Table 3). We performed additional analyses to assess the impact of exposure to therapeutic anticoagulation. Of the patients exposed to antiplatelet agents, 16.2% received concomitant antiplatelet medication with therapeutic anticoagulation. There was not a statistically significant increase in the rate of major hemorrhage administration for the combination of antiplatelet agent with therapeutic anticoagulation (HR 2.14, 95% CI 0.24 – 19.41, P = 0.50) compared to neither. However, therapeutic anticoagulation alone did increase the risk of major ICH compared to those not taking either medication (HR 6.43, 95% CI 1.74 – 23.71, P = 0.005) as well as the risk of all ICH events compared to those not exposed to either medication (HR 2.63, 95% CI 1.35 – 5.11, P = 0.004).

Glioblastoma subgroup analysis

For patients with glioblastoma, the largest tumor subgroup in the study, the cumulative incidence of any ICH at 1 year was 15.6% (95% CI, 7 - 24.2) in those receiving antiplatelet medications compared to 15.9% (95% CI, 9.8 – 21.9) in those not receiving these medications (P = 0.99, Gray test; Figure 3). The cumulative incidence of major ICH at 1 year was 4.1% (95% CI, 0 – 8.7) in those receiving antiplatelet medications compared to 4.3% (95% CI, 0.9-7.7) among controls (P = 0.76, Gray test).

Overall survival

There was no statistically significant difference in the median survival of patients exposed (28.3 months; 95% CI, 19.6 – 47.7) or not exposed (21 months; 95% CI, 16.8 – 31.9; Log-rank P = 0.10) to antiplatelet medications (Figure 4).

Discussion

The increased risk of life-threatening hemorrhage in the setting of intracranial malignancy complicates the decision to initiate or continue antiplatelet agents. While previous studies demonstrated an increased risk of ICH with exposure to therapeutic anticoagulation in primary brain tumors [17,20,21,23], data on the safety of aspirin in this setting are lacking. We report the findings of a matched cohort study of 387 patients with primary brain tumors and did not observe an association with antiplatelet medications and the development of ICH.

There is conflicting evidence whether aspirin and other antiplatelet agents increase the risk of ICH in the general population in the setting of atherosclerotic disease. While previous meta-analyses or population-level studies suggested increased risk of ICH, these observations often do not hold at the level of individual studies [11,14,24]. A matched cohort study of 199,079 aspirin users in the United Kingdom reported an overall relative risk of 0.90 (95% CI 0.72-1.13) for development of all ICH [12]. Interestingly, this study reported a protective effect of aspirin against subarachnoid hemorrhage (SAH), a finding that has been replicated in other studies [14,25,26]. This protective effect may arise from aspirin-mediated blockade of inflammatory constituents of aneurysm development [27]. Within our study population, we found only a single SAH occurring within the first year after brain tumor diagnosis representing 1.8% of all bleeding events, and no SAH occurred in the antiplatelet-exposed cohort. Aspirin use has also been associated with increased hematoma size, loss of functional capacity, and higher mortality in patients experiencing spontaneous ICH [28,29], although the greatest impact appears to be with the use of dual anti-platelet agents [30]. Based on the limited numbers, we cannot conclude whether antiplatelet agents affect ICH size in the setting of primary brain tumors.

Rates of spontaneous ICH in primary brain tumors differ based on the specific tumor subtype [15]. Glioblastoma are known to carry one of the highest incidences of major bleeding among all cancer types [4,31]. The present study did not demonstrate an elevated risk of any or major ICH after antiplatelet exposure in a subgroup analysis of patients with glioblastoma, the largest tumor

subtype in the study cohort (66.1%). Interestingly, aspirin exposure has been shown to be associated with lower incidence of glioma in the Glioma International Case-Control Study [32], though its impact on ICH outcomes in this setting has not been previously characterized. We observed a non-significant 7-month improvement in median overall survival among those taking antiplatelet agents.

To the best of our knowledge, this is the first study to specifically explore the impact of antiplatelet agents on the risk of ICH in patients with primary brain tumors. Strengths of this study include use of a blinded radiology review with strict criteria for ICH including objective classifications based on hemorrhage volume. Previous retrospective studies investigating ICH are challenging to interpret given wide variation and inconsistencies in definition ranging from radiologic evidence of trace blood products to large-volume, symptomatic hemorrhage. However, we acknowledge limitations to our study. As a limited sample size retrospective study, we cannot exclude the possibility that antiplatelet agents result in a small increased risk in ICH. However, based on the observed rates of ICH in the two arms, more definitive studies would require many thousands of patients. We also acknowledge that despite the matched cohort study design, residual confounding is possible. The decision to pursue treatment with antiplatelet agents relies on a clinical context that may have similarly impacted patient morbidity and mortality. As expected, there were more patients with cardiovascular disease in the antiplatelet cohort. Despite the potential for cardiovascular risk factors such as hypertension to confound the results due to contribution to ICH risk, reassuringly we observed no significant different in ICH rates between the two groups. We recognize that given aspirin is available over-the-counter, it is possible that the non-exposed cohort may have included patients taking aspirin. Reassuringly, the observed rate of ICH is similar to other studies that included cohorts not thought to be taking antiplatelet agents [4,17]. A potential corroborating statistical analysis would be time-varying analysis to explore the incidence of ICH during antiplatelet exposure. However, we were not able to capture the granularity required for such analysis, i.e. discontinuation dates or temporary periods off-treatment. As there were a limited number of patients exposed to concomitant antiplatelet and anticoagulation in our cohort, interpretation of these study results to patients

exposed to this combination therapy is limited. Further investigation is warranted to delineate the risk of ICH in patients with primary brain tumors exposed to both types of agents. The majority of patients (66.1%) in this study carried the diagnosis of glioblastoma, we cannot definitively establish the safety in less represented primary brain tumors. Finally, given that we excluded bleeding that occurred in the four-week period following neurosurgery or stereotactic radiosurgery given the high bleeding risk posed by these interventions, the results of our study cannot be extrapolated to establish safety of antiplatelet medications during this period.

In summary, this study reports safety of antiplatelet medications in patients with primary brain tumors. Additional investigations are warranted to analyze the impact of combined antiplatelet and DOAC therapy in this patient population.

Authorship Statement:

RP and JZ conceived the research study. SM, GW, EM, JM, SP, RS, AP, PE, and SS collected data. SM, RP, and JZ interpreted the data and drafted the manuscript. SR and DN performed statistical analyses. All other authors critically reviewed and approved the final manuscript.

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Conflicts of Interest:

JIZ reports prior research funding from Incyte and Quercegen; consultancy for Sanofi, CSL Behring, and Calyx. The other authors state that they have no conflict of interest.

References

[1] Wakai S, Yamakawa K, Manaka S, Takakura K. Spontaneous intracranial hemorrhage caused by brain tumor: its incidence and clinical significance. *Neurosurgery* 1982; **10**: 437–44.

[2] Velander AJ, DeAngelis LM, Navi BB. Intracranial hemorrhage in patients with cancer. *Curr Atheroscler Rep* 2012; **14**: 373–81.

[3] Carney BJ, Uhlmann EJ, Puligandla M, Mantia C, Weber GM, Neuberg DS, Zwicker JI. Anticoagulation after intracranial hemorrhage in brain tumors: Risk of recurrent hemorrhage and venous thromboembolism. *Res Pract Thromb Haemost* 2020; **4**: 860–5.

[4] Kaptein FHJ, Stals MAM, Kapteijn MY, Cannegieter SC, Dirven L, van Duinen SG, van Eijk R, Huisman M v, Klaase EE, Taphoorn MJB, Versteeg HH, Buijs JT, Koekkoek JAF, Klok FA. Incidence and determinants of thrombotic and bleeding complications in patients with glioblastoma. *J Thromb Haemost* 2022; **20**: 1665–73.

[5] Zoccarato M, Nardetto L, Basile AM, Giometto B, Zagonel V, Lombardi G. Seizures, Edema, Thrombosis, and Hemorrhages: An Update Review on the Medical Management of Gliomas. *Front Oncol* 2021; **11**: 617966.

[6] Navi BB, Reichman JS, Berlin D, Reiner AS, Panageas KS, Segal AZ, DeAngelis LM. Intracerebral and subarachnoid hemorrhage in patients with cancer. *Neurology* 2010; **74**: 494–501.

[7] Sansing LH, Messe SR, Cucchiara BL, Cohen SN, Lyden PD, Kasner SE, CHANT Investigators. Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH. *Neurology* 2009; **72**: 1397–402.

[8] Mora S, Manson JE. Aspirin for Primary Prevention of Atherosclerotic Cardiovascular Disease: Advances in Diagnosis and Treatment. *JAMA Intern Med* 2016; **176**: 1195–204.

[9] Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373**: 1849–60.

[10] Seshasai SRK, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, Ray KK. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012; **172**: 209–16.

[11] Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans C v. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016; **164**: 826–35.

[12] Cea Soriano L, Gaist D, Soriano-Gabarró M, Bromley S, García Rodríguez LA. Low-dose aspirin and risk of intracranial bleeds: An observational study in UK general practice. *Neurology* 2017; **89**: 2280–7.

[13] Gulati S, Solheim O, Carlsen SM, Øie LR, Jensberg H, Gulati AM, Madsbu MA, Giannadakis C, Jakola AS, Salvesen Ø. Risk of intracranial hemorrhage (RICH) in users of oral antithrombotic drugs: Nationwide pharmacoepidemiological study. *PLoS One* 2018; **13**: e0202575.

[14] García-Rodríguez LA, Gaist D, Morton J, Cookson C, González-Pérez A. Antithrombotic drugs and risk of hemorrhagic stroke in the general population. *Neurology* 2013; **81**: 566–74.
[15] Iyengar V, Patell R, Zwicker J. Challenges in anticoagulation for patients with brain tumors. *Best Pract Res Clin Haematol* 2022; **35**: 101350.
[16] Miller EJ, Patell R, Uhlmann EJ, Ren S, Southard H, Elavalakanar P, Weber GM, Neuberg D, Zwicker JI. Antiplatelet medications and risk of intracranial hemorrhage in patients with metastatic brain tumors. *Blood Adv* 2022; **6**: 1559–65.
[17] 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**: 3379–85.
[18] Yang W, Feng Y, Zhang Y, Yan J, Fu Y, Chen S. Volume quantification of acute infratentorial hemorrhage with computed tomography: validation of the formula 1/2ABC and 2/3SH. *PLoS One* 2013; **8**: e62286.
[19] Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3**: 692–4.
[20] Porfidia A, Giordano M, Sturiale CL, D'Arrigo S, Donadini MP, Olivi A, Ageno W, Pola R. Risk of intracranial bleeding in patients with primary brain cancer receiving therapeutic anticoagulation for venous thromboembolism: A meta-analysis. *Brain Behav* 2020; **10**: e01638.
[21] Carney BJ, Uhlmann EJ, Puligandla M, Mantia C, Weber GM, Neuberg DS, Zwicker JI. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. *J Thromb Haemost* 2019; **17**: 72–6.
[22] Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999; **94**: 496–509.
[23] 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**: 105–8.
[24] McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; **119**: 624–38.
[25] Gross BA, Rosalind Lai PM, Frerichs KU, Du R. Aspirin and aneurysmal subarachnoid hemorrhage. *World Neurosurg* 2014; **82**: 1127–30.
[26] Hasan DM, Mahaney KB, Brown RD, Meissner I, Piepgras DG, Huston J, Capuano AW, Torner JC, International Study of Unruptured Intracranial Aneurysms Investigators. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. *Stroke* 2011; **42**: 3156–62.
[27] Starke RM, Chalouhi N, Ding D, Hasan DM. Potential role of aspirin in the prevention of aneurysmal subarachnoid hemorrhage. *Cerebrovasc Dis* 2015; **39**: 332–42.
[28] Law ZK, Desborough M, Roberts I, Al-Shahi Salman R, England TJ, Werring DJ, Robinson T, Krishnan K, Dineen R, Laska AC, Peters N, Egea-Guerrero JJ, Karlinski M, Christensen H, Roffe C, Bereczki D, Ozturk S, Thanabalan J, Collins R, Beridze M, et al. Outcomes in Antiplatelet-Associated Intracerebral Hemorrhage in the TICH-2 Randomized Controlled Trial. *J Am Heart Assoc* 2021; **10**: e019130.

[29] Thompson BB, Béjot Y, Caso V, Castillo J, Christensen H, Flaherty ML, Foerch C, Ghandehari K, Giroud M, Greenberg SM, Hallevi H, Hemphill JC, Heuschmann P, Juvela S, Kimura K, Myint PK, Nagakane Y, Naritomi H, Passero S, Rodríguez-Yáñez MR, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010; **75**: 1333–42.

[30] Khan NI, Siddiqui FM, Goldstein JN, Cox M, Xian Y, Matsouaka RA, Heidenreich PA, Peterson ED, Bhatt DL, Fonarow GC, Schwamm LH, Smith EE. Association Between Previous Use of Antiplatelet Therapy and Intracerebral Hemorrhage Outcomes. *Stroke* 2017; **48**: 1810–7.

[31] Wang T-F, Zwicker JI, Ay C, Pabinger I, Falanga A, Antic D, Noble S, Khorana AA, Carrier M, Meyer G. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: Guidance from the SSC of the ISTH. *J Thromb Haemost* 2019; **17**: 1772–8.

[32] Amirian ES, Ostrom QT, Armstrong GN, Lai RK, Gu X, Jacobs DI, Jalali A, Claus EB, Barnholtz-Sloan JS, Il'yasova D, Schildkraut JM, Ali-Osman F, Sadetzki S, Jenkins RB, Lachance DH, Olson SH, Bernstein JL, Merrell RT, Wrensch MR, Johansen C, et al. Aspirin, NSAIDs, and Glioma Risk: Original Data from the Glioma International Case-Control Study and a Meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2019; **28**: 555–62.

Figure 1:
Cumulative incidence of ICH at 1 year. Figure 1A depicts all ICH and figure 1B depicts major ICH event in patients on antiplatelet agent (dashed red line) compared to control (solid blue line).

Figure 2:
Distribution of ICH size in patients not exposed to antiplatelet medications (upper panel) and patients exposed to antiplatelet medications (lower panel).

Figure 3:
Cumulative incidence of ICH at 1 year for the glioblastoma subgroup. Figure 3A depicts all ICH and figure 3B depicts major ICH event in patients on antiplatelet agent (dashed red line) compared to control (solid blue line).

Figure 4:
Kaplan-Meier curves for overall survival of intervention (dashed red line) and control (solid blue line) groups.

Table 1: Baseline patient demographics and characteristics

Characteristic	Antiplatelet, n = 130	Control, n = 257
Female (number, %)	48 (36.9)	137 (53.3)
Age (median, range)	67 (22 – 94)	65 (18 – 97)
Primary malignancy (number, %)		
Glioma	98 (75.4)	221 (86.0)
Glioblastoma	78 (60.0)	178 (69.3)
Anaplastic astrocytoma	5 (3.8)	16 (6.2)
Anaplastic oligodendroglioma	6 (4.6)	2 (0.8)
Diffuse astrocytoma	2 (1.5)	6 (2.3)
Miscellaneous[a]	7 (5.4)	19 (7.4)
Non-glioma	32 (24.6)	36 (14.0)
Craniopharyngioma	2 (1.5)	2 (0.8)
Ependymoma	3 (2.3)	5 (1.9)
Hemangioblastoma	7 (5.4)	4 (1.6)
Hemangioma	1 (0.8)	8 (3.1)
Meningioma	3 (2.3)	1 (0.4)
Schwannoma	7 (5.4)	5 (1.9)
Subependymoma	4 (3.1)	4 (1.6)
Miscellaneous[b]	5 (3.8)	7 (2.7)
Tumor location		
Frontal	36 (27.7)	83 (32.3)
Parietal	21 (16.2)	36 (14.0)
Occipital	7 (5.4)	10 (3.9)
Temporal	25 (19.2)	61 (23.7)
Multiple lobes[c]	4 (3.1)	21 (8.2)
Cerebellum	7 (5.4)	15 (5.8)
Brainstem (pons, medulla, or midbrain)	5 (3.8)	2 (0.8)
Cerebellopontine angle	7 (5.4)	4 (1.6)
Corpus callosum	4 (3.1)	4 (1.6)
Ventricle (third, fourth, or lateral)	9 (6.9)	8 (3.1)
Miscellaneous[d]	5 (3.8)	13 (5.1)
Comorbidities		
Hypertension	103 (79.2)	80 (31.1)
Chronic Kidney Disease	12 (9.2)	6 (2.3)
Prior ICH	0 (0.0)	8 (3.1)
Atrial fibrillation or flutter	5 (3.8)	12 (4.7)
Venous thromboembolism	0 (0.0)	9 (3.5)
Coronary artery disease	23 (17.7)	14 (5.4)
Hyperlipidemia	65 (50.0)	76 (29.6)
Peripheral vascular disease	1 (0.8)	4 (1.6)

Stroke or transient ischemic attack	6 (4.6)	12 (4.7)
Treatment of brain tumor		
Systemic therapy	75 (57.7)	144 (56.0)
Stereotactic radiation therapy	22 (16.9)	43 (16.7)
Involved-field radiation therapy	81 (62.3)	149 (58.0)
Neurosurgery	115 (88.5)	233 (90.7)
Anticoagulant exposure	21 (16.2)	39 (15.2)
Heparin	1 (0.8)	1 (0.4)
Enoxaparin	7 (5.4)	22 (8.6)
Apixaban	1 (0.8)	4 (1.6)
Rivaroxaban	1 (0.8)	0 (0.0)
Warfarin	4 (3.1)	4 (1.6)
Multiple	7 (5.4)	8 (3.1)
Median number of imaging studies (median, range)	7 (2-27)	7 (2-24)

Data presented as n (%).

[a]Miscellaneous glioma includes dysembryoplastic neuroepithelial tumor, ganglioma, giant cell astrocytoma, glioma NOS (non-biopsied suspected glioma), gliomatosis cerebri, gliosarcoma, pilocytic astrocytoma

[b]Miscellaneous non-glioma includes choroid plexus papilloma, craniopharyngioma, cystic teratoma, germ cell tumor, granular cell tumor, hemangiopericytoma, lymphoma, medulloblastoma, neurofibroma, pinealoma

[c]Multiple lobes includes patients with more than one of frontal, occipital, parietal, or temporal listed

[d]Miscellaneous location includes basal ganglia, optic chiasm, suprasellar, thalamus

Table 2: Characteristics of ICH Events

	Total (n = 55)	**Antiplatelet (n = 18)**	**Control (n = 37)**
ICH Category (%)			
Major	14 (25.5)	5 (27.8)	9 (24.3)
Measurable	19 (34.5)	5 (27.8)	14 (37.8)
Trace	17 (30.9)	8 (44.4)	9 (24.3)
Location of bleed			
Intraparenchymal	36 (65.5)	11 (61.1)	25 (67.6)
Subdural	12 (21.8)	4 (22.2)	8 (21.6)
Intraventricular	6 (10.9)	3 (16.7)	3 (8.1)
Subarachnoid	1 (1.8)	0 (0.0)	1 (2.7)
Presence of symptoms	13 (23.6)	5 (27.8)	8 (21.6)
ICH volume, mean +/- SD	10 +/- 20.5	12.5 +/- 23.7	8.9 +/- 19.4
Anticoagulation exposure	32 (58.2)	13 (72.2)	19 (51.4)

Table 3: Univariable analysis for factors predictive of measurable or major ICH.

	Hazard ratio (95% CI)	P-value
Age at diagnosis		
35-64 vs. 18-34	1.99 (0.26 – 15.52)	0.51
> 65 vs. 18-34	1.12 (0.14 – 8.99)	0.91
Hypertension	1.16 (0.59 – 2.30)	0.67
Surgery	3.10 (0.42 – 23.01)	0.27
Tumor location (supratentorial vs. infratentorial)	1.17 (0.40 – 3.37)	0.78
Anticoagulation		
All ICH		
Antiplatelet and Anticoagulation vs. Neither	2.80 (1.19 – 6.60)	**0.02**
Antiplatelet only vs. Neither	0.79 (0.39 – 1.60)	0.51
Anticoagulation only vs. Neither	2.63 (1.35 – 5.11)	**0.004**
Major ICH		
Antiplatelet and Anticoagulation vs. Neither	2.14 (0.24 – 19.41)	0.50
Antiplatelet only vs. Neither	1.85 (0.46 – 7.47)	0.39
Anticoagulation only vs. Neither	6.43 (1.74 – 23.71)	**0.005**