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ORIGINAL ARTICLE

Incidence and determinants of thrombotic and bleeding complications in patients with glioblastoma

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Abstract

Background: Glioblastoma patients are considered to be at high risk of venous thromboembolism (VTE) and major bleeding (MB), although reliable incidence estimates are lacking. Moreover, the risk of arterial thromboembolism (ATE) in these patients is largely unknown. Our aim was to assess the cumulative incidence, predictors, and prognostic impact of VTE, ATE, and MB on subsequent complications and mortality.

Methods: Cohort study of 967 consecutive patients diagnosed with glioblastoma between 2004–2020 in two hospitals. Patients were followed from 6 months before date of histopathological glioblastoma diagnosis up to 2 years after, or until an outcome of interest (VTE, ATE, and MB) or death occurred, depending on the analysis. Cumulative incidences were estimated with death as competing risk. Cox regression was used to identify predictors and the prognostic impact.

Results: A total of 101 patients were diagnosed with VTE, 50 with ATE, and 126 with MB during a median follow-up of 15 months (interquartile range 9.0–22). The adjusted 1-year cumulative incidence of VTE was 7.5% (95% confidence interval [CI] 5.9–9.3), of ATE 4.1% (95% CI 3.0–5.6), and of MB 12% (95% CI 9.6–14). Older age, type of surgery, and performance status were predictors of VTE. Incident VTE during follow-up was associated with MB (adjusted HR 4.7, 95% CI 2.5–9.0). MB and VTE were associated with mortality (adjusted HR 1.7, 95% CI 1.3–2.1 and 1.3, 95% CI 1.0–1.7, respectively).

Conclusion: We found considerable incidences of VTE and MB in glioblastoma patients, with both complications associated with poorer prognosis. Our observations emphasize the need for prospective studies to determine optimal thromboprophylaxis and VTE treatment strategy in these patients.

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KEYWORDS
anticoagulants, glioblastoma, hemorrhage, infarction, venous thromboembolism

1 | INTRODUCTION

Glioblastoma is the most common and aggressive primary brain tumor in adults, with an annual incidence of 3 per 100 000 persons and a median expected survival time of 15 months.[1] Venous thromboembolism (VTE) is a well-known complication in patients with a malignancy, and glioblastoma patients are particularly susceptible for VTE with reported incidences ranging from 8% to 39%,[2–6] depending on the use of thromboprophylaxis, VTE definition, and VTE detection method. The VTE risk is the highest in the postoperative period[7,8] but remains higher when compared with other malignancies throughout the course of the disease.[9,10] In line with the general cancer population, VTE in glioblastoma patients has been reported to be associated with increased mortality.[11]

More recently, arterial thrombosis (ATE) has also been recognized as a serious complication of cancer,[12] but for glioblastoma the incidence of ATE is not sufficiently studied. Small studies report a 1.3% to 9.0% incidence of stroke, but data on e.g., myocardial infarction are unavailable.[13–15] Notably, glioblastomas are highly vascular, and tumor-related intracranial hemorrhage (ICH) frequently occurs. Patients may occasionally present with an intralesional bleeding as the first symptom of glioblastoma (0.5%–3.4% of the cases[16,17]) or develop spontaneous intratumoral hemorrhage during the course of the disease (incidence 2%–8%[18]). Because of the potentially devastating consequences of ICH, physicians are hesitant to prescribe therapeutic anticoagulation after VTE or ATE is diagnosed.[19,20]

Available estimations of the incidences of VTE and bleeding are based on small cohort studies, with an often-heterogeneous patient population, and usually have focused on either thrombotic or bleeding complications. Furthermore, broad, not always clinically relevant, outcome definitions were used. Without accurate incidences, it remains challenging for physicians to determine the optimal VTE prophylactic and therapeutic strategy. Therefore, the aim of our study was threefold: (1) to provide reliable cumulative incidences of clinically relevant thrombotic and bleeding complications in a large practice-based cohort of glioblastoma patients; (2) to explore possible clinical predictors for VTE, ATE and MB; and (3) to assess the prognostic impact of thrombosis and bleeding on subsequent complications and all-cause mortality.

Essentials

- Glioblastoma patients are at high risk of developing venous thromboembolism (VTE) and bleeding.
- We studied the cumulative incidence, predictors and prognostic impact of VTE and bleeding.
- Both VTE and major bleeding were frequent and were associated with poorer prognosis.
- Prospective studies are needed to determine the best VTE treatment and prevention strategy.

2 | METHODS

2.1 | Study design, patients, and data collection

In this retrospective cohort study, consecutive adult patients treated for glioblastoma between 2004 and 2020 in Leiden University Medical Center (Leiden, The Netherlands) and/or Haaglanden Medical Center (The Hague, The Netherlands), were followed for the occurrence of venous and arterial thrombotic complications and bleeding complications. All patients had a histologically confirmed diagnosis of glioblastoma according to the World Health Organization criteria applicable at time of surgery.[1,21] The most recent World Health Organization classification (5th edition, 2021[22]) includes the isocitrate dehydrogenase (IDH) status (i.e., IDH-wildtype) as a necessary component of glioblastoma diagnosis, which was only available in patients diagnosed from 2017 on.

The standard of care for glioblastoma patients consisted of pursuing maximum "safe" resection in all patients. If tumor location or patient condition did not allow for surgical resection, a biopsy was performed for histological confirmation. Standard adjuvant anticancer therapy in patients <70 years old and Eastern Cooperative Oncology Group (ECOG) grade ≤1 was according to the Stupp protocol: 6 weeks of radiotherapy (30 × 2 Gy) with concomitant temozolomide chemotherapy (75 mg/m^2 once daily), followed by six cycles of temozolomide monotherapy (150 mg/m^2 once daily for 5 days per 28-day cycle). For patients ≥70 years or <70 years old and ECOG ≥2, the elderly Stupp (or Perry) scheme included concomitant chemoradiotherapy for 3 weeks (15 × 2.66 Gy), followed by six temozolomide cycles (equivalent dosing as Stupp protocol); a short 3-week course of radiotherapy only; or monotherapy with temozolomide in case of O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.[23]

Patients received pharmacological thromboprophylaxis during hospital admission (subcutaneous nadroparin 2850 IU once daily, or 5700 IU once daily when body weight >100 kg and/or presence of ≥1 additional VTE risk factor according to the simplified Caprini score[24]). Routine thromboprophylaxis was not prescribed in ambulant patients.

Patients were followed from 6 months before histopathological diagnosis until 2 years after, until last date of follow-up, until the end of data collection on 19 March 2021, or until death, whichever came first (resulting in a maximum observation period of 2.5 years).

This 6-month period before diagnosis was based on the usual window of several days to weeks between suspicion of a glioblastoma and histopathological confirmation, and the fast increasing risk of VTE and ATE in this period.[25] Patients who eventually became lost to follow-up were included in the analyses up to the last date with available information in the patient chart.

Data collection was performed by manually scrutinizing patient charts for baseline characteristics (demographics, ECOG performance status, and treatment details) and the occurrence of outcomes of interest, using a standardized electronic case report form. This study was approved by the local institutional review board of the two hospitals and informed consent was waived.

2.2 | Outcomes

The main study outcomes were (fatal) VTE, ATE, major bleeding (MB), and all-cause death. VTE consisted of either symptomatic or incidental pulmonary embolism, deep vein thrombosis of the upper or lower extremities, cerebral sinus vein thrombosis, or splanchnic vein thrombosis, and was confirmed by computed tomography, magnetic resonance, or ultrasound imaging.[26,27] ATE included ischemic stroke, myocardial infarction and peripheral arterial embolism. Ischemic stroke was confirmed by computed tomography or magnetic resonance imaging of the brain. Myocardial infarction was confirmed by corresponding electrocardiogram, echocardiogram, cardiac enzymes, and preferably coronary angiography. Peripheral arterial embolism was diagnosed with computed tomography angiography or Doppler ultrasound of the extremities. We followed the International Society on Thrombosis and Haemostasis (ISTH) definition of MB, defining MB as (1) fatal bleeding, (2) symptomatic bleeding in a critical area or organ, or (3) bleeding causing a fall in hemoglobin level of ≥1.24 mmol/L, or leading to a transfusion of ≥2 U of blood.[28] Postoperative MBs and ATEs were defined as intracranial bleeding or ischemia, respectively, in the surgical field within 7 days after surgery. Trace radiologic evidence of blood products or common postoperative venous infarction were not included. Endpoints were adjudicated by two independent experts (F.A.K. and J.A.F.K.), without any discrepancies.

2.3 | Statistical analysis

Patient characteristics were described using standard descriptive statistics. ECOG score was divided in a good (0–1) vs. a moderate to poor (≥2) performance status.

For our first study aim, cumulative incidences for the different outcomes were estimated using the Kaplan-Meier method and the cumulative incidence competing risk method, to adjust for the competing risk of death, and were calculated from the index date (i.e., 6 months before the date of histopathological diagnosis of glioblastoma). Because postoperative intracranial bleeding and ischemia may have a different pathophysiology, a sensitivity analysis was performed in which these postoperative events were excluded.

For our second aim, possible outcome predictors were identified with univariable Cox regression models. To assess the prognostic impact of occurrence of a thrombotic event (our third aim), Cox regression analysis was performed using VTE, ATE, or MB as time-dependent variables, adjusting for age, performance status, type of surgery (as known and available risk factors for at least VTE and mortality[2,8]), and sex (because not all sex-specific factors affecting prognosis are known or understood[29,30]). A sensitivity analysis was performed in patients with a known IDH-wildtype status. Per analysis, only those patients with complete data relevant to the particular analysis were used.

Statistical analyses were carried out in SPSS Statistics version 25.0 and RStudio version 1.3.1056.

3 | RESULTS

3.1 | Patients

A total of 967 patients with confirmed glioblastoma were included in the study. Patient baseline characteristics are presented in Table 1. The mean age was 63 years (standard deviation 12) and 580 patients (60%) were male. IDH mutation status was known in 373 patients (39%), of whom 350 were wildtypes (94%). Figure S1 illustrates the applied cancer treatment strategy in the included patients.

At the end of the observation period, 136 (14%) of the patients were still alive, 631 (65%) had died, and 156 (16%) were lost to follow-up; 44 (4.6%) had not yet reached 2 years of follow-up or an endpoint at the end of data collection. The median observation time was 15 months (interquartile range [IQR] 9.0–22).

3.2 | Venous thromboembolism

During the observation period 101 patients were diagnosed with VTE (10%), consisting of 51 isolated pulmonary embolisms (PEs; 50%), 46 DVTs of the lower extremities (46%), one confirmed PE with concomitant DVT, and three venous sinus thromboses (3.0%). Most VTEs were symptomatic (94/101, 93%), except for all three sinus thromboses, the concomitant PE and DVT, and three isolated PEs. Seven patients developed their VTE before the histopathological confirmation of glioblastoma (6.9%), of which five were within 1 month before diagnosis. Fourteen VTEs occurred within 4 weeks postoperatively (14%), and 40 VTEs (40%) were diagnosed during any type of active adjuvant therapy (chemotherapy, radiotherapy, and/or immunotherapy), of which 32 during initial adjuvant therapy, and eight during treatment of glioblastoma recurrence. The median time to VTE was 3.7 months (IQR 1.4–7.1) after glioblastoma diagnosis (i.e., 9.7 months after start of the observation period). Seventy patients used dexamethasone at time of VTE diagnosis (69%), and three patients developed a VTE under therapeutic anticoagulation (3%). Most patients started therapeutic anticoagulation therapy after VTE diagnosis (n = 93, 91%), of which the majority received

TABLE 1 Patient characteristics

Characteristic	N = 967
Age at diagnosis in years (mean, SD)	63 (12)
Sex (*n*, %)	
Male	580 (60)
Type of surgery at diagnosis (*n*, %)	
Biopsy	244 (25)
(Partial) resection	723 (75)
IDH status (*n*, %)	
Wildtype	350 (36)
Mutation	23 (2.4)
Unknown	594 (61)
Complete follow-up (*n*, %)	136 (14)
Incomplete follow-up (*n*%)	831 (86)
Died before end of observation	630 (65)
Lost to follow-up	157 (16)
Total follow-up in months (median, IQR)	15 (9.0–22)
Cause of death (*n* = 630) (*n*, %)	
Glioblastoma[a]	565 (90)
PE-related	4 (0.6)
Bleeding	12 (1.9)
Other	23 (3.7)
Myocardial infarction	1 (0.2)
Infection	20 (3.2)
Undetermined	26 (4.2)
Performance status at diagnosis (ECOG) (*n*, %)	
0–1	645 (67)
≥2	318 (33)
Recurrent glioblastoma (*n*, %)	533 (55)

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; IDH, isocitrate dehydrogenase; IQR, interquartile range; PE, pulmonary embolism; SD, standard deviation.

[a]Defined as resulting from tumor mass effect or any death in the terminal care setting in the absence of another more likely cause of death.

therapeutic low molecular weight heparin (*n* = 64, 63%). Nine patients developed recurrent VTE (9%) during the observation period, of which two were under therapeutic anticoagulation and one under prophylactic dose anticoagulation (after a recent bleeding).

The 1-year cumulative incidence of VTE, adjusted for the competing risk of death, was 7.5% (95% CI 5.9–9.3) (Figure 1 and Table S1). The 2.5-year adjusted cumulative incidence was 12% (95% CI 9.9–14), for an incidence rate of 8.1 per 100 patient years (95% CI 6.7–9.8).

3.3 | Arterial thromboembolism

Fifty patients developed an ATE during the observation period (5.2%), which were predominantly ischemic strokes (*n* = 46, 92%); two patients developed a myocardial infarction (4%), one patient a peripheral arterial thromboembolism (2%), and one patient a concurrent ischemic stroke and peripheral arterial thromboembolism (2%). Five ATEs occurred before histological glioblastoma confirmation (10%); 28 occurred postoperatively (56%) and three patients developed recurrent ATE (6%) within the observation period.

The adjusted cumulative incidence of all ATEs at 1 year was 4.1% (95% CI 3.0–5.6) and it was 5.6% (95% CI 4.2–7.3) at 2.5 years (Figure 1 and Table S1). This accounts for an incidence rate of 3.9 per 100 patient years (95% CI 3.0–5.1). In the sensitivity analysis (excluding postoperative ATEs), the adjusted 2.5-year cumulative incidence was 2.7% (95% CI 1.7–3.9), corresponding to an incidence rate of 1.7 per 100 patient-years (95% CI 1.1–2.6).

3.4 | Major bleeding

A total of 126 patients were diagnosed with MB (13%) during the observation period (after a median of 6.0 months, IQR 6.0–7.5), of which the overall majority was intracranial (*n* = 118, 94%), followed by gastrointestinal (*n* = 5), hematuria (*n* = 1), and cutaneous (*n* = 1). Twenty-five MBs occurred before first tumor surgery (20%), and it was the first presenting symptom of glioblastoma in 15 patients (12%); 61 MBs occurred within 1 week after surgery (48%). Sixteen of the 126 patients were using therapeutic anticoagulation at time of bleeding, of which 12 (75%) had started anticoagulation because of incident VTE during the observation period (of the others, two used anticoagulation for atrial fibrillation, one for a VTE before the observation period and one for a prosthetic heart valve). Thirteen patients had one or more recurrent MB (10%), of which two were under anticoagulation, both because of a VTE during the observation period. The adjusted 1- and 2.5-year cumulative incidences of MB were 12% (95% CI 9.6–14) and 14% (95% CI 12–16), respectively (Figure 1 and Table S1), for an incidence rate of 10 per 100 patient years (95% CI 8.6–12.0). In the sensitivity analysis (excluding postoperative bleeding events), the adjusted cumulative incidence was 7.3% (95% CI 5.7–9.2) at 2.5 years (incidence rate 5.1 per 100 patient years, 95% CI 4.0–6.5).

3.5 | Disease recurrence and survival

During the observation period, 533 patients (55%) developed recurrent glioblastoma (defined as progression or recurrence of the tumor after a period of disease control by therapy), after a median of 7.7 months (4.8–12). Of those, 292 (55%) received treatment for tumor recurrence (re-resection, radiotherapy, systemic therapy, or a combination).

The cause of death was predominantly from glioblastoma (*n* = 565/630, 90%; Table 1). Of the remaining deaths, four were PE-related (0.63%), 12 patients had a fatal major bleeding (1.9%; all intracranial), and one patient a fatal myocardial infarction (0.16%). Three of the 12 patients with fatal ICH were using therapeutic anticoagulation, all started because of a VTE during the observation period.

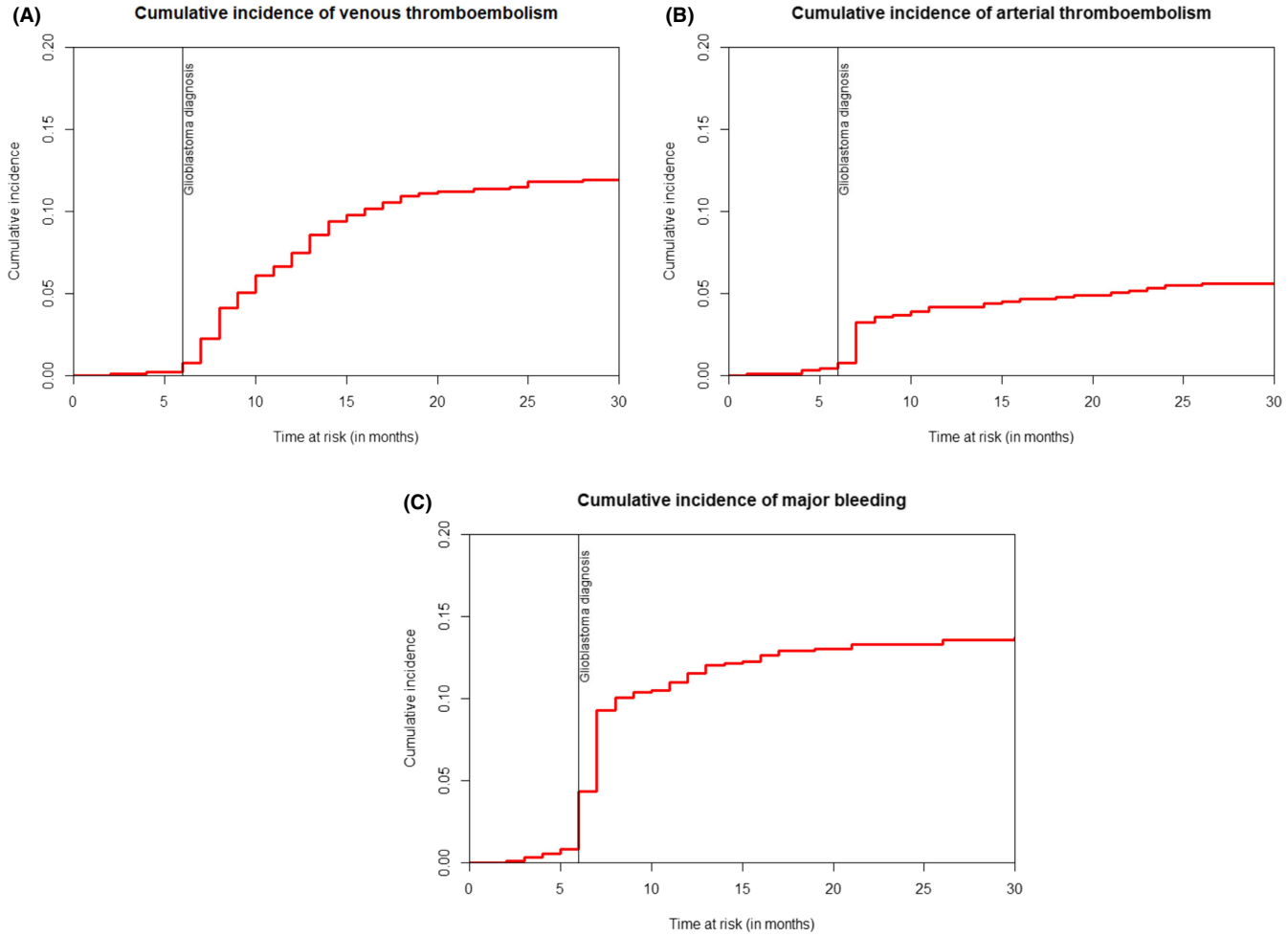

FIGURE 1 Cumulative incidences of venous thromboembolism (A), arterial thromboembolism (B) and major bleeding (C), adjusted for the competing risk of death

TABLE 2 Association between clinical variables and outcomes of interest

Variable	N[a]	VTE (HR, 95% CI)	MB (HR, 95% CI)	ATE (HR, 95% CI)	Mortality (HR, 95% CI)
Age (years)	967	1.03 (1.01–1.05)	1.01 (0.99–1.03)	1.0 (0.98–1.0)	1.04 (1.03–1.05)
Sex (female vs. male)	967	0.78 (0.52–1.2)	1.1 (0.77–1.6)	0.86 (0.48–1.5)	1.1 (0.91–1.3)
IDH status (wildtype vs. mutation)	373	1.4 (0.34–6.0)	1.6 (0.38–6.7)	0.53 (0.12–2.3)	2.5 (1.3–4.6)
ECOG status (≥2 vs. 0–1)[b]	951	2.0 (1.3–3.1)	1.4 (0.95–2.1)	1.5 (0.81–2.6)	2.5 (2.1–2.9)
Type of surgery (resection vs. biopsy)[b]	956	0.53 (0.33–0.84)	1.1 (0.66–1.7)	6.5 (1.6–27)	0.37 (0.31–0.44)

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IDH, isocitrate dehydrogenase; MB, major bleeding; VTE, venous thromboembolism.

[a]Number of patients with known value for corresponding variable.

[b]Only outcomes after diagnosis included.

3.6 | Outcome predictors

Regression analyses showed that older age was associated with VTE (hazard ratio [HR] 1.03 per year increase, 95% CI 1.01–1.05), as was an ECOG performance state of 2 or higher at the moment of the glioblastoma diagnosis (HR 2.0, 95% CI 1.3–3.1), or a (partial) resection (vs. biopsy; HR 0.53, 95% CI 0.33–0.84; Table 2). No predictors for MB were identified. Resection (vs. biopsy) was a predictor for ATE (HR 6.5, 95% CI 1.6–27), but this association was lost in the sensitivity analysis with only nonpostoperative ATEs (HR 2.0, 95% CI 0.45–8.5). For mortality, higher age, worse performance status and biopsy (vs. resection) were predictive, as well as IDH-wildtype status.

3.7 | Prognostic impact

The occurrence of a VTE during follow-up was associated with subsequent major bleeding (all MBs: adjusted HR [aHR] 4.8, 95% CI 2.5–9.3; nonpostoperative MBs: aHR 7.5, 95% CI 3.6–15; Table 3). There was no association between incident VTE, ATE, or MB and disease recurrence (aHR 1.0, 95% CI 0.77–1.4, aHR 0.86, 95% CI 0.54–1.4, and aHR 1.08, 95% CI 0.78–1.5, respectively). In the univariable analysis both VTE and MB were associated with increased mortality (Table 3). The association with VTE was lost in the multivariable analysis (aHR 1.1, 95% CI 0.88–1.4), but the association with MB maintained (aHR 1.8, 95% CI 1.5–2.3).

In the sensitivity analysis including only IDH-wildtype glioblastoma patients, the occurrence of a VTE during the observation period was also strongly associated with MB incidence (aHR 7.9, 95% CI 3.1–20). No significant association between thrombotic or bleeding complications and mortality was found in these patients (Table S2).

4 | DISCUSSION

Balancing the increased and competing risks of thrombosis and bleeding in cancer patients is complex, especially in glioblastoma, which has one of the highest thrombosis as well as major bleeding incidences among all cancer types. Our study confirms the high cumulative incidence of VTE, extending well beyond the postoperative period. Apart from general risk factors such as age, venous stasis in hemiparetic limbs, prolonged surgery, chemotherapy, angiogenesis inhibitors such as bevacizumab,[31] and possibly the use of dexamethasone,[32] several glioblastoma-specific mechanisms have been implicated in the mechanism causing VTE. Overexpression of tissue factor (activating the clotting cascade) and podoplanin (activating platelets) in glioblastoma cells, and the release of procoagulant microparticles (extracellular vesicles carrying for example tissue factor or podoplanin) by the tumor, promoting coagulation both locally and systemically, have been reported to predispose for VTE.[33–36]

Most arterial thrombotic events (46/50) in our cohort were ischemic strokes, of which more than half occurred during the early postoperative period, which is comparable to results from previous studies.[13,14] Other arterial thrombotic complications including myocardial infarction were uncommon, and this risk was not higher than described in other cancer types.[37] This suggests that the systemic hypercoagulable state in glioblastoma patients predisposes to venous rather than arterial thrombosis, and that ischemic strokes are perhaps more the result of local mechanisms rather than systemic, such as intraoperative damage, or direct mechanical compression, occlusion or infiltration of cerebral vessels by the tumor, as well as tumor-induced local inflammation and coagulation.[13,38,39]

We found a high risk of major bleeding, numerically slightly higher than that of VTE (adjusted 2.5-year cumulative incidence of 14% vs. 12%, respectively). Moreover, MBs were three times more often fatal than VTE events (12 vs. 4 fatal events, respectively). As expected based on literature, most MBs in our cohort were intracranial and largely postoperative, but the incidence of spontaneous (intracranial) major bleedings during the disease course was substantial as well (2.5-year cumulative incidence of 7.3%). Notably, our study showed that an incident VTE treated with anticoagulation was associated with marked increase in major bleeding events (aHR 4.8, 95% CI 2.5–9.3), highlighting the impact of VTE on the prognosis of glioblastoma patients. Our results are in line with a recent meta-analysis which found a 3.66-fold increased risk (95% CI 1.84–7.29) of ICH in glioma patients (tumor grade not specified) treated with anticoagulation for a VTE compared to those without.[40] It could be that the risk we found is not fully representative for modern anticoagulant treatment because in our cohort the majority of patients received LMWH, whereas nowadays direct oral anticoagulants (DOACs) are increasingly prescribed.[41,42] Notably, hardly any glioblastoma patients were included in the large phase 3 trials evaluating the safety and efficacy of DOACs in cancer patients with VTE.[43] Also, prospective studies regarding DOACs in glioblastoma patients are lacking, but available evidence does not show increased safety and (fatal) major bleeding events do occur when using DOACs.[44–46] Therefore, we do consider the incidences described in our study to be applicable to current clinical practice.

Although there is wide consensus on the strong indication for anticoagulation in the first 3 months after a VTE diagnosis, its

TABLE 3 Prognostic impact of thrombotic and bleeding events

	MB (HR, 95% CI)		Disease recurrence (HR, 95% CI)		Mortality (HR, 95% CI)[a]	
	Crude[b]	Adjusted[b]	Crude[b]	Adjusted[b]	Crude[b]	Adjusted[b]
VTE (yes vs. no)[c]	4.9 (2.6–9.3)	4.8 (2.5–9.2)	1.2 (0.90–1.6)	1.0 (0.77–1.4)	1.7 (1.3–2.1)	1.1 (0.88–1.4)
ATE (yes vs. no)[c]	2.1 (0.79–5.9)	2.0 (0.74–5.6)	0.83 (0.52–1.3)	0.86 (0.54–1.4)	1.1 (0.76–1.6)	1.2 (0.80–1.7)
MB (yes vs. no)[c]	N/A	N/A	1.1 (0.78–1.5)	1.1 (0.78–1.5)	1.8 (1.4–2.2)	1.8 (1.5–2.3)

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; MB, major bleeding; N/A, not applicable; VTE, venous thromboembolism.

[a]For mortality only events (VTE, ATE, and MB) after glioblastoma diagnosis are included.

[b]Crude HR derived from univariable Cox regression analysis. Adjusted HR derived from multivariable Cox regression, with adjustment for age, sex, Eastern Cooperative Oncology Group status (≥2 vs. 0–1) and type of surgery (resection vs. biopsy).

[c]Time-dependent variable.

optimal long-term management is debated. Standard duration of anticoagulation for cancer-associated thrombosis according to current guidelines is 6 months, and extended therapy may be offered when the cancer is still active, providing the risk-benefit ratio of anticoagulation is favorable. Glioblastoma is often regarded as a cancer type that is rarely stable for longer periods, and lifelong anticoagulation as secondary prophylaxis may be the target goal.[2,47] Our results, however, indicate that this risk-benefit ratio may not be favorable at all. It is currently unknown whether lower dose apixaban or rivaroxaban,[48–50] or alternatively factor XI inhibition,[51,52] are associated with a lower risk of bleeding. From our findings, we conclude that the decision on treatment duration in glioblastoma patients should be individualized, and the threshold for discontinuing treatment should be lower than for other cancer types.

Our findings may also have implications for primary thromboprophylaxis. Currently, thromboprophylaxis is standard practice postoperatively and during hospitalization in glioblastoma patients. Several guidelines recommend pharmacological thromboprophylaxis in ambulatory cancer patients at high risk of thrombosis, mainly based on the Khorana score.[53] An adapted score addressing the brain as "very high-risk site of cancer" has been used in several studies,[54,55] yet this score is poorly validated for primary brain tumor patients.[53–57] Importantly, the ISTH recommends against routine use of thromboprophylaxis in glioblastoma patients because of the high bleeding risk.[58] The only thromboprophylaxis trial in glioma patients, the PRODIGE trial (randomization between dalteparin 5000 IU OD [$n = 99$] and placebo [$n = 87$]), showed a trend toward decreased VTE (9.1% vs. 15% in 6 months, respectively) but increased ICH incidence (5.1% vs. 1.2%), although it had low statistical power (aimed sample size was 217 patients per group) because of slow accrual.[59] The Cassini trial, evaluating rivaroxaban, had primary brain cancer as an exclusion criterion, and in the AVERT trial, evaluating apixaban, only a small number of patients with primary brain tumors were randomized ($n = 24$).[55,60] Altogether, our findings of a high incidence of bleeding complications support the ISTH recommendation to not routinely start pharmacological thromboprophylaxis in ambulatory glioblastoma patients, although the benefit of low-dose anticoagulation (preventing VTE with subsequent, high-risk, therapeutic anticoagulation) might outweigh the risk in selected patients. Of note, molecular-genetic profiling has been implemented in standard care for diagnosis, prognosis, and targeted antitumor treatment of gliomas.[22] It remains to be investigated which molecular tumor profiles predispose for VTE and could help identification of glioblastoma patients at particularly high VTE risk and guide thromboprophylaxis management decisions in the future.

Our study has strengths and limitations. We have described the largest cohort of glioblastoma patients followed specifically for the occurrence of clinically relevant VTE, ATE, and major bleeding. Within their geographical region, all glioma surgeries were performed in the participating two hospitals, leading to a generalizable study cohort. Limitations include that patient charts of earliest cases in our cohort were largely nondigital with a higher risk of incomplete information compared with the more recent cases. Nevertheless, discharge letters and imaging reports were digitally accessible throughout the whole period, which decreased the risk of missing relevant outcomes. With respect to the third aim, not all established risk factors were available, and not all possible confounders might have been identified because of the retrospective design of the study. For example, we do not have information on previous VTEs in medical history, renal function, or the use of antiplatelet therapy. Further, we did not have an accurate overview of medication use 6 months before the ultimate diagnosis. Because of this, we were unable to estimate the overall bleeding risk associated with the use of anticoagulation during the study period. Also, although we excluded this period in the mortality analyses, the inclusion of 6 months before histopathological diagnosis in our observation period may cause "immortal time" bias. Last, because the World Health Organization classification of gliomas has recently changed because of new insights in and more common use of molecular diagnostics in primary brain tumors,[22] our cohort might include patients with tumors that would now be classified as "IDH mutant astrocytomas" instead of glioblastomas (because the IDH status of the majority of the patients was unknown), possibly with different risk profiles. Even so, the sensitivity analysis with only wildtype IDH tumors showed similar prognostic impact results, though not significant (most likely related to small size of the subcohort).

In conclusion, our study shows a high incidence of both MB and VTE in glioblastoma patients, with both complications associated with poor prognosis. Our observations emphasize the need for prospective studies to determine optimal thromboprophylaxis and VTE treatment strategy in these patients. For now, the particularly high bleeding incidence can be used as an argument to consider a limited duration of anticoagulant treatment (3–6 months, as VTE recurrence risk is highest during this period[61]) in glioblastoma patients diagnosed with incident VTE, and to follow ISTH guidance suggesting against routine pharmacological thromboprophylaxis in ambulatory patients.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

F.H.J. Kaptein: Gathered and verified data, performed the analyses, and primarily drafted the first version of the manuscript. M.A.M. Stals: Gathered data and revised the manuscript critically for important intellectual content. M.Y. Kapteijn: Revised the manuscript critically for important intellectual content. S.C. Cannegieter: Provided

methodological input and revised the manuscript critically for important intellectual content. L. Dirven: Revised the manuscript critically for important intellectual content. S.G. van Duinen: Revised the manuscript critically for important intellectual content. R. van Eijk: Revised the manuscript critically for important intellectual content. M.V. Huisman: Revised the manuscript critically for important intellectual content. E.E. Klaase: Gathered data and revised the manuscript critically for important intellectual content. M.J.B. Taphoorn: Revised the manuscript critically for important intellectual content. H.H. Versteeg: Revised the manuscript critically for important intellectual content. J.T. Buijs: Designed the study and revised the manuscript critically for important intellectual content. J.A.F. Koekkoek: Designed the study, verified data, and revised the manuscript critically for important intellectual content. F.A. Klok: Designed the study, analyzed and interpreted data, drafted the first version of the manuscript, and revised the manuscript critically for important intellectual content.

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SUPPORTING INFORMATION

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